# Ecology of Infectious Diseases in Natural Populations

EDITED BY

B. T. Grenfell and A. P. Dobson

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Ecology of Infectious Diseases
in Natural Populations

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# ECOLOGY OF INFECTIOUS DISEASES

## IN NATURAL POPULATIONS

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# Introduction

*A.P. Dobson and B.T. Grenfell*

## 1 Introduction

The epidemiology of infectious diseases is one of the great triumphs of applied ecology. In particular, the public health importance of parasites has lead to a large literature, exploring their impact on the population dynamics, population genetics and evolutionary biology of human populations. An important milestone was the Dahlem Conference on population biology of infectious diseases, held in 1981. The resulting book (Anderson and May 1982) lucidly summarised the contemporary state of parasite ecology and epidemiology. The meeting was also important in bringing together theoretical and empirical workers from a range of relevant disciplines. Their deliberations, in a series of group reports, set the scene for many developments in parasite ecology over the following decade.

Following the advent of HIV/AIDS, there has since been a particular flowering in the quantitative epidemiology of human infections (Anderson and May 1991). By contrast, work on diseases of naturally fluctuating animal and plant populations has had a lower profile. Although there are large bodies of published research on theoretical and empirical aspects of the ecology of infectious diseases in naturally fluctuating host populations, there has been no recent attempt to bring these together systematically. This is partly happenstance but, as we shall see, probably also arises from a lack of empirical knowledge about the details of many interactions. The Isaac Newton Institute programme on epidemic models, held during January–June 1993, provided the ideal venue for addressing this gap between theory and practice. This volume is based on a workshop which we convened during the second week of March 1993. We followed the Dahlem pattern, bringing together a collection of experts to provide overviews of the subject and produce group reports on important issues. This was a highly interdisciplinary group, ranging from biomathematicians to plant pathologists, veterinarians and wildlife managers. Their collective deliberations led to the synthesis which makes up the remaining chapters of this book.

Before summarising the structure and relationship of these contributions, we explore some broad philosophical issues.

## 2 What is $R_0$?? Who is Arnold?

The transfer of infection is fundamentally a contact process. The central quantity here is the speed of spread of infection through a host population under optimal conditions. This parameter is usually demoted by the symbol $R_0$, which can be defined in a variety of ways, depending on the nature of the host-parasite interaction (Heesterbeek and Roberts, Roberts *et al.* this volume). As students of theology will know, the naming of such a mystical quantity is always likely to be fraught with difficulty. Various names have been proposed for $R_0$: the basic reproduction (or reproductive) rate (or number, or ratio). We would not have the temerity to enter this debate, although a recent mistyping of a piece of dictation by one of us (APD) resulted in a new name for $R_0$ – *Arnold*. Though we hope this usage will spread, we have generally called $R_0$ the basic reproductive ratio in this volume.

## 3 How the book is organized

This is not a guide to the aetiology and pathology of infectious diseases. Instead, it provides a synthesis of current knowledge about the quantitative ecology and epidemiology of infections in naturally-fluctuating animal and plant host population. The word 'naturally' is relative here, since few populations have escaped direct or indirect human intervention. Our definition is therefore based on populations whose numbers are relatively unconstrained by humans, so that the impact of parasitism on 'natural' host dynamics (and of hosts on parasite dynamics) can be assessed. The main population dynamic question is obviously whether parasites tend to 'regulate' host abundance (i.e., reduce the tendency for unconstrained growth or fluctuation in numbers; see Anderson and May (1978) Holmes (1982)) or 'destabilise' it, contributing to variations in host population density (May and Anderson 1978). Which effect predominates in a particular interaction depends crucially on the nature of density dependent (nonlinear) processes in the host-parasite interaction (Roberts *et al.* this volume).

The background chapters present reviews of the current state of theoretical and empirical knowledge about the dynamics of infectious diseases in natural populations. During the meeting, we also convened working groups on four specialist areas: the population biology of microparasites and macroparasites, spatial dynamics of parasitism and genetic and evolutionary issues. Their deliberations are summarized by the four groups reports presented between the background papers below. The volume concludes with a glossary, which gives brief definitions of widely used technical terms, from both theoretical and empirical branches of the subject.

In terms of broad taxonomic and functional classification, we adopt the

standard division of pathogens into *microparasites* (viruses, fungi, bacteria, protozoa) and *macroparasites* (helminths and arthropods) (May and Anderson 1979, Anderson and May 1979). The biological and theoretical bases of this division are discussed extensively in the group reports on microparasites and macroparasites (Dye *et al.* this volume, Smith *et al.* this volume).

The group reports and background chapters are divided between three sections. We use the micro/macroparasite division in the first section, titled *Broad patterns and Processes*, which considers both observed patterns and techniques for modelling them. As these papers tend to focus on pathogens of vertebrate hosts, a number of important groups of interactions are not covered in detail in this sections (plant pathogens, vector borne-infections and insect micropathogens) We therefore devote the second section, *Pathogens, Insects and Plants*, to reviews of interactions between pathogens and non-vertebrate hosts. The main aim of this section is to draw out the special features of these interactions.

Much of the progress in parasite population biology in the last 15 years has been in analyzing the impact of various *heterogeneities* in the host or parasite population (Anderson and May 1984,1985, Nold 1980, Anderson and Gordon 1982, Burdon *et al.* 1989, Kallen *et al.* 1985, Dwyer 1991, Pacala *et al.* 1990, Barlow 1991). A variety of distinct, but not necessarily mutually exclusive, processes produce important heterogeneities in host parasite systems. We have classified them loosely under the following four headings: *immunological*, *spatial*, *genetic* and *ecological*. The final group of chapters focus on the effects these important heterogeneities have on host-parasite interactions in naturally fluctuating host populations.

# 4 The balance between theoretical and empirical research

A central implicit question for the meeting was: *what balance of new theory and empirical work do we need to advance the subject?* A major thrust of this book is that, currently, we particularly need to improve our empirical knowledge of interactions and our ability to manipulate them experimentally. New theoretical tools are also required – particularly in dissecting the dynamics of immunity (Grenfell *et al.* this volume), spatial infection processes (Bolker *et al.* this volume) and host-parasite population genetics (Read *et al.* this volume). However, these processes are often so complex that the models are best extended by reference to detailed empirical studies of particular systems (Gulland, Dobson and Hudson, Hudson and Dobson, all this volume). Constantly confronting new theoretical developments with empirical data allows the assumptions underlying the structure of new models to be examined from an empirical perspective. It also keeps theoreticians focused on real prob-

lems and encourages empiricists to have their results and biological insights clarified using the analytical perspective afforded by well-posed models.

We can divide the requirement for new empirical work into two broad areas. First, we need simply to know more about the diversity of host-parasite interactions – in particular, a greater empirical understanding of the impact of parasites on host-population dynamics is required if we are to resolve the endless 'compensatory versus additive' mortality debate (Holmes 1982, Gulland this volume). Such information is not won easily and depends crucially on a combination of long term detailed studies, controlled experiments, and, ideally, notification schemes for disease incidence. Unfortunately, there are only a limited number of National Centers which act as clearing houses and information centers for long-term data on infectious diseases in natural populations. The Center for Wildlife Diseases at Madison, Wisconsin provides an important model for this in the United States, but other countries – or groups of countries – need to examine the possibility of setting up similar centralized facilities. Only with this sort of information can our comparatively strong theoretical understanding of host-parasite population dynamics be tested and extended, for example, to provide more accurate predictions of the epidemiological impact of anthropogenic effects such as global-climate change.

Second, we require new technologies to dissect the dynamics of individual host parasite interactions. This is particularly important in terms of host immunity and host-parasite population genetics. For example, if sufficient variability can be discerned in molecular genetic studies of helminth parasite transmission stages, such as eggs, this could provide a method for non-destructively monitoring the dynamics of adult norm burden. Such developments would revolutionise epidemiological studies of many parasite groups.

# 5 A brief overview

This section synthesises the wealth of information and opinion generated in the background papers and group reports, in order to draw out common themes.

## 5.1 Microparasites

The empirical review of microparasite incidence concentrates on vertebrate examples (Dobson and Hudson this volume), whilst the chapter by Gulland surveys the impact and potentially regulatory role of pathogens in wild animal populations. The paper by Briggs *et al.* provides examples from studies of pathogens of insects, while Swinton and Anderson deal with plant pathogens. Heesterbeek and Roberts and Barlow provide respectively, an introduction

to mathematical models for microparasites and a 'field guide' to models that have been used in studies of infectious disease of wildlife. The microparasite group report (Dye *et al.* this volume) focused on the following major issues.

### 5.1.1 Persistence of infection in populations

Persistence is emerging as a problem in reconciling models for microparasites with observed patterns of empirical data. The group reports on microparasites and spatial processes and the background papers on observed patterns and impact all examine this problem from a variety of perspectives. Numerous recent studies emphasize the importance of spatial heterogeneity in perpetuating epidemic infections in host metapopulations (Bolker *et al.*, Dye *et al.* this volume). Though this insight is not new (Bartlett 1957), the development of individual-based models (and the computing technology necessary to implement them) has recently highlighted the importance of geographical and social space.

However, a careful balance is needed between emphasizing this particular heterogeneity and examining other biological phenomena which may be equally important, but less topical. For example, recrudescence of latent infections is probably very important in the persistence and re-emergence of herpesvirus infections (Grenfell and Smith 1990). Each of the discussions on this problem emphasizes the importance of sequentially adding ecological and epidemiological information to mathematical models. Similarly, we need to acknowledge the empirical fact that many microparasites persist in host species that live at low density, in social systems where contacts between individuals or social groups are minimal. In this case, we are likely to need individual-based models that more accurately reflect actual contact patterns, as determined by the host's social system.

We still need more experimental studies that address the importance of pathogens in regulating host populations and the role they play in determining the geographical range of species, both directly (by exclusion) and indirectly by apparent competition (Price *et al.* 1986,1988). In both these areas, the development of more powerful empirical tools that allow us to differentiate between infection and disease are needed (Gulland this volume). These will considerably strengthen our ability to effectively monitor endemic infections which may lead to disease outbreaks when a population is either stressed, or suddenly increases in density.

### 5.1.2 Conservation and disease control

The control of infectious diseases in natural population will increasingly become a problem as wildlife become concentrated into National Parks and reserves. The background papers aired the spectrum of opinion about the relative merits of two traditional forms of pathogen control: culling versus

vaccination (Heesterbeek and Roberts, Barlow this volume). Energetic discussion of the issue in the group sessions indicated that the 'best' approach indicated in published studies has usually been a function of model structure, economics, the availability of effective vaccines and public opinion. At present, culling is increasingly replaced by preventive vaccination for domestic animals, while culling continues to be used for wildlife. This asymmetry is changing, as more people emphasize the necessity of reducing human activities that have a detrimental impact on biodiversity. In this context, the widespread success of vaccination in the control of rabies in European wildlife is an excellent example of an ecologically sensitive campaign. In many cases, we need to take this exercise a stage further and examine the role that pathogen control can play in maintaining viable populations of many endangered species (Dobson and May 1986, May 1988, Thorne and Williams 1988, Scott 1988, Spalding and Forrester 1993). The strong consensus to emerge from these studies of pathogens and endangered species is that the small population size of many host species is likely to preclude them from maintaining species specific pathogens that are a major threat to their viability. Instead, the reduced levels of genetic diversity that characterize increasingly rare species may increase their susceptibility to epidemic outbreaks of pathogens acquired from more common species. To understand the epidemiology of these problems fully, we must turn to models for pathogens that infect a range of host species (Begon and Bowers this volume) and studies that examine interactions between pathogens and host genetic diversity (see Lively and Apanius, Read *et al.* this volume).

The properties of multi-species host-parasite models can be examined from two main perspectives: first, what happens when several species of parasite utilize a single host species and secondly, what happens when a single pathogen utilizes a range of hosts species (Holt and Pickering 1985, Hochberg and Holt 1990, Begon and Bowers this volume). A number of important questions remain to be addressed in this area. In particular, it is intriguing that models can be readily constructed that allow a single host population to support a large diversity of macroparasite species (provided each parasite species is sufficiently aggregated in its distribution) (Dobson and Roberts 1994, Roberts and Dobson 1995), while models for multiple microparasite strains usually require the addition of some form of spatial or other heterogeneity in the host population if more than one microparasite is not going to dominate and drive all others to extinction (Nowak and May 1994).

Further development of models for pathogens that infect more than one host species will allow us to examine other problems. In particular, we need to understand the role that 'natural' levels of biodiversity (number of species) in a region play in either buffering epidemic outbreaks, or providing a diversity of hosts species which mediate longer term pathogen persistence.

### 5.1.3 Microparasites and community structure

Such studies will also address the role that parasites play in food webs – a topic that is almost completely unexplored (Anderson and May 1986, Dobson and Hudson 1986, Dobson and Crawley 1994, Grenfell 1992). Nevertheless, everything we discuss in this book suggests that pathogens may have a bewildering array of potential effects on our understanding of food web structure. For example, counting the numbers of parasites in a food web will increase the numbers of species in an ecological community by a factor between 2 and 5, obviously, this will lead to increases in estimates of the number of species that each species interacts with. Ultimately, this may alter our traditional perspective of a food web as a pyramid of organisms with many producers on the bottom and a few consumers on the top, to a structure that more closely resembles a rhomboid, with each higher level of consumers being consumed by an increasing diversity of parasites. Moreover, there are a number of empirical examples where the introduction of pathogens into already complex communities have led to epidemics that drastically change the abundance of some species. Where these changes in density effect numerically dominant or 'keystone' species they can produce cascade effects that can generate major changes in the relative abundance of other species in the community and significant changes in ecosystem function (Dobson and Hudson 1986, Dobson and Crawley 1994).

### 5.1.4 The role of vectors

Dye and Williams (this volume) consider the conditions under which indirect transmission (via vectors or other intermediate hosts) will have 'special' dynamical effects, compared to direct transmission. They show that the degree of nonlinearity (density dependence) introduced by the vector, as well as the relative timescales of vector and definitive host components of the parasite life cycle, are crucial. They conclude that the vector component is so fast in its dynamics for microparasites that indirect transmission may not have a qualitative dynamical effect. A different tale may emerge for the more complex life cycles of macroparasites (Smith *et al.* this volume).

## 5.2 Macroparasites

Hudson and Dobson (this volume) introduce observed patterns of macroparasite infection, whilst the chapter by Gulland concentrates on parasite impact. Roberts, Smith and Grenfell (this volume) review models for host-macroparasite interactions and the paper by Grenfell, Dietz and Roberts considers immuno-epidemiological models in detail. The macroparasite working group (Smith *et al.* this volume) concentrated mainly on how current macroparasite models need to be refined to describe aggregation and other biological complexities. We review these, and other issues which arose, below.

### 5.2.1 Parasite aggregation

Macroparasitic infections tend to fluctuate less through time than microparasites (Dye *et al.* this volume), consequently, persistence is much less of an issue for the former than the latter. Instead, the main manifestation of heterogeneity in macroparasite abundance is in the *frequency distribution* of parasite burdens between hosts. The characteristically aggregated nature of this distribution is reflected both in observed patterns of parasitism (Hudson and Dobson this volume) and the associated theoretical literature (Roberts *et al.* this volume). The quantification and causes of aggregation are a major preoccupation of the macroparasite group report (Smith *et al.* this volume). Much still needs to be understood in this area, though both theoretical (see Woolhouse (1992) and Grenfell *et al.* (this volume)) and empirical studies (Smith *et al.* this volume) underline the importance of individual differences in host response (due to immunological or other inherent variations). Each of these approaches will provide important insights into the mechanisms producing aggregation in the distribution of parasites. However, a three-pronged attack should be mounted on this problem if we are to obtain a more complete understanding that encompasses interactions between processes that operate at very different temporal and spatial scales: (1) an experimental approach – this should examine the role of host genetics, prior experience, immunity, nutrition and spatial distribution of infective stages and susceptible hosts in determining resultant degree of aggregation; (2) the development of mathematical models which more explicitly consider heterogeneities (Grenfell *et al.* this volume); (3) comparative approaches that examine observed distributions from a wide variety of host and parasite communities (Dobson and Shaw in preparation).

### 5.2.2 Climate and seasonality

Much more work is needed to incorporate the effects of climate into models for macroparasites. There is a large literature on the effects of climate on survival of free-living stages and the potential for epidemic outbreaks (Levine 1963, Wallace 1961). Climatic factors are important in creating variability, which may aid or reduce persistence, and in 'stimulating' the evolution of traits such as arrestment (hypobiosis) and the evolution of complex life cycles. Ironically, work in these areas received reduced funding and consequent reduced interest once cheap drugs anthelmintic drugs became available in the 1950s and 1960s. Now that resistance has appeared to many drugs, it is likely that an understanding of how parasites are dependent upon the weather will receive new significance (Dobson and Carper 1992, 1993). If we are entering a period of global climate change, it is important that future models of parasite host dynamics consider the effect of changing climate on the distribution of parasites and their hosts.

A major component of the interaction between parasites and meteorological variation is seasonality. Most models for both macro- and microparasites ignore the potential influence of annual and diurnal variation on the dynamics of infection (though see Roberts and Grenfell (1992), Woolhouse *et al.* (1993)). Where these effects have been explored, they suggest that seasonal variation in transmission rates and host birth rates may have important forcing effects on the long-term dynamics of parasite-host systems (Roberts and Grenfell 1991,1992, Aron and Schwartz 1984, Yorke *et al.* 1979, Grenfell *et al.* 1995, Reif 1976).

### 5.2.3 Indirect transmission and complex parasite life cycles

With the exception of cestodes (Gemmell *et al.* 1986), a large lacuna is in mathematical models for helminths with indirect life cycles. When do the dynamics of the intermediate host become important? Obviously the relative time scales of the birth, death and transmission processes that operate at each stage of the life cycle are important in determining the population dynamic outcome. In many cases we can assume that the transmission stage mediated by the vector occurs on a fast time scale and will return to its equilibrium rate rapidly following perturbations. Under these circumstances, transmission rates will only be strongly dependent upon vector density when this is low (Hasibeder *et al.* 1992, Dobson 1988). When vector densities are much higher then limiting levels, the maximum parasite transmission rate will be constrained by other features of its life life cycle.

### 5.2.4 Community ecology of macroparasites

There is an increasing literature describing the observed structure of helminth communities (Bush, Aho and Kennedy 1990, Kennedy, Bush and Aho 1986, Sousa 1994). These studies have provided evidence that the local ecological conditions may overule phylogenetic constraints in determining the parasite assemblage observed in any host species in any particular location, and that communities of long-lived warm blooded hosts acquire more diverse assemblages of helminth parasites than those of short-lived poikilothermic hosts (Kennedy *et al.* 1986). Ironically, interest in parasite community structure has developed at a time when ecologists have shown increasing interest in metapopulations and habitat fragmentation. Most parasites live as populations which are fragmented into metapopulations on several spatial scales; each host operates as a patch on the most local scale, while the host's home range and the conspecifics that share this area with it create a second scale of habitat fragment for the parasite. Many of the mathematical frameworks developed for metapopulations probably apply best to macroparasites and their hosts, yet very few attempts have been made to examine parasite commmunities from this perspective. This lacuna emphasizes that more work is needed

on the processes determining the structure and dynamics of macroparasite communities. In particular, we need a more quantitative understanding of the role that different potential mechanisms play in allowing a diverse array of parasite species to coexist within the same host population. Key questions that need to be addressed here are: what are the relative roles of competition (direct and host mediated; interspecific and intra-specific), aggregation and life history strategies of parasites in determining the observed level of parasite biodiversity? (Dobson 1985, Dobson 1990, Dobson and Keymer 1990, Kennedy *et al.* 1986, Bush *et al.* 1990, Sousa 1994, Dobson and Roberts 1994, Roberts and Dobson 1995). On a larger scale we still need to understand the role that parasites play in determining the interactions between species that structure ecological communities and ecosystems.

## 5.3 Immuno-epidemiology

Lloyd (this volume) gives an extensive review of the immuno-epidemiology of parasitism in wildlife vertebrate host populations. Apart from a few studies, there is relatively little direct information, so that the review proceeds largely by analogy with the immunology of domestic animals. The immunology of persistent macroparasitic infections is rather better documented in wildlife populations than that of microparasites, so that Grenfell *et al.* (this volume) explore theoretical aspects of immuno-epidemiology in the context of (macroparasitic) nematode infections of ruminants.

Models including these immunological complexities must take account of a host's previous experience of infection (and therefore of host age). This is also the case with patterns of aggregation, so that Grenfell *et al.* examine how the development of immunity and aggregation influence patterns of parasitism. This exercise illustrates the importance of intrinsic differences between hosts in determining observed aggregation patterns and the potentially complex interaction between immunity and parasite-induced host mortality. However, these are still only equilibrium results and, again, we stress that dynamic models can only be produced in the context of detailed empirical knowledge of particular systems (Lloyd this volume). An exciting potential development is the inclusion of within-host immunodynamics into individual-based epidemiological models.

However, such models will require still more refined empirical knowledge for their construction. A particularly important area for modelling is to disentangle the epidemiological implications of neonatal tolerance, whereby early exposure to maternally-derived parasite antigens can 'tolerise' young animals to subsequent infection (Grenfell and Michael 1992, Lloyd this volume).

One crucial area that requires more empirical study is the interaction between immunity, stress and malnutrition (Lloyd this volume). Sadly, Anne Keymer's death has curtailed some very exciting work in this area. Her ex-

perimental demonstration that rats on a reduced protein diet are unable to immunologically control the rate at which they acquire nematode infections has profound implications for studies of pathogens in free-living host populations. Although our understanding of the immunological dexterity of a variety of domestic animals is increasing exponentially, it is crucial to consider which components of the immune system are most hampered by the frequent periods of low nutrition that face most free-living animal species.

## 5.4 Spatial Processes

As befits its importance, spatial heterogeneity is discussed in many parts of the book. The main reviews are the background chapter by Mollison and Levin, the spatial group report (Bolker *et al.* this volume) and Barlow's survey of wildlife disease models. Bolker *et al.* lucidly summarize the problems of measuring and modelling spatial heterogeneity, so that we restrict ourselves here to a few synthetic comments.

# 6 Representing spatial scale

This is a central problem in epidemiology. Since we cannot include the full hierarchy of spatial relationships, we must pick out a few important scales at which to analyze the behaviour of the system. A useful analogy here is with spatially well documented human diseases such as measles (Grenfell *et al.* 1995). There, we can measure transmission rates relatively well at local spatial scales (family level) and at the level of large populations. However, there are few data sets which allow us to measure $R_0$ at the intermediate spatial level (e.g. schools). Ironically, this is just where the nonlinearities in transmission are strongest. This underlines one of the most important uses of models – identifying where (in this case at which scale) we need to concentrate our efforts to collect appropriate empirical data.

Another important question is how the infection rate scales with host density and population size at different spatial scales (Barlow this volume). Much has been done theoretically in this area (Mollison and Levin this volume), though there is more to do in modelling the balance between population size and density in determining transmission rates at different scales in relatively weakly coupled metapopulations. However, the real need is for more empirical studies which explicitly measure the relationship between infection rate and host population density (de Jong *et al.* 1995) – ideally for hosts with different dispersion patterns (plants) or social systems (animals).

### Spatial models and data

Mollison and Levin (this volume) evaluate the different approaches (deterministic/stochastic, patches/individuals etc.) to allowing for spatial hetero-

geneities in epidemics. Spatial models have a beauty all their own, however (to return to the central theme of this volume) the most successful approaches confront models with data. Bolker *et al.* (this volume) outline a number of case studies along these lines. The advent of epidemiologically relevant data from remote sensing should provide a further significant impetus to the integration of models and data.

## 6.1 Evolution of Parasite-Host relationships

### 6.1.1 Virulence

The majority of work on coevolution has focused on microparasites and their hosts (Levin and Pimentel 1981, Fenner and Ratcliffe 1965, May and Anderson 1990, Dwyer *et al.* 1990, Frank 1992). It has proved much harder to examine the coevolution of virulence and resistance in macroparasites, though a number of studies are beginning to address this (Herre 1993, Jaenike 1993). Theoretical work suggests that increased virulence in a macroparasite will reduce the observed level of aggregation in the parasite's distribution (Anderson and Gordon 1982). Models that incorporate this effect recapture the result obtained for most microparasite models that strains of intermediate levels of virulence can usually outcompete macroparasites with negligible virulence (Dobson and Merenlender 1991). Nevertheless, because the aggregated distribution of each parasite strain increases its chances of persisting in the host population, it is quite possible for a host population to support a wide diversity of parasite strains that exhibit a range of levels of virulence.

Virulence is commonly perceived to manifest itself through direct damage to the host's tissues, however, it is also likely that both macroparasites and microparasites reduce their host's fitness through their indirect impact on the energy budget of the host. Although each individual parasite diverts only a small fraction of the host's diet to itself, hosts that are heavily infected with macroparasites, or malnourished hosts, are always the first to show acute symptoms of disease. This aspect of parasite virulence has not been explored in a theoretical framework. The rapid recent development of 'individual-based' models as a tool for examining interactions between populations and their resources (DeAngelis and Gross 1992, Kooijman 1993) provides a framework that could be used to more carefully examine the complex interaction between virulence and host nutrition.

### 6.1.2 Host behaviour and sexual selection

Parasite induced modification of their hosts behaviour is a subject that has received increasing attention in the last ten years (Dobson 1988, Lafferty 1992, Gotelli and Moore 1992). The best documented examples of parasites modifying host behaviour continue to be dominated by cases where the parasite

modifies the behaviour of an infected intermediate host in order to increase its rate of transmission to the next host in the life cycle. However, a variety of empirical and theoretical studies have stemed from the intriguing suggestion that parasites may play a crucial role in sexual selection; a topic that continues to generate interest ten years after it was first suggested by Hamilton and Zuk (Hamilton and Zuk 1982). The problem was only obliquely addressed in the discussions at this meeting; the present consensus suggests that although parasites may be an important selective agent for the evolution and maintenance of sexual selection, they are only one of a variety of mechanisms that may lead to the develop of secondary sexual characteristics (SSC's). Although some very elegant experiments provide some support for the importance of parasites that alter SSC's, comparative evidence for widespread interactions between parasite burden and degree of sexual dimmorphism remain equivocal (Hamilton and Zuk 1982, Read 1988, Balmford and Read 1991, Clayton *et al.* 1992, Clayton 1991).

### 6.1.3 Genetic variability and heterogeneity in susceptibility

There is increasing theoretical interest in this area. By contrast, there are very few good field data sets on the population genetics and coevolution of hosts and parasites. Our current understanding is based on very few path-breaking studies, which provide a tantalising glimpse of the potential role of parasites in maintaining host genetic diversity (May and Anderson 1983, Frank 1992, Gulland *et al.* 1993). Further long-term studies that combine molecular ecology with more traditional approaches are required to address these issues.

The evolution of resistance to chemotherapy by parasites and their vectors received less attention than we would have liked. Ironically, this is an area where classic evolutionary responses of pathogens to the selection pressure provided by anthelmintic drugs have been almost overlooked in the main stream of evolutionary studies. The evolution of drug resistance is a topic which may ultimately cause medicine to revert to a state more characteristic of the late 19th century, than the late 20th century. Resistant strains of tuberculosis are an increasing problem in hospitals in the United States and Europe, several vets at the conference independently reported the resurgence of TB in wildlife and veterinary studies.

## 7 Topics not covered in the book

There remain many fascinating problems still to be addressed in ecological studies of parasites and their hosts. The limited time available for our meeting meant that several important topics escaped our agenda. We focused on an exchange of ideas between theoreticians and empiricists. This left relatively

little time for the methodological discussions and epidemiological surveys, which are a major part of most wildlife disease meetings. This in no way detracts from our view as to the importance of these areas. Indeed they are the only way to address the incredible paucity of empirical studies on free-living host-parasite systems. This lack of empirical information means it may be some time before we can address more general ecological questions such as 'What is special about parasites when compared to predators?' We know, for example, that parasites have impacts on fecundity as well as mortality, plus in general faster population growth rates and ability to evolve faster than their hosts. How much do these and other factors increase their importance as natural regulators or destabilisers of free-living populations?

In terms of specific omissions, a section on parasites 'invasions' and emergence of new pathogens would have been useful – however this issue is covered in several chapters. More importantly, a specific section on the dynamics of host-parasite coevolutionary phylogenies would have been timely. In particular, why are hosts characterized by a few genes for resistance, while pathogens have a great variety of genes for virulence (Frank 1992)? Or is this only true for plants and fungal pathogens?

Finally, the impact of new developments in molecular biology on studies of infectious disease of wildlife was not a specific focus of this meeting. Such studies – for example, the extension of measles saliva tests to wild animal morbilliviruses – are likely to become crucial to the development of the subject.

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# The Impact of Infectious Diseases on Wild Animal Populations—a Review

*F.M.D. Gulland*

## 1 Introduction

It is well accepted that infectious diseases have been among the dominant selective forces influencing human populations over the past 10,000 years (Haldane 1949, McNeill 1976). However, despite theoretical studies suggesting parasites may be involved both in the regulation of host abundance and the maintenance of host genetic diversity (Anderson and May 1978, May and Anderson 1978, Anderson 1979 and 1981, Hamilton 1982, O'Brien and Evermann 1988) our understanding of the impact of infectious diseases on wild animal populations remains poor. Although parasitism, by definition, is associated with morbidity and mortality of the host (Anderson and May 1978, Price 1980), the traditional belief has been that 'well-adapted' parasites do little harm to their hosts, so as to prevent their own eradication (Grundman *et al.* 1976, Price 1980). This view is now questioned, as theoretical studies indicate that many co-evolutionary pathways may be followed, depending upon the relationships between parasite pathogenicity and transmission efficiency (Anderson and May 1982, May and Anderson 1990, Dobson and Merenlender 1991, Toft and Aeschlimann 1991). Thus, although the literature abounds with reports of infectious disease agents causing mortality in individual wild animals, these cases have been interpreted as resulting from an 'imbalance' in the natural host-parasite interaction. Such 'imbalances' may result from the introduction of an infectious agent into a naive wildlife population by man, classically exemplified by avian malaria in Hawaii and rinderpest in Africa (Warner 1968, Van Riper *et al.* 1986, Plowright 1982), or by an alteration of the host's resistance to infection.

Typically, diseases of wildlife have been investigated by performing pathological examinations on carcasses that are found incidentally, or producing lists of parasites identified in small samples of host species. There have been few attempts to assess the impact of a disease on the host population rather than upon an individual, or to describe the distribution of the disease agent in a manner sufficient to understand its epidemiology. The little information available on distribution of infectious diseases in wild animals comes mostly from large scale investigations into diseases that also infect man or his domestic stock (reviewed by Acha and Szyfres 1987, Brack 1987, Pastoret *et al.*

1988, Plowright 1988b, MacPherson and Craig 1991). However, as wild animal populations diminish and interest in their conservation increases, the importance of investigating the impact of disease in wildlife at a population level has been recognised (Dobson and May 1986, May 1988, Plowright 1988a, Scott 1988). The paucity of understanding of wildlife disease epidemiology thus arises not only from this oversimplified view of parasitism, but also from the traditional approach to investigating disease in wildlife and the difficulties involved in collecting such information (Plowright 1988a).

Infectious agents can exert important effects on host population dynamics both when they are endemic or epidemic. When endemic, their effects on host reproduction and survival can decrease host abundance. An important question is whether these effects are regulatory or not (i.e. host populations with the parasite are maintained at a lower density than those without). For a parasite to regulate a host population, it must have demonstrable density-dependent effects on either host reproduction or survival (Hassell 1982). Theoretical studies and experiments with laboratory animals demonstrate that parasites can regulate host populations (Anderson 1979 and 1981, Anderson and May 1978, May and Anderson 1978, Scott 1990, Heesterbeek and Roberts this volume, Roberts *et al.* this volume). However, apart from the well-documented example of *Trichostrongylus tenuis* in red grouse, *Lagopus lagopus*, (Hudson *et al.* 1985, 1992, Hudson and Dobson this volume), evidence from free-living populations is limited, as little data other than parasite mean prevalence and intensity is usually available.

Mass mortalities resulting from epidemics may play a more important role than density dependent factors in the dynamics of some populations (Harwood and Hall 1990). Epidemics can have severe consequences for wildlife if they reduce populations sufficiently to allow stochastic events to cause their extinction (Dye *et al.* this volume).

The aim of this paper is to review the available empirical information on the impact of infectious diseases on wild animal populations, concentrating on effects on vertebrate populations.

# 2 Methodology

To assess the impact of an infectious disease on a host population, both parasite and host distributions must be described – a process with enormous practical difficulties. Infection of wild animal populations may be determined directly or indirectly, the latter by detecting the response of the host to the presence of the parasite. The distinction between 'infection' and 'disease' has been clarified by Scott (1988), 'infection' simply referring to presence of the parasite within a host individual or population, while 'disease' refers to a clinical condition that can be observed or measured. Infection by macropar-

asites is usually detected by looking for the parasite or its offspring (eggs or larvae) in the host or its fomites and intensity of infection in individual hosts determined by counting macroparasites directly (MAFF 1971). This has important implications for the study of macroparasite dynamics, as these pathogens do not replicate in the host and the clinical picture is dependent upon the number of worms harboured by the host.

As most macroparasites tend to be over-dispersed within the host population, so that few individuals are heavily infected while most are lightly or uninfected (Anderson 1982, Anderson and Gordon 1982, Keymer and Dobson 1987), examination of only a small sample may miss heavily infected hosts (Scott 1988). In addition, a highly pathogenic parasite may kill its host before it is sampled, allowing only low infestation rates to be sampled. Microparasite infections can also be detected directly (by culture from tissue samples), but are often detected indirectly by detecting host antibody responses to infection, or using antibodies in vitro to detect antigenic products of the parasite (Voller and Bidwell 1988). Problems exist with interpretation of serological responses, as antibody production depends upon the ability of the host to develop an immune response and the longevity of the response, which in turn are influenced by such factors as host age, genetics and nutritional status. Definitions of sero-positivity and sero-negativity are often based on arbitrary levels determined from work in domestic stock. In addition, a positive result cannot usually distinguish between a previous or a current infection, and in young animals may result from transfer of antibodies from mother to offspring. To quantify infections in the host, difficulties in gaining access to and restraining wild animals for examination mean that sampling is often opportunistic, so that samples are rarely suitably age-stratified or diverse enough to detect heterogeneity in host-parasite associations (Bertram 1973). Difficulties in access to wild animals also mean that little is known about the relationship between infection and disease in these populations, although techniques are now being developed to examine animals without restraint (Thompson and Hammond 1992).

Determining the effects of infection on host population dynamics involves quantifying host reproduction and survival. These parameters are extremely difficult to determine in free-living populations, due to difficulties in finding and observing animals in their natural habitats. Wild animals tend to manifest few recognizable signs of disease, and often separate from others to hide when affected (Young 1969). If mortality is estimated from carcass recovery rather than censuses of the live host population, it may be underestimated due to the difficulty of finding carcasses (Scott 1988, Wobeser and Wobeser 1992, Philibert *et al.* 1993). In addition, infectious disease may increase susceptibility to death from other causes, such as predation (Rau and Caron 1979, Hudson *et al.* 1992), so that mortality from disease is underestimated. Once

a carcass is found, if infectious disease is not looked for, mortality may be attributed to other factors, such as weather and low nutritional plane, that can affect host mortality but may also directly increase host susceptibility to disease (see below). Most studies on free-living wildlife are observational rather than manipulative. This means that although negative correlations between parasite load and fitness components have been documented, the alternative hypothesis that both fitness and parasite load are affected by another factor cannot be ruled out (Lehmann 1993).

A number of graphical methods of analysis have been developed to detect parasite-induced mortality from data on parasite prevalence and intensity. These include peaked host age-parasite intensity curves concomitant with a decrease in the degree of dispersion of parasites in older classes of host (Anderson and Gordon 1982, Gordon and Rau 1982, Pacala and Dobson 1988); a slope of less than 2.0 for a log-log graph of variance versus mean intensity of infection (Anderson and Gordon 1982); major differences between truncated and non-truncated forms of a theoretical frequency distribution for the parasite (Crofton 1971, Lester 1977) and the use of confidence ellipses to compare multiple growth curves (Szalai *et al.* 1992). Because of the difficulties involved, the effects of disease on wild animal mortality have been considered to be compensatory rather than additive (Holmes 1982). However, this probably reflects the difficulty in documenting host population dynamics in the absence of disease agents compared to in their presence, without altering other factors influencing host population dynamics. Experimental studies on captive animals clearly demonstrate an additive effect of parasites on reduction of host reproduction and survival (Saumier *et al.* 1986, Scott 1990).

# 3 Impact on host reproduction

Parasites may reduce reproduction of a host population either directly by damaging reproductive organs, decreasing fecundity and/or neonatal survival, or indirectly, by decreasing growth rate and, therefore, age at first reproduction or modifying host behaviour. Direct effects resulting from host castration are common in invertebrates (Lauckner 1986), while effects on fecundity and neonatal survival have been reported in wild vertebrates. In addition, a number of recent experimental studies demonstrating pathogenic effects of ectoparasites on avian reproduction by reducing nestling survival have been performed (reviewed by Lehmann 1993). These effects on vertebrate reproduction are summarised in Table 1.

Reproduction of wild animals is often limited by behaviourial mechanisms such as territoriality, dominance hierarchies and mate choice. Parasites have been shown to influence movement and social behaviour of laboratory mice (Rau 1984, Hay *et al.* 1985). Although parasites are known to alter movement

| INFECTIOUS AGENT MICROPARASITES | HOST | REFERENCE |
|---|---|---|
| ** *Brucella* spp. | Wide host range | McCaughey 1968<br>Witter 1981 |
| | Bison | Wuerthner 1990 |
| * *Chlamydia psittaci* | Koala (*Phascolarctos cinereus*) | Brown and Grice 1984<br>Wiegler *et al.* 1988 |
| * *Plasmodium relictum* | Hawaiian crow (*Corvus hawaiiensis*) | Jenkins *et al.* 1989 |
| *** *Plasmodium mexicanum* | Fence lizard (*Sceloporus occidentalis*) | Schall 1983 |
| MACROPARASITES | | |
| *** *Trichostrongylus tenuis* | Red Grouse (*Lagopus lagopus*) | Hudson 1986<br>Hudson and Dobson 1991<br>Hudson *et al.* 1992 |
| ** *Scistocephalus solidus* | Three-spined stickleback<br>*Diplostomum gasterostei*<br>(*Gasterosteus aculeatus*)<br>*Echinorhynchus clavula* | <br><br><br>Pennycuick 1971 |
| ** *Cuterebra grisea* | *Microtus townsendii* | Boonstra *et al.*1980 |
| ** *Philornis* spp. | Pearly-eyed thrasher (*Margarops fuscatus*) | Arendt 1985<br>Uhazy and Arendt 1986 |
| | Puerto Rican Sharp-shinned hawk (*Accipiter striatus venator*) | Delannoy and Cruz 1991 |
| ** *Haemophysalis leporispalustris* | Snowshoe hare (*Lepus americanus*) | Keith and Cary 1990 |
| *** *Dermanyssus prognephilus* | Purple martins (*Progne subis*) | Moss and Camin 1970 |
| | Cliff swallows (*Hirundo pyrrhonota*) | Brown and Brown 1986 |
| | Bank swallows (*Riparia riparia*) | Hoogland and Sherman 1976 |

Table 1. The impact of infectious disease agents on reproduction of wild vertebrate populations.

* indicates studies are observational, ** indicates some degree of quantitative assessment has been made, *** indicates experimental manipulations and/or mathematical models have been used to investigate the importance of the disease at a population level.

| INFECTIOUS AGENT MICROPARASITES | HOST | REFERENCE |
|---|---|---|
| ** *Trichostrongyle* spp. | European rabbit (*Oryctolagus cuniculus*) | Dunsmore 1981 |
| ** *Protocalliphora hirundo* | Barn swallow (*Hirundo rustica*) | Shields and Crook 1987 |
| * *Ornithodorus amblus* | Guanay cormorant (*Phalacrocorax bougainvilli*)<br>Peruvian booby (*Sula variegata*)<br>Peruvian Brown Pelican (*Pelecanus occidentalis thagus*) | Duffy 1983 |
| ** *Ornithodoros concanensis* | Cliff swallow | |
| *Argas cooleyi* | (*Hirundo pyrrhonota*) *Oeciacus vicarius* | Chapman and George 1991 |
| * *Argas robertsi* | Cattle egret (*Ardeola ibis*) | McKilligan 1987 |

Table 1 (cont.). The impact of infectious disease agents on reproduction of wild vertebrate populations.

* indicates studies are observational, ** indicates some degree of quantitative assessment has been made, *** indicates experimental manipulations and/or mathematical models have been used to investigate the importance of the disease at a population level.

of wild animals (Steck and Wandeler 1980, Anderson and Trewhella 1985, Artois and Aubert 1985, Schall 1990) the interaction between parasitism and host behaviour in free-living populations remains unclear. Parasites may influence social status, and conversely, social status may influence resistance to infection. In host species in which dominance hierarchies are associated with conflict over access to food and mates, two conflicting theories on the relationship between dominance and parasite load exist. There is usually a positive correlation between social status and intake of preferred food (Appleby 1980). If preferred resources are associated with higher concentrations of infective stages, high social status will lead to increased risk of infection (Hausfater and Watson 1976, Halvorsen 1986). However, if good condition results from high status and confers increased resistance to infection, a negative correlation between status and intensity of infection would be expected (Prins 1987). This interaction between social status and infection can have

important consequences on host population dynamics. If parasites decrease reproduction yet are aggregated in the animals with the highest reproductive success, such aggregation would tend to increase suppression of host population growth. It may also counteract inbreeding within the dominant segment of the population and act as a method of stabilising selection (Halvorsen 1986, Folstad *et al.* 1989).

Parasite effects on host behaviour may also reduce host reproduction by modifying parental care of the young. For example, in bighorn sheep lamb survival is correlated with suckle duration, and ewes shedding higher levels of lungworm larvae in their faeces spend less time suckling lambs than do ewes with lower faecal larvae counts (Festa-Bianchet 1988).

Hamilton and Zuk (1982) have proposed that parasites and pathogens play an important role in the development of male traits that affect female choice. This theory has aroused considerable interest and controversy and results are conflicting, probably due to the complexity of the processes and number of confounding variables involved (Bradbury and Andersson 1987, Endler and Lyles 1989, Read 1988 and 1990, Harvey *et al.* 1991).

# 4 Impact on host survival

The devastating effects of epidemics such as Rinderpest in Africa and Phocine Distemper Virus (PDV) in Europe leave little doubt that infectious diseases can cause mortality of wildlife. In addition, as wildlife disease has traditionally been investigated by examining carcasses to determine cause of death, there is a vast literature describing mortality of individual wild animals associated with the isolation of infectious agents from their tissues (reviewed in Davis and Anderson 1971, Davis *et al.* 1981, Neiland and Dukeminier 1972, Dietrich 1981, Fowler 1981 and 1986, Kinne 1985, Benirschke 1986, Bengis and Erasmus 1988). Unfortunately, little is known about many such host-parasite interactions in the live animal. Increasingly, attempts are being made to evaluate the effects of infectious agents on survival of host populations rather than individuals. This is difficult to do, however, as it is difficult to control other factors that may cause host mortality. These factors may also modify the host-parasite interaction (see below), so that their control indirectly modifies the impact of the parasite on the host. It is really only when an infectious disease has been controlled and mortality of the host population shown to decrease that an infectious disease has been accepted to exert an effect on the host population dynamics. This situation is rare, due to the difficulties, expense and ethics of treating wildlife (see Hall and Harwood 1990). However, control of infectious agents that infect man or domestic animals as well as wildlife (such as rabies and rinderpest) do provide examples of wild populations increasing after the control of infectious agents (Steck 1982,

Dobson and Hudson 1986).

Historically, wild populations were believed to cope with perturbations such as disease, but as these populations dwindle, infectious agents causing relatively low levels of mortality are now considered to exert important effects on host demography, as well as genetics (May 1988, Thorne and Williams 1988, Cooper 1989, Harwood and Hall 1990). In addition, relatively non-pathogenic infectious diseases may be important in mediating competition between species, as classically suggested by Park (1948) and more recently by Schall (1992) with a study on *Anolis* lizards in the Caribbean. Infectious agents reported to reduce survival of wild populations, either due to the epidemic nature of the disease or as a result of relatively detailed ecological investigation and analysis of endemic diseases, are listed in Table 2.

# 5 Factors influencing the host-parasite intereaction

The impact of infection on the host will depend upon the virulence of the parasite, the infective dose and the resistance of the host to infection. These parameters can be modified by a number of factors, such as malnutrition and overcrowding, that also interact with each other, and have direct effects on host survival, complicating the dynamics of the host-parasite interaction. Mechanisms for the mode of action of factors influencing the host's resistance to infection are poorly understood despite extensive studies in man and laboratory animals (Slater and Keymer 1986, Abbott and Holmes 1990, Behnke 1990, Crompton 1991). Even less is understood about factors modifying the immune response in wild animals, but some field studies suggest alteration of the host-parasite interaction by external conditions has resulted in host mortality. These are summarised in Table 3 (see also Lloyd (this volume)).

# 6 Control

Control of infectious diseases in wild animals has generally only been attempted when the disease threatens man or his livestock. Where wildlife represent important vectors or reservoirs of infection, the aim of control has been to reduce transmission or remove the perceived source of infection. This is partially a result of the lack of drugs and vaccines developed for wild species and the difficulty and expense involved in treatment (a recent study on the vaccination of free-ranging bighorn sheep (*Ovis canadensis*) against *Pasteurella spp.* using biobullets from a helicopter was estimated to cost $200 per sheep Jessup 1991). It is also a consequence of the lack of knowledge of the impact of diseases in wildlife. As the primary concern of most wildlife

| INFECTIOUS AGENT | HOST | REFERENCE |
|---|---|---|
| *** Rinderpest | Artiodactyla | Berry 1981<br>Scott 1981<br>Plowright 1982<br>Shanthikumar *et al.* 1985 |
| | African buffalo (*Syncerus caffer*) | Sinclair 1974<br>Dobson and Hudson 1986<br>Prins and Weyerhaeuser 1987 |
| | Wildebeest (*Connochaetes taurinus*) | Talbot and Talbot 1963 |
| ** Foot-and-mouth disease | Artiodactyla | Hedger 1981<br>Thomson and Bosch 1991 |
| *** Rabies | Range of mammals (especially red fox badger, raccoon) | Moegle and Knorppf 1978<br>MacDonald 1980<br>Steck and Wandeler 1980<br>Steck 1982<br>Bacon 1985<br>Jenkins and Winkler 1987<br>Campbell and Charlton 1988 |
| *** Canine Distemper | Black footed ferret (*Mustela nigripes*) | Thorne and Williams 1988<br>Williams *et al.* 1988 |
| *** Phocine Distemper Virus | Common seal (*Phoca vitulina*) | Kennedy *et al.* 1988, Osterhaus and Vedder 1988, Kennedy 1990, Grenfell *et al.* 1992, Hall *et al.* 1992 |
| | Striped dolphin (*Stenella coeruleoalba*) | Domingo *et al.* 1990<br>Di Guardo *et al.* 1992 |
| | Common porpoise (*Phocoena phocoena*) | Kennedy *et al.* 1992 |
| *** Myxomatosis | European rabbit (*Oryctolagus cuniculus*) | Fenner 1953, Fenner and Ratcliffe 1965, Fenner and Myers 1978, Brothers *et al.* 1982 |
| * Epizootic Haemorrhagic Disease (*EHD*) | Cervidae | Brannian *et al.* 1983<br>Shope *et al.* 1955 |

Table 2. Impact of infectious disease agents on survival of wild animal populations. (a) Microparasites.
* indicates studies are observational, ** indicates some degree of quantitative assessment has been made, *** indicates experimental manipulations and/or mathematical models have been used to investigate the importance of the disease at a population level.

| INFECTIOUS AGENT | HOST | REFERENCE |
|---|---|---|
| * Avian Pox | Hawaiian land birds | Ralph and Van Riper 1985 |
| ** Arboviruses (> 200) | Wide range of vertebrates | |
| | Reviews: | Simpson 1968<br>Monath 1989<br>McLean 1991 |
| Louping ill | Red grouse (*Lagopus lagopus*) | Hudson 1986 |
| Yellow fever | South American primates | Simpson 1968 |
| * Newcastle Disease | Wide range of avian species | Lancaster and Alexander 1975 |
| * Duck viral enteritis Duck spp | | Hall and Simmons 1972<br>Snyder *et al.* 1973 |
| * Influenza | Wide range of avian species | Becker 1966 |
| | Harbour seal (*Phoca vitulina*) | Lang *et al.* 1981 |
| * European Brown Hare Syndrome | Hare (*Lepus europeus*) | Gavier-Widen and Morner1990<br>Dietz and Henriksen 1990 |
| * *Chlamydia psittaci* | Koala (*Phascolarctos cinereus*) | Brown and Grice 1984<br>Wiegler *et al.* 1988 |
| | Wide range of avian species | Page 1978<br>Simpson and Bevan 1989 |
| ** *Pasteurella haemolytica/ Pneumostrongylus* spp. | Bighorn sheep (*Ovis canadensis*) | Buechner 1960<br>Foreyt and Jessup 1982 |
| ** *Pasteurella multocida* | Wide range of avian species | Rosen 1972<br>Wobeser *et al.* 1979<br>Price and Brand 1984<br>Botzier 1991 |

Table 2 (cont.). Impact of infectious disease agents on survival of wild animal populations.
(a) Microparasites.
* indicates studies are observational, ** indicates some degree of quantitative assessment has been made, *** indicates experimental manipulations and/or mathematical models have been used to investigate the importance of the disease at a population level.

| INFECTIOUS AGENT | HOST | REFERENCE |
|---|---|---|
| ** Botulism<br>*Clostridium botulinum* | Wide range of avian species | Rosen 1971<br>Forrester *et al.* 1980<br>Smith 1982<br>Eklund and Dowell 1987<br>Brand *et al.* 1988 |
| ** Anthrax<br>*Bacillus anthracis* | Vertebrates | Ebedes 1976<br>Prins and Weyrhaeuser 1987<br>Turnbull 1990 |
| | Hippopotamus | Turnbull *et al.* 1991 |
| * *Mycobacterium* spp. | Flamingo (*Phoeniconaias minor*) | Sileo *et al.* 1979 |
| | Vole | Wells 1937 |
| *** | Badger (*Meles meles*) | Zuckerman 1980<br>Cheeseman *et al.* 1981<br>Anderson and Trewhella 1985<br>MAFF 1990 |
| ** *Yersinia pestis* | Prairie dogs (*Cynomys* spp.) | Christie 1982<br>Rayor 1985<br>Thorne and Williams 1988<br>Ubico *et al.* 1988 |
| * *Aspergillus fumigatus* | Range of avian species | O'Meara and Witter 1971 |
| ** *Glugea hertwigi* | Rainbow smelt (*Osmerus mordax*) | Nepszy *et al.* 1978 |
| ** *Plasmodium relictum* | Hawaiian land birds | Warner 1968<br>Van Riper *et al.* 1986<br>Van Riper 1991 |
| ** *Leukocytozoon simondi* | Range of avian species | Greiner 1991<br>Atkinson and Van Riper 1991 |
| ** *Toxoplasma gondii* | Voles (*Microtus agrostis*) | Elton *et al.* 1935 |
| ** *Apatemon gracilis* | Brook stickleback (*Culaea inconstans*) | Gordon and Rau 1982 |

Table 2 (cont.). Impact of infectious disease agents on survival of wild animal populations.
(a) Microparasites.
* indicates studies are observational, ** indicates some degree of quantitative assessment has been made, *** indicates experimental manipulations and/or mathematical models have been used to investigate the importance of the disease at a population level.

| INFECTIOUS AGENT | HOST | REFERENCE |
|---|---|---|
| ** *Diplostomum adamsi* | Yellow perch (*Perca flavescens*) | Lester 1977 |
| ** *Uvulifer ambloplitis* | Bluegill sunfish (*Lepomis macrochirus*) | Lemly and Esch 1984 |
| ** *Raphidascaris acus* | Yellow perch (*Perca flavescens*) | Szalai 1989 |
| * *Thermozyon cooperi* | Waterfowl | Oosthuizen and Fourie 1985 |
| *** *Eustrongylides ignotus* | Ciconiformes | Wiese *et al.* 1977<br>Spalding *et al.* 1993<br>Spalding and Forrester 1993 |
| * *Echinuria uncinata* | Waterfowl | Cornwell 1963 |
| * *Polymorphus minutus* | Waterfowl | Garden *et al.* 1964<br>Itamies *et al.* 1980 |
| ** *Cyathocotyle bushiensis* | Dabbling ducks | Hoeve and Scott 1988 |
| *** *Trichostrongylus tenuis* | Red grouse (*Lagopus lagopus*) | Hudson *et al.* 1992<br>Dobson and Hudson 1992 |
| ** *Skrjabingylus nasicola* | Mustelidae | King 1977<br>King and Moody 1982<br>Weber and Mermod 1987<br>Addison *et al.* 1988 |
| * *Baylisascaris procyonis* | Ground hogs (*Marmota monax*)<br>Cottontail rabbits (*Sylvilagus floridanus*) | Richter and Kradel 1964<br>Jacobson *et al.* 1976 |
| *** *Teladorsagia circumcincta* | Soay sheep (*Ovis aries*) | Gulland 1992 |
| * *Haemonchus contortus* | Sable antelope (*Hippotragus niger*) | Grobler 1981 |

Table 2 (cont.). Impact of infectious disease agents on survival of wild animal populations.
(b) Macroparasites.
* indicates studies are observational, ** indicates some degree of quantitative assessment has been made, *** indicates experimental manipulations and/or mathematical models have been used to investigate the importance of the disease at a population level.

| INFECTIOUS AGENT | HOST | REFERENCE |
|---|---|---|
| * *Paralaphostrongylus tenuis* | Ungulates, especially cervidae | Anderson 1972<br>Bergerud and Mercer 1989<br>Cole 1981<br>Nudds 1990<br>Comer *et al.* 1991<br>Bogaczyk *et al.* 1993 |
| * *Elaeophora schneideri* | Cervidae | Pence 1991 |
| ** *Stenurus* spp. | Cetaceans | Delyamure 1955 |
| * *Crassicauda* spp. | *Stenella attenuata*<br>Whales | Perrin and Powers 1980<br>Lambertsen 1991 |
| * *Uncinaria lucasi* | Northern fur seals (*Callorhinus ursinus*) | Olsen and Lyons 1965<br>Lyons and Keyes 1978 |
| ** *Otostrongylus circumlitis* | Ringed seals (*Phoca hispida*) | Onderka 1989 |
| ** *Wohlfahrtia vigil* | Microtus townsendii | Boonstra 1977 |
| ** *Rhipicephalus* spp. | *Papio ursinus*<br>Chacma baboons | Brain and Bohrmann 1992 |
| * *Psoroptes ovis* | Bighorn sheep (*Ovis canadensis*) | Lange *et al.* 1980<br>Welsh and Bunch 1983 |
| ** *Sarcoptes* spp. | Foxes (*Vulpes vulpes*)<br>Coyotes (*Canis latrans*) | Lindstrom and Morner 1985<br>Morner 1991<br>Pence *et al.* 1983 |
| * *Stomoxys calcitrans* | Lion (*Panthera leo*) | Fosbrooke 1963 |
| * *Sternostoma tracheocolum* | Gouldian finch (*Erythrura gouldiae*) | Tidemann *et al.* 1992 |

Table 2 (cont.). Impact of infectious disease agents on survival of wild animal populations.
(b) Macroparasites.
* indicates studies are observational, ** indicates some degree of quantitative assessment has been made, *** indicates experimental manipulations and/or mathematical models have been used to investigate the importance of the disease at a population level.

disease control schemes has been the protection of man and his economy rather than wildlife, many control programmes have depended upon reducing wild animal populations to reduce transmission rates, the gassing of badgers to control bovine tuberculosis being a well known example (Zuckerman 1980, Wilesmith *et al.* 1986). Rinderpest control has involved the vaccination of

both domestic cattle and wildlife, but the thrust of the control programme has been vaccination of cattle to reduce transmission rates (Plowright 1982). Similarly, elk (*Cervus elaphus nelsoni*) have been vaccinated against brucellosis in Wyoming, USA, in an attempt to reduce transmission to domestic cattle (Thorne *et al.* 1990).

As populations of some wild animals have become increasingly rare, public demand for protection of endangered species themselves from disease has lead to attempts at controlling infectious disease in wildlife to protect these populations. For example, large scale oral vaccination programmes to control rabies in foxes exist in France and are under trial to control raccoon rabies in the United States (Baer 1988, Blancou *et al.* 1988, Rupprecht *et al.* 1989, Linhart *et al.* 1991), but only recently has an attempt been made to control rabies in African Hunting Dogs (*Lycaon pictus*), as this host species has become threatened with extinction (Gascoyne *et al.* 1991). Similarly, the mountain gorilla (*Gorilla gorilla beringei*) has become severely endangered, so that when unusually large numbers of animals were suspected of dying from measles in the Parc des Volcans in Rwanda, animals were vaccinated with an attenuated human vaccine to protect them in the face of a possible disease epidemic (Hall and Harwood 1990). Control of macroparasites in wildlife has been attempted, in part to elucidate the role of these infections in host population dynamics (Hudson 1986, Gulland 1992, Hudson *et al.* 1992), but has not been undertaken on a large scale.

As little is known about the dynamics of disease (other than rabies) in wild populations, attempts at control must be carefully evaluated. Guidelines for the vaccination of wild animals have been outlined by Hall and Harwood (1990), but there is a need for increased understanding of the dynamics of infections and their effects on wild populations before extensive control of disease in wildlife is a real possibility.

# 7 Future directions

This review highlights the need for both experimental and theoretical developments in the study of wildlife disease. Predictive mathematical modelling is needed to increase understanding of the transmission dynamics of infectious diseases in wildlife and the role of disease in regulating wild animal populations. In addition, as increasing efforts are made to conserve endangered wild animals and vaccination of free-living populations is considered, models are required to predict the outcome of such control programmes. As wild animals are rarely exposed to a single infectious agent at a time, existing models for diseases in man and domestic stock need refining to understand multi-host and multi-parasite systems. The interactions between environment

| FACTOR HOST SUSCEPTIBILITY | HOST/PARASITE | REFERENCE |
|---|---|---|
| Nutritional plane | Voles, small game, owls/ *Franscisella tularensis* | Hornfeldt 1978 |
| | *Syncerus caffer*/ Helminths | Sinclair 1974 |
| | *Eudyptula minor*/ *Contracaecum spiculigerum* | Obendorf and McColl 1980 |
| | *Odocoiles virginianus*/ *Haemonchus contortus* | Davidson *et al.* 1980 |
| | *Clethrionomys glareolus*/ *Heligmosomum mixtum* | Henttonen *et al.* 1990 |
| | *Ovis aries*/ *Ostertagia* spp. | Gulland 1992 |
| Stress-overcrowding | *Sciurus vulgaris*/ Myxoma virus | Vizoso 1968 |
| | *Microtus agrestis*/ *Pneumocystis carinii* | Soveri *et al.* 1990 |
| | Microtine rodents/ endoparasites (review) | Wiger 1977 |
| | *Rangifer tarandus*/ bacterial infections | Leader-Williams 1982 |
| Stress-social dominance | Rangifer tarandus/ *Elaphostrongylus rangiferi* | Halvorsen 1986 |
| Stress-hormonal changes | *Antechinus stuartii*/ mixed infections | Lee *et al.* 1977 |
| Pollutants | *Zalophus californianus*/ *Leptospira pomona* | Gilmartin *et al.* 1976 |
| | *Phoca vitulina*/ *PDV* | Hall *et al.* 1992 |
| | Review | Peterle 1991 |

Table 3. Factors modifying the host-parasite interaction.

| FACTOR HOST SUSCEPTIBILITY | HOST/PARASITE | REFERENCE |
|---|---|---|
| Simultaneous infection | African ungulates/ *Trypanosoma brucei* | Allsopp 1972 |
| | *Isoodon macrourus*/ Ticks (*Ixodes and Haemophysalis* spp.) | Gemmell *et al.* 1991 |
| | European rabbit/ Myxomatosis | Boag 1988 |
| PATHOGEN | | |
| Infectious dose -climate | *Panthera leo*/ *Stomoxys calcitrans* | Fosbrooke 1963 |
| | *Alligator mississippiensis*/ *Aeromonas hydrophila* | Gorden *et al.* 1979 |
| | *Hippotragus niger*/ *Haemonchus contortus* | Grobler 1981 |
| Virulence -genetics | *Oryctolagus cuniculus*/ Myxomatosis | Fenner and Meyers 1978<br>Ross and Sanders 1987 |
| | Orbiviruses/ Seabirds | Nuttall *et al.* 1990 |

Table 3 (cont.). Factors modifying the host-parasite interaction.

(including food supply), host genetics and the immune response need to be further unravelled. Predictions about their interaction can then be tested experimentally, by using structured longitudinal field studies. Detailed field studies are also required to determine the distribution of infectious agents in live animal populations and the importance of heterogeneity in host exposure and susceptibility to infection in generating the observed variation in patterns of prevalence and incidence. In addition, the effects of species differences in life history patterns and behavioural spacing mechanisms on disease transmission need to be determined. Analytic field studies should be supported by experimental manipulations. Where this is not possible, mathematical and statistical models need to be developed which provide a range of techniques to estimate parameters such as thresholds of host density for the spread of disease, infective dose rates, host recovery rates, development and loss of immunity and death rate of the parasite within the host. Both field and experimental studies are also required to investigate the sub-clinical con-

sequences of infection, as these may have fitness costs important in ecology and evolution of wild populations. Such studies are not easy to perform in free-living populations, but with increased communication between theoreticians and field workers, disease investigations can be guided by mathematical models and used to test them, to increase understanding of the epidemiology of infectious diseases in wild animals and therefore their impact on wildlife populations.

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# Microparasites: Observed Patterns in Wild Animal Populations

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## 1 Introduction

Microparasites have been broadly defined to include viral, bacterial and protozoan pathogens (Anderson and May 1979). Mathematical models for microparasites characteristically divide the host population into susceptible, infectious and recovered and immune hosts (Anderson and May 1991). This reflects a bias towards studies of microparasites of vertebrates (especially viruses, rather than bacteria and protozoa). In this chapter we review observed epidemiological patterns in the population dynamics of microparasites in free-living animal populations.

Many microparasites are characterized by their tendency to produce a sustained immunological response in infected vertebrate hosts; recovered hosts are usually considered to be resistant to further infection. Ecological studies of microparasites in wild animal populations can only occasionally differentiate between the different epidemiological classes within the host population. More frequently tissue samples have to be collected so that serological tests may be used to differentiate between susceptible and recovered, or resistant animals. Similarly, not all pathogens produce a sustained immunological response, in some cases the pathogen is always fatal (for example, many bacterial and viral infections of invertebrates), in other cases recovered individuals simply re-enter the class of susceptible hosts. Furthermore, it is possible for infected individuals to show no overt symptoms of the disease. In some cases these individuals harbour latent infections which eventually develop and exhibit the characteristic symptoms of the disease in old, malnourished or stressed hosts. In other cases, the infected individuals show no clear symptoms, but are fully capable of transmitting the pathogen to susceptible hosts of the same or another species. For example, the herpes virus that causes duck plague is often disseminated by carrier mallards that show no serological evidence of the infection (Leibovitz and Hwang 1968, Jansen 1968, Friend and Pearson 1973).

The etiological characteristics of different pathogens have constrained the development of long term studies of microparasites in wildlife. The majority of studies for which data are available are for pathogens that may also infect humans, such as rabies in foxes and brucellosis in bison and elk, or of

pathogens that may also infect domestic livestock, such as bovine tuberculosis in badgers and possums, or rinderpest in wild artiodactyls. Occasionally, mass mortalities are observed in wild animal populations, such as occurs with anthrax outbreaks in African game parks (Prins and Weyerhaeuser 1987, Ebedes 1976, Berry 1993), avian botulism (Cliplef and Wobeser 1993) and duck plague epidemics in waterfowl (Leibovitz and Hwang 1968, Leibovitz 1994, Pearson 1994), or in the recent North Sea seal epidemic (Grenfell, Lonergan and Harwood 1992, Kennedy 1990, Harwood 1990, Heide-Jorgensen *et al.* 1992). These outbreaks allow the collection of large amounts of pathological data over a short period of time. In contrast, long term studies of endemic infections of microparasites in wild animal populations are comparatively rare, as are studies that examine the role that microparasites play in determining the lifetime reproductive fitness of individuals in wild animal populations.

Interactions between microparasites and their non-human hosts have direct and indirect impacts at the individual, population and community level. For example epidemic outbreaks of anthrax in African game parks lead to the deaths of many individual browsing animals, such as impala; this causes reductions in the size of the populations of these species, which in turn lead to reduced grazing pressure and the establishment of even-age stands of Acacia trees (Prins and van der Jeugd 1993, Dobson and Crawley 1994).

In this review, we present data from empirical studies of three different taxonomic groups of microparasite that suggest that microparasites directly and indirectly reduce the reproductive fitness of individual hosts and may reduce host populations to significantly lower densities than in the absence of the pathogen. Although the majority of examples are taken from studies of vertebrates, we have tried to include some invertebrate examples where they also reflect similar mechanisms.

We then consider the complexities (and logistic frustrations) that arise when trying to estimate transmission rates from the data usually collected in epidemiological surveys of wildlife. Although some sets of age-prevalence/serology data may allow estimates to be made of the basic reproductive ratio of the pathogen, $R_0$, most epidemiological surveys do not collect data that permit direct estimation of transmission rates and levels of pathogen induced host mortality. Furthermore, the presence of alternative reservoir hosts may confound the use of analytical techniques developed to estimate transmission rates for microparasites in human populations (Anderson and May 1991, Becker and Yip 1989, Becker 1989).

The potential role that pathogens play in regulating host populations is central to the long-running debate on compensatory and additive sources of mortality in wild animal populations (Holmes 1982, Erickson, Highby and Carlson 1949, Errington 1946). Unfortunately, the data to determine whether microparasites are reducing host population growth rates have not been sys-

tematically collected. Instead, we have to rely on data collected from perturbations that result from the two main mechanisms of disease control – vaccination and culling. These interventions can be regarded as experiments that allow researchers to monitor the response of the host population to reductions in disease prevalence. In some cases, these management experiments indicate that pathogen mortality is additive and is holding host populations at lower densities than would occur in the presence of the pathogen (for example, rinderpest in wildebeest and buffalo in the Serengeti). In other cases, the pathogen appears to have no effect on the host population and reductions in survival and fecundity due to the pathogen may be compensated for by increased survival and fecundity in the uninfected individuals.

In the final section of the chapter we discuss the role that microparasites play in determining levels of biodiversity in ecological communities. We conclude by describing how the addition or removal of microparasites may lead to changes in population density of hosts that lead to changes in the relative abundance of species throughout the community.

# 2 Impact on Individual Hosts

Microparasites can directly reduce both the survival and fecundity of their hosts. For example, studies of the blood parasites of Tengmalm's owls (*Aegolius funereus*) show that female owls with heavy infections of *Leucocytozoon ziemanni* produce significantly lower clutch sizes than uninfected females (Korpimaki, Hakkarainen and Bennett 1993). On a more subtle level, microparasites can indirectly reduce host fitness by manipulating, or altering, the behaviour of infected individuals. Possibly the most direct evidence of a microparasite manipulating host behaviour comes from studies of tsetse flies infected with trypanosomes (Jenni *et al.* 1980); a scanning electron microscope picture of the mouthparts of an infected tsetse fly showed the parasite actively wrapped around the tachoreceptors of the host. By manipulating these receptors while the host is feeding, the parasite interrupts the host's blood meal and induces it to feed more often. This allows the parasites in an individual infected host to infect a greater number of susceptible hosts.

It is also possible that parasites indirectly reduce host reproductive fitness by reducing their host's attraction to potential mates. A major growth industry in evolutionary ecology in the last ten years have been studies that examine the role that parasites may play in influencing mate choice. These comparative and empirical studies were inspired by the earlier work of Jaenike (1978) and Hamilton and Zuk (Hamilton and Zuk 1982, Hamilton 1982, Seger and Hamilton 1988, Zuk 1990) who suggested that sexual selection could be influenced by parasites. A number of recent reviews suggest that the impact of pathogens on body condition may be sufficient to allow females to differ-

entiate against infected males when selecting mates (Clayton 1991, Clayton, Pruett-Jones and Lande 1992, Read 1988).

One set of studies that provides comprehensive quantitative details of the impact of microparasites on their hosts is Schall's work on lizard malaria. These studies have examined the effects of saurian malaria, on host stamina, fecundity, growth and survival (Schall and Houle 1992, Schall 1983a,b, 1990b). The work illustrates the variety of ways in which infection with malaria leads to both direct and indirect reductions in host fitness in a range of lizard species (Figure 1). Early work on this system provided clear evidence that Western fence lizards (*Scleroporus occidentalis*) infected with *Plasmodium mexicanum* produced significantly smaller clutch sizes than uninfected lizards of the same size (Schall 1983b). This suggests that malaria infection has a significant impact on lizard fecundity. Alternatively, less fecund lizards may be less susceptible to malaria; there is no evidence in support of this alternative hypothesis.

As is often the case in studies of endemic infections, determining the impact of malaria on host survival was harder to establish. Infected fence lizards had a higher recapture rate in a mark-recapture studies under natural conditions (Schall 1990a), suggesting they may also be more susceptible to predation. However, there were no differences in the frequency of predator-produced injuries between infected and uninfected fence lizards, nor in African rainbow lizards studied under similar conditions (Schall 1990a). Comparative studies of the escape response of infected lizards showed no differences in the initial sprint speed, which is entirely dependent upon aerobic metabolism. In contrast, the stamina of infected lizards was significantly lower than that of uninfected lizards, suggesting that aerobic metabolism was affected by malaria and partially explaining why infected lizards may have greater difficulty in escaping from persistent predators (Schall 1990a). Furthermore, studies of the time budgets of infected and uninfected lizards showed that infected males and juveniles spent significantly less time in social activities, this may also have an indirect effect on their reproductive success.

Schall's work on lizard malaria illustrates that it is crucial to quantify observed pathology in terms of its impact on all components of host fitness. This work is almost unique in that it combines experimental studies on individuals with surveys of disease prevalence at the population level. This experimental approach is crucial in establishing a broader synthesis that directly addresses the question – 'How important are pathogens in determining the dynamics, distribution and abundance of wild and captive animal (and plant) populations?'

In the absence of long term monitoring and experimental studies, the potential impact of microparasites on their hosts has to be assessed indirectly using data collected from cross-sectional serological surveys, or from data

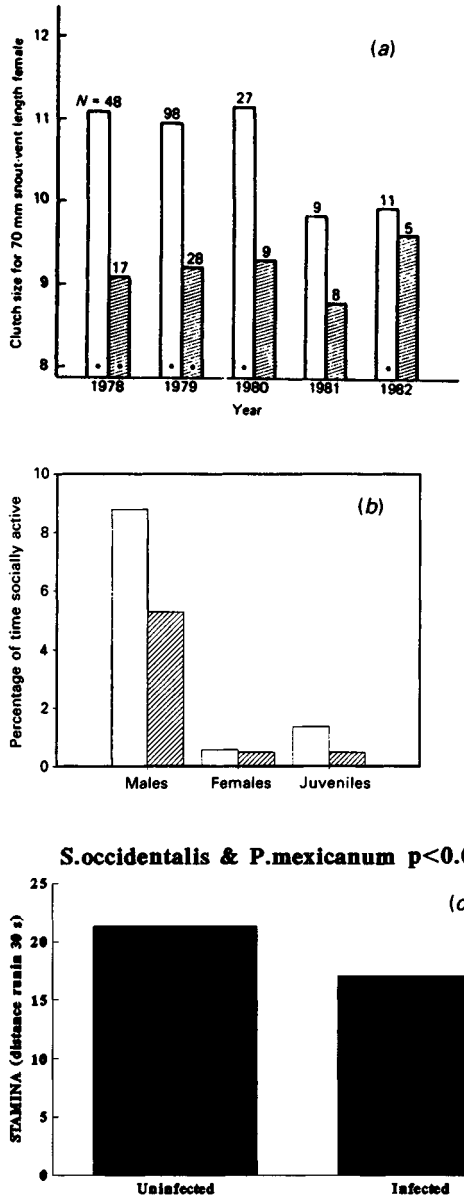



Figure 1. The influence of infection with malaria on different components of fitness for a variety of lizard species: (A) clutch size of *Sceloporus* lizards infected (hatched bars), or not infected (open bars), with *Plasmodium mexicanum*. (B) Percentage time spent in social activities for male, female and juvenile fence lizards infected, or not infected, with a malaria parasite (all after Schall 1983a). (C) distance run in 30 seconds by *Sceloporus* lizards infected and uninfected with *P.mexicanum*.

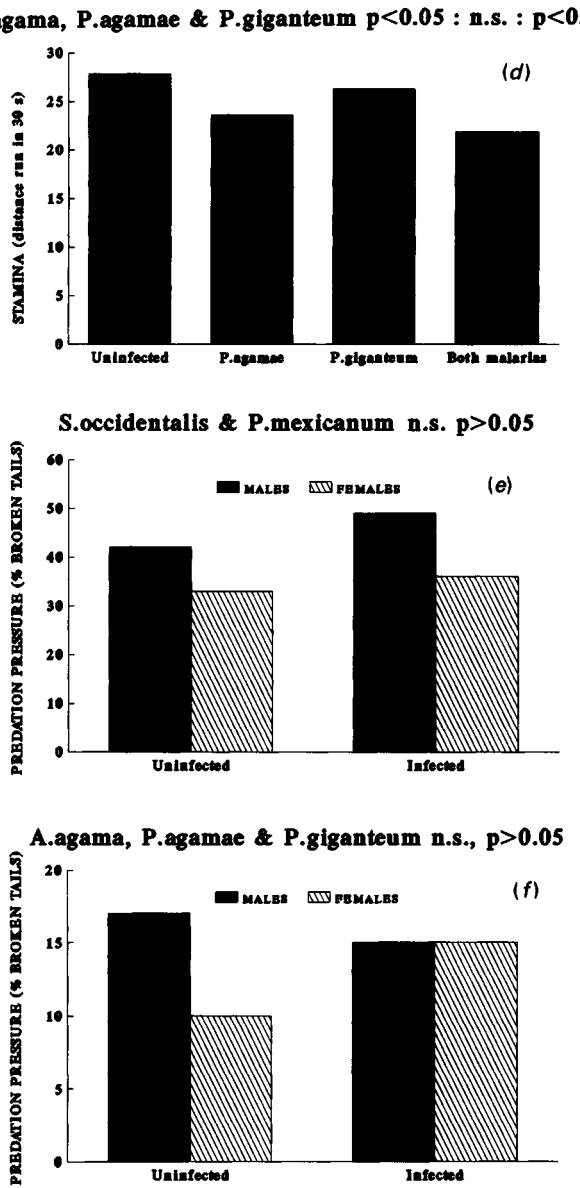



Figure 1 (cont.). The influence of infection with malaria on different components of fitness for a variety of lizard species: (D) distance run in 30 seconds by African rainbow lizards (*Agama agama*) infected and uninfected with *P.agamae* and *P.giganteum*. (E and F) Percentage of lizards with broken or regenerated tails, an index of predation pressure, comparing animals infected and uninfected with malarial parasites, (E) *S.occidentalis* infected with *P.mexicanum*; (F) *A.agama* infected with *P. agamae* and *P.giganteum*

collected from epidemic outbreaks of pathogens with readily characterized symptoms or pathology.

# 3 Observed Patterns at the Population Level

The majority of studies of microparasites in wildlife consist of surveys of host populations where cross-sectional data are collected from individuals of different known ages to determine either past levels of exposure to pathogens, or current levels of disease incidence (Spalding and Forrester 1993). These surveys can be divided into three broad categories:

1. closely-monitored disease outbreaks when the onset of disease in each individual in the population is recorded.

2. cross-sectional or horizontal surveys of seroprevalence from animals divided into known age or size classes.

3. broad surveys of disease prevalence and geographical distribution.

Many epidemiologists fantasize about data sets that combine all these attributes. Unfortunately, logistic problems constrain the possibility of obtaining such an ideal data set for any individual system. Instead, fragmentary data are available for some disease outbreaks, horizontal surveys are undertaken seredipitously when funding is available, and long term studies are occasionally set up if the severity of a pathogen presents a sufficient threat to humans or livestock. Extrapolations have to be made between systems and these always require cautious examination of the assumptions underlying the epidemiological model used to describe any particular system. The chapters by Heesterbeek and Roberts (this volume) and Barlow (this volume) discuss some of the assumptions underlying models for microparasites.

At the core of most epidemiological models is the assumption that transmission between infected and susceptible hosts may be characterized by some mass-action term. True mass action transmission assumes that transmission is a function of the density of each class of host, pseudo-mass action assumes transmission occurs at a rate determined by the numbers of each host (Diekmann *et al.* 1990, De Jong *et al.* 1995). These different assumptions about transmission lead to different expressions for the basic reproductive ratio of the pathogen, $R_0$, formally defined as the number of new infections produced when an infected individual is introduced into a population of susceptibles. Although the true mass action principle is the more accurate assumption, the majority of epidemiological models that have been applied to empirical data tend to assume 'pseudo-mass action' transmission (see Barlow this volume). Both models provide an equally good description of the data when fitted to

the comprehensive set of data produced in the classic laboratory studies of Greenwood *et al.* for mouse pasteurellosis (*Pasteurella muris*) (Greenwood *et al.* 1936, De Jong *et al.* 1995). However, the two models produce different expressions for the threshold population size at which the host population will continuously sustain the pathogen.

Where data are collected from closely monitored disease outbreaks, a number of statistical techniques have been developed for estimating rates of transmission. These methods have been applied to epidemiological data from an outbreak of swine fever in wild pigs (Hone *et al.* 1992, Inayatullah 1973) and to the recent outbreak of phocine distemper in the North Sea (Grenfell *et al.* 1992) (Figure 2). In both cases, the data were collected from populations of known density within a relatively restricted area, so true mass action transmission was probably a good assumption. Similarly, the data were collected in the form of the number of animals found dead in the months following the introduction of a small number of infected individuals into a population of susceptibles. In both cases, a simple epidemiological model provides a fairly good description of the transient dynamics of the epidemic as it spread through the host population. The data for swine fever in wild pigs allow Hone *et al.* (1992) to estimate that around 270 pigs, or 6.1 pigs/km$^2$ are required to permit an outbreak of the disease. The initial density of around 10.4 pigs per km$^2$ was sufficiently above this level to cause an outbreak.

Unfortunately, data as detailed as these are only occasionally collected; the majority of epidemiological data for wildlife populations tend to be collected as either surveys of average prevalence within a population, or from occasional serology surveys that at best aim to classify the population into individuals from relatively broad age- or size-classes.

## 3.1 Brucellosis in Bison and Elk

As an example of the types of pattern that are observed in surveys of this type consider data for brucellosis in bison populations in the United States and Canada. Brucellosis is a disease of ungulates caused by bacteria in the genus *Brucella*, it has been present in Yellowstone National Park in Wyoming for over 75 years. It was first diagnosed in 1916 when two bison aborted fetuses (Mohler 1917, Meagher and Meyer 1994). Since then, the bison and elk herds have been tested opportunistically, and occasionally systematically, for the presence of brucellosis (Meyer and Meagher 1995, Thorne *et al.* 1991). Unfortunately, the tests to determine the presence of *Brucella abortus* in elk and bison were originally developed for cattle. They were designed to determine whether the pathogen is present in a herd of cattle, rather than whether specific individuals are actually infected. Whereas the tests are fairly accurate at identifying infected herds when applied to cattle, they do not extrapolate readily to bison and elk (Meyer and Meagher 1995). In particular, the tests

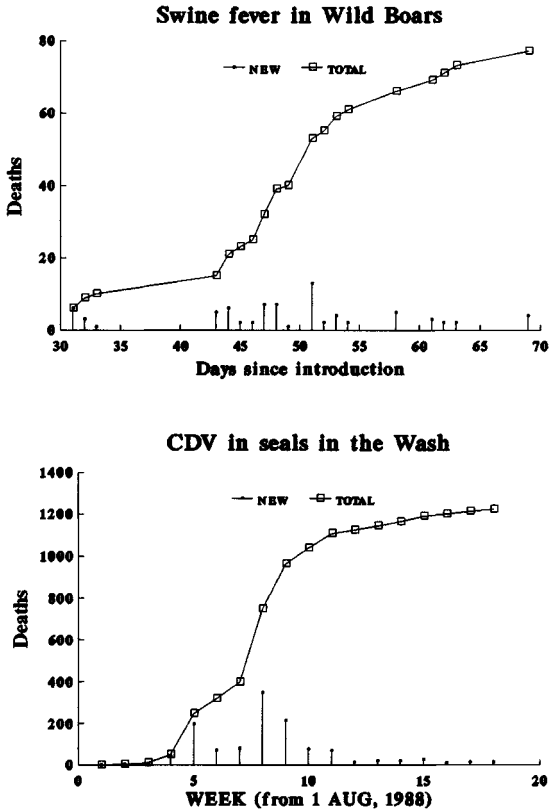



Figure 2. Observed mortality in outbreaks of (A) classical swine fever in wild pigs (Hone *et al.* 1992) and (Inayatullah 1973), and (B) phocine distemper, PDV, in seals in eastern England (Grenfell *et al.* 1992). In both cases a simple epidemiological model has been fitted to the observed data, and the transmission rate between infected and susceptible individuals estimated. In (A) transmission rate was estimated at 0.00099/day for a population of 465 pigs in a 44.6 km$^2$ forest in Pakistan; while in (B) transmission was estimated at 81/year for a population of around 5000 seals in the Wash estuary of East Anglia, UK.

tend to give unfortunately large numbers of false positive and negative results. Thus serological tests on blood may indicate the presence of *Brucella* antibodies in bison, but it is only possible to identify an animal as infectious for brucellosis if positive cultures are grown from tissue collected from that animal (Meyer 1992). Estimates of the incidence of *Brucella* should thus be treated with extreme caution unless accompanied by data from tissue culture. The proportion of false negative and positive results in the serology sample can then be quantified using the data from a large sample of individuals that

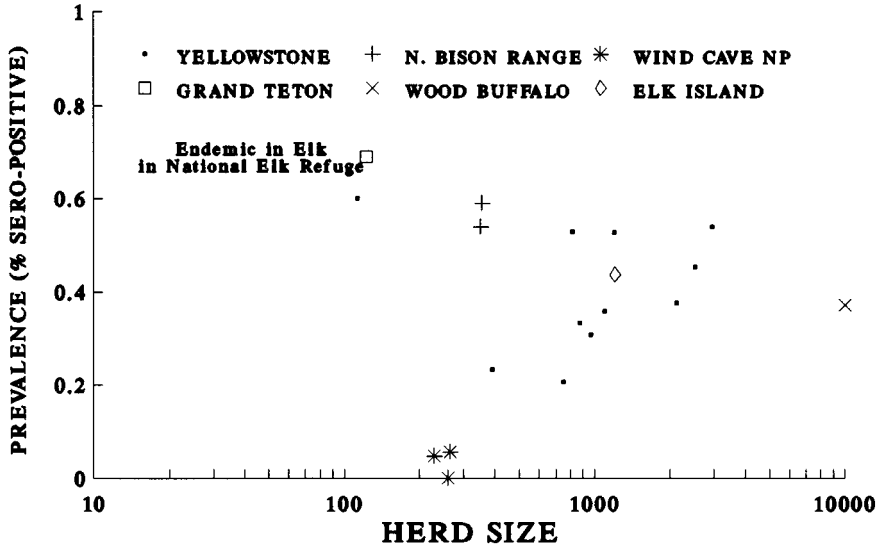



Figure 3. The relationship between population size and proportion of individuals infected with *Brucella abortus* for the bison population of Yellowstone (Meyer 1992) and bison populations in other US and Canadian National parks (Tessaro 1986, 1989).

have been tested both serologically and by tissue culture.

These caveats notwithstanding, it is possible to look at the relationship between herd size and brucellosis prevalence. The data in Figure 3 illustrate the proportion of samples which are sero-positive plotted against population size for the Yellowstone bison herd. Data from similar surveys of bison populations in other national parks in the United States and Canada are also included in this figure (Moore 1947, Choquette *et al.* 1961, Tessaro 1986, 1989), they suggest a similar trend underlies the data for each herd. The pattern complements those observed in studies of measles in human populations (Black 1966, Bartlett 1960). Essentially, sustained infections of brucellosis require bison herds in excess of a threshold density; in the case of *Brucella* in bison, a herd of at least two hundred animals.

These empirical surveys for brucellosis illustrate one of the central tenets of epidemiology: most pathogen have a relatively sharply defined threshold population density for the continued maintenance of a pathogen – this is usually termed the critical community size (Kermack and McKendrick 1927, Anderson and May 1991, Fine 1993). Microparasite persistence is only possible when host populations exceed the critical community size. Pathogens can establish in populations at densities lower than the critical community size, and the cumulative proportion of hosts infected increases as a relatively simple function of population density (Heesterbeek and Roberts this volume).

However, the disease outbreaks usually fail to maintain themselves and eventually die out. Population density is thus a major variable determining a population's ability to maintain a pathogen.

## 3.2 Impact of spatial structure

The influence of population density on rates of microparasite transmission is likely to be considerably modified by the spatial distribution of the host population. Hence, many diseases rapidly die out in species with small scattered populations; while they are more likely to persist in species with large, aggregated populations (Anderson and May 1991). These effects are important in interpreting pathogen distribution data at a variety of different spatial scales (see Mollison and Levin (this volume), and Bolker *et al.* (this volume)).

Work by Barlow on possums and bovine TB indicates that disease prevalence varies spatially and that foci of infection are present in different sections of transects across host populations (Barlow 1991a,b, 1993, May and Anderson 1984, 1990). Studies of rabies in striped skunks and bats in the United States reveal the presence of core areas where the pathogen is always present; these are surrounded by peripheral areas where rabies outbreaks occur when disease prevalence increases in the core areas (Pybus 1988, Burnett 1989, Gremillion-Smith and Woolf 1988).

At a larger spatial scale the geographical distribution of some macaque species may be determined by their susceptibility to malaria (Wheatley 1980), with some species being excluded from areas where malaria is present. Price *et al.* (1986) have suggested that this macaque example reflects a more general phenomena where hosts with large geographical ranges are able to use shared pathogens to outcompete species with more restricted geographical ranges. Data in support of this hypothesis are teasingly equivocal. In contrast, at local spatial scales, recent work on malaria in different South American primates indicates that the prevalence of malaria is dependent upon the size of the social groups which characterize the social system for each species (Davies *et al.* 1991). Although prevalence is observed to increase with group size, the data have to be interpreted cautiously as the larger, longer-lived primate species tend to live in larger groups. The observed higher prevalence may simply reflect longer average periods of exposure rather than higher transmission rates in larger groups.

## 3.3 Estimation of transmission rates

A variety of techniques have been developed for estimating the force of infection from age-prevalence data collected from serological surveys of infectious diseases of humans (Anderson and May 1991, Grenfell and Anderson 1985). If the microparasite is confined to a single species of host, these techniques

can be applied to serological data from age-structured serological surveys of wild animal populations. Examples of cross-sectional serology surveys are given for a number of microparasites in Figure 4. Most of these serology profiles show a steady increase in sero-prevalence with age. Unfortunately, the serology tests used to obtain these data often fail to differentiate between infectious individuals and individuals that have recovered from infection and are now immune. Where the data are obtained from pathogens whose dynamics conform to the basic SIR framework developed for measles and other humans pathogens, it should be possible to obtain approximate estimates of $R_0$, the basic reproductive ratio of the pathogen. If the host population and the pathogen are approximately at equilibrium, then an estimate of $R_0$ may be made using the average age of infection and estimates of host life expectancy (Anderson and May 1991, Grenfell and Anderson 1985, Dietz 1993).

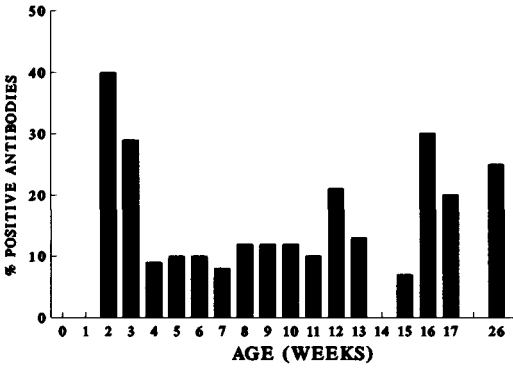
More powerful techniques are required to estimate age-and sex-specific transmission rates from the invasive and non-invasive surveys of serological data that are typically collected from wild populations. Significant biases can creep into these estimates unless information is available that allows us to quantify the way that the spatial distribution of the host species modifies estimates of $R_0$ (Barlow 1991a). May and Anderson (1984, 1990) and Anderson and May (1991) suggest a number of useful ways of handling the spatial heterogeneities in host distribution which may effect transmission rates.

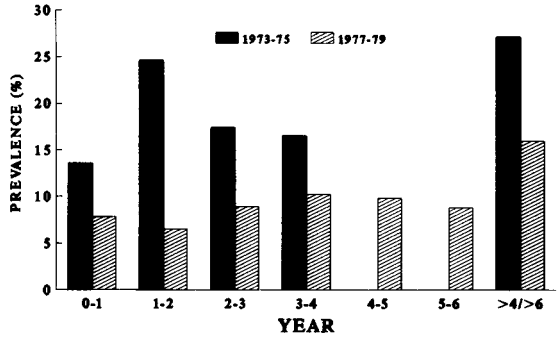
To fully determine the importance of spatial processes in determining transmission rates will require large scale data sets that monitor both the disease status of individuals and their spatial activity. The studies of Dwyer (1991) on insect viruses and Barlow on bovine TB in possums (Barlow 1991a, 1993), present some initial approaches to these problems. At present there are no long-term studies of vertebrates that contain data that could be used to test whether ecological methods can be used to parameterize transmission matrices.

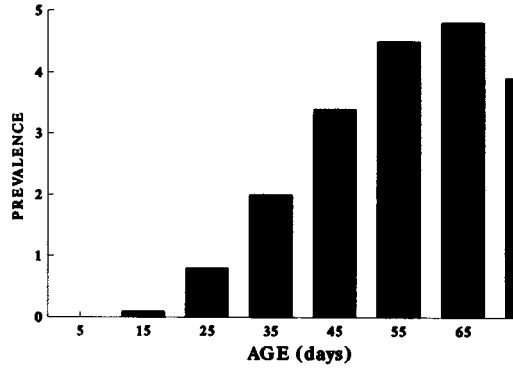
# 4 Long Term Trends

The available long term studies of microparasite infections of wildlife tend to fall into two categories: the majority of data sets consist of reports of numbers of infected animals reported in surveys undertaken of dead animals submitted for veterinary examination; a smaller number of data sets are from examinations of animals that have died in disease outbreaks in game parks or wildlife reserves.

In many cases the data collected are from disease outbreaks that have occurred following the introduction of a pathogen into a new area where potential hosts have no prior exposure. For example, the number of cases of both avian cholera and avian botulism in the United States have increased


Estimated seroprevalence for male and female bison collected on the Northern boundary of Yellowstone National pa
/91 (after Pac and Frey 1991); (B) myxomatosis in rabbits in UK (Ross *et al.* 1989); (C) badgers and bovine TB (Ande
5); (D) tsetse flies (*Glossina pallidipes*) infected with *Trypanosoma vivax* (Watson 1973)

significantly in the last 20 years, perhaps as a result of habitat alteration which reduces the available habitat for wildlife and concentrates migratory and resident birds into fewer and smaller areas and greatly increases the potential for disease transmission. Avian botulism has caused disease outbreaks where 50,000 birds die. Avian cholera was unreported in wild birds in the US prior to 1944, in an outbreak in Canada, around 100,000 geese were killed by an outbreak on their breeding grounds (Botzler 1991). Similarly, duck plague, caused by a herpes virus was unknown in the United States until an outbreak occurred in 1967 on a commercial duck farm on Long Island, New York (Jansen 1968, Leibovitz 1994). Following small isolated outbreaks of the disease, a major epizootic occurred at Lake Andes National Wildlife Refuge in North Dakota (Pearson 1994). An estimated 40,000 of 100,000 waterfowl died in this epidemic. Persistence of duck plague is mediated by the presence of carrier hosts who are immunologically silent and show no evidence of infection. There are large differences in susceptibility between host species. In a recent outbreak at Lake Cayuga in upstate New York, a high proportion of black ducks died, while a much smaller proportion of the more numerous mallards succumbed to infection.

Most surveys of disease outbreaks are obviously biased towards dead animals which may well have died because of the pathogen; there are very few long term systematic surveys of disease prevalence in natural populations. In some cases, such as the recent outbreak of distemper in lions in the Serengeti (Packer, personal communication), a considerable amount of information about the host population is available from long term ecological and behavior studies.

The most comprehensive data sets are for pathogens which also infect humans or domestic livestock, Figure 5 illustrates examples for rabies, bovine TB and canine parvovirus. These data illustrate three general trends: increasing prevalence through time (CPV in wolves in Superior National Forest), relatively constant prevalence (bovine TB in badgers, though some declines in prevalence have occured due to reductions in badger density), and low levels of prevalence with occasional epidemic outbreaks (rabies in mongooses and foxes). The dynamic behaviour observed in most of these studies contrast with the epidemic outbreaks illustrated in Figure 2. In all of these cases the pathogen persists in the host population for several years and either cycles in prevalence or remains at a relatively constant level. The one exception occurs with the CPV outbreak in wolves on Isle Royale; here the disease died out when the wolf population was reduced to a handful of animals left on the island, although it remained endemic in the wolf and domestic dog population on the mainland.

Mathematical models for microparasites display sustained cycles when hosts are infectious for only a short period time and then exhibit life long im-

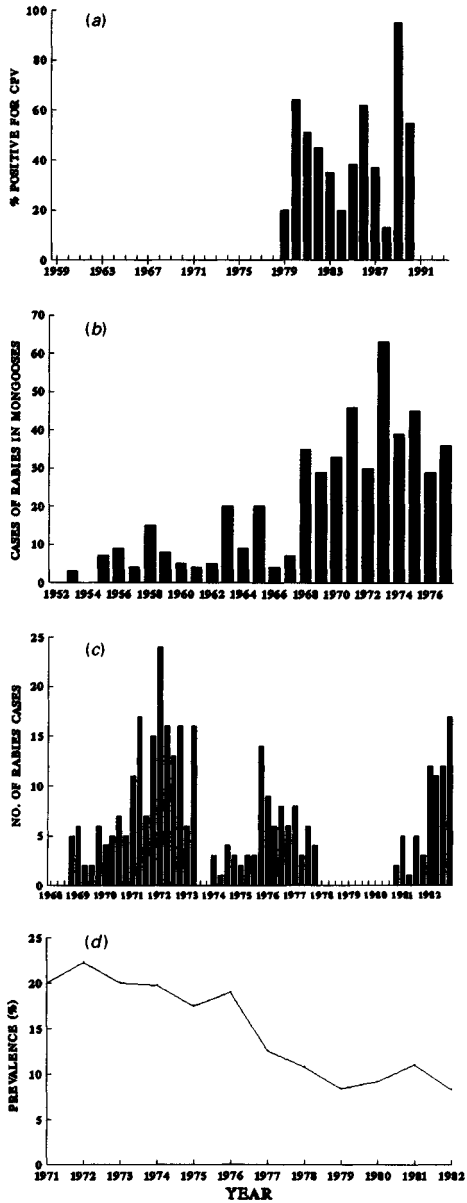



Figure 5. Long term dynamics observed for microparasites in wild populations of vertebrates: (A) percentage of wolves positive for canine parvovirus (CPV) from mainland Minnesota (Peterman and Page 1988; Mech and Goyal 1993); (B) cases of rabies in mongooses from Grenada, (Everard and Everard 1985); (C) cases of rabies in Red foxes in the Ardennes (Macdonald and Voight 1985); (D) prevalence of bovine tuberculosis in badgers in the counties of Gloucester, Avon and Wiltshire, England (Anderson and Trewella 1985).

munity, or when pathogens exhibit a long incubation period and produce high levels of host mortality (Anderson and May 1991, Heesterbeek and Roberts this volume). The aetiology of rabies corresponds to this second pattern, and most species infected with rabies tend to show cyclic epidemic outbreaks. In contrast, bovine TB and *Brucella* have long development periods, longer periods of infectiousness and produce relatively low mortality in their hosts, these pathogens tend to exhibit constant levels of prevalence. These longer term dynamics should be borne in mind when age-prevalence data from cross-sectional studies are examined. Thus, endemic pathogens will tend to produce steadily increasing levels of prevalence with age, in contrast, pathogens that tend to exhibit periodic epidemic outbreaks, will be characterized by a 'saw-toothed' serological age-profile. Some of these feature are apparent in the age-prevalence data illustrated earlier in Figure 4.

In cases where the pathogen is increasing in prevalence, for example rabies in striped skunks (*Mephitis mephitis*) and raccoons (*Procyon lotor*), these increases at the regional level also reflect increase in the geographical distribution of the disease (Pybus 1988, Gremillion-Smith and Woolf 1988). In some cases, these changes in geographical distribution reflect invasive spread of the pathogen into a new area, such as the current outbreak of rabies in raccoons that is making its way up the East coast of the United States. In other cases, rabies is endemic in a few core areas, but periodic epidemic outbreaks cause spillover into the individuals that live in the surrounding area. This pattern is observed fairly consistently in the long term reports for rabies in skunks in Illinois, where annual reports are collected from each county in the state. Data for the recorded cases of wildlife rabies in the United States reflect a similar pattern (Figure 6), but at a much coarser resolution (Torrence *et al.* 1992, Jenkins, Perry and Winkler 1988, Anthony *et al.* 1990); whenever the total number of recorded cases of rabies increases during a periodic outbreak, the number of 'spillover' counties recording outbreaks also increases, while the number of states recording outbreaks remains roughly constant (Gremillion-Smith and Woolf 1988). Both of these indices of prevalence decline after an outbreak and the disease retreats to low prevalence in the core districts. Models for the spatial spread of microparasites that describe some of these patterns are discussed in the chapter by Mollison and Levin (this volume).

It is worth mentioning here that recent developments in geographical information systems and the availability of satellite images are beginning to prove invaluable in examining the spatial patterns of disease distributions (Rogers and Williams 1993, Epstein *et al.* 1993); the melding of this technology with theory developed to examine the spatial dynamics of epidemics should allow important new insights to be gained in our understanding of the spatial distributions of different animal pathogens.

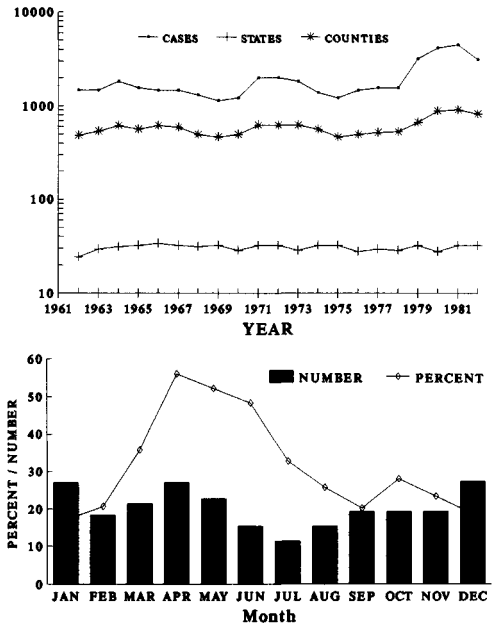



Figure 6. Spatial and seasonal components of rabies infection in striped skunks; (A) changes in the spatial incidence of rabies at three spatial scales: national (top line), county (middle line), state (line). (B) The seasonal incidence of rabies in skunks in Illinois; the vertical bars indicate the number of skunks submitted for testing, the diamonds indicate the percentage testing positive each month (after Gremillion-Smith and Woolf (1988)).

## 4.1 Seasonal patterns in single species

Seasonal variation in host birth rate and social behaviour may lead to seasonal variations in the force of infection. In rabies for example both annual and biannual cycles are superimposed upon the longer 4 to 10 year cycles in disease incidence; see Figure 6 (Gremillion-Smith and Woolf 1988). The annual incidence of rabies in skunks reflects several aspects of the host population biology, some regions illustrating a peak of prevalence in the fall and early winter and others exhibiting a double peak with one in the spring and one in the fall. Peaks are probably caused by increases in transmission when the animals either den communally, or when young animals migrate and contact rates between individuals increases.

## 4.2 Long-term trends in multi-species pathogens

Pathogens, such as anthrax, rabies, rinderpest and trypanosomiasis can utilize a range of hosts species. Although one species may act as the principle reservoir, disease outbreaks rapidly spread to other species. Long term data for this type of pathogen are again usually obtained from records of dead

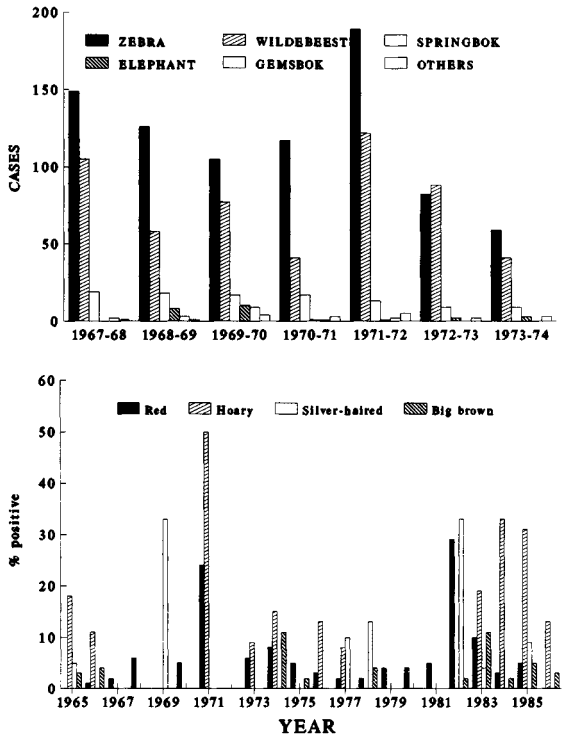



Figure 7. Temporal incidence of pathogens that infect a range of host species. (A) cases of anthrax in different wildlife species (zebra, wildebeest, springbok elephant, gemsbok and 'others') in Etosha National Park, Namibia (after Berry 1993). (B) Prevalence of rabies in four different species of bats (Red, Hoary, Silver-haired, Big-brown) in Illinois (Burnett 1989).

animals in outbreaks; Figure 7 illustrates examples for anthrax and rabies. In the former case persistence of the pathogen is probably achieved by long lived spores that remain in the soil and are transmitted to susceptible hosts when droughts lead to the overgrazed conditions that promote spore uptake. In Etosha National Park in Namibia mortality due to anthrax and rabies has been recorded intensively since 1966 and 1975 respectively (Turnbull *et al.* 1989, Berry 1993). While the majority of recorded anthrax deaths occurred in zebra (54%), with the remaining deaths occurring predominantly in wildebeest (35%), springbok (6.7%) and elephant (1.7%). In contrast, rabies deaths were mainly in kudu (54%), jackals (26%) and bat-eared foxes (11.3%). The differences in death rates reflect the abundance of each host species, their feeding ecology and their susceptibility to infection.

Where pathogens infect a range of wildlife species low rates of transmission between different host species may lead to different genetic and immunological

strains of the pathogen infecting different host species whose ranges overlap, for example rabies in bats, raccoons and skunks (Carey and McLean 1983). There is also increasing evidence which suggests that geographic structuring of the host population will produce geographic 'races' or varieties of the pathogen. The rabies that infects skunks in the southern US is immunologically, and genetically, distinct from the rabies present in skunks in California, the great plains and the north-eastern US (Smith *et al.* 1986).

The long term records for bat rabies in Illinois contain some important examples of the subtle role that host ecology plays in determining transmission rates. The prevalence of rabies in colonial-living bat species is lower than the prevalence in more solitary species (Burnett 1989, Carey and McLean 1983). Three reasons have been suggested to explain this: colonial species may be less aggressive when infected with rabies than solitary species, this is partly supported by many examples of solitary bat species attacking other individuals when infected. Secondly, it could be that different strains of rabies are present in each bat species and the strains present in colonial species have less of an influence on host behaviour. Both the lack of sychronicity in rabies outbreaks in different bat species and immunological differences in rabies strains isolated from different bats support this contention. Finally, it may be that the stress of migration increases the susceptibility of solitary bat species to rabies (Burnett 1989).

## 4.3 Interspecific transmission

Acknowledging that pathogens exist which infect a range of potential host species has stimulated the development of more complex epidemiological models (e.g. Holt and Pickering 1985, Begon *et al.* 1992, Begon and Bowers this volume). These models require a considerable increase in the number of transmission rates that have to be estimated from a restricted number of data points. In many cases quantification of transmission rates will be impossible unless independent information is obtained that quantifies the transmission rates within and between potential host populations. A rapidly developing area in the study of infectious diseases in humans, is the development of models that explicitly consider differential rates of disease transmission between individuals of different age and sex (Dietz and Schenzle 1985, Anderson and May 1991, Anderson *et al.* 1989, Blythe and Castillo Chavez 1989, Sattenspiel and Simon 1988). Where pathogens infect a range of host species these techniques can be modified to quantify the rate at which pathogens spread within and between species. To examine the dynamics of a pathogen which infects a range of host species we will potentially need to estimate not only rates of transmission between individuals of different age, sex or social status for each individual species, but also transmission rates between different age and sex classes of different species!

How can we reduce this complexity? A number of different ecological and physiological factors are likely to be important in determining the relative rates of within and between species transmission. Population densities and spatial heterogeneity will still be of primary importance in determining whether pathogens that infect several species of host will be able to establish in one particular species (see Begon and Bowers this volume). However, the presence of infected individuals of another species can allow a pathogen to establish in a population in which it would otherwise be unable to persist (Holt and Pickering 1985, Begon *et al.* 1992).

The initially daunting task of quantifying inter-specific transmission rates may be simplified if the physiological and ecological constraints that determine rates of transmission can be independently quantified. Physiological factors are a primary component in determining the potential of any species to transmit a pathogen. Here a variety of factors, such as the quality and quantity of mucus and saliva produced and the rate at which an infected animal coughs and sneezes all affect its ability to produce viable pathogen transmission stages. The influence of these physiological factors on transmission rates is likely to be very hard to quantify empirically, particularly as both host physiology and behavior may be modified by the pathogen to increase its transmission or as a side effect of other aspects of its pathology.

In contrast, from an ecological perspective, distances between animals are likely to be crucial in determining rates of pathogen transmission. These can fairly readily be quantified in the field. As in other ecological processes, it is not only the mean distances between animals that are important in determining transmission rates, but also the heterogeneity in these distances. In the case of intra-specific transmission the observed population densities and levels of aggregation are determined both by the habitat in which the animal lives and its social system.

As an example of a pathogen that infects a range of species consider the dynamics of rinderpest in a community of African ungulate species. Rinderpest is a member of the Morbillivirus genus in the order Paramyxoviridae (Scott 1964). Understanding the transmission dynamics of rinderpest requires the construction of a WAIFW matrix (Who Acquires Infection From Whom, (Anderson and May 1985,1991, Dietz and Schenzle 1985). The matrix quantifies the rates of transmission between different classes of individuals in the pool of potential hosts. In the case of rinderpest, which is transmitted by aerial plumes,the average distance between members of different species will be important in determining rates of interspecific disease transmission. It therefore seems sensible to assume that the relative magnitudes of interspecific transmission rates scale inversely with the distance between individuals of different species (Dobson 1995). Because the ratios of interspecific to intraspecific transmission are important in determining the prevalence of

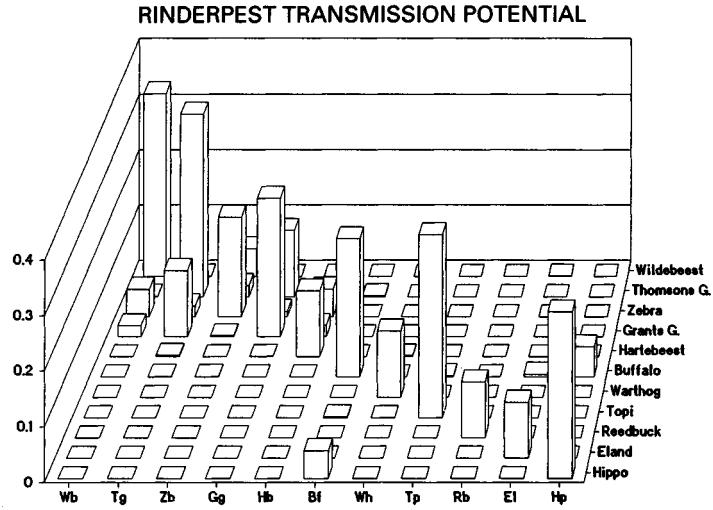



Figure 8. WAIFW (Who Acquires Infection From Whom) matrix for transmission within and between the main ungulate species in Ngorongoro Crater. The estimates of transmission rates are the inverse of samples of nearest neighbour distance for each ungulate species in the crater. The estimates were obtained in August 1989 by driving around the reserve and estimating the distance to the nearest conspecific and the nearest member of another species for between one and five animals in each social group of ungulate observed each day. The surveys have been repeated in the wet and dry season for each of two years (Dobson 1995).

infection in different host species, these simple quantitative measures of transmission potential will provide qualitative insight into the likely course of a disease outbreak in the host community.

The potential for disease transmission between different ungulate species in a natural community is illustrated in Figure 8. The data are taken from surveys of the spatial distribution of ungulates in Ngorongoro crater (Dobson 1995). The matrix is constructed from data collected only during the day and so reflect only a subset of the full range of distances that contribute to the observed patterns. Nevertheless, the surveys suggest that if the distances between members of different species are important in determining rates of intra-specific transmission, then transmission rates within a species are likely to be much larger than rates between species. If the WAIFW matrix were completely dominated by the diagonal elements that reflect within species transmission, this would lead to independent outbreaks occurring in each potential host species. However, the observed shape of the matrix suggests that interspecific transmission may occur readily between some species (e.g. Thompson's and Grant's gazelles), while hardly at all between others (e.g. wildebeest and topi). When combined with the WAIFW matrix determined

from the spatial distribution of different species throughout the ecosystem this may lead to complex patterns of disease outbreaks which may allow the pathogen to appear in small localized outbreaks and persist for many years after a major epidemic.

## 4.4 Vector borne diseases

Many diseases of wildlife are transmitted by vectors such as tsetse flies and ticks (see Dye this volume). When the vector uses a range of host species then the population dynamics of the pathogen can become tortuously complex. Transmission in vector borne diseases depends on the host being bitten by a vector that has already bitten an infected host and is capable of transmitting the pathogen. In these microparasites the basic reproductive ratio depends on the square of the vector biting rate, since pathogen transmission requires transmission from host to vector and again from vector to host. The probability of a host being infected will increase with the number of times the host is bitten, which in turn is a function of the vector to host ratio. When the vector to host ratio is low, changes in the prevalence of the disease will be strongly dependent upon changes in vector density. Epidemics can occur in years when vector numbers increase due to environmentally favourable conditions, or the presence of alternative host species which amplify vector abundance. In contrast, in areas of high vector density, the vector to host ratio is high and the disease may become endemic at a high level of prevalence.

Louping ill, is a disease of red grouse caused by a flavivirus that is transmitted between hosts by the sheep tick, *Ixodes ricinus*; the pathogen illustrates several of the characteristics described above. Although many aspects of the population dynamics of red grouse can be explained by the impact of the nematode *Trichostrongylus tenuis* and predators (Hudson, Newborn and Dobson 1992, Dobson and Hudson 1992, Hudson, Dobson and Newborn 1992), there are a number of grouse moors where ticks are abundant and where louping ill is known to kill 80% of infected individuals (Hudson 1992). In parts of the north Yorkshire moors, ticks and Louping ill are known to be present but the abundance of ticks is low and the disease is present at low levels with occasional outbreaks where the percentage of grouse that test seropositive varies from 2% to 20%. In contrast, in northern Scotland, the abundance of ticks is much higher, due to favourable habitat and abundant alternative hosts such as the mountain hares. In these areas the percentage of grouse that are seropositive remains high and relatively stable, between 40% and 60% (Hudson 1992). Population data collected from these endemic sites show high mortality during the breeding season when the vectors are active. Because mortalities due to the disease exceed recruitment, grouse populations in these areas can only be sustained by immigration.

# 5 Population Regulation by Microparasites

Population regulation is usually associated with either the survival or fecundity rate of the host population declining as the host population density increases. More formally, population regulation by a microparasite requires the per capita impact of the pathogen to exceed the intrinsic growth rate of the host population (May 1983). Unfortunately, it is frequently impossible to accurately estimate the magnitude of these parameters from the data collected in cross-sectional serology surveys, or occasional disease outbreaks. Even long term population studies only occasional provide the data necessary to estimate case mortality rates and host birth and death rates in the absence of the pathogen. This paucity of data has led to a continuing debate on whether parasites can actually regulate their hosts, or whether, mortalities due to pathogens are compensated for by increased fecundity and reductions in mortalities due to predators or starvation (Holmes 1982, Scott and Dobson 1989).

The best way to address this debate is to undertake experiments that either introduce a pathogen to a host population and demonstrate a significant reduction in host density, or remove a pathogen from a population and demonstrate an increase in population density. There are considerable logistic and ethical constraints in the design of such experiments. The classic studies of Greenwood in mice provide the best examples of how such a study could be designed (Greenwood *et al.* 1936). An alternative approach is to examine natural and human-induced introductions, or removals, of pathogens in areas where host populations can be carefully monitored.

Studies of rinderpest in East Africa and myxomatosis in rabbits provide potential 'natural' examples of host population regulation by a microparasite. In both cases the pathogen was introduced into a population with no prior exposure. The myxomatosis example is described in detail in Fenner (1983), Fenner and Ratcliffe (1965), May and Anderson (1983) and Dwyer *et al.* (1990), and in chapters by Apanius and Lively and by Read *et al.* (both this volume). The introduction of the myxoma virus to Australia and several European countries (UK and France) initially led to widespread reductions in rabbit populations. In both areas the rabbit population was an introduced species that had escaped from captivity and increased to sufficiently high densities to qualify as a major pest species. Unfortunately, the initial success of the myxoma virus as a biological control agent was short-lived as the initial virulent strains of the pathogen were replaced by strains with lower virulence. Selection in the virus was complemented by selection in the rabbits for strains that were more resistant to infection by myxomatosis. A better understanding of the dynamics and evolution of virulence in microparasites in natural populations requires more quantitative studies on virulence and its expression in natural populations. The classic studies on myxomatosis and

rabbits need to be extended to other species.

Rinderpest provides a less studied, but equally engaging example of the impact of a pathogen on host population dynamics. Understanding the influence of rinderpest on populations of buffalo, wildebeest and other wildlife species is made possible by the presence of long-term monitoring schemes which have tracked the densities of all large mammal species in the Serengeti ecosystem (Sinclair 1973,1979, McNaughton 1983). Up until 1890, the Sahara desert acted as an efficient barrier for the spread of rinderpest into the southern half of the African continent (Dobson 1988), primarily because the ungulate species that live in the desert exist at such low population densities that they are unlikely to support a continual infection of rinderpest. At the end of the last century a major pandemic of rinderpest was initiated by the accidental introduction of a few infected cattle into the horn of Africa. The epidemic caused massive mortalities in wild and domestic livestock that took 10 years to spread from Somalia to Cape Town. The levels of mortality in some species may have been as high as 95%, confirming that sub-Saharan ungulate populations had no previous exposure to the pathogen (Plowright 1982, Scott 1964, Simon 1962).

The development of an effective vaccine for rinderpest ultimately led to its eradication in much of East Africa (Plowright 1968,1982,1985, Scott 1964). Following the initiation of the vaccination scheme in cattle surrounding the Serengeti in the late 1950's, wildebeest numbers in the Serengeti increased from around 300,000 to around 1.5 million (Sinclair 1973,1979, Dublin *et al.* 1990). Increases also occurred in numbers of buffalo and in lions and hyenas that are the main predators of these two species. These increases were matched by the initial disappearance of the virus from wildebeest, buffalo and eland (Figure 9). The disappearance of rinderpest was matched by the decline in 'yearling' disease which had previously produced levels of mortality in immature wildebeest that were estimated to be as high as 40% (Talbot and Talbot 1963). All of this evidence implies that rinderpest was holding ungulate populations at a much lower density than the habitat could support and that predator numbers are dependent upon prey density, rather than acting as a regulatory constraint.

Although there have been no major epidemics of rinderpest in the Serengeti/Ngorongoro region since vaccination schemes were modified to use cell-culture vaccine, there have been a number of outbreaks that have led to significant localized mortality in cattle, buffalo and eland. In particular, an outbreak at Lobo in the Northern Serengeti in March 1982 killed many buffalo. This was followed by an outbreak in the Ngorongoro crater area in June of the same year when two to four thousand buffalo and a number of giraffe, warthog and eland also died. Sera from tissue collected from both these areas indicated the presence of rinderpest antibody (Rossiter *et al.* 1983,

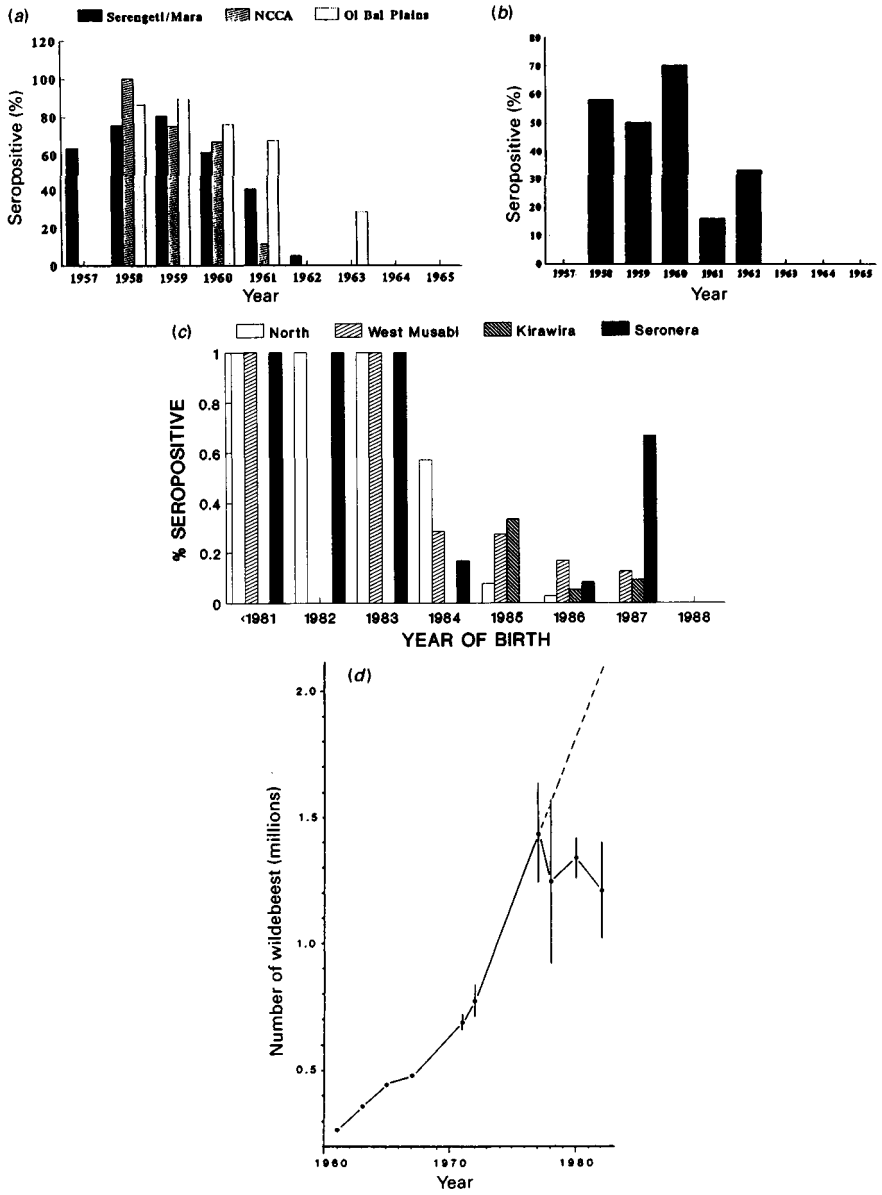



Figure 9. Serology profiles from (a) wildebeest, (b) eland, (c) buffalo in different parts of the Serengeti ecosystem following the onset of vaccination in cattle in the late 1950s (data from Plowright and McCullough (1967), Taylor and Watson (1967) and Anderson *et al.* (1990)). The wildebeest samples were collected in the Northern Serengeti and Masai Mara (dark bars), Ngorongoro conservation area (hatched bars) and the OlBal plains (open bars). The eland samples are all from Ngorongoro conservation area and the buffalo samples were from 4 different areas of the Serengeti: North, West Musabi, Kirawira, Sevanira. (d) The size of the wildebeest population in the Serengeti (1962–1984) after Dublin *et al.* (1990)).

1987). Subsequent serological surveys suggested that the disease persisted in the buffalo population for a number of years before fading out (Figure 9). However, it should also be noted that these data, which were collected from animals of different ages over the course of 2–3 years, could also be interpreted as reflecting the continued presence of the virus in the buffalo population. The change in prevalence with age might simply reflect continued low level exposure of animals to the virus. The absence of any pathological evidence would suggest that if it is present, it is a very mild strain of the virus.

## 5.1 Microparasites as biological control agents

The long term studies of rinderpest and myxomatosis provide tantalizing empirical demonstrations of the potential of microparasites to reduce host densities. The use of pathogens as biological control agents for introduced vertebrate pests on oceanic islands provides further support for arguments that microparasites are capable of regulating host abundance. Perhaps the best documented study comes from the introduction of feline panleucaemia (FPL) virus to the introduced cat population on Marion island in the south Atlantic (Howell 1984, van Rensburg *et al.* 1987). Here the introduction of FPL reduced the cat population from around 3400 in 1977 to around 600 in 1982, an annual decrease of around 30%. The study provides an important applied example of how pathogens may be used to reduce population to lower densities.

## 5.2 Disease control and its impact

Rabies epitomises the three different approaches made to the control of infectious diseases of wildlife (Pybus 1988): these approaches could be classified as passive acceptance, active disease constraint, and active host control. In the first case the presence of rabies in wildlife is accepted and the vaccination of domestic pets is accompanied by widescale public education programs. In many instances this is sufficient to reduce the spread of the disease. In the second case, free-ranging individuals are vaccinated in an attempt to constrain the spread of rabies. In the final case individuals in wild populations are culled in order to directly reduce the host population and its potential to infect humans or domestic livestock.

Control of infectious diseases of wildlife may be carried out by chemotherapy and vaccination campaigns, or by culling. While chemotherapy reduces the incidence of the disease by treating infected individuals, vaccination and culling attempt to control the pathogen by reducing the pool of susceptible hosts below the threshold for establishment. In general, vaccination and chemotherapy are more commonly used when the pathogens uses domestic livestock as their main reservoir host, although it is increasingly being tried as

a control measure when wild life can be treated relatively easily (e.g. Coyne and Smith 1992). In contrast, culling of wildlife is usually undertaken when populations of wildlife form a significant reservoir for a disease that poses a health problem to domestic animals or human populations. Increasing emphasis on ethical considerations in environment management should mean that vaccination will be used more often as a tool in wild populations while culling will have to be used more circumspectly (Anderson and Trewhella 1985).

## 5.3 Culling bison in Yellowstone

The long term data on population growth in the Yellowstone bison herd may be used to examine the efficacy of culling, or removal, as a means of eradicating *Brucella* from the bison herd. A simple model of the relationship between recruitment, population size and brucellosis prevalence suggests that eradication of *Brucella* from bison may require the reduction of the bison herd to less than 200 animals, essentially below the critical community size for maintenance of the disease, (Figure 10). Sustained culling at this level could rapidly drive the Yellowstone herd to extinction. At present the herd is expanding into a much larger range (Meagher 1989a,b) and numbers around 4,000 animals. Even a cull of this magnitude is not guaranteed to lead to the disappearance of brucellosis, as it will take quite some time to fade out in the reduced population. Similarly, the presence of more than one hosts species (or more than one strain of the bacteria) may confound attempts to control brucellosis by simply reducing any individual host species. Although the bison herd is perceived to present the major threat as a reservoir of the pathogen, a significant proportion of elk ( 2%) also test positive for *Brucella*. As there are 35,000 elk in Northern Yellowstone, and perhaps 100,000 in the Greater Yellowstone Ecosystem, the numbers of infected elk in the Yellowstone area are equivalent to the numbers of infected bison. This suggests that elk are as great a threat to cattle as are bison and should be subject to the same control regime. A potential vaccine has been tested on elk in Grand Teton national park (Herriges *et al.* 1989), but problems remain with both efficacy and delivery.

## 5.4 Vaccination against rinderpest in the Ngorongoro region

The control of rinderpest in East Africa presents a marked contrast to attempts to control brucellosis. Rinderpest eradication has been achieved entirely through the vaccination of cattle. No wild animals have ever been treated, indeed this would be both a dangerous and logistically impossible task (Plowright 1982). Cattle in the Ngorongoro Conservation Area are vac-

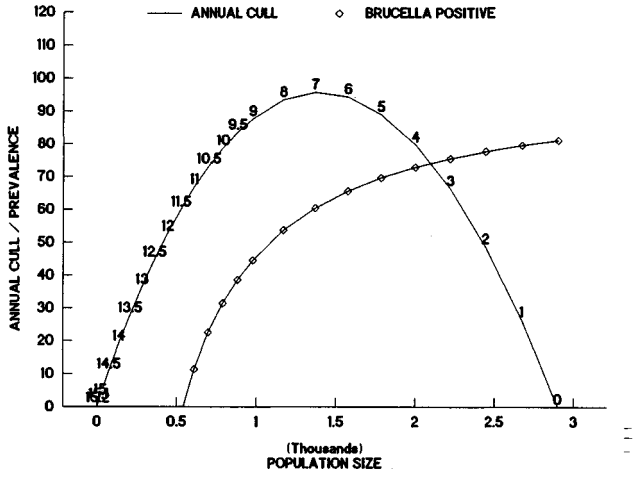
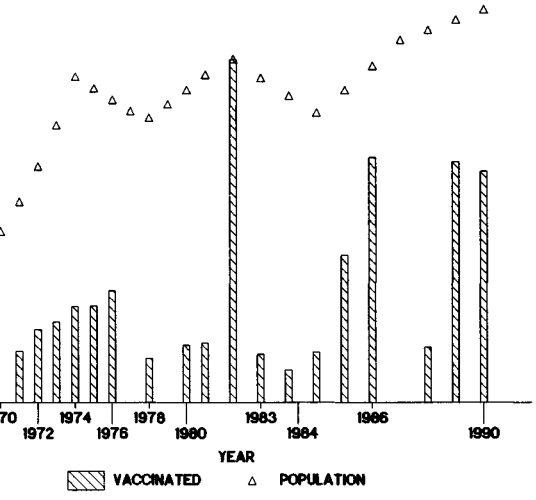
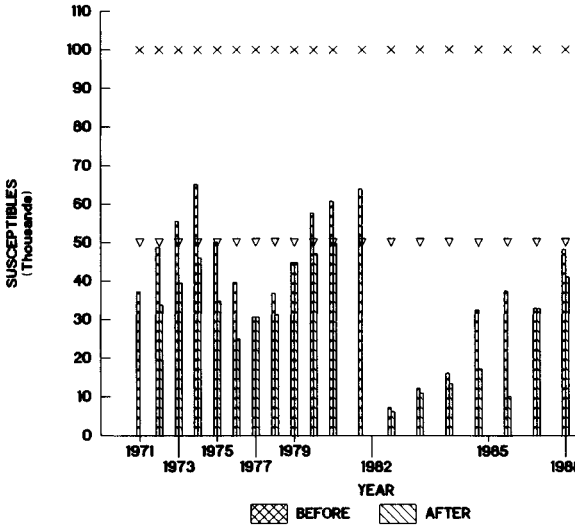



Figure 10. The relationship between bison population size and recruitment in Yellowstone National Park. The numbers superimposed upon this stock-yield relationship give the estimated annual percentage cull required to reduce the population to this level. The broken line is the relationship between population size and estimated seroprevalence of brucellosis (Dobson and Meagher in press).

cinated annually with a live attenuated virus vaccine. Figure 11 illustrates the total number of adult and juvenile cattle inoculated in the entire NCCA region for the years 1971-90. Although coverage in the early years of the vaccination campaign was occasionally erratic, the level of coverage has increased steadily so that by the late 1980's around 90,000 out of 130,000 cattle (approximately 70%) are protected at any one time. If Plowright's estimate that around 100,000 susceptible cattle are required to maintain the pathogen in the population (Plowright 1968), then the present level of coverage should be sufficient to prevent the disease re-establishing (see Figure 11).

Occasionally the illegal introduction of infected cattle from adjacent countries (particularly at times of civil unrest), leads to rinderpest outbreaks. This occurred in 1982, when rinderpest spread from transient cattle to wildlife and killed large numbers of buffalo. A larger epidemic was prevented by mounting a massive vaccination campaign which may have inoculated around 99% of the cattle in the region. The result underlies the importance of vaccination in containing the disease and in preventing future outbreaks. Furthermore it should be noted that the outbreak occurred in NCCA where the vaccination coverage is fairly high. In areas where the vaccination coverage is lower, the potential for rinderpest persistence is higher. This may explain why (Rossiter *et al.* 1987, Anderson *et al.* 1990) found evidence for rinderpest in buffalo from the Northern part of Serengeti where illegal cattle movements have been




otal numbers of cattle present in the Ngorongoro district of Tanzania between 1970 and 1990 and the numbers vacc obson 1994). The vaccination campaign lasts throughout the dry season, from July through until September. The data i numbers of adult animals, which are branded immediately before vaccination (on left after 1982), and calves which ar unch (on right after 1982). (B) Estimates of the numbers of susceptible cattle in NCCA in the period 1970 to 1990. Th numbers of susceptible individuals in the population, before and after vaccination, in each year. These estimates were ob evious inoculation lasts for life, but that the number of cattle brought for inoculation includes animals who have been i verage survival and fecundity rates of cattle have been estimated for the region (Homewood and Rodgers 1991); so it i he proportions of susceptible, resistant and multiply-inoculated animals in the host population. Two estimates of the hreshold for rinderpest to establish are also skectched: the upper value at 100,000 susceptible hosts ($\times$ $\times$ $\times$) represents P lower value at 50,000 (the solid triangle) is based on an estimate of transmission rate using the observed serology profile ation was widely used (Dobson 1995).

a common occurrence.

# 6 Conclusions: Pathogens, Disease Control and Biodiversity

Many long-term ecological studies of vertebrates have been disrupted by disease outbreaks that lead to increased mortality, reduced fecundity and reduced population densities. For example, the classic long term study of wolves on Isle Royale was completely disrupted when the wolf population was reduced from a long term average of 40-50 wolves in the 1960's and 1970's to a population of 10 to 15 animals following an outbreak of canine parvovirus in 1980 (Peterson and Page 1988, Mech and Goyal 1993). The long term studies of lions in the Serengeti are at present being disrupted by an outbreak of canine distemper (Packer, personal communication). The collection of epidemiological data from outbreaks in populations whose dynamics have been monitored for a long period of time before the disease introduction are particularly important for testing and developing the next generation of epidemiological models. The consequences of disease outbreaks and of disease control needs to be better understood in terms of the role they play in the maintenance of biodiversity in natural and captive communities (Dobson and Hudson 1986, Dobson and Crawley 1994).

Furthermore, the role that pathogens play in structuring ecological communities needs to be examined in more detail from both a theoretical and empirical perspective. In communities where the same pathogen infects a range of host species, we need more studies of the role that pathogens play in modifying interactions between species and determining the relative abundance of different host and non-host species. A number of theoretical studies have examined the population dynamics of systems involving one pathogen and two host species (Holt and Pickering 1985, Dobson and May 1986a,b, Begon *et al.* 1992, Begon and Bowers this volume). Understanding the population dynamics of such systems is crucial in systems involving pathogens that infect both wildlife and domestic species, particularly in situations where economic, health and political factors are important. Determining the most cost-effective and least damaging ways to control pathogens will considerably enhance the ability of wildlife managers to control similar diseases in other situations where they pose a major threat to the preservation of species diversity.

Unfortunately, very few surveys of disease in wildlife populations are organized so that data are collected on both host population density and pathogen prevalence. Although standard textbooks of wildlife epidemiology routinely describe disease symptoms and their characteristic pathology, information on disease prevalence in hosts populations of different sizes are rarely given. A

more detailed empirical synthesis of the population sizes required for disease establishment and rates of transmission in populations at different densities is essential if wildlife epidemiology is to progress from description to quantitative understanding. This will require increased dialogue between ecologists and epidemiologists interested in diseases of wildlife and the veterinarians and wildlife biologists who regularly collect data on diseases of wildlife. Similarly, the development of statistical techniques which allow the quality of epidemiological tests to be incorporated into the analysis of survey data is a major area for future research in wildlife epidemiology.

Ecological epidemiology has developed very rapidly as an important new branch of ecology. As threats to natural animal populations continue to mount, it is crucial that the role diseases play in perturbing and regulating natural populations be more completely understood.

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# Mathematical Models for Microparasites of Wildlife

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## 1 Introduction

In this chapter we review some of the basic theory of deterministic modelling of microparasitic diseases of wild animal populations. As discussed by Dobson and Grenfell in the Introduction to this volume, the special feature of wildlife diseases is that host population size is a dynamic variable. This requires significant modifications to classical epidemic theory based on constant host populations. Particularly since the seminal work of Anderson and May (1979), there has been a large body of research in this area (reviewed by Barlow, Begon and Bowers, Briggs *et al.* (this volume)). Here we review some basic issues in the modelling of microparasitic infections in naturally-fluctuating animal populations. The paper is not intended as an in depth study of microparasite models, but should be seen more as a summer exhibition at a museum with little bits of everything, as a guide to the art of elementary modelling and the less accessible more mathematical literature where the exhibits are usually stored.

There are many purposes for using mathematical models in epidemiology (see Anderson and May (1991), Hethcote and Van Ark (1992) for an extensive list). Among the main 'justifications' are, firstly, the fact that models provide *insight* into the relative importance of factors that influence spread, and improve our understanding of the relationship between mechanisms that operate on the level of the individual and the phenomena that result on the population-level (after Diekmann 1991). Secondly, the formulation of mathematical models requires precision about the underlying hypothesis and could make one aware of *working hypotheses* that might otherwise go unnoticed and which, once discovered, might deserve scrutiny. The analysis of mathematical models can lead to the introduction of *new concepts* that turn out to play an vital role. The most important example of this is the idea of a threshold quantity for epidemic development (the basic reproduction ratio $R_0$). Another use of models is in clarifying which parameters are critical in their influence on the dynamical behaviour. This may lead to the discovery of *key-parameters* whose numerical (range of) value(s) could still be unknown. Finally, we mention the dominant use of models in performing *thought experiments* with respect to, for example, the evaluation of the efficacy of given

(or even still imagined) control measures, in cases where actual experiments are impossible because of practical, ethical or economic constraints.

The main use of mathematical models is, perhaps surprisingly, not in predicting future trends. One of the reasons for this is that the most complex models for specific diseases are still (highly) oversimplified. Furthermore, our knowledge of the values of many parameters in the transmission process is often poor and making models more complex rapidly leads to a proliferation of these parameters, the values of which are difficult to determine with accuracy. Accurate quantitative predictions are therefore practically impossible, particularly given the potential complexities of dynamic wildlife host populations noted above.

In Section 2 of this paper, we introduce some simple concepts from epidemic theory. Starting with the general approaches of Kermack and McKendrick (1927) and Ross and Hudson (1917), we specialise to the compartmental approach to disease modelling that is most prominent in the literature today. We discuss concepts such as invasion (connected to the basic reproduction ratio $R_0$), epidemic, final size, endemic state, and control. The general Kermack and McKendrick model and the way that compartmental models are contained in it as special cases, are treated in Appendix A. In Section 3, we first introduce a simple (but not too simple) basic compartmental model, which we then proceed to extend in various directions, describing the dynamic behaviour of the models so obtained. The impact of host population dynamics is a particular focus here. The evaluation of control strategies such as vaccination and culling is discussed, with reference to the basic model, in Section 4. In Section 5, we briefly study the inclusion of heterogeneity in infection rates in the model, and finally, Appendix B is devoted to the definition and calculation of $R_0$ in heterogeneous populations.

Even the largest summer exhibition cannot cover all aspects of art, and happily there is no need for this because summer comes to museums everywhere. There are, first, a number of general useful books devoted to epidemiological modelling. In order of appearance we mention Bailey (1975) (stochastic aspects), Anderson (1982b) (a collection of papers, partly on human diseases, partly on animal diseases), Hethcote and Yorke (1984) (gonorrhea, but with much insight to modelling infectious diseases in general), Becker (1989) (data analysis), Anderson and May (1991) (a major tome, providing many insights on human disease epidemiology) and Busenberg and Cooke (1993) (a good introduction to mathematical modelling of infectious diseases, much broader than its title suggests). We do not discuss stochastic models, although we briefly go into stochasticity connected with fade-out in Section 2.4 (see also the Dye *et al.* this volume). Stochastic models of wildlife microparasites are mainly concerned with the spatial spread of rabies (see e.g. papers by Ball, Mollison and others in Bacon (1985)). For recent

advances in stochastic modelling of infectious diseases we refer to Gabriel *et al.* (1990), Mollison *et al.* (1991) and Gabriel *et al.* (1993). On a smaller scale but mainly devoted to wildlife diseases, we refer to Mollison and Levin (this volume), Bolker *et al.* (this volume) and Swinton and Anderson (this volume) for aspects related to spatial spread of animal diseases. For an excellent review of the modelling of spatial spread see Metz and Van den Bosch (1995). For vector transmitted diseases we refer to Dye and Williams (this volume), and for multi-host/multi-parasite interactions see Begon and Bowers (this volume). Finally, see Barlow (this volume) for an extensive critical evaluation of models for wildlife microparasitic diseases.

## 2 Some elementary epidemic theory

An important characteristic of the class of disease-causing organisms referred to as 'microparasites' is that, once infection has taken place, the disease develops within the body of the host individual without influence from the external environment (Dobson and Hudson this volume). In general, the microparasites reproduce within the host's body at such a high rate that any additional infection by the same parasite will go unnoticed. This observation is due to Ross and Hudson (1917) and Kermack and McKendrick (1927) in their seminal contributions to the mathematical theory of epidemics. Following this observation, both papers essentially describe the expected infectivity of an infected individual as a function $\mathcal{A}(\tau)$ of $\tau$, the time elapsed since that individual became infected. The idea is that $\mathcal{A}$ is the average taken over all possible stochastic time evolutions of the internal population of microparasites and the concomitant reaction occuring in the immune system of the host. The precise nature of $\mathcal{A}$ is, of course, determined by the particulars of the disease under study. In Figure 1, we give two examples of this function $\mathcal{A}$. The first graph represents a herpes infection in (wild)fowl (with recrudescence in carriers at irregular intervals after 6-8 weeks), the second graph represents rabies in foxes (both graphs are from G. Smith, personal communication). Note the difference in time-scale between the two examples.

In this paper we will focus on the more familiar compartmental models because they are the most frequently used in the literature. A concise description, connecting the more flexible infectivity function approach with compartmental models of disease progression, is given in Appendix A. For a recent review of mathematical modelling involving the infectivity function $\mathcal{A}(\tau)$ see Diekmann *et al.* (1995). For a recent review of compartmental models for infectious diseases we refer to Anderson and May (1991), Hethcote (1994).

In the compartmental approach, one generally distinguishes four classes, the *susceptible* individuals $S$, the *latent* individuals $E$ (i.e. infected individuals

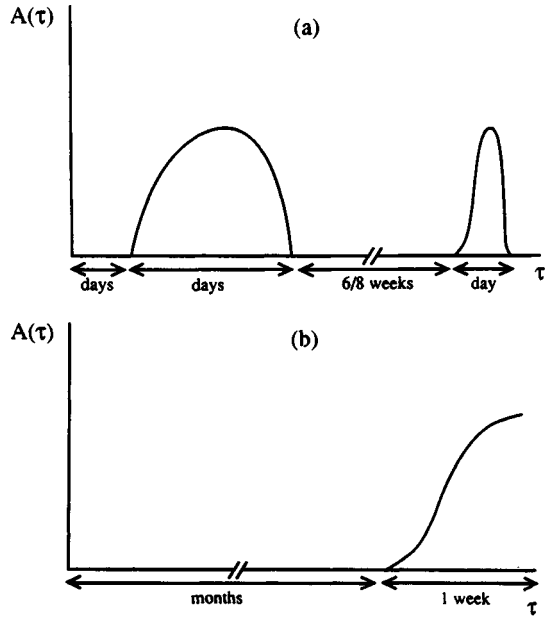


Figure 1. Examples of the shape of the function $\mathcal{A}(\tau)$: (a) For a disease with a short infectious period followed by recrudescence, and (b) for a disease with a long pre-infectious period.

that are not yet infectious, $E$ stands for 'exposed'), the *infective* individuals $I$ (i.e. individuals that are infectious) and the *removed* class $R$ (consisting in general of individuals that have been infected but are no longer infectious, and are not susceptible, where the interpretation of 'removed' can vary from (temporarily) immune to dead).

## 2.1 Simple model

For the simplest compartmental description of an epidemic caused by a microparasite we make the following assumptions: the population is closed (i.e. we assume that the time-scale of the epidemic processes of transmission and recovery is much shorter than the time-scale on which the population size changes due to natural births and deaths). This assumption will be removed when we consider the impact of host population dynamics in Section 3. Animals recover from the infection at a rate $\gamma$, after which they are immune to further infection; contacts between individuals are made at random; there is a constant transmission rate $\beta$. Consider a large population of *constant* size $N$, of which $S$ animals are susceptible to a given disease, $I$ are infective and $R$ animals have been removed. How many new cases arise per unit of time? The $I$ infectives make on average $\beta I$ potentially infective contacts per unit of

time. Only a fraction $S/N$ of those contacts is with a susceptible. So, $\beta IS/N$ is the number of new cases arising per unit of time.

The above assumptions lead to the following system of differential equations for the susceptible, infective and removed classes

$$\begin{aligned} \frac{dS}{dt} &= -\frac{\beta}{N}SI \\ \frac{dI}{dt} &= \frac{\beta}{N}SI - \gamma I \\ \frac{dR}{dt} &= \gamma I. \end{aligned} \tag{2.1}$$

In Appendix A it is shown that the infectivity function that describes the same situation is given by $\mathcal{A}(\tau) = \beta e^{-\gamma\tau}$.

Compartmental models are usually named after the types of compartment that occur in progression. System (2.1) is therefore an example of an SIR-model (if there were no recovery, i.e. if $\gamma = 0$, one would speak of an SI-model, whereas with an added latency period it would be an SEI-model, etc.).

## 2.2 Invasion

The first question one could ask when studying the disease dynamics under the assumptions listed above, is whether or not an epidemic develops when a small number $I_0$ of infectives is introduced into a large population of size $S_0$ where everyone is susceptible ($S_0 + I_0 = N$). This question is answered by the value of the basic reproduction ratio $R_0$, i.e. the expected number of secondary cases produced by one typical primary case during the entire period of infectivity in a population consisting only of susceptibles. Under the assumptions that lead to (2.1) we have

$$R_0 = \frac{\beta}{\gamma}$$

because on average one infective individual meets and infects $\beta$ susceptible individuals per unit of time, and it does this for a period of time of average length $1/\gamma$. An epidemic can develop if $R_0 > 1$ (if each infected individual on average causes more than one new infection, a chain reaction will ensue), whereas the disease will disappear from the population without causing a chain reaction of new cases if $R_0 < 1$.

Given that $R_0 > 1$, the solutions to system (2.1) typically look like the curve in Figure 2. The number of infectives will at first rise steadily, will then reach a maximum value and decrease until it reaches zero and the infection disappears. The decrease can be understood by observing that the susceptible population becomes too small after a certain point in time for an infective individual to come into contact with susceptibles sufficiently often during the

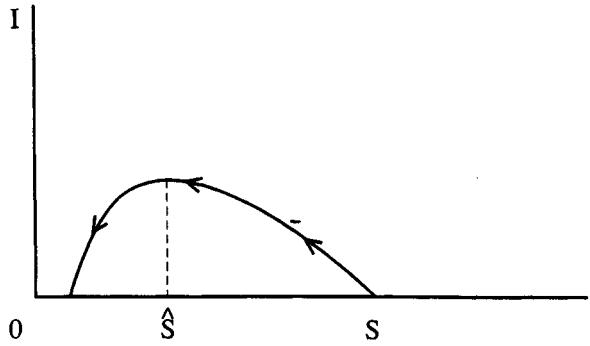


Figure 2. Typical solution trajectory for equation (2.1) in the $S, I$-plane. Note that $I$ achieves its maximum when $\hat{S} = S/N = \gamma/\beta$.

infectious period in order to cause new cases. Furthermore, the infectious period is of limited length, after which the individual becomes immune.

Remember that $R_0$ is defined in a virgin population, i.e. one consisting of susceptibles only. If $R_0 > 1$ and the epidemic progresses, then the susceptible population will decrease. In a non-virgin population, where a fraction $S/N < 1$ is still susceptible, an infective individual will on average cause a number of new cases less than $R_0$ ($R_0$ is an upper bound). One could use the term *current* (or effective, see Anderson (1982a), Busenberg and Cooke (1993)) reproduction ratio and denote it by $R_c(S)$, which depends on the currently available number of susceptibles, to describe the expected number of new cases per infective in a non-virgin changing population. Note that $R_c(S)$ is a function of time (because $S$ is), whereas $R_0$ is not. In the present case

$$R_c(S) = \frac{S}{N} R_0 = \frac{S\beta}{N\gamma}.$$

The epidemic reaches its maximum value (i.e. the maximum number of infectives present at the same time) at $dI/dt = 0$. From the second equation of (2.1), we see that this occurs when the susceptible population has reached the value $\hat{S} = \gamma N/\beta$. This is equivalent to the value of $S$ where $R_c(S) = 1$ (i.e. when, on average, each infective causes exactly one new infection in the non-virgin population). If $S < \hat{S}$, then $R_c(S) < 1$ and the infection cannot persist in the population (we already intuitively described this above).

## 2.3 Final size

In this simple epidemic model, the size of the susceptible population will steadily decrease and approach a limit $S_\infty$. The question is whether $S_\infty = 0$ (i.e. does the disease persist until every individual has suffered from it?). The

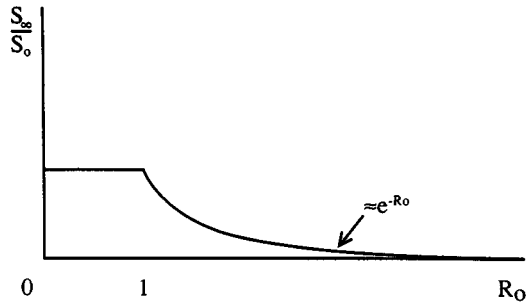


Figure 3. The ratio of the final size of the susceptible population to its initial size, for a simple epidemic model.

answer is already given by Kermack and McKendrick: no! More precisely, the following holds in good approximation (i.e. when $I_0$ is so small that $S_0 + I_0 \approx S_0$, for details see, e.g., Busenberg and Cooke (1993)):

- if $R_0 > 1$ then $S_\infty$ is found by solving the so-called 'final value' equation

$$\ln \frac{S_\infty}{S_0} = R_0\Big(\frac{S_\infty}{S_0} - 1\Big)$$

In Figure 3, this relation is depicted graphically, and one can observe that the bigger $R_0$ is, the smaller $S_\infty/S_0$ will be. From the relation it follows that for large $R_0$ we have $(S_\infty/S_0) - 1 \approx -1$, so $S_\infty \approx S_0 e^{-R_0}$.

## 2.4 Inflow of new susceptibles

The behaviour of (2.1) is very simple: if an epidemic occurs ($R_0 > 1$) then it will follow the general pattern of the curve in Figure 2 and we can calculate when it reaches its peak (when $R_c(S) = 1$), and what the final size is. Of course, in (2.1) we focused on a very short time-scale, where the demographic changes that might occur in the meantime could be neglected. If we widen our view to a longer time-scale, then we have to take into account that fresh susceptibles join the population to replenish the susceptible 'pool'. The model would then become somewhat more complicated, and the dynamics of the solutions diversify. In Section 3, we review this in detail for compartmental models. Here we only give some general comments.

If we include inflow of new susceptibles (by births or migration) we can still retain the assumption that the time-scales of demographic and disease processes are different. In that case, the generic picture changes into that depicted in Figure 4. After the epidemic has run its course and the disease has died out, the susceptible population will again build up on the demographic time-scale, and after it has passed the critical level for $R_c(S) > 1$, a new epidemic can occur if the disease is reintroduced.

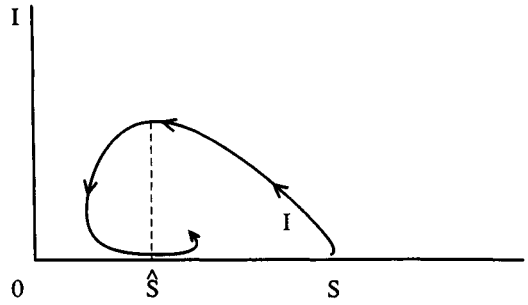


Figure 4. Typical solution trajectory in the $S, I$-plane for a simple epidemic model with birth or immigration of susceptibles, where the demographic time-scale is long compared to the disease time-scale.

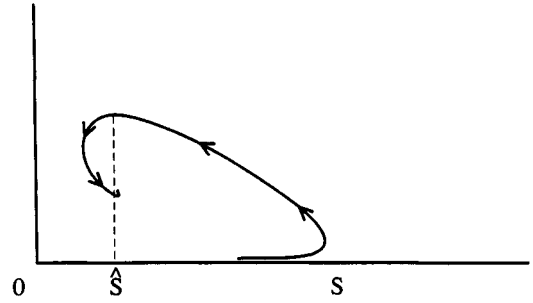


Figure 5. Typical solution trajectory in the $S, I$-plane for a simple epidemic model with birth or immigration of susceptibles, where the demographic and disease time-scales are similar.

If inflow of new susceptibles is important on the epidemic time-scale, then one can encounter various types of dynamic behaviour. One possibility is that a stable steady *endemic* state obtains, at precisely that level of the susceptible population where the corresponding $R_c(S) = 1$ (when, on average, each case generates exactly one new case). This value of $S$ is often called the critical community size (see Bartlett (1960) and Schenzle and Dietz (1987)). If the susceptible population is above this size, then an infection can persist. This situation is depicted schematically in Figure 5. Alternatively, the system can show regular or irregular oscillations around an unstable endemic steady state. If no steady state exists, then the susceptible population can either show a steady increase, with the infected population increasing steadily as well (and a question can be whether the disease causes the population to grow at a slower rate than it would have done in absence of the disease), or the disease can die out. We discuss simple models in Section 3 that show this range of behaviour.

As far as the disappearance of a disease from a population is concerned, it is useful to distinguish at least two types of stochastic aspects, linked to the recurrent epidemics and the endemic steady states described above (see Diekmann *et al.* (1995) for a more detailed discussion):

1. If population turnover is slow relative to disease transmission, we reach almost the final size situation of the closed epidemic before the gradual inflow of new susceptibles has any effect. In this case, there are very few infecteds and the size of the susceptible population is of the order of $S_0 e^{-R_0}$, which is far below threshold. It will take a long time before the density is above threshold again, and during this period demographic stochasticity may easily lead to the extinction of the infectious agent. This is referred to as epidemic fade-out in Anderson and May (1991, p.20).

2. Even if the infective agent escapes extinction after the first outbreak and becomes established, there is still the possibility of extinction as a result of chance fluctuations. This is called endemic fade-out in Anderson and May (1991).

We end this section with some elementary remarks about control. If some control strategy (e.g. vaccination or culling) were being considered for a given endemic disease, then it would be interesting to evaluate its efficacy in eradicating the disease. Let us take vaccination in a homogeneous population as an example and consider the possibility for invasion in the partly vaccinated population. If a fraction $v$ of the susceptible population is made immune to infection at any given time, due to vaccination, then a fraction $(1-v)$ of the susceptibles remains available. If the vaccination strategy is to be successful, it has to bring the reproduction ratio $R_v$ in the vaccinated population below one. Note that $v = 0$ (no vaccination) brings us back to the invasion problem in a virgin population. In the situation described by the model (2.1) we get $R_v = (1-v)\beta/\gamma$ as the expected number of secondary cases. For success we want $R_v < 1$ which is equivalent to

$$v > 1 - \frac{\gamma}{\beta} = 1 - \frac{1}{R_0}.$$

In Section 4, we discuss control strategy evaluation for more 'realistic' models.

## 2.5 Density models

In the literature one encounters models expressed not in absolute numbers of animals but in densities. Usually density refers to number of animals per unit area, but other density-measures may be important as well. For example, in

the context of the larch-budmoth and its granulosis virus, Baltensweiler (see e.g. Baltensweiler (1968), Briggs *et al.* (this volume)) uses number of larvae per 7.5 kg of branches as a measure of density (see also Bowers *et al.* (1993)). For the rest of this section we will only consider spatial density.

If the area occupied by a population remains constant, then an increase in numbers is equivalent to an increase in density, and one might as well formulate the model in terms of absolute numbers as these are often intuitively easier to grasp. If the population expands the area it occupies when numbers increase, then the density could stay roughly constant and it depends on the type of problem one is studying whether the sizes of the various classes are better expressed in numbers than in densities. For example, when studying effects of the environment on host population dynamics (limits in growth) one might opt for densities (see however Section 3.3).

The main reason for the use of densities is the immediate connection to the law of mass-action from chemical reaction kinetics which underlies the transmission term in many epidemic models. The mass-action assumption originally states that the rate at which molecules of types A and B collide (i.e. the number of collisions per unit volume per unit of time) in a well-stirred reaction vessel, is proportional to the product of the concentrations of A and B. Translated into susceptible and infective individuals making pairwise contacts in a homogeneously mixing population, the assumption reads that the number of contacts per unit area per unit of time is proportional to the product of the density of susceptibles $s$ and the density of infectives $i$. The main assumption, apart from homogeneity, underlying this is that locally the probability per unit of time of a contact between two individuals is the same for any pair. In the situation of model (2.1) this leads to a transmission term of the form $\hat{\beta}si$, where $\hat{\beta}$ is the transmission rate constant. In De Jong *et al.* (1995), both theoretical and experimental results are discussed that show that the correct counterpart of mass-action if one expresses class-sizes in absolute numbers is given by transmission terms of the form: $\beta SI/N$, as in (2.1).

In Dwyer and Elkington (1993), a model for a nuclear polyhedrosis virus in Gypsy moths is discussed where the description in densities is particularly apt (Briggs *et al.*, this volume). One of the variables is the quantification of infectious virus-particles in the environment which can of course only be expressed as a density (here number per unit volume) because absolute numbers are, as in chemical reactions, not appropriate.

# 3 Adding various complexities

## 3.1 The basic SI-model

In the present section we will add more biological complexity ('realism') to the simple model (2.1) and describe the dynamic behaviour of the models thus

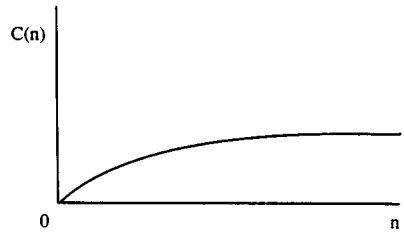


Figure 6. The contact rate $C$ as a function of population density $n$.

obtained. In this subsection we add a few basic details, in further subsections we then look at various extensions with examples and applications. We start however, by disregarding recovery (i.e. take $\gamma = 0$), and defer study of the influence of an '$R$-class' to Section 3.6. For a detailed review and analysis of SI-models, including many of the extensions given below, see Zhou and Hethcote (1993).

In deference to its potential importance for wildlife diseases, we first of all relax the requirement that the population size $N$ is constant. Furthermore, let each individual make contact with $C(N)$ other individuals per unit of time. The definition of contact depends upon the mode of transmission of the disease under study. Given that the contact is between an infective and a susceptible individual, the transmission rate is $\beta C(N)$. For each contact the probability that the 'contactee' is susceptible is $S/N$ (we assume homogeneous mixing), and hence the total number of infectious contacts per unit time is $\beta C(N)IS/N$. The expression $\beta C(N)I/N$ is often referred to as the *force of infection* (Anderson and May 1991), being the fraction of the susceptible population that the infectives are able to contact and infect per unit of time.

The opportunity for contact depends upon the local population density. Heesterbeek and Metz (1993) have shown that, when it is taken into account that contacts have a non-negligible average duration, the relationship between the contact rate $C$ and the (spatial) population density $n$ in a homogeneously mixing population is as shown in Figure 6. The density itself may change as a function of population size $N$. If we consider a wild animal population then at low numbers the area occupied will not change initially as the number of animals slowly increases (i.e. density will increase linearly with population size). After some critical density has been reached animals will disperse or widen the territory occupied and density will temporarily drop only to increase again as numbers rise further to take up the enlarging area. As a caricature one could picture the relationship as shown in Figure 7 (dotted line) and approximate the general trend by a saturating curve (solid line). Combining the 'shapes' of Figures 6 and 7, one can easily show that $C$ as a function of $N$ is as in Figure 8, which is similar to the form $N/(c_1 + c_2N)$ postulated by Dietz (1982).

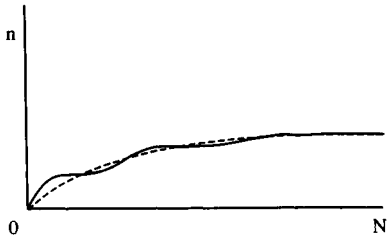


Figure 7. Population density $n$ as a 'heuristic' function of population size $N$.

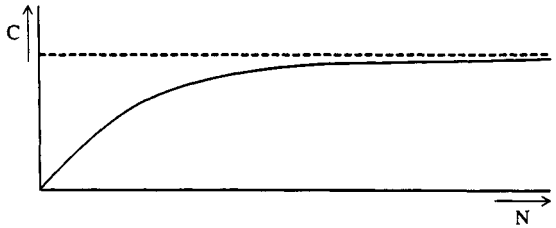


Figure 8. The contact rate $C$ as a function of population size $N$. Reproduced from Roberts and Heesterbeek (1993), with permission.

A more careful argument along similar lines, see Diekmann *et al.* (1994), results in a counterintuitive $S$-shaped relation between population size and contact rate. This might prove to be the correct relation certainly for animals that display territorial behaviour or have specific contact structures like the seal population they discuss. There is a clear need for more detailed submodels of the contact process.

We now add rudimentary demographics of the animal population to the basic model, and include a general contact rate function $C(N)$. As pointed out by Anderson and May (1979), a central question here is: can the parasite regulate the size of the host population? The only way to leave the infected class $I$ is by death, either due to the disease or from natural causes. Let the (constant) per capita birth and death rates in the absence of disease be $a$ and $b$ respectively, and assume $a > b$ (hence the population increases exponentially in the absence of disease). The model (2.1) becomes

$$\frac{dS}{dt} = aN - bS - \beta\frac{C(N)}{N}SI \tag{3.1}$$

$$\frac{dI}{dt} = \beta\frac{C(N)}{N}SI - (\alpha + b)I, \tag{3.2}$$

where $\alpha$ is the increase in host mortality due to disease. It is often more convenient to work in terms of the total population size $N$ and the number of infectives $I$. Adding (3.1) and (3.2) (and copying (3.2) with $S = N - I$) we obtain

$$\frac{dN}{dt} = (a - b)N - \alpha I$$

$$\frac{dI}{dt} = \beta\frac{C(N)}{N}(N-I)I - (\alpha+b)I. \tag{3.3}$$

System (3.3) has steady state solutions defined by $(N,I) = (0,0)$ and $(N^*,I^*)$ with

$$I^* = \frac{a-b}{\alpha}N^* \tag{3.4}$$

$$C(N^*) = \frac{\alpha(\alpha+b)}{\beta(\alpha+b-a)}. \tag{3.5}$$

As equation (3.5) does not explicitly define $N^*$, an obvious requirement for the steady state to exist is that (3.5) has a solution. This is not a problem if, for example, $C(N)$ is as in Figure 8, with the limit for large $N$ sufficiently large (i.e. larger than the right-hand side of (3.5)). Most authors proscribe that $C(N)$ must be an increasing function of $N$, with some technical requirement to ensure that $N^*$ is defined uniquely (see, e.g., Thieme (1992) and the references given there). If (3.5) indeed has a unique solution, then a positive steady state exists, and the disease can regulate the population when $\alpha > a - b$. This requirement may be interpreted as regulation being achieved if the disease-induced mortality rate exceeds the intrinsic growth rate of the population. In this context, regulation means that a population that is increasing in size in the absence of the disease, is limited to a steady size in the presence of the disease (Anderson and May 1979). Diekmann and Kretzschmar (1991) proved that the steady state defined by (3.4-5), if it exists, is globally asymptotically stable, i.e. solutions will always tend to that steady state over time.

A related question is what happens to the dynamics of (3.3) if the steady state (3.4-5) does not necessarily exist. From (3.3b) it is apparent that if $I$ is very small, then $dI/dt < 0$ whenever $\beta C(N) < \alpha + b$. Diekmann and Kretzschmar (1991) investigated the special case

$$C(N) = \frac{N}{c+N} \tag{3.6}$$

in detail. Formula (3.6) has the general shape given in Figure 8. The dynamics of solutions of (3.3) may, with this choice for $C(N)$, be summarised as follows, in terms of the value of the transmission rate constant $\beta$ in relation to the other parameters:

| | |
|---|---|
| (i) $0 \le \beta < b+\alpha$ | $N \to \infty, I \to 0$ |
| (ii) $b+\alpha < \beta < a+\alpha$ | $N \to \infty, I \to \infty$ |
| | $I/N \to 0$ |
| (iii) $a+\alpha < \beta < \ell$ | $N \to \infty, I \to \infty$ |
| | $I/N \to (\beta-\alpha-a)/(\beta-\alpha) > 0$ |
| (iv) $\beta > \ell := \alpha(\alpha+b)/(\alpha+b-a)$ | $N \to c\ell/(\beta-\ell)$, |
| | $I/N \to (a-b)/\alpha$. |

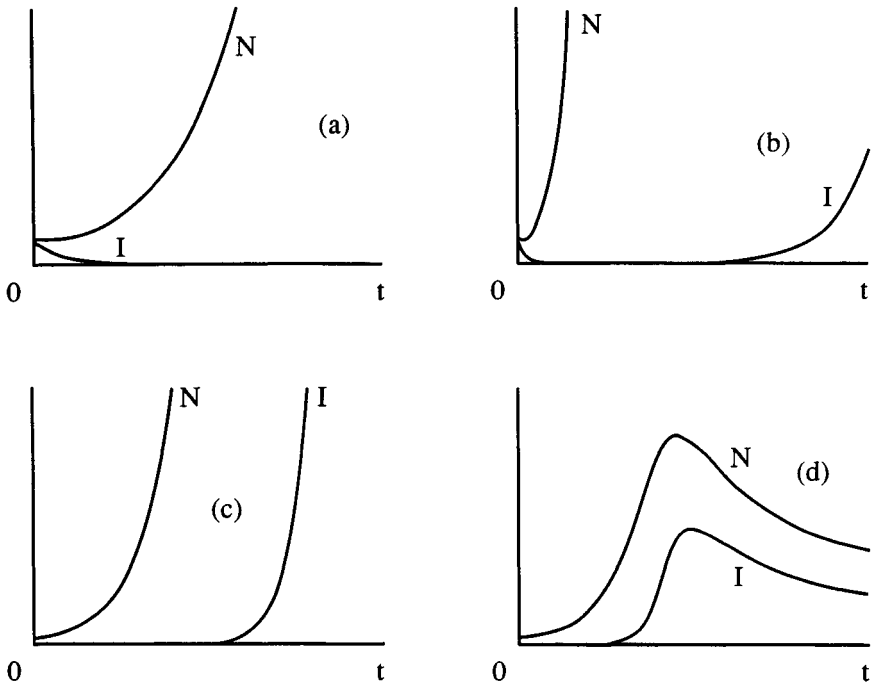


Figure 9. Numerical solutions of equation (3.3) with $a = \alpha = 2, b = 1, C(N) = N/(5 + N)$ and a) $\beta = 2$; b) $\beta = 3.5$; c) $\beta = 5$ and d) $\beta = 8$; satifying conditions (i)-(iv) above, respectively. Reproduced from Roberts and Heesterbeek (1993), with permission.

Inspection of the proofs in Diekmann and Kretzschmar (1991) makes it clear that similar results hold true if $C(N)$ is any increasing function. In words, the four possibilities are, for increasing values of the transmission rate $\beta$: i) the disease becomes extinct and the host population grows without bound; ii) both the susceptible and infective populations grow without bound, but the proportion that are infective tends to zero; iii) both the susceptible and infective populations grow without bound, but the proportion that are infective tends to a positive finite limit; and iv) both the susceptible and infective populations tend to a bounded steady state ((3.4-5)). The four possibilities are illustrated schematically in Figure 9.

If the contact rate $C(N)$ is a constant for all $N$, then equation (3.5) can only be solved if the constant happens to be equal to the right-hand side of

(3.5). For this case we have the same possibilities (i)-(iv) from the previous paragraph, but the bounded steady state of (iv) is now the steady state $(N, I) = (0, 0)$ (see Busenberg and Van den Driessche 1990).

## 3.2 Disease-dependent host demographics

In many cases diseases will reduce the fertility of the host animal (for an excellent biological discussion see Gulland, this volume). Examples are fungal infection of geese (Smith and Dobson 1992), brucellosis causing abortions in elk (Peterson *et al.* 1991) and microsporidian infection of flour beetles (Onstad and Maddox 1990). See Dobson and Hudson (this volume) for additional evidence from data of reduced host fitness and reduction to lower population densities in the presence of pathogens (for microparasites from three different biological classes). Briggs *et al.* (this volume) provide an extensive discussion of the relationship between disease and host demography for microparasites of insects.

In Diekmann and Kretzschmar (1991) this effect on the birth-term is modelled by including a rudimentary description of pair formation. A pair can be formed between two susceptibles, a susceptible and an infective (in which case the rate of producing offspring is reduced by a factor $\xi$) or two infectives (reduction by factor $\xi^2$). This leads to

$$\frac{dN}{dt} = a\frac{(N - (1-\xi)I)^2}{N} - bN - \alpha I. \tag{3.7}$$

The system (3.3b,3.6,3.7) was analysed by Diekmann and Kretzschmar (1991), who determined the following dynamic behaviour. There exist two threshold parameters $\xi_T$ and $\xi_P$. If $\xi > \xi_T$ then the behaviour of solutions is qualitatively the same as that of solutions to (3.3,3.6) (which corresponds to $\xi = 1$). If $\xi_P < \xi < \xi_T$, there exists a range of the parameter $\beta$ for which there is bistablility (long term behaviour dependent on initial conditions). If $0 < \xi < \xi_P$ there exists a range values of $\beta$ for which stable periodic solutions occur.

In Zhou and Hethcote (1993) reduction of fertility is also studied, but with a birth-term which is not quadratic. In this case no cyclic behaviour is possible.

As an extension of (3.7), it may be interesting to study the following variant

$$\frac{dN}{dt} = a\frac{(N - (1-\xi)I)(N - (1-\eta)I)}{N} - bN - \alpha I$$

which could mimic different effects of the disease on the fertility of males and females (Hethcote, personal communication), or different effects on female fertility depending on whether a susceptible female contacts an infective male or whether the female is itself infected.

## 3.3 Host population dynamics

Host populations do not grow in an unbounded manner. In reality the birth and/or death rate will depend on the host population density, birth rate being a non-increasing function of density and death rate non-decreasing. The derivation in the previous subsections was in terms of size rather than density, but as in the argument for the contact rate function in 3.1, there is a direct correspondance between the two. We will continue to use population size as a variable. Consider the equation

$$\frac{dN}{dt} = \big(A(N) - B(N)\big)N - \alpha I \tag{3.8}$$

where $A$ and $B$ are birth and death rates, respectively, as functions of $N$ with $dA/dN \leq 0$ and $dB/dN \geq 0$. Equation (3.8) is the analogue of (3.3a), for density dependent population growth. The term in brackets ensures that in the absence of disease the population size tends over time to the carrying capacity $K$, where $A(K) = B(K)$, with positive growth if $N < K$, and negative growth if $N > K$. Often logistic population regulation is assumed with $A(N) - B(N) = r(1 - N/K)$ (where $r = a - b$). Nonlinear effects in population growth are in response to the local population density, and an examination of the community structure is necessary to ensure that any model is correctly defined. For models with a constant rate of recruitment (i.e. $N$-independent) or immigration into the population, see Zhou and Hethcote (1993) and the references given there. Of course, wild animal populations do not, in general, breed continuously throughout the year, but have a seasonal pattern. These periodic birth patterns could be modelled by taking $A(N) = a(1 + \epsilon\phi(t))N$, where $\phi$ is a periodic function of time. We will not discuss this complication in more detail but refer to Roberts *et al.* (this volume), Grenfell (1992), Bolker and Grenfell (1993) and the references given there.

Equation (3.3b) becomes

$$\frac{dI}{dt} = \beta\frac{C(N)}{N}(N - I)I - \big(\alpha + B(N)\big)I. \tag{3.9}$$

The above system (3.8-9) has three steady state solutions: the trivial one $(N, I) = (0, 0)$ which is unstable, the disease-free steady state $(N, I) = (K, 0)$, and the endemic steady state $(N^*, I^*)$ which only exists if the basic reproduction ratio

$$R_0 = \frac{\beta C(K)}{\alpha + B(K)}$$

is greater than one. The solution dynamics of (3.8-9) may be summarised as follows. If $R_0 < 1$, the disease cannot persist, and all solutions tend to the disease-free steady state $(K, 0)$. If $R_0 > 1$, the disease persists in the population, and solutions tend to the endemic steady state $(N^*, I^*)$, where

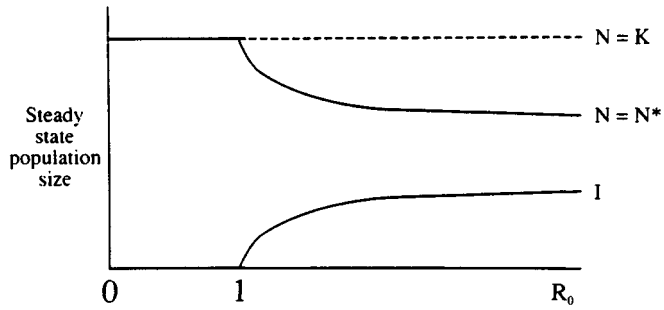


Figure 10. Steady state population size $N$ and the size of the infectious population $I$ as functions of $R_0$ for equations (3.8-9). The broken line signifies an unstable steady state. Reproduced from Roberts and Heesterbeek (1993), with permission.

$N^* < K$. The steady state value $N^*$ as a function of $R_0$ is given in Figure 10.

As $R_0$ depends on $K$ an alternative way of expressing the threshold theorem is to define $K_T$ as that carrying capacity for which $R_0 = 1$. The threshold for disease persistence can then be expressed as $K > K_T$, where

$$\frac{\beta C(K_T)}{\alpha + B(K_T)} = 1.$$

The validity of this as a threshold, or indeed the existence of a unique solution for $K_T$, depends upon the precise form of the functions $B(N)$ and $C(N)$. For example, for the extreme case $C(N) = N$, with $B(N) = b$, constant, $K_T = K/R_0$ with $R_0 = \beta K/(\alpha + b)$. For the other extreme $C(N)$ a constant (=1), $R_0 = \beta/(\alpha + b)$ (compare Section 2). For the latter case, both the contact rate $C$ and $R_0$ are independent of population size, and the concept of $K_T$ is meaningless. In Bouma *et al.* (in preparation) and in De Jong *et al.* (1995), both theoretical arguments and experimental evidence are discussed that show that $R_0$ does not depend on population size at constant population density.

## 3.4 Vertical transmission

Vertical transmission of a parasite occurs when it is passed from mother to offspring either before or at birth. Examples include venereal spirochaetosis of rabbits (transmission at birth) (Smith and Dobson 1992) and insect baculoviruses (see Briggs *et al.* (this volume) for a review). Pseudo-vertical transmission is the term used when the disease is passed from mother to offspring after birth, due to unusually close contact. An example of this is

tuberculosis in possums (Roberts 1992), where the young are infected while being carried in the pouch. For both cases the mathematics are essentially the same. Equation (3.9) is modified by a term specifying the addition to the infective class due to births to infective parents

$$\frac{dI}{dt} = pA(N)I + \beta\frac{C(N)}{N}(N-I)I - \Big(\alpha + B(N)\Big)I. \tag{3.10}$$

A complete analysis of the SI-model with vertical transmission for constant births and deaths, for $C(N) = N$, and with density-dependent (logistic) host death can be found in Busenberg and Cooke (1993).

## 3.5 The effect of long latency periods

Many diseases have a long latency period before the individual becomes infective. This may be modelled by introducing the $E$-class, $N = S + E + I$, see Section 2. Equation (3.9) is replaced with separate equations for the $E$ and $I$ classes,

$$\frac{dE}{dt} = \beta\frac{C(N)}{N}(N-E-I)I - \Big(\sigma + B(N)\Big)E \tag{3.11}$$

$$\frac{dI}{dt} = \sigma E - \Big(\alpha + B(N)\Big)I \tag{3.12}$$

where $\sigma$ is the rate at which infected animals become infective (so, the duration of the latency period is assumed to be exponentially distributed with average value $1/\sigma$). As explained at the end of Appendix A, $R_0$ would not be affected by an $E$-class if no deaths occured in this class. In the present model, deaths do occur and this factor has to be taken into account. Only a fraction $\sigma/(\sigma + B(K))$ of the latent individuals is expected to survive the latency period in a virgin population, so

$$R_0 = \frac{\sigma\beta C(K)}{(\sigma + B(K))(\alpha + B(K))}.$$

Rather than present an analysis of equations (3.8,3.11-12) in the abstract, we proceed to discuss a specific example.

**Example: Rabies in foxes**

A model for the dynamics of rabies in European foxes discussed by Anderson *et al.* (1981) featured a density dependent death rate regulating the host population in the absence of disease, a constant birth rate, but only susceptible foxes giving birth, and contact rate function $C(N) = N$. In our notation the equations are

$$\frac{dN}{dt} = r(1 - \frac{N}{K})N - a(E+I) - \alpha I$$

$$\begin{aligned}\frac{dE}{dt} &= \beta(N-E-I)I-(\sigma+b+r\frac{N}{K})E\\ \frac{dI}{dt} &= \sigma E-(\alpha+b+r\frac{N}{K})I.\end{aligned}$$

This model has been extensively analysed by Anderson (1982a). The condition for persistence of the disease is

$$R_0=\frac{\sigma\beta K}{(\sigma+a)(\alpha+a)}>1 \quad \text{or} \quad K>K_T=\frac{(\sigma+a)(\alpha+a)}{\sigma\beta K}.$$

The appearance of $a$ instead of a death rate in the denominator of the expression for $R_0$ seems surprising at first, but when $N=K$ (at carrying capacity), births and deaths balance (i.e. $a=r+bK/K$).

However, the regulated population state may be a constant value or a stable cycle, depending upon the parameter values. If there is a constant steady state solution trajectories exhibit damped oscillations as they tend towards it, and for typical parameter values the damping period is long (3-4 years). Anderson (1982a) showed that stable cycles would occur if both the fox carrying capacity $K$ and the mean latency period $1/\sigma$ were high. The stability of the limit cycles has been confirmed analytically by Swart (1989). If the latency period is short cycles do not occur. As we saw earlier, cyclic behaviour is impossible in the SI-model that is obtained from Anderson's model in the limit $\sigma\to\infty$ or $1/\sigma\to 0$. This is therefore a situation where a delay in transmission caused by a long latency period can destabilise the steady state of a system, and cause the population size and the number of diseased animals to exhibit periodic cycles (see also Bolker *et al.*, Dye *et al.* both this volume).

We see that there are at least two ways in which to get cyclic behaviour if one starts off with the basic SI-model: one is to introduce a time-delay, as outlined above, the other is to introduce special nonlinear feedback in the birth-term, as outlined in Section 3.2. For recent reviews of periodic behaviour in epidemic models, both compartmental and more general, see Hethcote and Levin (1989) and Liu (1992).

## 3.6 The effect of acquired immunity

Until now in this section, we have assumed that once an infection is acquired there is no recovery. This is not the case for many infections, and in some cases, the host animal is immune to contracting the infection again for some period after its recovery, or indeed for life. It is common to model this by the introduction of an $R$ (removed) class (see Section 2). For our simple model, equation (3.8) remains unchanged, and equation (3.9) becomes

$$\frac{dI}{dt}=\beta\frac{C(N)}{N}(N-I-R)I-\big(\alpha+B(N)+\gamma\big)I \qquad (3.13)$$

where $\gamma$ is the probability per unit of time of recovery from the disease and $N = S + I + R$. The dynamics of the $R$-class is expressed by

$$\frac{dR}{dt} = \gamma I - \big(B(N) + \rho\big)R, \tag{3.14}$$

where $\rho$ is the probability per unit of time of loosing immunity (upon which the individuals re-enter the susceptible class with rate $\rho R$). The system (3.8,3.13-14) has, apart from the trivial steady state, a nontrivial disease-free steady state $N = S = K, I = R = 0$, and an endemic steady state exists when $R_0 > 1$, where

$$R_0 = \frac{\beta C(K)}{\alpha + B(K) + \gamma}.$$

For a detailed analysis of SIRS-models with $A(N) = a$ and $B(N) = b$, constants, see Thieme (1992). Greenhalgh and Das (1993) do a similar analysis with a density dependent death rate (logistic deaths). Both papers review most of the literature on this problem. See also Anderson and May (1991), Hethcote (1994).

Examples of diseases where a removed class plays a role in the dynamics, include avian pox virus in hawks (Graham and Halliwell 1986) and pigeon pox in (wild) pigeons (Cubb 1986). In the former case, the host is permanently immune after recovery, in the latter it becomes susceptible again after at least one year.

# 4 Control aspects

A model is primarily a means by which the dynamics of the infection may be understood, but the motivation for the construction of the model is often to aid in the planning of control. The type of control measure that is proposed will depend on the desired end result in terms of both the disease prevalence and the population density. For example, if a wild animal population is acting as a reservoir for a disease of humans or domestic livestock, then killing animals on a regular basis may be the most appropriate way of decreasing the host population size, and hence the amount of disease present. Alternatively, if the reason for control is that the disease is present in a population that is being conserved, then killing animals is not a suitable control measure, and vaccination may be considered. Vaccination will, however, reduce host mortality and may increase the population above desired levels. In this section models for a variety of different strategies for the control of hosts and/or pathogens are discussed. See also Anderson (1982a,b).

## 4.1 Culling

Consider a program with a fixed per capita culling rate $\delta$. Equations (3.8-9) become

$$\begin{aligned} \frac{dN}{dt} &= \big(A(N) - B(N)\big)N - \delta N - \alpha I \\ \frac{dI}{dt} &= \beta\frac{C(N)}{N}(N-I)I - \big(\alpha + B(N) + \delta\big)I \end{aligned}$$

and $R_\delta$, the basic reproduction ratio in the presence of control, is defined by

$$R_\delta = \frac{\beta C(K_\delta)}{\alpha + B(K_\delta) + \delta}$$

where $A(K_\delta) - B(K_\delta) - \delta = 0$ (the expression reduces to $R_0$ from subsection 3.3 when $\delta = 0$). Hence, regular culling of host animals may eradicate the disease from the population if

$$\delta > \beta C(K_\delta) - (\alpha + B(K_\delta))$$

which would reduce the size of the remaining disease-free population to $K_\delta < K$. Similar models where culling has been investigated as a method of reducing the prevalence of a wildlife disease include tuberculosis in possums (Roberts 1992), rabies in foxes (Anderson 1982a), rabies in raccoons (Coyne *et al.* 1989), and tuberculosis in badgers (Anderson and Trewhella 1985). See also Dobson and Hudson (this volume).

When only infected animals are killed upon discovery, this effectively means an increase in the differential mortality rate $\alpha$. A successful example of this type of control concerns dourine (*Trypanosoma equiperdum*) in wild horses and zebra (Smith and Dobson (1992), see also Section 5).

## 4.2 Vaccination

Vaccination of a wild animal population may, for example, be achieved by the spreading of baits containing an oral vaccine. The effects of this control measure may be modelled by introducing a new class, $V$, for animals that are immune to infection due to vaccination. For our simple model, equation (3.8) remains unchanged and in (3.9), $N - I$ is replaced by $N - I - V$, because now $N = S + I + V$. If we introduce a per capita vaccination rate $q$, then

$$\frac{dV}{dt} = q(N - I - V) - \big(B(N) + \nu\big)V$$

where it has been assumed that vaccination has no effect on animals in the $I$-class, and where $\nu$ is the rate of loosing the protected status due to, for

example, loss of memory in the immune system of the host. The basic reproduction ratio $R_q$ under vaccination is given by

$$R_q = \frac{\beta C(K)(B(K)+\nu)}{(\alpha + B(K))(B(K)+\nu+q)}. \tag{4.1}$$

Hence, regular vaccination of host animals may eradicate the disease from the population if

$$q > (B(K)+\nu)(R_0 - 1) \tag{4.2}$$

which would increase the size of the population to $N = K$, with a proportion $v = V/N = q/(B(K)+\nu+q)$ of these immune due to vaccination. If we do not vaccinate at a rate $q$, but vaccinate in such a way that at any given time a fraction $v$, as defined above, is vaccinated, we find from (4.1) and (4.2) that the criterion for success is

$$v > 1 - \frac{1}{R_0},$$

an equality we derived for the simple model (2.1) in Section 2.4 (with a different $R_0$ of course).

Examples of vaccination strategies include, rabies in foxes (Anderson 1982b), rabies in raccoons (Linhart *et al.* 1991), and brucellosis in elk (Peterson *et al.* 1991). See also Dobson and Hudson (this volume). The strategy may be to spread baits containing an oral vaccine (for example to control rabies in foxes), or to capture animals, vaccinate and release them (for example seals with phocine distemper virus; Grenfell *et al.* (1992)).

## 4.3 Chemotherapy

The effect of mass chemotherapy to control disease may be modelled in a similar way to that of culling and vaccination discussed above. Equation (3.8) remains unchanged, but if infected animals are successfully treated with a per capita rate $h$, then equation (3.9) is replaced by

$$\frac{dI}{dt} = \beta\frac{C(N)}{N}(N-I)I - \big(\alpha + B(N) + h\big)I.$$

It is easily seen that the basic reproduction ratio $R_h$ of the disease under chemotherapy is

$$R_h = \frac{\beta C(K)}{\alpha + B(K) + h}$$

and chemotherapy is successful if

$$h > (\alpha + B(K))(R_0 - 1). \tag{4.3}$$

Note that the effect of introducing chemotherapy into the model is the same as the effect of increasing the rate at which the host animal recovers from the disease.

### 4.4 Comparison of control strategies

The similarity between equations (4.2) and (4.3) suggests that the efficacy of different strategies could be compared. In fact, the ratio of the proportion of hosts that must be vaccinated annually to the proportion that must be treated by chemotherapy is $q/h = (\nu + B(K))/(\alpha + B(K))$. Hence, if $\nu > \alpha$ the rate of vaccination required to achieve disease eradication is higher than the rate of treatment required for the same purpose. If the majority of the cost is due to the logistics of the operation, rather than the chemical agents employed, then this formula provides a simple means of comparing the two options on a financial basis.

It is more difficult to compare the effects of culling and vaccination or chemotherapy, as this option establishes a new population size $K_\delta < K$, which may reduce both the host mortality rate $B(N)$ and the contact rate $C(N)$. If the host species is regarded as a pest in its own right this could be desirable (for example possums, rabbits, foxes), but as we mentioned in the introduction to Section 4, a culling strategy would defeat the purpose of a disease control operation that was part of a wildlife conservation plan. A comparison of relative rates of culling and the other two strategies is dependent on the precise forms of the functions $B(N)$ and $C(N)$, and will therefore differ between diseases and host demographic situations.

## 5 Heterogeneity

If we add more realism to the basic models of Section 3, by taking into account the fact that not all individuals are the same, matters quickly become much more complicated. There are many types of heterogeneity that could have important influences on susceptibility, infectivity and the structure of the contact process (who meets whom how often). Important types are age (in sexually transmitted diseases, viral diseases, maybe always important), spatial location (for example with respect to rabies if one is interested in spatial spread, see Mollison and Levin (this volume), gender (influences on behaviour, for example in sexually transmitted diseases), social structure (for example families, home ranges), different host species in the life cycle of the parasite (for example vector transmitted diseases, see Dye (this volume)), genetic diversity (see Lively and Apanius (this volume)) and others.

Heterogeneous characteristics may be qualitative (e.g. male/female), quantitative and discrete (e.g. number of offspring) or continuous (e.g. age). Most results on the dynamic behaviour of heterogeneous models are for the case where a finite number of different subgroups of individuals is recognised. Analysis of infinite dimensional heterogeneous models is predominantly aimed at age-structure and spatial structure (e.g. characterising rates of spatial spread of diseases, see the review by Metz and Van den Bosch (1995)). We

will not go into details here about the dynamic properties and formulation of heterogeneous models in general, for recent guides to the literature see Anderson and May (1991) and Diekmann *et al.* (1995).

For this paper we restrict ourselves to a specific two-dimensional example of a sexually transmitted disease. Sexually transmitted diseases (STD's) of animals, including wildlife (such as herpes in baboons, STD's of rabbits, crabs, geese, and *Chlamydia* infections of the koala) have recently been reviewed in Smith and Dobson (1992). For illustrative purposes we give below a simple model for the STD dourine of wild horses and zebra. This example captures some of the essentials of the host-pathogen system. We recognise two types of animal in the population, females (mares, 1) and males (stallions, 2) and take into account the following: transmission rates differ for male to female and female to male; there is only heterosexual transmission; the disease is fatal in males whereas females often recover to become susceptible again. We can model this situation using an extension of system (2.1) to include differential mortality $\alpha_i$ (i.e. mortality due to the disease) and recovery without immunity $\rho_i$, $i \in \{1,2\}$ (we take the removal rate $\gamma_1 = \gamma_2 = 0$, because immunity is generally absent in STD infections). We obtain at first the more general system

$$\begin{aligned} \frac{dS_i}{dt} &= a - \beta_{i1} I_1 \frac{S_i}{N_i} - \beta_{i2} I_2 \frac{S_i}{N_i} + \rho_i I_i - b S_i \\ \frac{dI_i}{dt} &= \beta_{i1} I_1 \frac{S_i}{N_i} + \beta_{i2} I_2 \frac{S_i}{N_i} - \rho_i I_i - \alpha_i I_i - b I_i \end{aligned} \tag{5.1}$$

for $i \in \{1,2\}$, with $N_i = S_i + I_i$, where we have assumed a constant inflow of susceptibles into the population and a per capita death rate $b$. Under our assumptions for dourine we can assume $\beta_{11} = \beta_{22} = 0$ (no homosexual transmission), $\rho_2 = 0$ (neglect recovery for males), $\alpha_1 = 0$ (neglect disease-induced death of females), and $\beta_{12} \neq \beta_{21}$. Model (5.1) is an example of an SIS-model, frequently encountered in the study of human STD's (see, e.g. Hethcote and Yorke 1984). Models like (5.1) with various complications added and with obvious generalisation to an arbitrary number of $n$ types of individual have been analysed extensively over the last years as a direct result of the HIV-epidemic in humans (see e.g. Hethcote and Van Ark 1992). See also Begon and Bowers (this volume), where multispecies models with a similar structure are discussed. Criteria for the existence and stability of steady states have been given for many cases and the area is very much one, to use Hethcote's words, of 1001 variations on the same theme (Hethcote 1994).

In Appendix B it is shown that the basic reproduction ratio for the situation described by (5.1), simplified by the assumptions on the parameters

below it, is given by

$$R_0 = \sqrt{\frac{\beta_{21}}{\alpha_2}\frac{\beta_{12}}{\rho_1}}.$$

If we study the effect of killing infected animals that are discovered, we could mimic this control strategy by increasing $\alpha_1$ and $\alpha_2$ by an amount $k$ which could represent the rate at which infected animals are detected (with an available diagnostic test on capturing). The reproduction ratio $R_k$ is then given by

$$R_k = \sqrt{\frac{\beta_{21}}{\alpha_2 + k}\frac{\beta_{12}}{\rho_1 + k}},$$

leading to a criterion for success

$$k > \frac{1}{2}\Big(\sqrt{(\rho_1 + \alpha_2)^2 + \alpha_2\rho_1 R_0^2} - (\rho_1 + \alpha_2)\Big).$$

Of course, for horse-herds living in captivity, the detection rate $k$ will be much higher than in the wild. This control method for *T. equiperdum* has been applied successfully in various parts of the world (Smith and Dobson 1992).

# 6 Conclusion

This chapter presents a range of mathematical tools which can be used to explore the rich and increasingly well-documented dynamics of microparasitic diseases in wildlife host populations. Starting from the basic mathematical background, we have tried to show that the resulting models can be used to address fundamental epidemiological questions (how do we model the infection process? what is the effect of host population fluctuations and density dependence? etc.) As such, and to reprise our exhibition analogy, we would hope that these ideas be on permanent display for use in interdisciplinary studies.

# Appendices

# A The Kermack–McKendrick model

For the more mathematically interested reader, we briefly describe the Kermack-McKendrick model from 1927 in terms of the general infectivity function $\mathcal{A}$, and show how compartmental models are obtained as a special cases, where we use system (2.1) as an example.

Under the assumptions that led to system (2.1), but with transmission rate not necessarily constant, we can write

$$\frac{dS}{dt} = -S(t)\lambda(t), \tag{A.1}$$

where $\lambda(t)$ is the *force of infection* at time $t$, i.e. the fraction of the susceptible population that the infected individuals are able to meet and infect per unit of time. To express $\lambda(t)$ in familiar terms, observe that the infective individuals that have disease-age $\tau$ at time $t$, are expected to contribute infectivity $\mathcal{A}(\tau)$ towards susceptibles. How many infected individuals are there who have disease-age $\tau$ at time $t$? These are of course precisely those individuals that became infected themselves at time $t - \tau$. We then have to integrate over all disease-ages and hence,

$$\lambda(t) = -\frac{1}{N}\int_0^\infty \mathcal{A}(\tau)\frac{dS}{dt}(t-\tau)d\tau. \tag{A.2}$$

Note that $\lambda(t)$ is positive because $dS/dt$ is negative.

As an example, we derive $\mathcal{A}(\tau)$ for the compartmental disease progression as described in Section 2.1. Assume that the time periods spent in each consecutive class are exponentially distributed with some appropriate rate constant. $\mathcal{A}(\tau)$ is in this case the product of the probability of (still) being in the infective class $I$ at time $\tau$ after infection and the transmission rate at that time. Suppose we ignore the latency period and let $\gamma$ be, as before, the probability per unit of time for an infective individual to be removed. Then $e^{-\gamma\tau}$ is the probability of remaining infective after being infected for a time $\tau$, and if transmission occurs at a constant rate $\beta$ in state $I$, then $\mathcal{A}(\tau) = \beta e^{-\gamma\tau}$.

If we add a latency class $E$ with average duration $1/\sigma$ (exponentially distributed) then similar reasoning as above leads to

$$\mathcal{A}(\tau) = \frac{\beta\sigma}{\gamma - \sigma}(e^{-\sigma\tau} - e^{-\gamma\tau}). \tag{A.3}$$

As in the case without a latency period, $\int_0^\infty \mathcal{A}(\tau)d\tau = \beta/\gamma$, independent of $\sigma$. It is easy to check that with an infinitely short latency period (i.e. $\sigma \to \infty$) we 'rediscover' $\mathcal{A}(\tau) = \beta e^{-\gamma\tau}$.

The example illustrates that we can either imagine a discrete disease-state variable with a stochastic jump process (where the holding times in the various compartments do not necessarily have to be exponentially distributed as in our examples above) to describe the progression of the disease, or a continuous disease-state variable $\tau$ with steady progression and an infectivity function $\mathcal{A}$; see Figure 11. The two representations in Figure 11 are equivalent when (A.3) holds. The $\tau$-representation is suited for a more general class of models since $\mathcal{A}$ can, in principle, be any nonnegative function.

In the special case $\mathcal{A}(\tau) = \beta e^{-\gamma\tau}$ we obtain system (2.1) from (A.2-3) by noting that the number of infective individuals at time $t$ is obtained by integrating over all recruitment into the infective class before time $t$ while taking into account the probability of being removed before $t$ is reached.

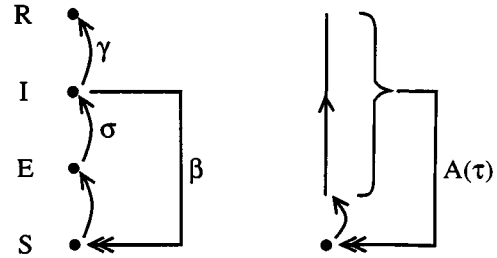


Figure 11. Metaphorical comparison of the discrete disease-state model and the continuous disease-state model.

Mathematically this means that

$$I(t) = -\int_{-\infty}^{t} e^{-\gamma(t-\tau)}\frac{dS}{dt}(\tau)d\tau = -\int_{0}^{\infty} e^{-\gamma\tau}\frac{dS}{dt}(t-\tau)d\tau. \qquad \text{(A.4)}$$

If we substitute $\mathcal{A}(\tau) = \beta e^{-\gamma\tau}$ into (A.2) and use (A.4) then (A.1) is the same as the first equation in system (2.1). We obtain the differential equation for the infectives in (2.1) by differentiating (A.4) with respect to $t$.

Kermack and McKendrick showed that the basic reproduction ratio in the general case is given by

$$R_0 = \int_0^\infty \mathcal{A}(\tau)d\tau.$$

For the special cases treated in this example, we rediscover $R_0 = \beta/\gamma$. Note that $R_0$ is the same in this case with and without a latency class, because we neglect death in this simple model (the infected individual cannot die before reaching the infective class) and the average duration of the infective period is not affected by the latency class. See subsection 3.5 for an example where it does affect $R_0$.

# B $R_0$ for heterogeneous models

In the homogeneous model (2.1), $R_0 = \beta/\gamma$. The corresponding heterogeneous model with two types of individuals is given by

$$\begin{aligned} \frac{dS_i}{dt} &= -\frac{S_i}{N_i}\sum_{j=1}^{2}\beta_{ij}I_j \\ \frac{dI_i}{dt} &= \frac{S_i}{N_i}\sum_{j=1}^{2}\beta_{ij}I_j - \gamma_i I_i, \end{aligned} \qquad \text{(B.1)}$$

$i \in \{1,2\}$, $N_i = S_i + I_i$. Let us interpret, for example, $i = 1$ as female individuals and $i = 2$ as males. In the same heuristic way as for (2.1), we could then for the heterogeneous system (B.1) calculate a quantity $m_{11}$ say, which gives the expected number of new male cases that are caused by one

male infected individual in a population consisting only of male susceptibles. In the same way one could calculate quantities $m_{12}, m_{21}$ and $m_{22}$ with obvious interpretations. So, instead of the single number we had before, we now have four different numbers. The basic reproduction ratio for the heterogeneous population will be some average of these four $m_{ij}$'s, the question we want to answer is: how should we take this average in order to arrive at a quantity which possesses the threshold property that an epidemic can develop if it is bigger than one, whereas no epidemic will develop if it is less than one?

By just applying the biological interpretation of the $m_{ij}$'s we can obtain expressions for them from the model equations. We arrange the four expressions into a matrix

$$M := \begin{pmatrix} m_{11} & m_{12} \\ m_{21} & m_{22} \end{pmatrix} = \begin{pmatrix} \beta_{11}/\gamma_1 & \beta_{12}/\gamma_2 \\ \beta_{21}/\gamma_1 & \beta_{22}/\gamma_2 \end{pmatrix}.$$

If we now regard *generations* of infected individuals (i.e. the initially infected animals are the first generation, all animals that become infected through contacts with members of the first generation are collectively called the second generation, etc.), then the matrix $M$ relates the number of infected male and female animals in the present generation, represented by a vector $X = (x_1, x_2)^T$, to the respective numbers in the next generation given by the vector $MX$. One can easily see that this is a good interpretation of the matrix $M$ because, for example, the first component of $MX$ is given by $x_1\beta_{11}/\gamma_1 + x_2\beta_{12}/\gamma_2$, which is precisely the total number of new male cases that we expect will become infected by the combined 'efforts' of $x_1$ infected males and $x_2$ infected females. It is clear that the matrix $M$ (called the *next-generation matrix*) contains information that can answer our question. Note that, because we are dealing with biological quantities, all entries of the next-generation matrix will be non-negative. $M$ therefore is a *positive* matrix.

Let $\omega > \mu$, with $\omega > 0$, be the two eigenvalues of the positive matrix $M$ with eigenvectors $W$ and $U$ (so, $MW = \omega W$, and $MU = \mu U$), then we can write any vector $X = (x_1, x_2)^T$ as a linear combination of $W$ and $U$, $X = a_1 W + a_2 U$, where the $a_i$ depend on $X$. If we apply the matrix $M$ to both sides we obtain

$$\begin{aligned} MX &= M(a_1 W + a_2 U) = a_1 MW + a_2 MU \\ &= a_1 \omega W + a_2 \mu U \end{aligned}$$

and applying $M$ $n$ times leads to

$$\begin{aligned} M^n X &= a_1 \omega^n W + a_2 \mu^n U \\ &= \omega^n \Big( a_1 W + a_2 (\frac{\mu}{\omega})^n U \Big). \end{aligned}$$

From this last expression we see that the behaviour of the infected population of males and females will, after many generations, be determined by the dominant eigenvalue $\omega$ of $M$ and its eigenvector. Indeed, for $n \to \infty$, $(\mu/\omega)^n \to 0$

and

$$M^n X \approx a_1 \omega^n W.$$

So, if $\omega > 1$, the consecutive generations will increase in size, whereas for $\omega < 1$ the generation sizes will approach zero. After many generations, each generation will be $\nu$ bigger than the previous one, and the distribution of infected individuals over males and females will become fixed and is given by $W$.

These properties of $\omega$ motivate the following definition of the basic reproduction ratio $R_0$ in a heterogeneous population

$$R_0 = \omega = \text{ the dominant eigenvalue of the matrix } M.$$

Thus, $R_0$ is defined on a generation basis. One can show that $R_0 > 1$ indeed leads to an increase in the infected population in real time and that $R_0 < 1$ leads to a decrease in real time.

For the example given in Section 5 (system (5.1)) we find that the next-generation matrix $M$ has elements $m_{ij} = \beta_{ij}/(\rho_j + \alpha_j)$ (expected number of new $i$-cases caused per unit of time by $j$-infective, multiplied by average duration of infectious period) and under the special parameter assumptions listed in Section 5, we find

$$M = \begin{pmatrix} 0 & \beta_{12}/\alpha_2 \\ \beta_{21}/\rho_1 & 0 \end{pmatrix}$$

and the dominant eigenvalue can easily be calculated from the characteristic equation $\det(M - \lambda Id) = 0$, where $Id$ is the identity-matrix. We find

$$R_0 = \sqrt{\frac{\beta_{21}}{\alpha_2}\frac{\beta_{12}}{\rho_1}}.$$

The above ideas can be found in Hethcote and Yorke (1984). If one recognises $n$ (sub)groups of animals, then $M$ will become an $n \times n$-matrix with the element $m_{ij}$ being the expected number of new cases among members of group $i$ that are caused by infected members of group $j$. $R_0$ is again the dominant eigenvalue of $M$ (Hethcote and Yorke 1984). In general, if there are $n$ types of individuals, calculating $R_0$ would mean first calculating the matrix $M$, and then numerically determining the dominant eigenvalue. In De Jong *et al.* (1994) an explicit algorithm is given to calculate the matrix $M$ for multigroup models from basic model ingredients and assumptions.

In one special case it is easy to calculate $R_0$, in fact even an explicit formula can be given. The assumption that makes this possible is that every element $m_{ij}$ of $M$ can be written as

$$m_{ij} = f_i g_j$$

which means that contributions to $m_{ij}$ by the susceptible individual (type $i$) and that of the infective individual (type $j$) are separated. This is called separable mixing (the well-known proportionate mixing is a special case of this when $g_j = cf_j$, where $c$ is a constant). The biological interpretation of separable mixing is that the types of individuals that can be infected by a given infective animal are independent of that animal's own type. Under that assumption

$$R_0 = \sum_{i=1}^{n} m_{ii}$$

being the sum of the elements on the diagonal of $M$. In the case of model (B.1), this leads to

$$R_0 = \frac{\beta_{11}}{\gamma_1} + \frac{\beta_{22}}{\gamma_2}.$$

The mathematics of defining and calculating $R_0$ in populations with any given heterogeneity structure can be found in Diekmann *et al.* (1990) and Heesterbeek (1992).

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# Microparasite Group Report: Persistence of Microparasites in Natural Populations

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## 1 Introduction

Afer initial discussions, the group decided to focus on a central question: how do microparasites persist in their wildlife host populations? The question of

persistence arose in three different ways: by looking at the results of simple SEIR theory, by examining the criteria under which parasites regulate their host populations, and by considering disease patterns in natural populations.

Models of human diseases which tend to occur in epidemics, like measles, have difficulty in explaining observed patterns without invoking unrealistically low levels of infection in inter-epidemic periods. Similar problems arise with existing models of wildlife diseases. For fox-rabies, deterministic models can produce epidemics and spatially spreading waves, but they also generate very small fractions of foxes between epidemics. Stochastic models which do not allow fractional foxes also have problems accounting for persistence; for example the model of Voigt *et al.* (1985) requires immigration of small numbers of rabid foxes to maintain persistence.

The problem of persistence for microparasites is most acute when the contact rate between infectious and susceptible individuals is high (so that infection travels rapidly through a population), when the infectious period is short, and when the rate of production of new susceptibles is low, either because the birth-rate is low or because immunity is durable and fully protective. Many macroparasites have more stable populations than microparasites because their infectious periods tend to be long, often many years, and because partial and short-lived immunity permits reinfection (Smith *et al.* this volume). Broadly speaking, fluctuations in case number or parasite population size are greatest for (epidemic) viruses and least for (endemic) helminths, with protozoa like *Plasmodium* and *Leishmania* lying somewhere in between.

Regulation here refers to density-dependent (negative feedback) processes that maintain a population within a certain range or level, which could be a stable equilibrium point, a stable cycle or even an apparently chaotic trajectory, depending on the details of the birth and death processes (Sinclair 1989). Limitation, by contrast, refers to density-independent effects on population growth. In host-parasite (and prey-predator) systems, we often ask which regulatory processes stabilize host population size, but these same processes regulate that of parasites too. We are really interested in the stability of the system, from which the persistence and endemicity of the parasite follow. The pathogen is not only maintained in its host population, but it may also satisfy, for example, the characteristics required of a biological control agent.

Accounts of the natural histories of infectious diseases often contain data suggesting that pathogens appear in and disappear from wild animal populations. For example, the recent epidemic of seal distemper in the North Sea is no longer news, rinderpest seemed to disappear from wildlife when cattle were vaccinated during the 1960s, peste des petits ruminants (PPR) is sporadic in the sheep and goats of Sahelian farmers, isolated cases of rabies arise in the low-density domestic dog populations around the Serengeti, and insect baculoviruses are invisible in their host populations for most of the time.

With this background, and drawing only on the prevailing wisdom of participants (rather than an extensive literature search), we asked: Do microparasites really disappear from their wildlife host populations between epizootics, or is poor surveillance the explanation? If they are continuously present, what details of their various life histories explain persistence? What are the best methods of monitoring infections in wild animal populations? Which persistence mechanisms are density-dependent? Which microparasites tend to be enzootic rather than epizootic? If infections do disappear from populations between epizootics, from where are they reintroduced and how are they maintained on larger spatial scales? How can modelling usefully take us beyond the limits of qualitative argument?

Undoubtedly the bounds of the discussion were influenced, if not foreordained, by background papers covering both the theory (Heesterbeek and Roberts, Barlow, both this volume) and observed patterns (Dobson and Hudson this volume). Given the analytical leaning of participants, we began with the theoretical background, and then considered further the available data.

# 2 Theoretical Background

## 2.1 Persistence between epidemics

Models of measles (a morbillivirus) infections in large, dense human populations are a good starting point. Measles epidemiology has been closely observed, and the luxurious quantity of data has been extensively analyzed.

In semi-isolated human populations smaller than a critical community size (CCS), also known as the threshold population size, of about 250,000–300,000 people, measles fails to persist because the inflow of new susceptibles (birth rate) is too low for the rate of epidemic spread (Bartlett 1957,1960, Black 1966). Traditional SEIR models for the complex dynamics of measles match the data in many ways (e.g. inter-epidemic period) but fail to predict the CCS to within several orders of magnitude (Olsen and Schaffer 1990, Rand and Wilson 1991). For example, a seasonally-forced SEIR model gives not only a CCS greater than 50 million but also an unrealistically low minimum number of infectives of $10^{-12}$ of the population in troughs between epidemics.

If more realism in the form of age-structure and seasonality is added to the models, the CCS drops to about 1.5 million (Bolker and Grenfell 1993), a value which could be reconciled with the data, taking into account the lack of true isolation from other sources of disease and the small seasonal variation in some places. Unfortunately, these models also remove the complex dynamic pattern. Stochastic model analogues recapture the complex dynamics but once again do not allow persistence. There are therefore no models at present which explain both persistence of the virus and the irregular dynamics

observed in some measles data sets. Empirically and theoretically, the most likely explanation for persistence may be some form of population structure, such as clustering into families and schools at a small level or into cities and villages on a metapopulation level.

## 2.2 Persistence in the context of population regulation

This is a much explored topic (Anderson and May 1979, Begon and Bowers, Heesterbeek and Roberts, both this volume) and is currently of considerable interest in the context of multispecies host-parasite interactions. We outline the basic picture, and some multispecies extensions of it, in the Appendix.

# 3 Empirical Evidence

## 3.1 Morbilliviruses

The problem of pathogen persistence between epidemics in measles may apply directly to other morbilliviruses infections occurring in wild, feral and domestic animals. We briefly considered three examples:

### 3.1.1 Phocid Distemper Virus (PDV)

Simple SEIR models of the epidemiology of phocid distemper suggest that the rate of transmission of PDV was sufficient to ensure eradication of infection in the common seal populations of the North Sea by the end of the first outbreak in 1988 (Grenfell *et al.* 1992). The combined North Sea population of seals, irrespective of species, is theoretically too small to maintain the infection – models predict the fade out and disappearance of the virus. However, the data show that 54% (21/38) of grey seals born since 1988 have been exposed to antigen (presence of serum antibody) even though there has been little evidence of overt PDV infection since 1988. So the virus appears still to be present in seal populations.

The mechanisms underlying the persistence of this virus are not known, but recent evidence points to vertical transmission. In 1991 grey seal pups from a small number of seropositive females were vaccinated with two doses of the inactivated canine distemper vaccine at approximately 3 and 8 days of age. CDV specific immunoglobulin sub-classes (IgM and IgG) were measured using monoclonal antibodies (King *et al.* 1994). Some individuals showed the classic pattern of primary exposure to antigen, with an increase in IgM preceding a slower increase in IgG. Others showed no initial IgM peak, but a very rapid rise in IgG, indicative of secondary exposure. These data are difficult to interpret but suggest that pups have been pre-exposed to virus,

either in utero or just after birth. Females which show no clinical signs of infection may harbour virus in tissues such as lymph nodes and provide immunogenic stimulus to these animals and their offspring. The question of persistence depends critically on whether these animals are ever infectious.

### 3.1.2 Rinderpest

Since rinderpest was introduced into East Africa in the 1870s, there have been a series of outbreaks of clinical disease involving cattle and/or wild ungulates. It is not clear whether the virus disappeared during the inter-epizootic periods, nor how new epizootics were started, although infected cattle introductions occurred in some instances. Vaccination since the 1950s has clouded the epidemiological picture still further.

Although a range of wildlife species are variably susceptible to rinderpest virus, wildlife hosts do not appear to be a reservoir of infection. When vaccination of cattle was implemented in the 1960s in northern Tanzania, infection died out both in cattle and wildlife, and led to an eruption of the ungulate herds of the Serengeti-Mara ecosystem (Plowright 1968,1982, Sinclair 1979, Dobson and Hudson this volume). Domestic hosts appeared to have acted as a reservoir of infection for wildlife and not vice versa; wildlife species do not therefore seem to be responsible for virus persistence.

What is clear is that rinderpest had a devastating impact on the ecology of East African grazing systems. The reduction in the abundance of game animals caused by this disease not only caused a major perturbation of the ecology of the Serengeti-Mara, but may also account for major epidemics of human sleeping sickness which occurred when tsetse flies switched to man as hosts in the absence of game animals. On the other hand, the rise in abundance of wildebeest since rinderpest control by vaccination has led to more intense competition with cattle for pasture, and more frequent transmission from wildebeest to cattle of malignant catarrhal fever.

### 3.1.3 Goat Plague/Peste des Petits Ruminants (PPR)

The virus causing PPR, although sharing antigenic links, is distinct from rinderpest virus. In domestic ruminants, overt disease is seen only in goats and sheep, with goats being the primary host in West Africa and the Middle East, whereas in India sheep are more severely affected. Naturally acquired disease has also been confirmed in wild ruminants such as nilgai in India, with a range of other wild hosts being susceptible in captivity. The epidemiology in India and in the Middle East has been poorly-studied and it is possible that many of the reported outbreaks of rinderpest were actually PPR.

In the Sahel region of Africa, from Senegal to western Ethiopia, the disease is apparently endemic in the livestock of pastoralists such as the Fulani. Prevalence rates of serum antibody approach 75% suggesting that although

offspring are susceptible when they lose their colostral antibody, clinical disease is muted or sub-clinical.

More important epidemics of disease occur at the beginning and end of the wet season among the stock of settled farmers to the south of the Sahel. Such outbreaks are perhaps explained by variation in the susceptibility of different sheep and goat breeds, and by the migration pattern of the Fulani pastoralists. The migrant herds travel south at the start of the dry season and graze land occupied by settled farmers. Any young nomadic livestock still shedding virus will transmit the disease to the highly susceptible settled stock, with case mortality rates of 60–70%. Similarly, at the onset of the wet season, the nomadic tribes sell off excess stock. These animals are often bought by the settled tribes for sacrifices at one of the many seasonal festivals and outbreaks of PPR can occur if these animals mix with susceptible village goats.

Assuming this morbillivirus behaves like others (e.g. no latent infection), the key question is how virus is maintained in the herds of migrant pastoralists. Are these herds sufficiently large, and by analogy with measles, above the relevant CCS for viral persistence? Is the large-scale population structure of these herds important for persistence? Although the density of wild animals in the Sahel is very low, can they play a role either by effectively inflating community size, or as reservoirs of infection?

## 3.2 Rabies

We have already said that models of rabies (mostly fox rabies) have difficulty in explaining the observed persistence of the virus. The density of natural populations is such that they seem to exist below the CCS, and persistence in stochastic models like that of Voigt *et al.* (1985) requires reintroduction of infected animals. This is true even though host species typically have high birth rates so that epidemics are fed with a high rate of production of susceptibles.

Discussions of rabies persistence are increasingly asking about the importance of departures from the classic picture of high mortality, with no recovery and no post- infection immunity. Do alternate reservoir species, long periods of latency and communicability, carriers and refractory hosts play a significant part in persistence?

Against a role for alternate reservoir species is the observation that rabies viruses isolated from most major host species are antigenically distinct, as determined by reaction patterns to monoclonal antibody panels (Wiktor *et al.* 1980). In North America, for example, virus isolated from any species in a skunk rabies area is different from that isolated from a fox rabies area. There is also evidence that susceptibility varies between strains and hosts. Foxes infected with fox rabies virus show a high level of susceptibility to infection, a high proportion of salivary virus excretion and low post-infection immunity,

whereas foxes infected with dog virus show a low level of susceptibility, moderate proportion of salivary virus excretion, and high post-infection immunity (Blancou 1986). So the disease seems to be maintained in independent cycles of infection with only one major host occurring in a given geographical area. Other species, like cattle, suffer sporadically from rabies infections but make little or no contribution to the spread of infection.

On the other hand, adaptation of rabies viruses to different hosts may explain the appearance of new epidemics. For example, the European fox rabies epidemic which began after the Second World War may have originated from an adapted domestic dog or arctic fox virus.

The presence of antibody may indicate recovery, with or without subsequent infectiousness. Serum neutralizing antibodies have been found in skunks (Carey and McLean 1983), raccoons (McLean 1972), mongooses (Everard and Everard 1985), and domestic dogs (Andral and Serie 1957, Gascoyne unpublished). In rare cases (5 dogs out of 1065) rabies virus has been isolated over the course of several years from healthy dogs (Fekadu 1972). One experimentally infected dog recovered from rabies and excreted virus in saliva for 9 months (Fekadu *et al.* 1981). Very long incubation and latent periods have also been observed in dogs (Tierkel 1975), and might commonly result from low- dose infections; this too would aid persistence.

The true frequency with which all these phenomena occur in rabies host populations is not known, and there have been few quantitative explorations of their potential significance. One exception is due to Coyne *et al.* (1989), who investigated the dynamics of raccoon rabies in the USA. Raccoon rabies was first confirmed in Florida in the early 1940s, but has since spread to neighbouring states such as Georgia, and by translocation further north to West Virginia. From there, cases have been reported throughout many of the eastern states, even reaching New Jersey, New York and Massachusetts latterly. Case notification rates for the USA have levelled off in recent years but, since current raccoon densities are not known, nothing can be said about changes in the persistence of infection. Populations of raccoons appear to show highly damped oscillations in abundance in affected areas. About 20% of raccoons exposed to virus (and therefore seropositive) never develop rabies and never shed virus. When this class of raccoons was included in a simulation model, damped oscillations in raccoon abundance occurred, just as seen in the data (Coyne *et al.* 1989). Presumably, the resistant fraction of the raccoon population provides the more steady supply of susceptibles needed to maintain endemicity.

## 3.3 Insect baculoviruses

Briggs *et al.* (this volume) provide a detailed survey of insect host-microparasite interactions. Here, we focus on questions of persistence. The insect

baculoviruses are relatively well studied for two reasons. First, this class of viruses (nuclear polyhedrosis viruses, NPV, and granulosis viruses, GV) encompasses a large proportion of insect pests. Second, they offer the potential for effective biological control by virtue of their virulence and their specificity to each insect species (Harper 1987). Host larvae become infected on consuming food contaminated with free-living infective virus. In successful infections, virus particles spread throughout much of the larval tissue, eventually killing the larva and leaving a cadaver packed with virus particles which are then released (Entwistle and Evans 1985).

Persistence of baculoviruses between outbreaks of disease is undoubtedly a problem that requires a solution because the majority of baculovirus diseases are undetectable in host populations for most of the time. There are a number of possible mechanisms for persistence of baculoviruses outside their hosts:

### 3.3.1 Environmental reservoirs

Although virus particles are protected by a protein coat, it is likely that virus mortality is high unless they occupy a habitat such as soil, which affords additional protection, especially from UV light (Benz 1987). The survival of infective particles in soil is well documented (e.g. Thompson *et al.* 1981), but the importance of such reservoirs in disease persistence is unclear, since particles must be transferred back to the active sites of the hosts to become infective. 'Rain-splash' may occur in agricultural pests feeding on low-growing crops, but it is harder to invoke this mechanism where hosts are forest insects, even though virus has been found in the soil beneath trees (e.g. NPV infections of spruce sawflies, *Gilpinia hercyniae*; Evans and Entwistle (1982)).

### 3.3.2 Latency/vertical transmission

A large body of circumstantial evidence suggests that vertical transmission of latent virus infection occurs. Environmental stressors, such as high host density or high temperature, or inoculation with heterologous virus may trigger activation (Tanada and Fuxa 1987). Recently, PCR has revealed that NPV is present in all stages of *Mamestra brassicae*, and that NPV can be reactivated in larvae (Fuxa 1992, Hughes *et al.* 1993). This mechanism potentially gives much flexibility to the pathogen which can remain latent in hosts through unfavourable periods and then break into overt infection when conditions are suitable.

### 3.3.3 Long distance transmission/metapopulations

Baculoviruses may also be opportunistically transported between populations by vectors such as parasitoids or birds. Birds, which have greater ambits than parasitoids, have been shown to defecate live baculovirus some distance from where they consumed infected larvae (Entwistle *et al.* 1977).

### 3.3.4 Alternative hosts/reservoirs

Baculoviruses could potentially invade a new host from an alternative host species. There is, however, little direct evidence because all potential host species are not of course continuously surveyed.

## 3.4 Louping ill in red grouse populations

Louping ill is a disease of sheep and grouse (*Lagopus lagopus*), caused by a flavivirus transmitted between hosts by the sheep tick *Ixodes ricinus*. Diseased individuals exhibit polioencephalomyelitis and other nervous disorders, obvious symptoms being poor locomotion (Dobson and Hudson this volume). Sheep and grouse are the only hosts known to produce a sufficiently high viraemic response for clinical signs to be exhibited or for ticks to be reinfected, but the ticks will feed on a wide range of species including deer, mountain hares and rodents. Case mortality rates in sheep vary between 10% and 60%, but have been found to be 80% in experimentally infected grouse (Reid 1975). Key factor analysis of grouse population data shows that the disease causes greater mortality than many other factors, including nematode parasites. It holds the population at a reduced density, where the population is sustained through immigration (Hudson 1992). The virus appears to limit but not regulate the grouse population since mortality rate through the disease is independent of density. In some populations the disease appears to be enzootic with high seroprevalence (60%), whereas other populations with lower numbers of ticks and fewer mammalian hosts appear to have epizootic outbreaks with the level of seropositivity varying from 5% to 45% between years (Hudson 1992).

At present we do not have a complete explanation for these patterns. However, the relationship between tick abundance and prevalence rates in ticks and grouse is becoming clearer as a result of recent work which points to trans-ovarial transmission in ticks, and which suggests that grouse chicks can be infected by eating ticks.

## 3.5 Brucellosis in wild ungulates

Up to now we have been discussing viral infections. Brucellosis is caused by a bacterium, *Brucella abortus*, which is transmitted sexually and to susceptible individuals licking an aborted foetus. Two main foci of infection of *Brucella* occur in Wyoming. First, in Yellowstone National Park, bison (*Bison bison*) form the main reservoir, with 5–8% of culled animals producing positive culture tests (and around 20% of older animals testing positive with the more unreliable serology test). Only one abortion has been observed in the bison herds that have been studied for more than 25 years. Only 1–2% of elk tested serologically produce positive titres, but none have been tested using

a culture test. Nevertheless, with over 30,000 elk in the region as opposed to 4000 bison, there are likely to be as many infected elk in the region as infected bison. Female elk (*Cervus elaphus*) will abort the first calf carried after *Brucella* infection.

The second focus is in Grand Teton National Park where elk herds supporting endemic brucellosis are concentrated into a small area during the peak calving period. In the late 1970s, a small herd of bison were introduced to Grand Teton. Occasional abortions have been subsequently observed in this herd and individuals now also test positive for *Brucella*. If no other pathogen, such as *Neospora caninum*, is causing these abortions, it is possible that *Brucella* is exhibiting different pathogenicity towards bison when predominantly cycling in elk.

Variable pathogenicity to primary and secondary reservoir hosts implies that the course of infection differs in other respects too e.g. with respect to infectiousness and the periods of latency and communicability. If this is true, elk and bison are epidemiological apples and oranges, in the same way as dog and fox hosts of rabies – their numbers are not simply additive in the calculation of CCS.

## 3.6 Bovine tuberculosis in possums

The first possum with tuberculosis in New Zealand was identified in 1967. Feral deer, cats and ferrets also carry TB, but possums are the most important wildlife vector on account of their abundance (70 million), their extensive contact with cattle (infectious animals often die on pasture, cattle lick the carcasses then insert tongues into their nostrils) and because they are highly infectious.

The natural history of TB is quite different from those viruses already described. Typically, the latent and infectious periods are about 3–4 months long, with the contact rate estimated at 7/infected animal/year from models. Possum-to-possum transmission from open lesions is concentrated around den sites through contamination of sequentially-shared den sites, scent marking, mating and fighting. There is also pseudo-vertical transmission from mother to pouch young. Contact rate is thought to be independent of carrying capacity (determined by den site availability) and this is supported by the apparent independence of disease prevalence and possum abundance (Barlow this volume, Dobson and Hudson this volume).

Overall, prevalence of disease is low, 5% or less, but occurs patchily with local rates as high as 40%. Possum density appears to be unaffected by the presence of infection. Recently, a larger area (several $km^2$) of uniformly high prevalence and possibly substantially reduced host density has been discovered. Insufficient long-term data are available to determine whether

patches are fixed, suggesting environmentally-determined disease hotspots, or wandering and at the mercy of stochastic processes.

Given the natural history of TB in possums, there is no obvious problem in explaining persistence qualitatively. But whether the precise levels of prevalence and patchiness can be mimicked with mathematical models is an open question.

## 3.7 Anthrax

Anthrax is an important pathogen in some large mammal populations being responsible, for example, for more than 50% of all deaths recorded in the Etosha National Park, Namibia between 1966 and 1974 (Ebedes 1976). In principal, the persistence of anthrax between recurrent outbreaks is not hard to explain. Bacteria are shed in small numbers during the early phase of infection and in large numbers when the host dies. Under the right conditions, bacteria sporulate rapidly and spores can persist for up to 50 years. Infection can occur following inhalation, ingestion or entry of spores through the skin, although relatively high doses ($10^6$–$10^8$ spores) may be required. In addition, there is laboratory evidence that, if environmental conditions are favourable, spore germination followed by vegetative multiplication and subsequent resporulation can occur outside the host (Van Ness 1971). Thus spores may become locally concentrated.

This system seems to provide an adequate explanation of the recurrent outbreaks of anthrax in the Kruger National Park, South Africa which have been modelled by Hahn and Furniss (1983). There, kudu, roan antelope and buffalo are most severely affected. Outbreaks of disease normally occur at the end of the dry season, when herbivores are both in poor condition and may have abrasions to the lining of the mouth, which facilitates spore entry.

However, it less easily explains the pattern of disease in Etosha National Park, where outbreaks occur during the rainy season when animals are in good condition. Despite the proposition that gravel diggings in Etosha act as reservoirs for recurrent infection (Berry 1981), there is no evidence that high concentrations of spores occur in these diggings (Turnbull *et al.* 1989). Moreover, kudu rarely die from anthrax in Etosha. Instead, wildebeest, elephants and zebra suffer the highest mortality, although these species are rarely infected in the Kruger. These observations suggest that mechanisms other than sporulation may explain the persistence of anthrax between outbreaks.

## 3.8 *Ligula intestinalis*: an honorary microparasite

*Ligula intestinalis* is a cestode parasite of fish which behaves like an epidemic microparasite. The history of recent invasions into the community at Slapton

Ley, an isolated lake in south Devon, appears typical (Kennedy and Burroughs 1981).

Historically the fish community of Slapton Ley comprised one predator (pike) and three other species – rudd, perch and roach. Roach were the least abundant species until the late 1960s when they were increasingly favoured by eutrophication. During the 1970s the growing roach population apparently satisfied an astonishingly elaborate threshold condition for the establishment of *L. intestinalis*. First, their abundance attracted great crested grebes to the lake, and the grebes introduced *L. intestinalis*. Second, the roach were so abundant by 1973 that intra-specific competition had led to a significant reduction in own their size-age relationship, and a significant reduction in the abundance of competing perch and rudd. Numerous diminutive roach were therefore feeding on plankton up to two years of age, which aided the spread of *L. intestinalis* after its introduction.

*L. intestinalis* prevalence reached 32% in yearling roach in just three years. The parasite sterilizes roach; it also causes a behavioural change which enhances transmission at the same time as increasing winter mortality. The resulting decline in roach numbers reduced intra- specific competition, allowing roach to improve their size-for-age and decreasing the time they spent feeding on plankton. This decline also eased inter-specific competition. Thereafter roach growth improved and the transmission success of *L. intestinalis* declined until prevalence fell to about 3% in 1984.

A catastrophic collapse of fish populations in the winter of 1984–5 was followed by a slow recovery. In 1987 rudd dominated the fishery, but in 1989 roach reappeared. By 1991 the rudd had again declined, the roach began to show stunted growth, and *Ligula* had reappeared and reached 65% prevalence. This second epidemic has followed the same trajectory as the first, but over a much shorter period. Persistent, endemic *L. intestinalis* infections have not been observed, and quantitative epidemiology has not addressed the problem.

# 4 Conclusions

## 4.1 Quality of the data

The above stories are mostly incomplete accounts of a selection of epizootic and enzootic microparasites in their wild animal host populations. Important questions of detail are thrown up everywhere. How many recent cases of seal distemper have gone undetected? Is PPR epizootic in Fulani livestock populations, and hence susceptible to fade-out? How many recorded cases of PPR have actually been rinderpest? How sensitive are methods for detecting anthrax spores? How sensitive and specific is the serological test for *Brucella* applied to elk, bison and moose?

These are questions about the effort which has been put into collecting data, about study design, and about the reliability of techniques used for measurement and diagnosis. The lack of effort devoted by veterinarians to investigating wild reservoirs rather than domestic animals is partly explained by the relative difficulty of doing so. Ecologists are accustomed to working with wild animals and will cheerfully face these difficulties, but the way in which ecological theory has developed has drawn fieldworkers towards competition and predation, and to concentrate on parasitoids rather than true parasites.

Studies of wildlife diseases are carried out at the boundary between ecology and epidemiology, but the design of these studies has not yet made the methodological best of both worlds. The textbooks of epidemiology are most explicit about the relationship between inference and design, and their lessons have not yet been assimilated by all ecologists. For example, correlation is often mistaken for causation: a cross-sectional study showing reduced fecundity in the presence of a microparasite does not necessarily mean that the microparasite is responsible. Susceptibility to infection could be greater in those individuals who are less fecund for some other reason. Proof requires a prospective or longitudinal study, preferably a controlled experiment. As a general rule, complex data analysis (including modelling) rarely makes up for poor study design.

As for diagnostic techniques, those who work with major infectious diseases of medical and veterinary importance are aware that the tests often have severe limitations, despite much effort invested in their development. The sensitivity and specificity of serological tests is an excellent example – for many parasitic diseases, the perceived need to choose a cut-off point from a continuous distribution is an enduring problem, and tests which cross- react with closely related parasites are commonplace. Serological studies of wildlife diseases are now being carried out with tests lifted from human and veterinary medicine, but the sensitivity and specificity of these tests used in another context have rarely been examined.

Despite all these uncertainties, the data are not universally poor, and some firm statements can be made from those we have discussed here. The absence of rinderpest infection in spectacularly growing Tanzanian wildebeest populations, together with other evidence, makes the persistence of infection in these animals highly unlikely. By contrast, the data on bovine TB make it clear that the infection is now persistently enzootic in New Zealand possums.

## 4.2 Explanations for observed patterns

Where observed patterns are convincing, can they be explained? We began with the problem of measles persistence, which may ultimately have a complex explanation in terms of transmission in spatially-structured populations.

Some wildlife diseases, for example PPR and epidemics of *L. intestinalis*, might also have to be explained in the same way. For other pathogens, we can more or less confidently invoke other mechanisms, and qualitative argument suggests that they will aid persistence – vertical transmission of PDV, baculoviruses and louping ill; carriers of rabies; durable spores of anthrax; long periods of infectiousness in brucellosis and tuberculosis; reservoirs and alternative hosts for louping ill and other pathogens. But in all these cases we need better measurements of their frequency of occurrence, and further quantitative investigations of the way they influence disease population dynamics.

Our third and most oblique angle on persistence was from the perspective of population regulation. The discussion was dominated by theory, which is not altogether explained by the proclivities of participants (see Appendix). Given that many accounts even of the presence and absence of infection in populations are sketchy, definitive analyses of non-linear processes are understandably few. There are some good examples of epizootics arising in host populations as they exceed a critical threshold (CCS), from which disease-induced mortalities push these host populations back to low density (*L. intestinalis* may be one of them). In such cases, the contact rate between susceptibles and infectives (and hence $R_0$) must increase with host population size, but we have little idea of the form of the contact rate - host abundance relationship.

Over the last 15 years there has been considerable progress in developing theories to explore the regulatory, or destabilising, effects of microparasites on host-parasite dynamics (Anderson and May 1979,1981,1986, Heesterbeek and Roberts this volume). However, for obvious logistical and financial reasons, there has been much less empirical progress in this area. Holmes (1982) thought that the best examples of regulation by diseases should be found in invertebrate populations. Given the relative ease of field and laboratory work in these systems, this is likely to be an area in which some progress can be made in understanding the dynamical effects of parasitism (Briggs *et al.* this volume)

# 5 Recommendations for research

1. Find out whether the problem of fade-out in models of measles can be solved by more carefully considering space and scale. Investigate the application of these findings to morbilliviruses and other parasites (rabies, *L. intestinalis* etc.) of wild animals.

2. Measure the frequency with which various persistence mechanisms occur – reservoirs, carrier states, persistent stages, latency and recrudescence, and vertical (including transovarial) transmission.

3. Investigate the quantitative implications of these various persistence mechanisms. Do this for specific host-parasite systems, rather than for host-parasite systems in general, using everything we know about their natural history to constrain model structure and parameter values. Analyses of this kind will surely help to identify priorities for field research.

4. Carry out trials which will lead to the adaptation and proper epidemiological interpretation of routine diagnostic methods for use in wildlife disease epidemiology – serology, parasite isolation, DNA probes, PCR etc.

5. Develop new methods in the experimental (as opposed to observational) epidemiology of wildlife diseases. Most ecologists will have something to learn from the rigorous approach to study design commonplace in human disease epidemiology (where the penalty for making mistakes is often thought to be higher!). What is needed is a methodological blend from the catechisms of ecology and epidemiology.

6. Investigate further whether the effects of parasites on mortality and fecundity are additive or compensatory (still needed after all these years), and the extent to which parasitism acts non-linearly (density dependent positive and negative feedback).

# Appendix

We first consider the conditions for regulation, and hence persistence, in a system with one host and one pathogen. We then outline some new results (Bowers unpublished), relying on heuristic arguments rather than resorting to formal proofs. See Begon and Bowers (this volume) for a review of the previous literature on which this Appendix builds.

## One pathogen species in one host species

The following is a simple model of a pathogenic microparasite acting on its host population size:

$$\frac{dN}{dt} = (a-b)N - \alpha I \qquad \text{(A1)}$$

$$\frac{dI}{dt} = \beta C(N)(N-I)I/N - (b+\alpha)I \qquad \text{(A2)}$$

Here, $a$ and $b$ represent the per capita birth and death rate in the host population ($N$) in the absence of parasitism, $\alpha$ is the increase in death rate imposed by the parasite, $\beta$ is the probability of transmission, $I$ is the number

of infected hosts and $C(N)$ is the contact rate. Furthermore, it is assumed that $\alpha > a - b > 0$, that is $R_0 > 1$. Only weak conditions on the contact rate function $C(N)$ (e.g. $C(N)$ is non-negative and increasing iin $N$, such as $C(N) = N$) ensure that parameter regions exist where the system tends to a globally stable equilibrium, in other words regions exist where the pathogen persists in its host population and where the host population is regulated. If $C$ is a constant for all $N$, then the stable equilibrium of (A1), (A2) is $(N, I) = (0, 0)$, hence the pathogen cannot regulate the population and survive. This will occur, for example, when the contact rate depends on population density and when density remains constant even though population size increases. This might happen when animals are territorial or when animals move in a herd.

This is one of a range of simple microparasite models exploring the regulation of one host species by one pathogen species (see Heesterbeek and Roberts (this volume) for more detailed arguments); others can be found in Anderson and May (1979).

## One pathogen species in two host species

Now the pathogen imposes death rates $\alpha_1$ and $\alpha_2$ on each of its two host species. We assume direct transmission of the parasite from host to host although, with simple modification, the argument would work for a parasite with free living stages. In which of *the two host species do we expect to see the microparasite persist*? Consider two situations:

### Without other regulatory factors acting on the host.

If $Y_1^*$ and $Y_2^*$ denote supposed equilibrium densities of infecteds for each host alone with the pathogen, and the transmission coefficients $\beta_{ij}$ are defined in the usual way, then $\beta_{12}Y_2^*$ denotes the force of the interspecific infection felt by a susceptible of host 1 when attempting to invade equilibrium $Y_2^*$. Correspondingly, $\beta_{11}Y_1^*$ is the force of infection felt and tolerated by an individual of host 1 in an equilibrium of its own species and the pathogen. If

$$\beta_{12}Y_2^* < \beta_{11}Y_1^*, \tag{A3}$$

an individual of host 1 can invade the equilibrium of host 2 and the pathogen. If both hosts are regulated by the pathogen when they exist on their own, if there are no other regulatory factors, and if the pathogen is shared, then the following outcomes could occur:

1. $\beta_{12}Y_2^* < \beta_{11}Y_1^*$ and $\beta_{21}Y_1^* < \beta_{22}Y_2^*$. In this situation, both hosts can invade and we expect coexistence. *The pathogen persists in both host populations.* (Note $\beta_{12}\beta_{21} < \beta_{11}\beta_{22}$ is implied).

2. $\beta_{12}Y_2^* < \beta_{11}Y_1^*$ and $\beta_{21}Y_1^* > \beta_{22}Y_2^*$. Here, host 1 can invade, while host 2 cannot and we expect *host 1 to survive with its pathogen* whereas host 2 is eliminated.

3. $\beta_{12}Y_2^* > \beta_{11}Y_1^*$ and $\beta_{21}Y_1^* > \beta_{22}Y_2^*$. In this case, neither host can invade. Either host could outcompete the other; one host will survive and the other will be eliminated. Initial relative host densities will determine which host does which, and *hence which host appears to support the pathogen* (Note $\beta_{12}\beta_{21} > \beta_{11}\beta_{22}$ is implied).

These alternative outcomes are highly analogous to those of Lotka-Volterra models where there is direct competition. We can therefore refer to apparent competition occurring in this example too.

The role of pathogenicity is expressed through the effect of $\alpha_1$ and $\alpha_2$ on the densities of $Y_1^*$ and $Y_2^*$. As a specific example, think of the case where the pathogen is being used for biological control. Here host 2 is a pest whereas host 1 is a non-target species. The value of $\alpha_1$ should then be such that when it acts alone, it only just regulates host 1, which will be at high density in these circumstances. Correspondingly $Y_1^*$ will also be high with any reasonable prevalence, although detailed argument suggests prevalence will be near 1. By a similar argument, $Y_2^*$ should be low and so $Y_1^* \gg Y_2^*$. Outcome (2) is therefore likely. In this scenario, the non-target host survives more or less unaffected, but the pest is controlled by the pathogen.

**With other regulatory factors acting on the host.**

In a two host system where a pathogen affects both hosts and where other factors regulate host density, let $Y_1^*$ denote infected densities in the presence of all factors, but where the other host is absent. Let $\hat{Y}_1$ denote these values if all factors other than the pathogen are absent. To account for this new situation, inequality (A3) is replaced by

$$\beta_{12}Y_2^* < \beta_{11}\hat{Y}_1 \qquad \text{(A4)}$$

The term on the right is now the maximum force of infection that the susceptible host can tolerate. The entire classification of possible outcomes (1), (2) and (3) now has inequality (A3) replaced by (A4). The outcome of the biological control example is, however, unchanged because we can argue that $\hat{Y}_1 \gg Y_2^*$ and $\hat{Y}_2 \ll Y_1^*$.

Without the extra regulatory factors, the pathogenicities had to be sufficiently high to regulate the hosts, but these conditions no longer automatically apply. *The hosts must, however, support the pathogen* (e.g. threshold host density must be less than host carrying capacity). However, a further condition must be added: that the pathogenicity experienced by a host (which we

have said in (2) or (3) cannot invade) is sufficiently high to eliminate it in the average circumstances. In this case, invading individuals must suffer higher death rates than birth rates and therefore the conditions

$$\alpha + b > a \text{ or } \alpha > r = a - b \tag{A5}$$

are required. This condition is automatically fulfilled when the hosts are regulated only by pathogens. In the present example, however, condition (A5) is required for hosts to be eliminated in (2) and (3). In these cases, when (A4) does not hold, coexistence occurs. Thus low $\alpha$ favours coexistence through what may be called the mechanism of resource mediation.

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# Macroparasites: Observed Patterns in Naturally Fluctuating Animal Populations

*P.J. Hudson and A.P. Dobson*

## 1 Introduction

The parasitic helminths and arthropods (ticks and fleas) are usually classified as macroparasites. The definition embraces the nematodes, cestodes, trematodes, acanthocephalans and the lice, fleas and ticks (Anderson and May 1979). In these species, reproduction usually occurs via the transmission of free-living infective larval stages, although many species have complex life cycles involving several obligatory host species. Macroparasites do not usually have direct reproduction within their definitive hosts, but asexual reproduction occurs in the intermediate hosts of the digenean trematodes and some cestodes and nematodes. When compared with the microparasites (the protozoans, viruses and bacteria), the macroparasites are relatively large, have long generation times and are immunologically characterised by a diversity of antigens. Infections by macroparasites are generally chronic leading to morbidity rather than mortality (see Lloyd this volume). It is therefore important to consider the sub-lethal effects of macroparasites on host fitness rather than more obvious lethal effects as both have important consequences for the dynamics of the interaction between the host and parasite populations.

Despite the very large number of parasites known to infect wild animals, relatively few ecologists have investigated the role of parasitic helminths and arthropods in regulating host abundance or distribution. This is surprising when one considers the numerous studies that have investigated the regulatory role of other natural enemies such as parasitoids and predators (Crawley 1992). On the one hand, ecologists and wildlife managers have traditionally seen parasites as benign symbionts living in equilibrium with their host. When environmental factors disturbed this careful balance, then the epidemic outbreaks of macroparasites could cause massive host mortalities, but these were thought to be unusual exceptions to this general rule. On the other hand, parasitologists carried a different perspective and saw parasites as organisms that benefited at the expense of their host (Crofton 1971, Kennedy 1975). Even so the majority of ecological studies of parasites concentrated on basic taxonomy (with an almost Freudian fascination for mouth-parts), surveys of parasite diversity, or examined interactions between parasites and

hosts at the level of the individual host. It was not until the 1970's that ecological studies began to consider interactions between parasites and hosts at the population level. The volume by Kennedy (1975) provided an important first synthesis in this area.

The views of ecologists have changed over the past fifteen years following the early work of Crofton (1971) and the synthesis of the principles of population biology with those of parasitology (Anderson and May 1978, May and Anderson 1978). These studies showed that parasites were capable of regulating their host populations and that certain features of the interaction could also potentially destabilize parasite-host relationships and cause oscillations in parasite and host numbers (May and Anderson 1978). Furthermore, extensions of the work implied that benign parasites would not necessarily be at a selective advantage, since the lifetime reproductive success of parasites does not depend upon survival alone, but on the interactions between survival, reproduction and transmission which determine the parasite's ability to establish breeding offspring in new hosts (Anderson and May 1982, Dobson and Merenlender 1991, Herre 1993, Lively and Apanius this volume).

While the mathematical framework for a clear understanding of parasite-host relationships is now available (Anderson and May 1978,1991, Roberts *et al.* this volume), only a few empirical studies have examined the processes in naturally fluctuating animal populations and linked theory with field data. This is partly because suitable systems have to be identified, partly because long term studies are required which fail to attract the attention of funding bodies, and partly because of methodological problems in understanding the components of transmission.

This paper provides an introduction to observed epidemiological patterns in the population dynamics of macroparasites in wild animal populations. Discussion of the impact of helminths on their hosts is given in the chapter by Gulland (this volume), while the group report by Smith *et al.* (this volume) considers some of the problems introduced here in more detail and from a number of different perspectives. We have concentrated upon examining either long-term studies of parasite-hosts systems, or insightful experiments on laboratory systems; our main goal has been to describe and interpret general phenomena that should occur in other systems. Throughout we have concentrated upon the impact of the parasites on individual hosts and the consequences of this for the abundance and distribution of the host population. The paper is also designed to complement the chapter on modelling the population dynamics of macroparasites (Roberts *et al.* this volume) and the chapter on observed patterns in microparasites (Dobson and Hudson this volume). A final aim has been to highlight areas of future research for both the empiricist and the theorist. We emphasize that the chapter is not a comprehensive review, but an identification of general patterns. Throughout, the general contention is that macroparasites frequently have an important sub-

lethal impact on their hosts with interesting consequences for the dynamics of both the parasite and the host populations.

## 2 Impact in individual hosts

Parasites act both directly and indirectly to reduce host survival and fecundity (see Gulland this volume). The majority of experimental studies suggest that the impact of parasites on host survival is directly related to worm burden (Figure 1). Although the impact of macroparasites on host fecundity is also a function of parasite burden, the ability of some cestodes and digeneans to reproduce asexually within their intermediate host means that only one successful infection is required to produce significant reductions in host fecundity and survival. In many instances, experimental studies designed to quantify the direct effects of macroparasites on host survival have also revealed interesting sublethal levels of infection. For example, infection with *Schistosoma mansoni* significantly increases and then reduces the locomotory activity of golden hamsters (Kavaliers and Podesta 1988). Treatment of the infected hamsters with opiate antagonists reduces the changes in activity in parasitized hosts, suggesting that the pathogens produce substances that resemble neuropeptides, or neuropeptide precursors, which mimic the opiates of the hosts. These indirect effects are generally associated with moderate worm burdens, the increased morbidity observed in the host may produce increased mortality through other causes: predation, accident, infection with other parasites, or reductions in host fitness that reduce the host's competitive ability. Many acanthocephalans, trematodes, cestodes and nematodes have also been shown to alter the behaviour of their intermediate hosts in order to increase their susceptibility to predation by the definitive host in their life cycle (Dobson 1988).

A number of experimental studies have provided evidence that both parasitic helminths and arthropods have a significant impact on the energy budgets of their hosts (Bailey 1975, Connors and Nickol 1991, Jokela *et al.* 1993, Booth *et al.* 1993). Deer mice (*Peromyscus leucopus*) infected with the cestode *Hymenolepis citelli* show a 2% reduction in digestion efficiency, which does not seem to have any major impact on host fitness (Munger and Karasov 1991). In some cases infected hosts can respond to this by increasing their rate of food consumption, as occurs when starlings (*Sturnus vulgaris*) are infected with the acanthocephalan, *Plagiorhynchus cylindraceus* (Connors and Nickol 1991). Similar results are reported for rock doves (*Columba livia*) infected with feather feeding lice (Booth *et al.* 1993). However, chronic infections often lead to increased metabolic rate and reduced body mass which may have a long term impact on host fitness. In many invertebrate systems, the energetic costs of parasitism are paid for by reducing reproductive effort (Minchella 1985). For example, fresh-water clams, *Anodonta piscinalis*,

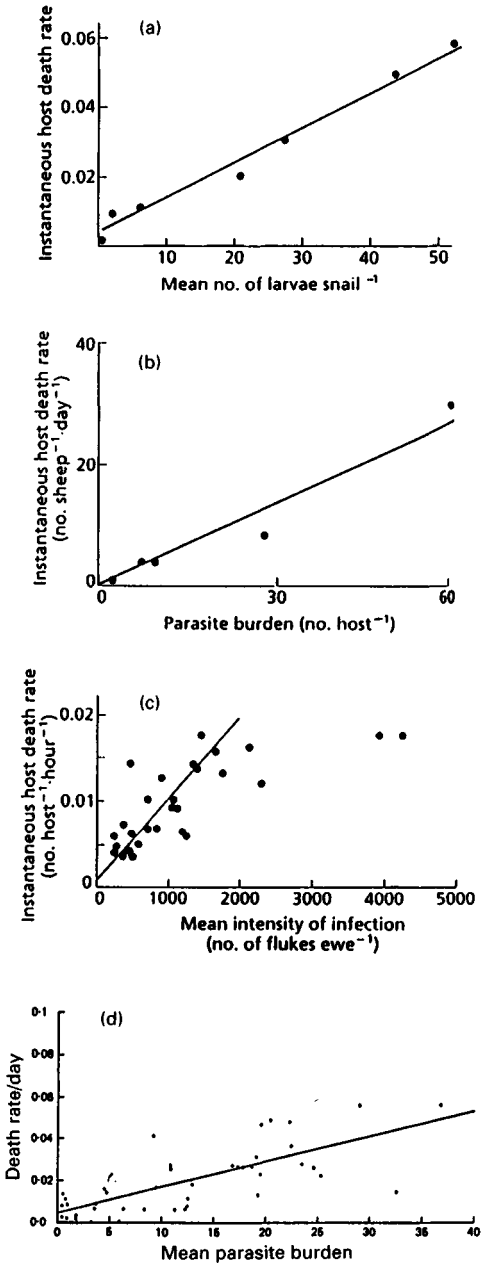


Figure 1. The relationship between the death rate of hosts and the burden of parasites indicating that parasites reduce host survival rate in a linear manner (a) *Elaphostrongylus rangiferi* in the snail *Arianta arbustorum* (Skorping 1985); (b) *Hymenolepis diminuta* in the beetle *Tribolium confusum* (Keymer 1981); (c) *Fasciola hepatica* in sheep (Boray 1969); (d) *Gyrodactylus bullatarudis* in guppies (Scott and Anderson 1984).

infected with the castrating trematode *Rhipidoctyle fennica*, lack gylcogen reserves and are lighter, but contain more fat, than uninfected clams (Jokela, *et al.* 1993). By castrating their hosts the parasites utilize the energy the hosts would otherwise use to produce its own offspring.

## 2.1 Parasite induced reduction in host survival

The three main methods of assessing parasite induced mortality in free-living populations are: (i) compare the worm burden of animals that have died from parasitism with those from a random sample of the host population; (ii) record survival of animals with known worm burdens; and (iii) undertake field experiments that manipulate worm burdens and monitor the subsequent survival and fecundity of the control and treatment hosts.

A large number of veterinary studies have recorded the parasite burden of animals killed or found dead, although pathological examination indicates parasites as the likely cause of death, these studies usually omit to obtain estimates of worm burden from a living sample of wild animals. This makes it almost impossible to obtain an estimate of parasite induced host mortality rates. Nevertheless, one of the interesting features of this type of field data is the large variance observed between individual hosts, some of which are capable of withstanding much greater worm burdens than others (Hudson *et al.* 1992). Even in the laboratory experiments of Scott and Anderson (1984), where constant environmental conditions and abundant food were provided for fish used as hosts, there was still large variation in the parasite burdens of hosts that had died or survived infection.

## 2.2 Parasite induced reduction in host fecundity

There is growing evidence from a wide range of systems that parasites can have either a direct or indirect impact on host fecundity. In some parasites this may act through direct castration, but in many of the parasites of vertebrate hosts an increase in parasite burden reduces the physiological condition of the host and the ability of parents to produce or rear offspring (Figure 2). One of the clearest examples of this reduction in breeding production occurs in red grouse infected with the nematode parasite *Trichostrongylus tenuis*. There is a direct association between parasite burdens and clutch size, hatching success and survival of grouse chicks (Hudson 1986, Hudson *et al.* 1992). Experimental reductions in parasite burdens resulted in a subsequent increase in these parameters and a clear relationship between breeding production and worm burden (Figure 2).

In a similar study of pheasants, there is initial evidence that parasites directly influence female breeding production and indirectly influence male fitness by reducing their ability to defend females. Earlier research on *Heterakis* had shown that this parasite will reduce body fat but can also cause

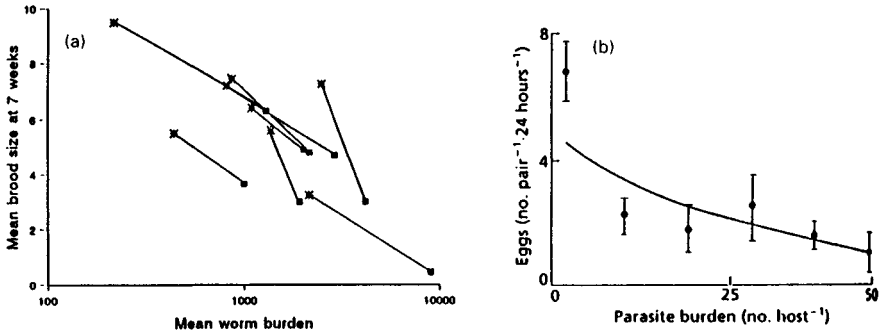


Figure 2. The relationship between host breeding production and parasite burden (a) *Trichostrongylus tenuis* in red grouse (Hudson *et al.* 1992); (b) *Hymenolepis diminuta* in *Tribolium confusum* (Keymer 1981).

the immune system to release corticosterone which will suppress testosterone. Treatment of females with an anthelmintic to remove internal parasites (in particular *Heterakis sp.*) increased nesting attempts, hatching success and overall brood production (Woodburn 1993). Treated males spent longer with the wattles above their eyes fully inflated (an indication of dominance) and defended five times more females in their harems than untreated females. Unfortunately, this result was not replicated in sites where male density was lower and competition for mates less pronounced (Woodburn 1993).

## 2.3 Indirect effects on host competitive ability

The growth and developmental rates of hosts infected with parasites may be significantly slower than uninfected hosts (Figure 3) and reductions in the hosts stored energy reserves may reduce its ability to survive in times of stress. These indirect effects of parasitism reduce the host's ability to compete for resources or mates, and this may have an impact on the fitness of individual hosts which will have dynamical consequences for the population. For example, Saumier *et al.* (1994) showed that when larval stages of *Trichinella pseudospiralis* are injected into American kestrels they became established in the birds musculature and reduce the birds ability to fly. Since these birds depend on hovering and aerial manoeuvrability to catch their prey, *Trichinella* infections reduce the bird's ability to obtain food for themselves and their young. Similar infections may lead to a reduction in social status and reduced access to resources in mice; individuals injected with *Trichinella spiralis*, showed evidence of decreased dominance status perhaps also as a result of direct damage to the musculature (Rau 1983).

Alteration in host movement patterns may also influence the transmission of the parasite. Mice infected with *Syphacia obvelata* showed decreased exploratory activity compared with uninfected controls (McNair and Timmons 1977). In contrast, mice 1985), this may make them more vulnerable to preda-

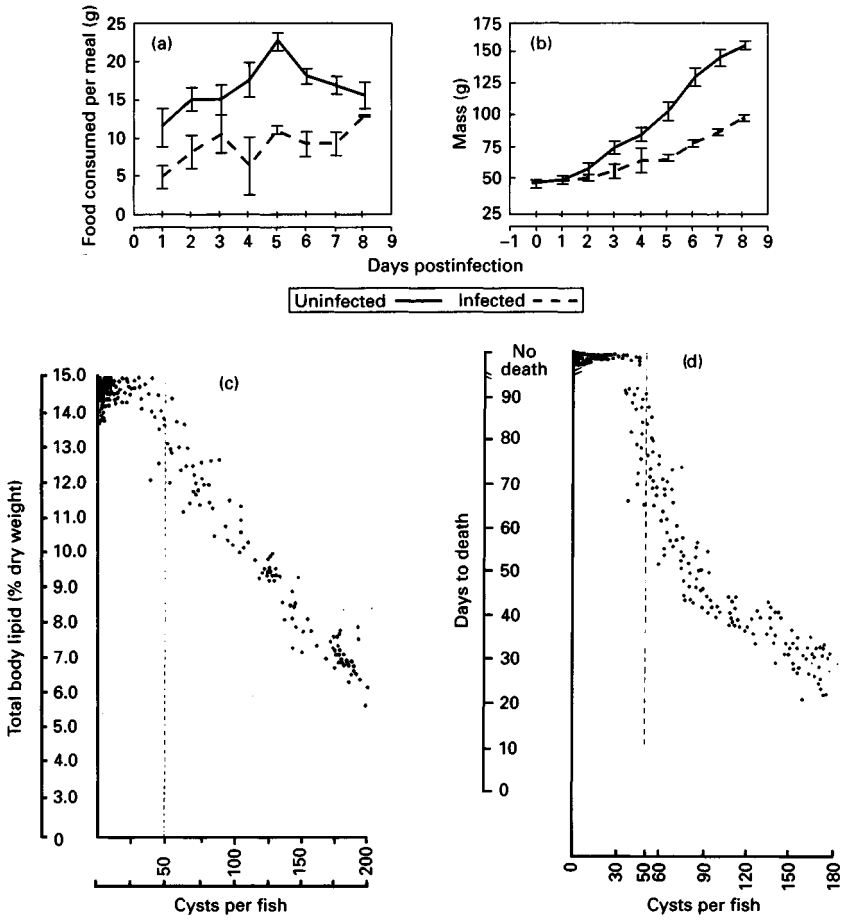


Figure 3. The indirect effect of parasites on their hosts. Tricolored heron nestlings infected with *Eustrogyliedes ignotus* larvae, (a) food consumed per meal by infected and uninfected birds; (b) body mass gained per day for infected and uninfected chicks (after Spalding *et al.* 1994). (c) The relationship between parasite burden and total body lipid content (% dry weight) in bluegill sunfish infected with cysts of the trematode *Uvulifer ambloplitis*; (d) the relationship between number of cysts per fish and days of progressive temperature drop until death (after Lemly and Esch 1984).

tory dogs, the principle host of this parasite. While these effects on mice may, or may not, have an impact on the competitive ability of the host, they may be a direct manipulation of host behaviour by the parasite to increase rates of parasite transmission (Dobson 1988, Lafferty 1992).

Parasites may act to reduce fecundity by reducing the attractiveness of their host to potential mates. Male laboratory mice mounted females infected with *T. spiralis* less often than uninfected females. These effects appear to be due to differential receptivity of the females, as opposed to preference by the males (Edwards and Barnard 1987). Parasites may also influence secondary

sexual characteristics such as behavioural displays, ornaments or colouration in a manner that allows hosts to select mates on the basis of indications of fitness (Read 1990). For example, male sage grouse have large air sacs which they inflate during lekking behaviour. Lice cause haematomas on these air sacs and infested males are less likely to obtain matings while lekking than are lice free males (Johnson and Boyce 1991). To test whether the females used the haematomas as cues, Spurrier *et al.* (1991) conducted a series of experiments that artificially added haematomas as red marks on the air sacs of grouse. The results showed that males with real or experimental haematomas were not selected by the females. Studies of the monogenean *Gyrodactylus turnbulli* on guppies have shown that parasites reduce the carotenid colours of males so that females discriminate against recently infected males (Lyles 1990, Houde and Torio 1992).

We conclude this section by emphasizing that there are still some major questions that need to be examined experimentally in a greater variety of systems if we are to fully understand interactions between parasites and hosts at the individual host level. In particular we need to know why there are large variations in the effects of parasites on host mortality. Are these differences driven by genetic variation in the host, or through environmental factors? Similarly, the interaction between parasitism, stress and nutrition requires further experimental and theoretical study. We know that the impact of the parasites on host fecundity and survival is often related to the nutritional status of the host (Keymer and Tarlton 1991). Poorly nourished hosts are more vulnerable to increased mortality because of the increased nutritional burden of the parasites, but they may also be more vulnerable to infection as they are less able to launch a strong immunological response (Slater and Keymer 1986,1988).

# 3 Observed epidemiological patterns

The majority of published data sets for parasitic helminths are 'one-off' field surveys of the prevalence and worm numbers found in a large sample of dissected hosts. In some cases the data are obtained when a large number of hosts die during harsh weather, or due to a local environmental contamination. Occasionally, long-term field studies collect information on the prevalence of specific pathogens using faecal samples; other studies collect more detailed information on worm burdens by systematicaly removing individuals from the population (Kennedy 1975,1987, Kennedy and Rumpus 1977, Burrough 1978, Montgomery and Montgomery 1988,1990, Gregory *et al.* 1992). Where estimates of parasite infection are obtained from a population whose individuals can be accurately aged, then information about the rate of acquistion of parasites can be obtained from the age-prevalence curve. In the absence of controlled experiments, these data provide the most important

information from which to determine rates of parasite transmission and the possible impacts of the parasite on the host, and vice versa.

## 3.1 Age prevalence and intensity

Age-intensity curves can reveal patterns that may allow quantification of rates of transmission and parasite mortality (Anderson and May 1991). As very few parasitic helminths are transmitted vertically from an infected female to her unborn offspring, the majority of age-intensity curves show an initial increase after the age at which an animal is first susceptible to infection (Figure 4 and 5). Similarly, because macroparasites tend not to reproduce directly within their definitive hosts, the increase is usually due to the acquistion of new infective larval stages (the major exception to this generality are the monogeneans and many parasitic arthropods). Any change in the parasite burden of an individual host is thus a result of the balance between the rates of parasite infection (immigration) and mortality processes operating on the parasite population in the host. If both rates are constant then an age intensity curve for a group of animals will show a rise in parasite burden to an asymptote, the level of which is determined by the balance between infection and mortality.

Examination of the data from a number of systems provides examples of age intensity curves that can be classified as one of three types (Figures 4 and 5): the first show a continual rise in intensity of infection, the second show a rise to an asymptote determined by a balance between infection and mortality, the third type are convex, with numbers of parasites per host reaching a peak and subsequently declining. Providing immigration of parasite transmission stages into the host exceeds their death rate in the hosts, and there is no reduction in infection due to prior exposure to the pathogen, then we would expect worm burdens to increase with host age (Type I). In contrast, if the net mortality rate of the parasites becomes roughly equal to their rate of establishing in the host, we would expect to see worm burdens rising to an asymptote (Type II). A number of biological processes could generate the convex age-intensity curves observed in some studies (Type III); these include parasite-induced host mortality, age dependent changes in infection rate, such as changes in host behaviour, age related changes in exposure and the development of resistance to infection through either reduced macroparasite survival and/or a reduction in establishment. In some systems, all of these processes will play a role and it is important to realize that, when operating at low levels, they may produce curves that either asymptote or show only a reduced increase in worm burden with age. Nevertheless, there is growing evidence from both human and non-human mammalian hosts that a major factor causing convex age-intensity curves is the development of acquired immunity (Anderson and Crombie 1984, Crombie and Anderson 1985, Lloyd this volume). In humans, convex age-prevalence curves are frequently

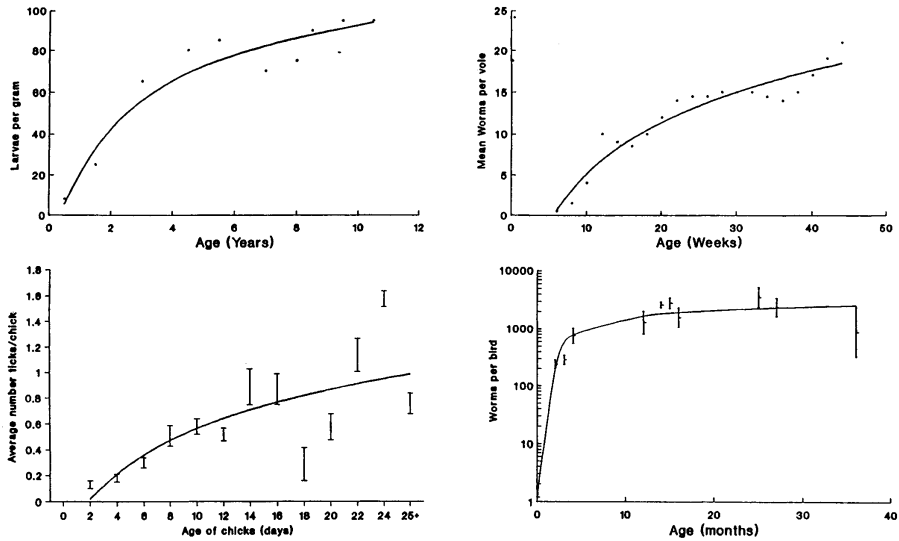


Figure 4. Age intensity curves from a number of macroparasite systems – all of these curves show a steady rise to an asymptote (a) *Elaphostrongylus rangiferi* in reindeer (Halvorsen 1986b); (b) *Heligmosomum polygyrus* in voles (Quinnell 1992); (c) *Ixodes ricinus* on grouse chicks (Hudson 1992); (d) *Trichostrongylus tenuis* in red grouse (Hudson 1992).

a consequence of acquired immunity (Anderson and Medley 1985, Anderson and May 1991, Grenfell *et al.* this volume).

One of the clearest example of convexity in age intensity curves for a wild animal species is seen in *H. polygyrus* infections of wood mice where intensity of infection peaks at 8 months of age (Gregory, Montgomery and Montgomery 1992). Experimental work implicates acquired immunity as the principal cause of convex age-intensity curves in this system (Quinnell 1992), this convexity is generated in the absence of parasite induced host mortality (Gregory, Keymer and Clarke 1990). In contrast, in the red grouse-*T.tenuis system*, there appears to be little if any acquired resistance, the rate of acquisition of new parasites far exceeds the parasite mortality rates, so the age intensity curve increases throughout the life of a bird (Hudson, Dobson and Newborn 1992, Hudson *et al.* 1992).

An important limitation of age intensity curves is that they should ideally be constructed from longitudinal data where the individuals of the same age cohort are sampled in successive days, weeks, months or years. This is straightforward when ectoparasites are being counted, but sampling endoparasites often requires the removal of individuals from the population. This may lead to changes in the age structure and density of the host population which can have repercussions for future sampling. An alternative method is to collect cross-sectional data from one point in time. Unfortunately, previous variations in exposure rate due to past variations in the force of infection may distort the observed age-intensity curve. Moreover it is likely that the observed patterns of prevalence and intensity can vary greatly according to host gender, social status, and previous control programmes; all of which can have an impact on the survival of both hosts and free-living parasite infective stages.

Age prevalence curves are more ambiguous indicators of the interaction between the parasite and host. Obviously if prevalence increases with age, then hosts are either always susceptible or increase their susceptibility to infection with age. However, any convexity or asymptote in the age-prevalence curve could indicate either a change in the diet of the host, the clearing of infections by previously infected hosts, or the loss of infected individuals from the population (see Grenfell *et al.* this volume). Although large changes in mean intensity can occur when a few heavily infected individuals die, or are otherwise removed, from an age cohort, such effects may have little impact on prevalence. In general, age-intensity curves for macroparasites are more powerful for the detailed analysis of epidemiological processes, yet age-prevalence curves can often be more readily obtained using non-invasive techniques such as the examination of feacal material for eggs. More sophisticated diagnostic tools should soon become available to quantify worm burdens in infected hosts using non-destructive immunological techniques (see Lloyd this volume).

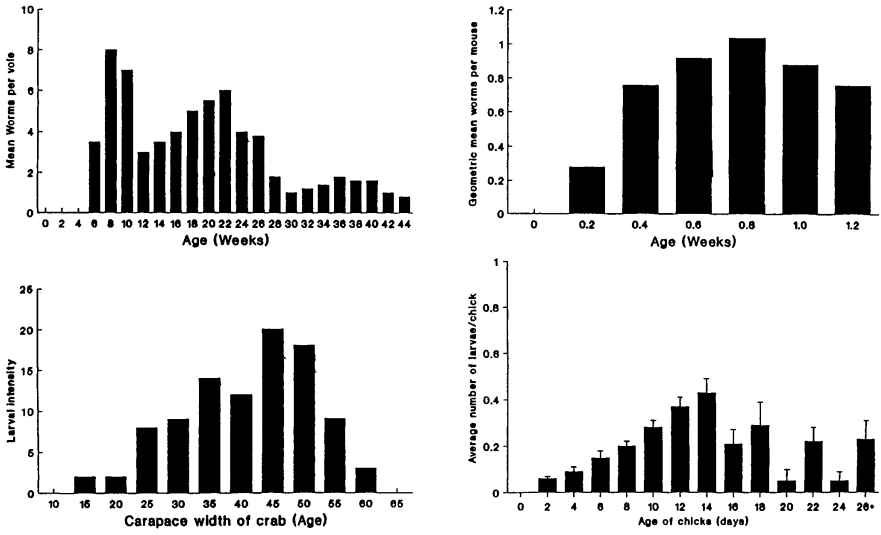


Figure 5. Age intensity curves from a number of macroparasite systems – all of these curves illustrate a more convex shape than those in Figure 4 – after an initial rise the mean worm burdens decline with increasing age. (a) *Syphacia obvelata* in voles (Kisielewska and Zubczewska 1973); (b) *H. polygyrus* in wood mice (Gregory *et al.* 1992); (c) Larval *Profilicollis botulus* in shore crabs (Liat and Pike 1982); (d) *Ixodes ricinus* larvae on red grouse chicks (Hudson 1992).

## 3.2 Transmission and fecundity of parasitic helminths

The fecundity of parasitic worms is several orders of magnitude greater than their free-living counterparts, this may partly be due to the relatively sedentary existence enjoyed by parasites in a habitat where they are essentially bathed in a highly nutritious food source (Skorping *et al.* 1991, Calow 1979,1983, Dobson *et al.* 1992). It also reflects the high incidence of asexual and parthenogenic reproduction in many parasite species.

Nevertheless, the proportion of parasite eggs that manage to produce a successful infection in a host is very small (of the order, 0.01 to 1%, Hudson and Dobson (in press)) and is principally determined by abiotic factors. This implies that meteorological effects are likely to have a major impact on parasite geographical distributions and the abundance of adult stages. The old adage that 'Worms work by the weather' (Gordon 1948) is obviously over simplistic, but it may come back to haunt parasitologists if current predictions of global climate change allow parasitic helminths to invade new regions.

## 3.3 Patterns of parasite distribution within host populations

Hosts provide a very clear sampling unit for studying parasites and identifying population processes. Such advantages are lost once we start considering the distribution and abundance of the free-living stages. Up to this point we have followed the historical precedent of attempting to obtain a quantitative understanding of host-macroparasite associations using only two epidemiological measurements: parasite prevalence and intensity, the proportion of hosts infected and the mean worm burden. Because there are pronounced differences in the worm burden of hosts, it is also important to consider the frequency distribution of parasite burdens in the host population (Crofton 1971, Anderson and May 1978,1991). A general characteristic of the macroparasite-host relationship is the aggregation of parasite population into a small proportion of the host population – characteristically the variance in parasite numbers per host exceeds the mean (Figure 6). Frequency distributions of this type are usually described by the negative binomial distribution, it is characterised by two parameters: the mean and a parameter $k$, which is an inverse measure of the degree of aggregation (see Smith *et al.* this volume).

The observed statistical distribution of parasites within their host population reflects both the biological processes determining parasite births, transmission and deaths and the methodological processes that have been used to sample the host population. At the simplest level, hosts are not usually distributed at random in their environment, so exposure to infection of even randomly distributed infective stages may well generate an aggregated distribution of parasites in the host population (Keymer and Anderson 1979). It follows that, if the hosts are not distributed at random, it seems unlikely

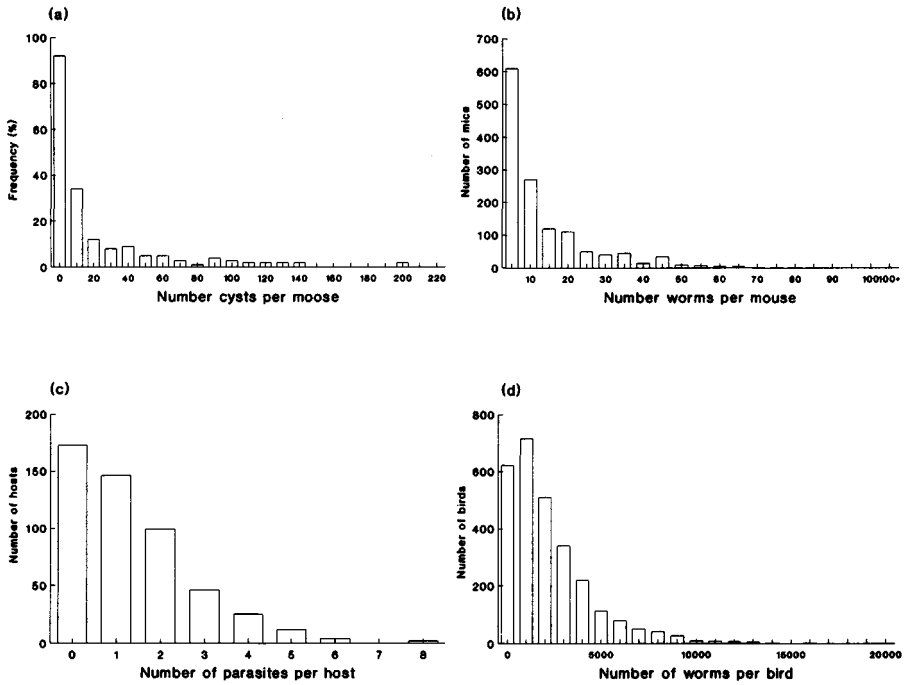


Figure 6. Frequency distributions of parasites from a number of wild host species demonstrating that many exhibit an aggregated distribution of parasites within the host population (a) *Echinococcus granulosus* from moose (McNeil 1983); (b) *Heligmosomum polygyrus* in wood mice (Gregory *et al.* 1992); (c) *Polymorphus minutis* in *Gammarus minutis* (Crofton 1971); (d) *Trichostrongylus tenuis* from adult red grouse in northern England (Hudson 1986).

that the spatial distribution of infective stages would remain random when the next cohort of transmission stages are passed from infective hosts. In many cases transmission stages will be passed in pulses (e.g. with faeces or other excreta) and these larval stages may utilise intermediate hosts which themselves are aggregated within the habitat of the definitive host. Hence spatial variability in exposure to infection is likely to crucially influence the observed degree of aggregation (Anderson and Gordon 1982, Grenfell *et al.* this volume). Differences in exposure will be further compounded by differences in susceptibility beween hosts (Anderson, *et al.* 1978), these can either be innate and dependent upon the genetic, physiological or morphological characteristics of individual hosts (Wakelin 1984); immunological differences due to differences in prior exposure to infection will also lead to differences in susceptibility between hosts (see Grenfell *et al.* this volume, Lloyd this volume).

Sampling biases often confound attempts to obtain an accurate estimate

of the parameters that characterize an observed parasite distribution. Here it is fundamental to realize that both the mean and the variance of the parasite distribution are dynamic entities which will change temporally and spatially. Furthermore, it is important to appreciate that attempts to increase precision by combining samples from different age or sex classes may lead to over-estimation of the degree of aggregation in some age classes, and under-estimation for others (Pacala and Dobson 1988). Finally, it is important to bear in mind that the pattern of the distribution is influenced by the often small number of heavily burdened hosts; small sample sizes will often fail to locate or identify these individual hosts (see Smith *et al.* this volume).

Where patterns of distribution change with age, social class and gender, then combining data may misrepresent the overall degree of aggregation and hide important trends in the observed data. Male rabbits carry three times the burden of *Trichostrongylus retortaeformis* burdens than females (Boag and Kolb 1989). Reindeer calves of dominant females had access to more food than calves of low dominance females and consequently carried higher burdens of *Elaphostrongylus rangiferi* (e.g. Halvorsen 1986a). Furthermore there is a tendency for the pattern of distribution to change with age from a random distribution in the age class first exposed to infection and to become more aggregated as the hosts become older (Gregory *et al.* 1990, Hudson 1986, Pacala and Dobson 1988).

The aggregation of parasites into a small proportion of the host population has important consequences for the dynamics of the parasite-host system; concentration of a large proportion of the parasite population into a small proportion of the hosts tends to focus interactions that regulate parasite numbers so that they influence a larger proportion of the parasite population. Concomitantly, the impact of the parasites on the hosts is applied to a smaller proportion of the host population. Thus the aggregated distributions tend to stabilise parasite-host interactions, whereas random or regular distributions tend to destabilise the relationships (Anderson and May 1978, May and Anderson 1978).

Many macroparasites have $k$ values in the region of 0.1 to 1.0 (Figure 7a). These values reflect an underlying tendency for the variance of the parasite distribution to increase at rates faster than the mean (Figure 7b). Aggregated distributions of parasites in hosts are the general rule in parasite-host associations. Nevertheless, considerable care must be exercised when interpreting estimates of aggregation in population studies as many of the biases involved in collecting the data will tend to over-emphasise the degree of aggregation (see Smith *et al.* this volume). In natural systems where parasites have been shown to have a dramatic impact on host numbers (Grouse-*T.tenuis* and Soay sheep-*Teladorsagia* systems; see later) the value of $k$ is high relative to that reported for other animal and human populations. For example, studies of *T. tenuis* in adult red grouse, found the variance to mean ratio of

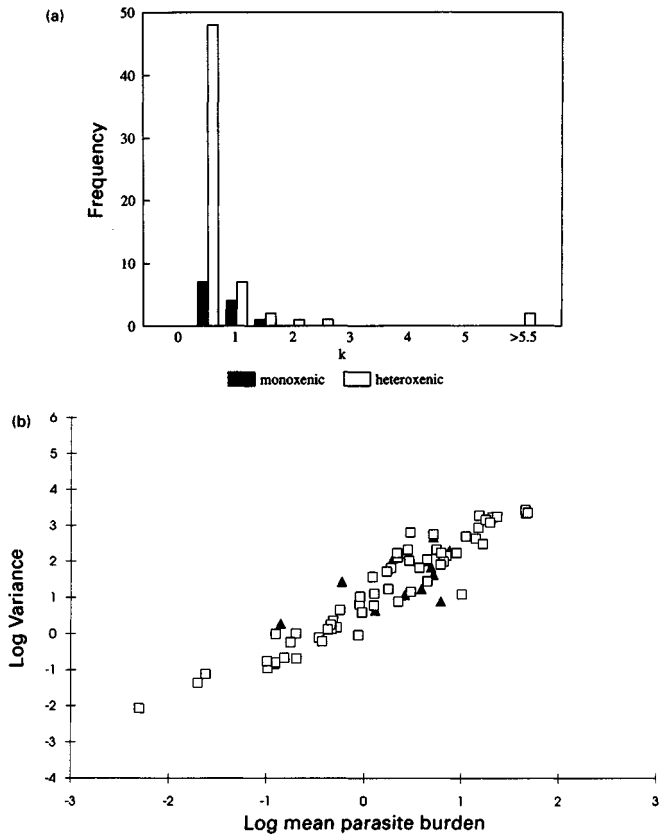


Figure 7. (a) Frequency distribution of $k$, the aggregation coefficient, from heteroxenic and monoxenic parasitic species identified in terrestrial ecosystems (Dobson and Shaw in preparation). (b) The relationship between log mean parasite burden and log variance of parasite burden for data from 292 parasite species sampled in their natural host populations. The solid triangles are for parasites with single host (monoxenic) life cycles; the open squares are for parasites with multiple host (heteoxenic) life cycles. The best fit slope through these data has a slope significantly greater than unity (Dobson and Merenlender 1990, Dobson and Shaw in preparation)

parasites in adult grouse varied from 0.8 to 3.1 during a 10 year study (Hudson *et al.* 1992) with similar variance between populations (Hudson 1986).

## 3.4 Predisposition

The observed differences in worm burden between hosts of the same age reflect both the susceptibility of the host to infection and its cumulative experience of differential exposure to parasite infective stages (see Grenfell *et al.* this volume). It is therefore important to know more about the conditions which have produced the few heavily infected individuals. Are they simply heavily

infected by chance, or are they predisposed to be so because of exposure or susceptibility to infection? One of the clearest ways of addressing this type of question is to undertake controled experiments that treat and monitor individuals in the population in order to assess their subsequent rate of reinfection. Two types of response are seen: in the first case heavily infected individuals subsequently become infected at a faster rate than hosts who had lower worm burdens; in the second, rates of re-infection show no correlation with the previous level of infection (Schad and Anderson 1985, Munger *et al.* 1989).

Where significant results are obtained that indicate predisposition to infection it is important to differentiate between habitat and genetic differences between hosts. Predisposition is influenced both by host susceptibility and exposure, the relative importance of each effect is likely to vary between species and habitats. Variations in exposure can reflect an individuals social status, or they may relate to genetic and nutritional processes. Unfortunately, relatively few studies have been conducted which examine predisposition in wild animal populations. Since level of infection needs to be determined before and after treatment it is often hard to obtain accurate and compatible estimates of worm burden.

A subsection of studies of predisposition should address the question; are heavily infected individuals becoming infected by their own macroparasites? This could be examined by comparing the variation in genetic relatedness between worms within, and between, individuals within a population (Mulvey *et al.* 1991). If it were so then it could influence the immune response of the host to the worm and have consequences for the fitness of the parasite population and the evolution of virulence (Herre 1993, Nowak and May 1994).

# 4 Temporal dynamics of macroparasite populations

A number of long-term studies of macroparasites in their natural hosts have been undertaken (Figure 8). These reveal a variety of patterns of long-term dynamics that range from long-term stability (in Kennedy and Rumpus's study of the acanthocephalan parasites of fish (Kennedy and Rumpus 1977), through long-term cycles in parasite prevalence that vary both seasonally (helminths in field mice (Montgomery and Montgomery 1988) and reindeer (Bye and Halvorsen 1983, Halvorsen 1986b, Halvorsen and Anderson 1982)), and on longer time scales (*T.tenuis* in red grouse). In other long-term studies, declines or increases in parasite prevalence are observed – in many cases these can be linked to biotic or abiotic changes in the habitat occupied by the host. For example the arrival of Great Crested Grebes on a small lake (Slapton Ley), studied by Kennedy and colleagues (Burrough 1978, Kennedy 1987), led to the introdution of a second species of eye fluke, *Tylodelphys*

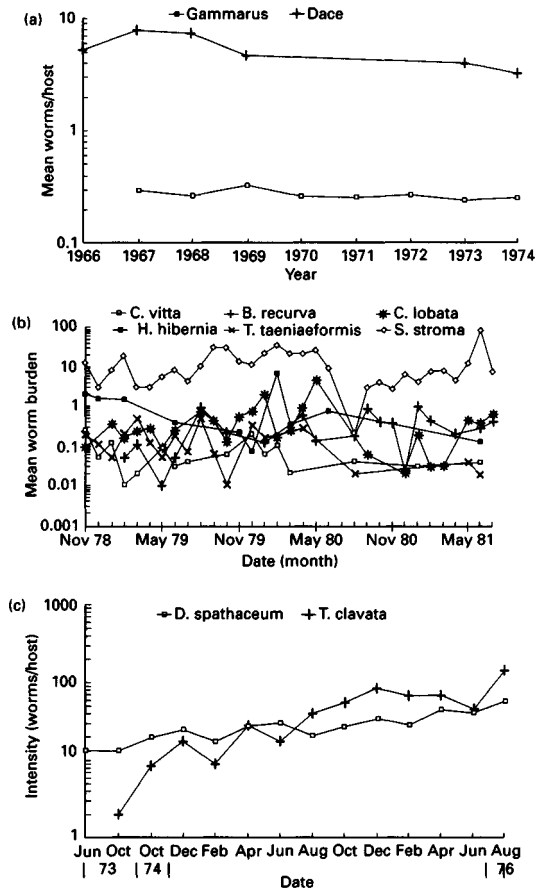


Figure 8. The observed long-term abundance of parasites in a number of field studies. (a) the acanthocephalan *Pomphorynchus laevis* in both its definitive (Dace) and intermediate host, *Gammarus* (Kennedy and Rumpus 1977). (b) Six species of parasitic helminth in a woodland population of *Apodemus sylvaticus* at Clandboyne, Northern Ireland (Montgomery and Montgomery 1988), (c) two species of parasitic eyefluke (*Diplostomum spathaceum* and *Tylodelphys clavata*) in roach species in a small lake in south-west England (Burrough 1978).

*clavata*, which changes both the abundance of a parasite species (*Diplostomum spathaceum*) occupying the same niche in the fish population and a decline in the abundance of the dominant species in the fish community (Burrough 1978). In many cases long-term studies have recorded major changes in the abundance of parasite abundance and diversity as a consequence of anthropogenic changes to the habitat (Aho *et al.* 1982). As the survival of macroparasite transmission stages are often dependent on temperature and humidity, it seems likely that the distribution and abundance of many parasites will change in response to long-term climate changes. The pos-

sible consequences of this are only beginning to be explored (Dobson and Carper 1992).

## 4.1 Density dependent processes

If consistent patterns of abundance are observed in host and parasite populations through time, it implies that some form of regulation is operating in either the parasite or the host population. Several density dependent processes can occur at each stage of a parasite's life cycle (Anderson and May 1991). As each individual host is a discrete unit or 'patch' of habitat for the parasite then it is relatively easy to define the arena within which intra-specific competition will operate, when compared with density dependent processes in other animal populations (Hassell 1986, Hassell *et al.* 1989). Nevertheless, counting the parasites in natural infections will invariably require destruction of the host, and hence details of the mechanisms operating may be lost (Shostak and Scott 1993).

Parasite processes that may respond to increased density include establishment in the host, development and maturation time, adult survival and fecundity, and duration of dormancy (arrested development or 'hypobiosis' in nematodes) (Keymer 1982, Shostak and Scott 1993). These effects may operate in either the definitive or the intermediate hosts, and any single one of these potentially regulatory processes could be large enough to constrain population growth, provided it effects a significant proportion of the parasite population (Keymer 1982). In many natural systems, relatively minor regulatory effects may be amplified by the aggregated distribution of the parasites; the large number of parasites that are in the few heavily infected hosts will exhibit either higher mortality or lower fecundity and developmental rates than the individual parasites in lightly infected hosts.

The resulting dynamic effect depends on the degree to which the parasites are aggregated in the host population and the relative impact of the parasite on host survival and fecundity (Anderson and May 1978, May and Anderson 1978). Where parasite induced reductions in host survival are more pronounced than reductions in fecundity, then the parasites may regulate the host population to a steady density, particularly if the parasites are aggregated in their distribution. In contrast, where parasite impacts on host fecundity are more pronounced than their impact on host mortality, then the system may exhibit sustained cyles of host and parasite abundance – particularly if the parasites exhibit low degrees of aggregation.

Parasite induced host mortality is potentially a major form of density dependent parasite regulation in systems where host mortality rate increases with worm burden, since the death of a host leads to the loss of a large number of parasites. However, in some systems death of the host is obligatory for parasite transmission (Dobson 1988, McCallum and Singleton 1989), in

these systems increased worm burdens may increase transmission between the intermediate host, often a prey species, and the predators which act as definitive hosts. At the level of the individual host, adult worm survival could be reduced when there is strong competition for space and an individual is more likely to be displaced by either other parasites, or through the disintegration of host tissue (Shostak and Scott 1993). When there is a heavy worm burden – and consequently severe competition for food – reductions in parasite growth, survival or fecundity have been recorded in laboratory experiments (Read 1951, Bailey 1975, Dobson 1986, Goater 1992). If there is a trade off between fecundity and survival, there is always the possibility that smaller parasite individuals are less fecund but survive longer and thus generate a positive association between survival and parasite density (Keymer and Slater 1987).

Naturally there are exceptions to many of the situations described. One interesting example is that of *Capillaria hepatica* found in wood mice (Barker, *et al.* 1991, McCallum and Singleton 1989). This parasite may cause the death of the host, but transmission is dependent on host death since eggs are deposited in the liver and only liberated by cannibalism, necrophagy and possibly predation (Singleton and McCallum 1990). In this instance, the death of the host is not a stabilising density dependent constraint on parasite population growth but a destabilizing influence.

In ectoparasites, the concentration of parasites on particular parts of the host body could result in additional parasites being forced to utilise areas where they are exposed to host grooming or preening behaviour and thus may die or receive fewer resources. Tick fecundity is a function of the size of the blood meal and meals may be smaller on hosts carrying many ticks (Hudson 1992).

The condition of the hosts may also play an important role in mediating mechanisms that regulate parasite numbers. Malnourished hosts frequently suffer from a depression in the immune response and this can influence the pattern of density dependent depression in worm fecundity (Montgomery and Montgomery 1989, Slater and Keymer 1988, Lloyd this volume). In Soay sheep, Gulland (1992) compared estimates of *Teladorsagia* fecundity from sheep that were on a high plane of nutrition, with worm fecundity in sheep that had become immunosuppressed during a population crash. The parasite population in sheep with natural infections exhibited pronounced density dependent reductions in egg production, in contrast the parasites in the malnourished, immunosuppressed sheep showed no reduction in fecundity. Furthermore, worm fecundity in the immunosuppressed sheep was similar to the maximum level of egg production seen in the sheep on a high plane of nutrition. This would imply that the differences in egg production were due to the immune response of the host. However, as the author herself notes there can be genetic differences in the *T. circumcincta* populations in sheep from

different sections of the population. These and other contributory factors associated with a reduced plane of nutrition could encourage worms in dying hosts to increase their egg production (Gulland and Fox 1992, Gulland 1992).

If there is a high degree of variation in the immune response which influences the relationship between worm fecundity and worm burden then inverse density dependant fecundity may be observed when comparisons are made between individual hosts (Keymer and Slater 1987). Thus, in a host with a strong immune response, worm burden and fecundity could be greatly reduced, whereas a host with a mild immune response, could carry a high burden of parasites with high fecundity. Such an inverse density dependent relationship has been recorded for *H. polygyrus* in an enclosed population of wood mice (Quinnell 1992).

It should also be borne in mind that measuring parasite fecundity in relation to worm population size is not simple. The obvious method is to conduct *in utero* counts of eggs from animals which have been killed so that both worm burden and egg counts can be conducted. However the presence of eggs reflect the standing crop of eggs and not the rate of egg production. Care should therefore be taken in the statistical detection of density dependence, since only a few individuals carry high parasite burdens and the variables of fecundity and macroparasite burden are not independent. In some cases, errors in the measurement of worm burden may bias the data towards a negative correlation (Keymer and Slater 1987, Shostak and Scott 1993). Experimental studies are needed where individuals are treated and density dependence recorded within and between individuals.

To summarize this section, we conclude that although density dependent constraints potentially regulate the size of the parasite population, counter-intuitive and equivocal results have been obtained in experimental studies of some host parasite systems. Nevertheless, the long-term stability of many natural host-parasite systems implies that some regulatory mechanisms are operating. Unfortunately, the complexity of many parasite life cycles make it almost impossible to identify where density dependent effects are operating in many natural systems.

# 5 Impact at the population level

If macroparasites reduce the growth rate of their host population in a density dependent manner, through their impact on host survival and fecundity, they will regulate host population density. However, demonstrating regulation is not simple in natural populations and previously heated debates continue to smoulder as to whether reductions in host fitness due to the presence of parasites act in an additive or compensatory fashion (Anderson 1979, Holmes 1982, Scott and Dobson 1989). Formally demonstrating regulation of host abundance by a parasite requires examination of systems where the popu-

lations of both host and parasite can be experimentally perturbed and the subsequent changes in both parasite and host fecundity, survival, dispersal and density can be monitored. Unfortunately, these conditions are rarely met in field studies of free-living populations, so no wild animal population has been examined to a sufficient extent to determine if parasites are truly regulating host abundance.

In free-running laboratory conditions, parasites have been shown to dramatically reduce the size of the host population. In particular, increases in host density have produced increases in parasite burdens that in turn produce reductions in host survival or fecundity. Scott and Anderson (1984) investigated the effects of the monogenean *Gyrodactylus bullatardis* on guppies in long term experimental conditions in the laboratory. They showed that the parasites had a dramatic impact in reducing host abundance below the level it would have been without infection although after about 95 days the parasite subsequently became extinct. In another free-running experiment Scott (1987) introduced the parasite *H. polygyrus* to mice kept in large enclosures and showed that under conditions where a wet peaty substrate provided high transmission rates, the parasites were capable of regulating the size of the mouse population for a period of 16 weeks, after which anthelmintic treatment resulted in an increase in the population (Figure 9).

One of the simplest cases where parasites reduce host fecundity and cause oscillations in host numbers is in the infection of red grouse by the parasitic nematode *Trichostrongylus tenuis*. In this system parasite induced reductions in host-fecundity tend to destabilize the parasite-host relationship and generate oscillations in parasite and host numbers (Figure 10). Observational work over thirteen years shows that mortality and breeding losses of grouse were positively correlated with worm burdens (Hudson *et al.* 1992, Hudson 1992). The influence of these effects on the dynamics of red grouse populations were examined using an extension of the mathematical model developed by Anderson and May (1978). The models show that interactions between the parasite and grouse can generate population cycles of the correct period and amplitude (Dobson and Hudson 1992). This approach also implies that removal or significant reductions of the parasites will cause the system to stop cycling. Preliminary experimental results from a number of study sites suggest that this is the case (Hudson, Newborn and Dobson in preparation).

A second system where parasites contributed to cyclic population crashes was investigated in the Soay sheep population that inhabit the St Kilda archipelago. Sheep numbers crash every 3 or 4 years in this population through an overcompensating density dependent mortality (Grenfell *et al.* 1992). The population crashes are rapid with two-thirds of the population dying during a 12 week period. However, the interaction between the parasites and the hosts is superimposed on the potentially cyclic interaction between the sheep and their food resources. Examination of the corpses indicates

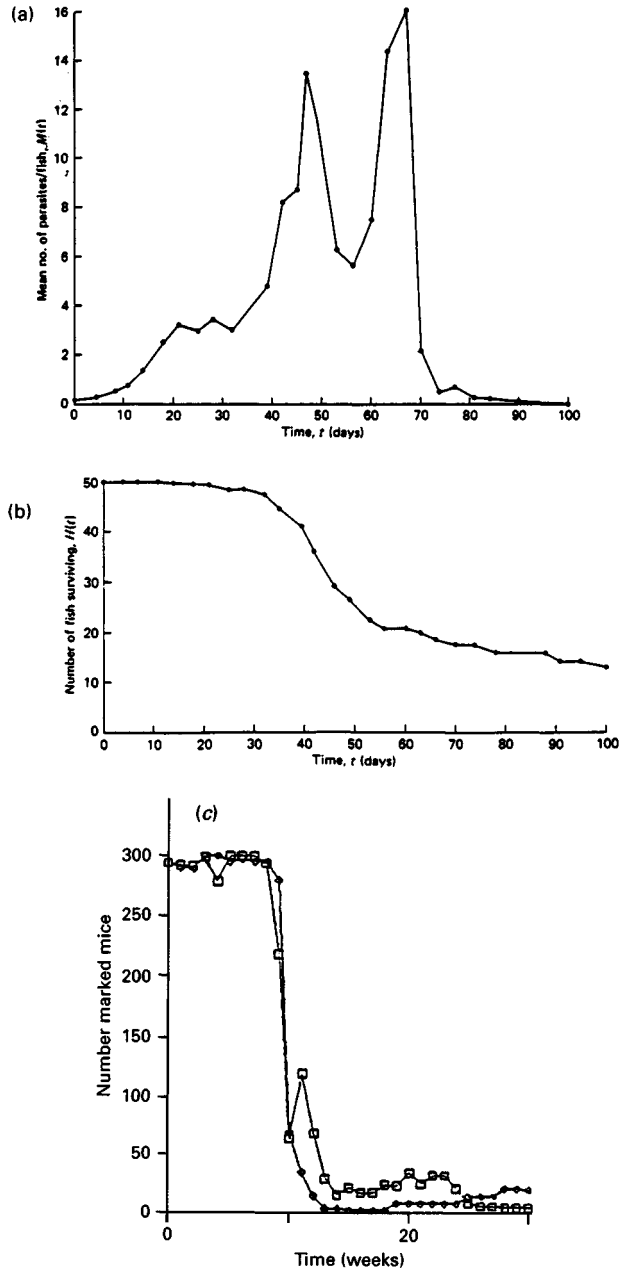


Figure 9. The results of two free-running experiments on the effects of parasites on laboratory populations animals: (a) mean parasite burden of the monogenean *Gyrodactylus bullatarudis* on guppies; (b) the number of fish surviving in the population during the same time period (Scott and Anderson 1984). (c) The results of an experiment that introduced the nematode *H. polygyrus* into two laboratory population of mice. In both cases the parasites were introduced eight weeks after the mice populations had settled to a steady state (Scott 1987).

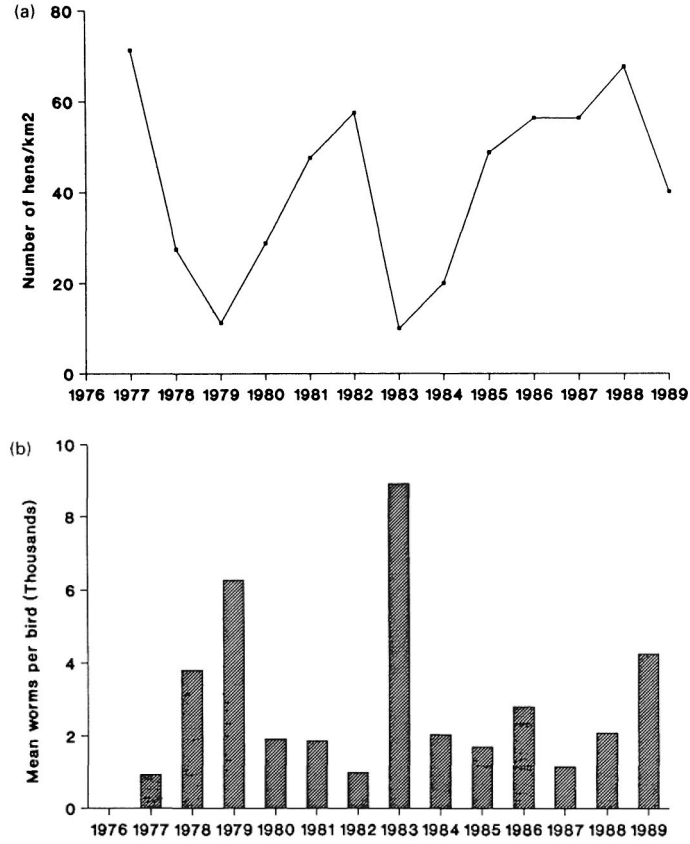


Figure 10. Changes in the density of a wild host species and a parasite of that species (a) breeding density of red grouse at Gunnerside (N. Yorks) between 1976 and 1989. (b) Mean worm burden of the parasitic nematode *T. tenuis* in the birds over the same time period (Hudson 1992).

high burdens of gastrointestinal nematodes (principally *Teladorsagia circumcincta*) coupled with severe protein deficiency (Gulland 1992). Immunological data from the hosts and data on nematode fecundity indicate that the hosts were immunosuppressed. In contrast, in an experiment in which sheep on a high plane of nutrition were compared to wild sheep infected with similarly high numbers of worms, there was no evidence of clinical signs or mortality. The study could not elucidate the relative importance of parasites and food shortage during the population crash (Grenfell *et al.* 1992, Gulland 1992, Read *et al.* this volume), but individuals experimentally treated with an anthelmintic survived longer than untreated individuals, demonstrating that the parasites were at least a contributory factor.

# 6 Impact on host distribution

While there have been some clear examples of microparasites influencing the geographic distribution of their hosts, there is only weak evidence that macroparasites may have such an influence. For example, the presence of the nematode *Parelaphostrogylus* in white-tailed deer has been suggested as the principal reason why other ungulates, such as moose, are absent from areas occupied by white-tailed deer (Anderson 1972, Price *et al.* 1986,1988). Recent theoretical work by Schmitz and Nudds (1993) suggest that rather restricted conditions are required for one host species to exclude a potential competitor through the presence of shared parasites.

# 7 Conclusions

Macroparasites exhibit a range of characteristics which indicate they are capable of having a large impact both on the fitness of individual hosts and the dynamics of host populations. Empirical studies have demonstrated a range of direct and indirect impacts of macroparasites on host fitness including reduced host survival and fecundity, increased susceptibility to predation and the decreased ability to defend resources. Many of these characteristics of the macroparasite-host relationship are a function of the number of parasites harboured by the host; for example parasite impacts on host survival and fecundity increase with the worm burden of individual hosts. Nevertheless, there has been considerably less theoretical work on the dynamics of macroparasites and a range of challenging theoretical and empirical problems remain comparatively unexplored.

In contrast to microparasites, the parasitic helminths and arthropods exhibit more sluggish dynamics, but are less susceptible to fade-out (local extinction). This may be a consequence of the many adaptations that allow helminth and arthropod larval stages to live for long periods of time in a dormant state; or, it may be a consequence of the complex, multi-host life cycles that have evolved to allow parasites to use different host species at different times of the year, or in different parts of their hosts habitat.

There is still much empirical and theoretical work to be done on macroparasites and their hosts. In particular there have been very few explorations of the population dynamics of species with complex life cycles (Dobson 1988, Dobson and Merenlender 1990). Considerable interest has developed in the community ecology of parasitic helminths (Sousa 1993,1994, Kennedy *et al.* 1986, Esch *et al.* 1988, Bush *et al.* 1990a,b, Bush and Holmes 1986, Holmes 1973, Holmes and Price 1986) and this has proved to be an area where mathematical models can also provide an alternative perspective on the dynamics of parasite host interactions (Dobson 1986, Roberts and Dobson 1994, Dobson and Roberts 1994).

Perhaps the largest lacuna in our understanding of macroparasite population biology occurs in the area of co-evolution and population genetics (Dobson and Merenlender 1990). A number of empirical studies have provided information about the genetic basis of susceptibility to different parasitic helminths in different systems (see Read *et al.* this volume). Recent work on genetic polymorphism in Soay sheep on St Kilda indicate the potential importance of gastrointestinal nematodes in maintaining heterozygote advantage at the adenosine deaminase locus (Gulland *et al.* 1993). These detailed studies on the genetic basis of susceptibility and virulence at the individual population level are complimented by studies of the evolution of host specificity in parasitic nematodes adapting to new or novel host species (Jaenike 1993) and comparative studies of the relative susceptibility of insect hosts to the acanthocephalan, *Moniliformis moniliformis* (Frehling and Moore 1993, Moore and Crompton 1993).

Similarly, more empirical and theoretical studies are needed on the potential role of host genetic heterogeneity in determining observed levels of parasite aggregation within the host population. However, the degree of aggregation within these distributions will depend both on biological features such as host genotype and heterogeneity in the spatial distribution of infective stages and hosts (Grenfell *et al.* this volume, Woolhouse 1992). These biological phenomenon will then be distorted by non-biological features such as unintended, biased sampling of the population.

At the population level there is some evidence that macroparasites may regulate host numbers and there is also evidence that delayed density dependent effects can lead to large scale changes in host numbers. Such effects may act directly, as in the grouse-*Trichostrongylus tenuis* system or as a consequence of immunosuppression, as in the Soay sheep-nematode system on St Kilda. Although these situations are comparable to those seen in studies of microparasites in natural populations, there are still too few experimental tests of the role that parasites play in regulating host abundance.

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# Mathematical Models for Macroparasites of Wildlife

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## 1 Introduction

### 1.1 The nature of macroparasitic infections

Parasites harm their hosts (Figure 1). That is one of the reasons we are interested in them. The notion that parasitism had some adverse effect on the mortality or fecundity of the host was an explicit part of Anderson and May's definition of the relationship (Anderson and May 1978), but is often attacked on the grounds that many host-parasite relationships seem to result in no discernable harm to the host. It is not difficult to find instances in the literature (usually case studies) in which individual animals or sometimes whole populations are found to have died as a result of infection with one or more species of parasite. Examples include dolphins and killer whales that have become stranded because nematode or trematode infections of the eustachian tube or cochlea have interfered with echolocation (Dailey and Ridgeway 1976, Stroud and Roffe 1979, Morimitsu *et al.* 1987); anaemia and pneumonia caused by excessively large nematode burdens resulting in the death of an opossum (Nettles, Prestwood and Davidson 1975); a similarly overwhelming trematode infection causing the death of a cougar (Kistner *et al.* 1979); and nematode infections as the cause of substantial mortality in populations of egrets and white tailed deer (Wiese *et al.* 1977, Davidson *et al.* 1980). Such instances are often dismissed as involving unusually high levels of parasitism or abnormal or aberrant hosts and are contrasted with those studies which report no discernable consequences of parasitism. For example, Pence *et al.* (1988) found no evidence that the helminth infections they described 'were responsible for morbidity or mortality in [a] feral swine population'; Davidson *et al.* (1980) found that 'lesions [in Bobwhite quail] attributable to helminths were rare and involved minimal tissue damage', and Keith, Keith and Cary (1986) found 'no compelling reason to believe that parasitism was a significant factor in the overwinter decline in [a] population of snowshoe hares'.

Given observations like these is it still possible to define parasites in terms of the harm they do to their hosts? One response might be to invoke the concept of 'sub-clinical' effects that has proved useful in evaluating the costs of parasitism in domestic species. The argument here is simply that the

harm parasites do may be too subtle to detect given the normal constraints of field work. We list just three illustrative instances: trichuriasis in man adversly affects the cognitive functions of school children (Nokes *et al.* 1992), dominance relationships in mice are perturbed by nematode infections (Rau 1984) and parasitized stickle-backs consume smaller prey than unparasitized controls (Milinski 1984). An alternative response might be to accept that there are instances in which parasites appear to do no measurable harm to their host and to ask why? For example, strongyloidiasis, caused by the nematode *Strongyloides stercoralis*, is usually a well tolerated infection of man and dogs. Nevertheless there are fatalities attributable to this parasite. They occur in immunocompromised hosts in which the parasite undergoes repeated cycles of autoinfection leading to hyperinfection and host death. Clearly, in this case, hosts with properly functioning immune responses are able to constrain the infection to levels which apparently cause no obvious health problems. For these hosts, the cost of parasitism is the cost of mounting an immune response.

Anderson and May (1978) specified the harm that parasites do to their hosts in terms of an effect on host mortality and fecundity because they wished to demonstrate that parasites could potentially regulate their host population density. Few now would disagree that parasites which do adversly affect host survival and fecundity can potentially affect patterns of host population abundance (Hudson and Dobson this volume). However, many more might disagree that parasites *necessarily* adversely affect the productivity of the host population, a proposition inherent in Anderson and May's definition of parasitism. We can reconcile the two schools merely by reinterpreting the word 'harm' to encompass some cost to the host. The cost may be expressed as increased mortality, reduced fecundity, or the energetic cost required to mount an immune response which maintains parasite burdens at tolerably low levels. Implicit in this formulation is the idea that sometimes the cost of mounting an adequate immune response will be affordable and sometimes it will not. For example, animals maintained on a high plane of nutrition will frequently be able to cope with a much greater parasitic challenge. These animals will be exposed to parasites but will experience no measurable reduction in survivorship or fecundity. Animals on a lower plane of nutrition will not be able to afford the cost of mounting an adequate immune response and this will be expressed in terms of reduced productivity.

## 1.2 Modelling host-macroparasite interactions

Macroparasites have profound influence on both human health and the productivity of agricultural systems. In consequence, there is a plethora of models for specific macroparasitic infections of man and his domestic animals (see

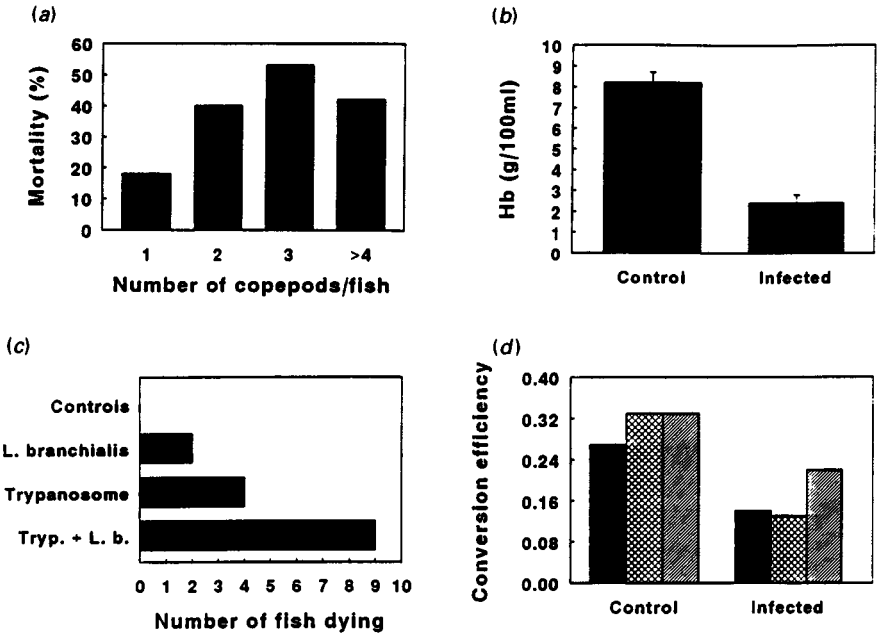


Figure 1: Effect of *Lernaeocera branchialis*, an ectoparasitic copepod, on Atlantic cod. (a) Host mortality at different intensities of infection, (b) Depression of haemoglobin levels in parasitised sub-adult cod, (c) Effect of concomitant infection with *Trypanosoma murmanensis* on host mortality, (d) Effect on food conversion efficiency in cod fed to satiation. Data from Khan (1988).

Smith (1994) for a review). In many instances the intent is to understand how we might limit the infection, whether by drugs, vaccines or management strategies. In a smaller number of cases the objective is to find out if it is possible to regulate a host species which is itself a pest, or which acts as an intermediate host or reservoir for a parasite that affects a man or a host species of importance to man. On the other hand, there are rather few *specific* models of macroparasitic infections of wildlife species (Barlow this volume), except in so far as some of the models already referred to involve non-domestic intermediate host species from various phyla. We shall allude to these models whenever they may be of relevance to wildlife populations, but otherwise we shall focus our attention on the architecture and properties of more generic models. These fomulations have been developed to explore fundamental ecological role of parasites, particularly their effects on (and influence from) patterns of host abundance (Hudson and Dobson this volume) and the genetic and evolutionary interactions of hosts and parasites (Read *et al.* this volume) Initially we shall describe models for endoparasites with

simple direct life cycles that include infective free-living stages (sections 2–7). We discuss models for endoparasites with indirect lifecycles in section 8, models for ectoparasitic infections in section 9, and finally, competition between parasite species in the same host in section 10. Throughout, we focus on the question *What are the special properties of macroparasite interactions with their hosts, compared to microparasites or 'true' predators?* (Smith *et al.* this volume).

# 2 Models for endoparasitic infections with a simple direct life-cycle

## 2.1 Early stochastic approaches

An early model for macroparasite populations was that presented by Tallis and Leyton (1966). It was not an epidemic model, but a stochastic description of the dynamics of the parasite population in a host population, motivated by the need to model parasite populations in sheep. The model was restricted to female parasites. Given that the probabilities that a female parasite gains entry to the host in the time interval $(x, x + \Delta x)$ and matures in the time interval $(y, y + \Delta y)$ are $\lambda(x)\Delta x$ and $\alpha(y, x)\Delta y$ respectively, then the probability generating function (p.g.f) for the number of mature female parasites at time $t$ is

$$F(z,t) = \exp\left[\int_0^t \int_0^y \lambda(x)\alpha(y,x)\,dx\,dy\,(z-1)\right] \tag{1}$$

Furthermore, if a female parasite that matured at time $y$ produces offspring at time $t$ with p.g.f $g(z,t,y)$, then the p.g.f for the number of offspring produced is

$$G(z,t) = \exp\left[\int_0^t \int_0^y \lambda(x)\alpha(y,x)[g(z,t,y)-1]\,dx\,dy\right] \tag{2}$$

The authors remarked that the distributions for mature parasites, and the distribution for the total number of parasites are Poisson. They also noted as an example that if the input function $\lambda$ were constant, independent of time, $\alpha(y,x)$ were an exponential distribution ($\alpha e^{-\alpha(y-x)}$), and $g(z,t,y)$ were Poisson, independent of $t$ with parameter $\gamma$, then (1) and (2) would become

$$F(z,t) = \exp[\Lambda(t)(z-1)] \tag{3}$$

and

$$G(z,t) = \exp[\Lambda(t)(e^{\gamma(z-1)}-1)] \tag{4}$$

respectively, where $\Lambda(t) = \lambda t + (\lambda/\alpha)(e^{-\alpha t} - 1)$. The distribution of mature female parasites (3) is therefore Poisson, and that for the production of offspring (4) is Neyman Type A, both with a time-varying parameter $\Lambda$.

This was an important, if frequently overlooked, result because many workers have assumed that the overdispersed distribution of fecal egg counts that is typical of infections in domestic species necessarily reflected an overdispersed distribution of mature parasites.

A second model was presented by Tallis and Leyton (1969). The exposure rate $\lambda$ was now taken to be constant, but parasites were assumed to enter the host with p.g.f $h(z)$. The p.g.f of the number that have entered by time $t$ is now

$$L(z,t) = \exp[\lambda t(h(z) - 1)] \tag{5}$$

and given that the probability that a parasite that enters the host at time 0 survives until time $t$ is $M(t)$, the p.g.f for the number of live parasites at time $t$ is

$$\Pi(z,t) = \exp\left[\lambda \int_0^t (h(1 + M(t-x)(z-1)) - 1)dx\right] \tag{6}$$

The 'equilibrium distribution' was found by letting $t \to \infty$ in (6). Once again special cases were considered, and it was noted that if $h(z) = pz/(1 - qz)$, $p + q = 1$, a truncated geometric distribution, and $M(t) = e^{-\mu t}$, then the probability generation function for the number of parasites tends to

$$\Pi_\infty(z) = \left(1 + \frac{m}{k}(1 - z)\right)^{-k} \tag{7}$$

the negative binomial distribution with mean $m = \lambda/(\mu p)$ and variance $m(1 + m/k)$. The parameter $k = \lambda/(\mu q)$ is an inverse measure of the degree of overdispersion, $\Pi_\infty$ tends to a Poisson distribution as $k \to \infty$. Tallis and Leyton (1969) used the negative binomial distribution to discuss the relationship between parasite prevalence and disease severity, with reference to hookworm infections of humans. They pointed out that if the average number of parasites per exposure was small (2 in their example), and the parasites were long-lived in relation to the exposure rate ($\lambda/\mu > 5$), then most people (>99%) would harbour a few worms (mean/infected individual $\approx$ 10, standard deviation $\approx$ 4.5). Hence the prevalence of the parasite would be high, but the prevalence of disease would be low. On the other hand if the average number of parasites per infection were high (256 in their example), and the parasites were short-lived ($\lambda/\mu < 1/8$) then there would be a low prevalence of parasites, but some individuals would have high parasite burdens and hence severe disease (average worms/infected individual $\approx$ 64, standard deviation $\approx$ 120).

The work by Tallis and Leyton (1966, 1969) showed that it would be difficult to develop a realistic stochastic model of a parasite life-cycle that was mathematically tractable. Their models, which were essentially models for trickle infections, required restrictive and arbitrary assumptions in order to provide distributions, such as the negative binomial, that are easily characterised (7). While deterministic models are clearly easier to deal with, it is

still necessary to incorporate some method of representing parasite frequency distributions. This problem was addressed by Crofton (1971a,b) who used a deterministic model to investigate the long-term behaviour of host and parasite populations. Using the proposals that parasite populations have overdispersed distributions that may be approximated by the negative binomial; parasites kill heavily infected hosts; and the parasite species has a higher reproductive potential than the host; computer simulations were produced that showed host and parasite numbers tending to an equilibrium. Although Crofton (1971b) was not explicit about the mathematical structure of the model, his proposals were reinterpreted by May (1977) who was able to make comparisons with the later models by Anderson and May.

## 2.2 Deterministic models

Anderson and May (1978) proposed a model for the dynamics of macroparasites in a host population that would grow exponentially in the absence of infection. They modelled the dynamics of the host population size ($H$) by the differential equation

$$\frac{dH}{dt} = (a - b)H - \alpha P \tag{8}$$

and that of the total size of the parasite population ($P$) by

$$\frac{dP}{dt} = \frac{\lambda PH}{H_0 + H} - (b + \mu)P - \alpha HE(i^2) \tag{9}$$

Here the birth and death rates of the host are $a$ and $b$ respectively, and the death rate of the parasite is $\mu$. The other terms in the model are derived as follows. Let $p_i$ be the probability that a host contains $i$ parasites, and $\lambda$ be the rate of production of transmission stages per parasite. Then the total production of transmission stages is

$$\lambda H(t) \sum_{i=0}^{\infty} ip_i = \lambda P(t) \tag{10}$$

and it is assumed that the proportion of these stages that become adult parasites is $H(t)/(H(t)+H_0)$ (see section 6). Hence the effects of all stages of the parasite outside the host are approximated by one transmission efficiency constant $H_0$. The increase in the rate of mortality of the host due to a single parasite is $\alpha$. Hence the net rate of loss of hosts due to parasitism is

$$\alpha H(t) \sum_{i=0}^{\infty} ip_i = \alpha P(t) \tag{11}$$

remembering that by definition $\sum ip_i$ is the mean number of parasites per host, $= P(t)/H(t)$. The model assumes that when hosts die so do their

parasites. The net loss of parasites due to parasitism is therefore

$$\alpha H(t) \sum_{i=0}^{\infty} i^2 p_i = \alpha H(t) E(i^2) \tag{12}$$

where $E(i^2)$ is the mean-square number of parasites per host, which will in general be a function of $t$. By assuming that $E(i^2)$ is a function of the mean number of parasites per host, equations (8,9) may be written in a closed form for $H$ and $P$. Hence we have a deterministic set of equations for the dynamics of the host-parasite system, that incorporates some information about the distribution of the parasites among hosts but falls short of a full stochastic description of the system. Anderson and May (1978) assumed that the distribution of parasites could be approximated by a time independent negative binomial distribution (7), for which $E(i^2) = m + m^2(1+k)/k$, where $m = P/H$. Equation (9) may therefore be rewritten as

$$\frac{dP}{dt} = \frac{\lambda P H}{H_0 + H} - (b + \mu + \alpha)P - \frac{\alpha(1+k)}{k} \frac{P^2}{H} \tag{13}$$

Anderson and May (1978) tabulated estimates of $k$ from data for many parasite species, which are mostly in the range 0.1–0.7. The negative binomial distribution is an approximation, but a useful one, to a distribution which in a full stochastic model is strictly determined by the dynamics of the system.

Hadeler and Dietz (1984) represented the parasite/host system as a birth and death process with killing, that also included host age as an independent variable. Hence if the number of hosts with age $a$ and $r$ parasites at time $t$ is $n(t, a, r)$, a number generating function may be defined by

$$N(t, a, z) = \sum_{r=0}^{\infty} n(t, a, r) z^r \tag{14}$$

which satisfies the partial differential equation

$$\frac{\partial N}{\partial t} + \frac{\partial N}{\partial a} + g(z) \frac{\partial N}{\partial z} - [\phi(t)(z-1) - \mu(a)]N = 0 \tag{15}$$

where the host death rate is $\mu(a) + \alpha r$ and parasite population parameters are subsumed within the quadratic function $g(z)$. The parasite infection rate $\phi(t)$ was assumed to be a function of the mean number of parasites per host, and newborn hosts were assumed not to carry parasites. Hadeler and Dietz compared the qualitative dynamics of this model with that of (8,13), and determined that there was broad agreement. More recently, however, Adler and Kretzschmar (1992) have compared solutions of (8) and (9) with numerical solutions of a complete stochastic system, and questioned whether a two-dimensional system could ever capture the properties of the full system (see also Grenfell *et al.* (this volume)).

# 3 Host and parasite population regulation

Equations (8,13) have steady state solutions (i.e. $dH/dt = dP/dt = 0$)

$$P^* = \frac{a-b}{\alpha} H^* \tag{16}$$

$$H^* = \frac{H_0 \Lambda}{\lambda - \Lambda} \tag{17}$$

Hence a positive steady state solution can only exist if

$$\lambda > \Lambda = \mu + \alpha + a + (a - b)/k \tag{18}$$

If (18) holds then the host/parasite system tends to the globally stable steady state (16,17) over time, and therefore the parasite regulates the host population. If (18) does not hold then the host population continues to grow exponentially until constrained by other processes not included in the model. Letting $k \rightarrow \infty$ in (13,17,18) the equations for a parasite population randomly distributed among hosts are recovered, which generate neutrally stable oscillations (Anderson and May 1978). Equation (18) may be interpreted as: the host population is regulated if the parasite 'birth rate' exceeds the host birth rate plus the parasite death rate, by an amount determined by the intrinsic rate of growth of the host population and the degree of overdispersion of the parasite population.

The analysis presented so far has concentrated on the ability of the parasite to regulate the host population. A complementary question is: what happens to the parasite population if the host population is not regulated? From (13) it is apparent that if $\lambda < b + \mu + \alpha$ then $dP/dt < 0$ and the parasite population dies out over time. If, however, $\lambda > b + \mu + \alpha$, the parasite population grows, either tending to $P^*$ if (18) holds, or exponentially if regulation does not occur. Hence the basic reproduction ratio is

$$R_0 = \frac{\lambda}{b + \mu + \alpha} \tag{19}$$

If $R_0 > 1$ the parasite population can invade the host population, or maintain itself in the population if already present. If $R_0 < 1$ the parasite population cannot invade, or if already present will become extinct. For macroparasites $R_0$ is defined not as the number of new cases arising from an infected case as for microparasites, but as the number of 'next generation' adult parasites that would arise from one adult parasite in a totally susceptible population (Anderson and May 1982).

This analysis still does not provide a complete description of the dynamics of the host/parasite assemblage. By assumption the host population would increase exponentially in the absence of the parasite. From (13) the parasite population becomes extinct if $\lambda < b + \mu + \alpha$, and from (18) both host and

parasite populations tend to a steady state if $\lambda > a + \mu + \alpha + (a - b)/k$. The dynamics for intermediate values of $\lambda$ become clear by rewriting (13) in terms of the mean number of parasites per host, $m = P/H$, to obtain

$$\frac{dm}{dt} = \left[\frac{\lambda H}{H_0 + H} - (a + \mu + \alpha)\right] m - \frac{\alpha}{k} m^2 \tag{20}$$

The solution for $m$ as $H \to \infty$ is readily discernable from (20). The long-term behaviour may now be summarised as follows.

If

$$\begin{array}{rl}
0 \leq \lambda < b + \mu + \alpha & H \to \infty,\ P \to 0 \\
b + \mu + \alpha < \lambda < a + \mu + \alpha & H \to \infty,\ P \to \infty \\
 & P/H \to 0 \\
a + \mu + \alpha < \lambda < \Lambda & H \to \infty,\ P \to \infty \\
 & P/H \to k(\lambda - (a + \mu + \alpha))/\alpha > 0 \\
\lambda > \Lambda = a + \mu + \alpha + (a - b)/k & H \to H^*,\ P \to P^*
\end{array}$$

In words, the four possibilities are, for increasing values of the transmission rate $\lambda$: the parasite population becomes extinct and the host population grows without bound; both host and parasite populations grow without bound, but the mean number of parasites per host tends to zero; both host and parasite populations grow without bound, but the mean number of parasites per host tends to a positive finite limit; and both host and parasite populations tend to a bounded steady state.

# 4 Destabilising effects

In a sequel to their 1978 paper May and Anderson (1978) modified their model to investigate factors that may destabilise the host population. For example, assume that the parasite induces a reduction in the host's rate of reproduction, proportional to its number of parasites. Equation (8) must now be replaced with

$$\frac{dH}{dt} = (a - b)H - (\alpha + \beta)P \tag{21}$$

equation (13) remains unchanged, and the steady state solutions of (13,21) are

$$P^* = \frac{\alpha + \beta}{a - b} H^* \tag{22}$$

$$H^* = H_0 \left( \frac{\lambda}{\mu + \alpha + a + \frac{a-b}{\alpha+\beta}(\frac{\alpha}{k} - b)} - 1 \right)^{-1} \tag{23}$$

Hence a positive steady state solution can only exist if

$$\lambda > \mu + \alpha + a + \frac{a-b}{\alpha+\beta}\left(\frac{\alpha}{k} - \beta\right) = \Lambda - \frac{a-b}{\alpha+\beta}\frac{\beta(k+1)}{k} \tag{24}$$

Equation (24) shows that if a parasite decreases the fecundity of the host ($\beta > 0$), the parasite 'birth rate' $\lambda$ required to regulate the host population is lower than that required to regulate the population if $\beta = 0$. If $\beta < \alpha/k$ the dynamics may be summarised in a similar manner to that in the previous section. However, if $\beta > \alpha/k$ the steady state solution (22,23) becomes unstable and limit cycles occur. May and Anderson (1978) described this effect of parasite induced reduction of host reproductive potential; parasite reproduction within a host that directly increases parasite population size; and time delays in parasite reproduction and transmission; all of which are destabilizing processes.

An alternative formulation of this problem was discussed by Diekmann and Kretzschmar (1991). Instead of the assumption that each parasite reduced the host's fertility by an amount $\beta$, it was assumed that each parasite reduced fertility by a proportion $1-\xi$. Hence the effect is multiplicative rather than additive. Instead of equation (21) the host population dynamics is now modelled by

$$\frac{dH}{dt} = \left(a\left[\frac{kH}{(1-\xi)P + kH}\right]^k - b\right)H - (\alpha+\beta)P \tag{25}$$

Diekmann and Kretzschmar (1991) point out that this formulation avoids a possible difficulty with host birth rates being negative for large parasite populations (which was acknowledged by May and Anderson (1978)), but this is unlikely to occur if $\beta$ ($\sim a(1-\xi)$) is small. The qualitative dynamics of the two models are the same. The resulting delayed density dependence can have profound effects on the dynamics of the host-parasite association (Hudson and Dobson this volume).

# 5 Parasite population regulation

Host populations are regulated by factors other than their parasites, and it is common to include either density-dependent birth or death rates in equations for population dynamics (Heesterbeek and Roberts this volume). In the simplest cases where the parasite does not affect host mortality or fecundity we may consider the host population size $H$ to be constant, and $\alpha = 0$. Equation (13) becomes

$$\frac{dP}{dt} = (b+\mu)(R_0 - 1)P \tag{26}$$

where

$$R_0 = \frac{\lambda H}{(H_0 + H)(b + \mu)} \tag{27}$$

Whether the parasite population grows or becomes extinct now depends on $H$, as $R_0 > 1$ implies that $H$ exceeds a threshold value $H_T$ defined by (cf. Anderson and May (1991), p.475)

$$H_T = \frac{H_0(b + \mu)}{\lambda - b - \mu} \tag{28}$$

The parameter $H_T$ is usually referred to as a threshold density. When considering the use of $H_T$ as a threshold parameter it is necessary to carefully consider the utilisation of space by the host population. In many cases an increase in population size would be partially compensated for by an increase in territory, with population density increasing at a lesser rate (De Jong *et al.* 1995).

In reality the parasite population will not grow exponentially as suggested by equation (26), just as density-dependent factors would ultimately limit the host population size. Density dependent factors that could limit the parasite population size while maintaining a constant host size are concomitant immunity, parasite-induced reduction in parasite fecundity and parasite-induced increase in parasite mortality (Bradley 1972, Anderson and May 1991). Introducing one or more of these mechanisms into the model leads to an equation of the form

$$\frac{dP}{dt} = (b + \mu)(R_0 f(P) - 1)P \tag{29}$$

where $f(0) = 1$ and $f$ is nonincreasing in $P$ (Anderson and May 1991). The function $f$ contains information about the density-dependent mechanisms that regulate the parasite population, and may depend on the distribution of parasites among hosts (i.e. be a function of $k$). At equilibrium $R_0 f(P^*) = 1$, which again requires $R_0 > 1$.

For example, Anderson and May (1985, 1991) considered the situation where the production of new infective stages decreases as parasite burden increases. In particular, if a host animal has $i$ parasites, then each parasite produces new infective stages at the rate $\lambda_0 \delta^{i-1}$ for some $\delta < 1$. The total rate of production of transmission stages $\lambda P$ is then equal to

$$\lambda_0 H \sum_{i=1}^{\infty} i p_i \delta^{i-1} = \lambda_0 P [1 + \frac{P}{Hk}(1 - \delta)]^{-(k+1)} \tag{30}$$

where a negative binomial distribution of parasites among hosts is assumed. Hence we have

$$f(P) = [1 + \frac{P}{Hk}(1 - \delta)]^{-(k+1)} \tag{31}$$

$R_0$ is given by (23) with $\lambda$ replaced by $\lambda_0$. The steady state size of the parasite population is

$$P^* = \frac{kH}{1-\delta}(R_0^{1/(k+1)} - 1) \tag{32}$$

Once again, in the absence of regulation ($\delta = 1$) the parasite population would grow exponentially, but in this case regulation is by effects directly impinging on the dynamics of the parasite population, rather than indirectly through the dynamics of the host population.

The analysis so far has assumed either that the parasites are hermaphrodite, or if dioecious that all female parasites are mated. This may be true when parasite intensity is high, but for low parasite intensities the likelihood that a host animal has both a male and female parasite will be reduced. This has been addressed by May (1977) (see also Anderson *et al.* (1989), Anderson and May (1991)). The problem of finding a mate is not an instance of density-dependent regulation, as it introduces a mechanism by which the transmission rate is decreased at low densities.

Parasite populations may be regulated by acquired immunity, that is an immunity to infection manifested by the host in response to its previous history of exposure to infection. This host response may serve to reduce the probability that an exposure leads to a mature parasite in the host, either by preventing establishment or interfering with the maturation process, or interfering with established parasites by reducing their fecundity or increasing their mortality (Roberts and Grenfell 1991). Tallis and Leyton (1966) introduced an 'antigenic information trajectory' into their stochastic model in an attempt to convey this concept. Roberts and Grenfell (1991), in a model for nematodes in farmed animals which in this aspect applies equally to wild animals, introduced a variable $r$ as a measure of the average level of immunologically significant experience of infection in the host population. The value of $r$ was assumed to increase with exposure to infection, and decrease with time, so for our system

$$\frac{dr}{dt} = \frac{\lambda PH}{H_0 + H} - \sigma r \tag{33}$$

As $r$ depends not on the present number of parasites $P$, but on the history of $P$ over past time, equation (29) must now be modified to obtain

$$\frac{dP}{dt} = (b+\mu)(R_0 f(P,r) - 1)P \tag{34}$$

where $f(0,0) = 1$ and $f$ is nonincreasing in $P$ and $r$. The steady state value of $P$ is obtained by solving $R_0 f(P^*, r^*) = 1$, where $\sigma r^* = \lambda(r^*)P^*H/(H_0 + H)$.

For a model that provides a fuller description of the effects of acquired immunity on helminth populations; see Grenfell *et al.* (this volume).

# 6 Free-living stages

The factor $H/(H_0+H)$ was introduced in equation (9) to approximate transmission through those parts of the life-cycle that exist outside the definitive host. For nematode parasites these are the egg and (free-living) larval stages. For other parasites they may also include stages within intermediate host animals (see section 8).

The population dynamics of the free-living stages of nematodes have been the subject of many extensive investigations, ranging from models with one variable for the population size (Anderson 1982a, Anderson and May 1991, Roberts and Grenfell 1992) to detailed descriptions of the dynamics of the free-living stages (reviewed in Roberts (1991)). These stages are exposed to the environment, and therefore their transmission rates depend in general on factors such as temperature and humidity. Nonautonomous models, where time has been used to model seasonal changes in these factors, have been used to model the dynamics of the egg and larval stages of nematodes of farmed animals (Grenfell *et al.* 1987, Leathwick *et al.* 1992, Roberts and Grenfell 1992, Smith 1990). In particular, Roberts and Grenfell (1992) used an equation equivalent to

$$\frac{dL}{dt} = q(t)\lambda P - (\rho(t) + \beta(t)H)L \tag{35}$$

and employed a transfer function argument to investigate the comparative dynamics of this model and the autonomous model equivalent to (cf. Anderson and May 1991)

$$\frac{dL}{dt} = \lambda P - (\rho + \beta H)L \tag{36}$$

In these models $q$ is proportional to the probability that an egg develops into an infective larva, $\lambda$ is the rate of production of infective stages by adult parasites, $\rho$ is the natural loss (death) rate of infective stages and $\beta$ is the infectious contact rate. The method used to compare (35) and (36) was similar for that used to investigate seasonal host population dynamics, which is reviewed in section 7.

With a separate equation for the free-living stages, equation (9) (with $\alpha = 0$) becomes

$$\frac{dP}{dt} = \beta H L - (b+\mu)P \tag{37}$$

Our original formulation is recovered by assuming that characteristic times in the free-living stages are short in comparison to those of adult parasites, hence setting $dL/dt = 0$, and therefore $L = \lambda P/(\rho + \beta H)$ from (36). This assumption is valid for a variety of helminth parasites of man in particular (May and Anderson 1979) but would not apply to trichostrongylid infections in ruminants, for example. Substituting for $L$ then recovers our model (9),

with $H_0 = \rho/\beta$ and $\alpha = 0$. The basic reproduction ratio (27) is unchanged. Environmental factors are density independent mechanisms that may modify but do not regulate parasite populations. Equations (35,37), or (36,37), as they stand are linear in $L$ and $P$, and to make this a biologically realistic model it is necessary to introduce some sort of regulatory mechanism, either parasite regulation of the host combined with host population dynamics as in section 3 and 4, or regulation of the parasite population with or without acquired immunity as in section 5.

In more complex models where, for example, the host is involved in a plant/herbivore cycle, explicitly allowing for the dynamics of the free-living stages can produce a 'storage effect' that reduces the tendency for host and parasite population fluctuations (Grenfell (1992); see also next section).

# 7 Environmental and ecological influences

Host-parasite interactions do not exist in an ecological vacuum. Other factors (notably host feeding and predation on hosts) may also have a significant effect on the parasite. Barlow (this volume) summarises the conclusions of published models that have incorporated such interactions. The interactions between parasitism and other ecological processes can lead to stabilising or destabilising effects (Anderson 1979), or even chaotic fluctuations in some instances (Grenfell 1992).

Wild animal populations do not, in general, breed continuously throughout the year, but have a seasonal pattern. This is a major distinguishing feature between these and farmed populations, which although seasonal are controlled by the farmer. The parasite may also exert a seasonal influence, as we saw in the last section, where development rates of free-living stages could vary with the time of the year. In the rest of this section we include periodic patterns of host births and parasite transmission in the basic model (8,13), and present a method for determining the extent to which these seasonal patterns perturb the dynamics in the situation where the host and parasite populations are otherwise regulated.

Consider now equations (8,13), but include a seasonal birth rate for the host and a seasonal development rate for the free-living stage of the parasite. Hence (8) is replaced with

$$\frac{dH}{dt} = a[1 + \epsilon\phi(t)]H - bH - \alpha P \tag{38}$$

and (13) with

$$\frac{dP}{dt} = \frac{\lambda[1 + \epsilon\psi(t)]PH}{H_0 + H} - (b + \mu + \alpha)P - \frac{\alpha(1+k)}{k}\frac{P^2}{H} \tag{39}$$

where the forcing functions $\phi(t)$, $\psi(t)$ are periodic, $|\phi(t)|$, $|\psi(t)| \leq 1$. As birth and development rates must remain positive we may assume $\epsilon < 1$. Near the equilibrium $(H^*, P^*)$ defined by (16,17) equations (38,39) may be written with $H = H^* + \epsilon x$, $P = P^* + \epsilon y$, as

$$\frac{d}{dt}\begin{pmatrix} x \\ y \end{pmatrix} = J\begin{pmatrix} x \\ y \end{pmatrix} + \begin{pmatrix} aH^*\phi(t) \\ \lambda P^* H^* \psi(t)/(H_0 + H^*) \end{pmatrix} + O(\epsilon) \qquad (40)$$

where

$$J = \begin{pmatrix} a-b & -\alpha \\ \frac{a-b}{\alpha}\left(\frac{(a-b)(k+l)}{k} + \frac{\Lambda(\lambda-\Lambda)}{\lambda}\right) & -\frac{(a-b)(k+l)}{k} \end{pmatrix} \qquad (41)$$

is the Jacobian matrix of the autonomous system at $H = H^*$, $P = P^*$. Here $\Lambda = a + \mu + \alpha + (a-b)/k$. For small $\epsilon$ the solution of (40) is

$$\begin{pmatrix} x(t) \\ y(t) \end{pmatrix} = \frac{1}{2\pi}\int_{-\infty}^{+\infty} \mathrm{T}(\eta)\begin{pmatrix} aH^*\tilde{\phi}(\eta) \\ \lambda P^* H^* \tilde{\psi}(\eta)/(H_0 + H^*) \end{pmatrix} e^{i\eta t}\, d\eta \qquad (42)$$

where the tilde denotes Fourier transform, i.e.

$$\tilde{\phi}(\eta) = \int_{-\infty}^{+\infty} \phi(t) e^{-i\eta t}\, d\eta \qquad (43)$$

and $\mathrm{T}(\eta) = (i\eta I - J)^{-1}$, $I$ is the identity matrix. It is easy to see from (41) that the eigenvalues of $J$ have negative real parts, so T is well-defined. The magnitude of the response of the system to the components of the forcing functions with frequency $\omega$ may therefore be determined from the magnitude of $\mathrm{T}(\omega)$, recalling that the Fourier transform of $\cos\omega t$ is $\pi[\delta(\eta-\omega)+\delta(\eta+\omega)]$. Roberts and Grenfell (1992) scaled the components of T for a more complex system to obtain transfer functions for the response of the steady state of the autonomous system to periodic forcing. For our case the magnitude of the responses to $\phi$ in $H$ and $P$ are $a|\mathrm{T}_{11}(\omega)|$ and $aH^*|\mathrm{T}_{21}(\omega)|/P^*$ respectively, with phase lags $\theta = -\Im(\mathrm{T}_{ij})/\Re(\mathrm{T}_{ij})$ as appropriate, and similar results hold for the response to $\psi$.

Nisbet and Gurney (1982) discussed the characteristics of the response of autonomous systems to periodic forcing via plots of transfer functions against the forcing frequency, $\omega$. Of prime interest here, however, is the response of the system to an annual forcing cycle, i.e. the magnitude of $\mathrm{T}(2\pi)$, and the relative magnitudes of the responses to $\phi$ and $\psi$.

The ratio of the magnitude of the response in $H$ to annual forcing of host birth rate to the response in $H$ to annual forcing of parasite transmission rate is

$$\left|\frac{a(H_0 + H^*)\mathrm{T}_{11}(2\pi)}{\lambda P^* \mathrm{T}_{12}(2\pi)}\right| = \frac{a(k+1)}{\Lambda k}\left|1 + \mathrm{i}\frac{2\pi k}{(k+1)(a-b)}\right| \qquad (44)$$

and the equivalent relationship for the response in $P$ to the two seasonal influences is

$$\left(\frac{a(k+1)}{\Lambda k} + \frac{a(\lambda-\Lambda)}{\lambda(a-b)}\right)\left|1 - \mathrm{i}\frac{2\pi}{a-b}\right|^{-1} \tag{45}$$

If expression (44) is large ($\gg 1$) then the seasonal variation in host reproduction has a greater influence on the within-year variation in host numbers than the seasonal variation in parasite transmission. Alternatively, if this quantity is small ($\ll 1$) then it is the variation in parasite transmission that is responsible for seasonal variation in host numbers. A similar argument applied to (45) determines the relative importance of these two mechanisms in generating the seasonal variation in parasite numbers. Once the dominant seasonal influence is determined, it is of course necessary to calculate the relevant component of $\mathrm{T}(2\pi)$ in order to determine the absolute importance of these factors.

# 8 Models of macroparasites with indirect life-cycles

## 8.1 Cestodes

Cestodes exist in a variety of predator-prey life cycles, some of which have man as the definitive host and others have wild or domestic animal life-cycles with man as an accidental intermediate host (Keymer 1982). Although cestodes are very frequent parasites of wildlife populations and are of major international importance as zoonosese, few models have been developed to explain their life-cycles. Such as there are include a model for *Caryophyllaeus Laticeps* in the bream (Anderson 1974), a model for *Hymenolepis diminuta* (Keymer 1982) and models for *Echinococcus granulosus*, *E. multilocularis*, *Taenia hydatigena* and *T.ovis* (Roberts *et al.* 1986, 1987, Roberts and Aubert 1995).

Keymer's model for *H. diminuta* is a straightforward example of generalizing the precepts of the Anderson and May formulation for direct life-cycle parasites to a parasite with an indirect life-cycle. Adult *H.diminuta* live in the small intestine of a range of small mammals, often rats. The mammalian hosts become infected when they predate insects infected with cysticercoid larvae. The insects (e.g. *Tribolium confusum*) become infected when they ingest free living eggs. The system has a number of interesting features, particularly with respect to the intermediate host: under laboratory conditions there is a non-linear relationship between the egg ingestion rate and egg density (a functional response), and, although there is no parasite induced host mortality, host (beetle) fecundity is adversely affected (Keymer 1981). In addition, experiments by Hesselberg and Andreassen (1975) indicate that the

parasite is regulated by density dependent constraints on the survival of adult parasites in the rat.

Keymer's model is an interesting example of how judicious simplifications can render an otherwise intractable system susceptible to analysis. She began with three equations representing the mature parasites in the rat population ($P_1$), the cysticercoids in the beetle population ($P_2$), and the free-living eggs ($E$). Under the assumption that the parasite population distribution could be adequately described by the negative binomial probability distribution, the model was

$$\begin{aligned}
\frac{dP_1}{dt} &= \beta_1 H_1 D_1 P_2(t - T_1) - (b_1 + \mu_1 + \delta)P_1 - \frac{\delta(k+1)P_1^2}{kH_1} \\
\frac{dE}{dt} &= \lambda P_1 - \mu_3 E - \beta_2 H_2 E \\
\frac{dP_2}{dt} &= \beta_2 D_2 H_2 E(t - T_2) - (\mu_2 + b_2)P_2 - \beta_1 H_1 P_2
\end{aligned} \tag{46}$$

The model is constructed along standard lines, $\mu_i$ being the intrinsic parasite death rates at each stage and $b_i$ being the natural mortalities of the hosts. Since the model dealt with mature parasites on the one hand ($P_1$) and developed cysticercoids ($P_2$) on the other, the parameters $D_i$ represented the proportion of infected parasites that survived the requisite developmental times, $T_i$. Regulation of parasite abundance was achieved by incorporating a density dependent rate of parasite mortality ($\mu + \delta P_1$). In order to simplify things somewhat, Keymer assumed that, under natural conditions, the functional responses of the two predatory hosts was of trivial significance. Net transmission was therefore a simple linear function of predator/prey abundance ($\beta_1 H_1 P_2$, and $\beta_2 H_2 E$). Further simplification was effected by noting that the life spans of the parasitic stages were orders of magnitude longer than that of the free living eggs and that the developmental time delays were also rather short. Recasting the model in terms of mean parasite burdens ($M_1$ and $M_2$ respectively) and taking into account the relative time scales led to

$$\begin{aligned}
\frac{dM_1}{dt} &= \beta_1 D_1 H_1 M_2 - (b_1 + \mu_1 + \delta_1)M_1 - \frac{\delta(k+1)M_1^2}{k} \\
\frac{dM_2}{dt} &= \frac{\lambda H_2 \beta_2 D_2 M_1}{\mu_3 + \beta_2 H_2} - (\mu_2 + b_2)M_2 - \beta_1 H_1 M_2
\end{aligned} \tag{47}$$

This reduction in the number of equations was achieved by assuming that egg density reached its equilibrium value so quickly that the transient behaviour of the equation for $E$ is of trivial significance for the overall dynamics of the model. Thus it is possible to substitute the equilibrium value $(\lambda P_1/(\mu_3 + \beta_2 H_2))$ for $E$ in the equation for $M_2$. Notice that if we define $H_0$ as $\mu_3/\beta_2$

we can rewrite the first part of the equation for $M_2$ as

$$\frac{dM_2}{dt} = \frac{\lambda M_2 D_2 H_2}{(H_0 + H_2)} - \cdots \tag{48}$$

which is identical to the Anderson and May format discussed earlier (equation (9)). As mentioned previously, the saturation transmission term $\lambda PH/(H_0 + H)$ of the Anderson and May model represents the case where the 'time scale for infective stages to be transmitted is shorter than any other relevant time scale in the model' (May and Anderson 1978).

The dynamical behaviour of the two equations (47) is such that there are two stable equilibria. Either the parasite persists within the host population or it does not. Unlike models for direct life cycle dioecious helminths, which manifest multiple stable states for parasite persistence, hermaphrodite tapeworms like *H.diminuta* appear to have only one positive equilibrium. An index of the threshold for parasite persistence can be obtained by noting that the life span of the cysticercoids is much less than the life span of parasites in the mammalian host. It is thus possible to substitute the equilibrium value for $M_2$ into the equation for $M_1$ and show by simple inspection that $dM_1/dt$ is positive provided

$$H_1 H_2 > \frac{\mu_3(\mu_2 + b_2)(b_1 + \mu_1 + \delta)}{\lambda \beta_1 B_2 D_1 D_2} \tag{49}$$

This inequality assumes that $\beta_1 H_1 \ll \mu_2 + b_2$ and $\beta_2 H_2 \ll \mu_3$ and can be discarded. The striking feature of this system is that the critical threshold density of beetles for parasite persistence turns out to be astonishingly low (15 beetles per hectare when rat density is 20 per hectare (Keymer 1982)). In indirect life cycle parasite systems, the threshold for parasite persistence is a multiplicative property of the respective host densities. Parasite persistence in low density definitive hosts is therefore assured by the passage of an intermediate stage through a host of guaranteed high density. This may have provided a major selection pressure for the evolution of life cycles involving more than one host (Anderson 1982b).

The models of *E.granulosus* and *E.multilocularis* described by Roberts *et al.* (1986, 1987) and Roberts and Aubert (1995) have been used to inform policy decisions concerning parasite control. Although more usually associated with domestic infestations, *E.granulosus* is found in a variety of wildlife associations, including its original wolf-caribou cycle and the dingo-wallaby cycle in Australia (Gemmell *et al.* 1987). In many instances *E.granulosus* serves as a reservoir for infections in domestic animals. Current models for this parasite only deal with the domestic (sheep-dog) cycle but probably have application in wild life cycles. Control programmes against *E.granulosus* have been successful in many regions of the world (Gemmell *et al.* 1986, 1987).

It has been found that although intermediate host animals are capable of acquiring an immunity to infection, in the domestic situation the infection pressure is so low that this effect is minimal (Roberts *et al.* 1986). The definitive host only acquires immunity at very high infection pressures, and the parasite does not increase the mortality of the host. Hence, in the domestic situation $R_0$ for *E.granulosus* infections is invariably only just above one, and control programmes are successful.

*Echinococcus multilocularis* usually has the fox as the definitive host, and small rodents as intermediate hosts. It is found throughout Europe and Asia, and in North America (Roberts and Gemmell 1994). If man becomes accidentally infected with the intermediate stage, the consequences are often fatal. Initial attempts to model the life cycle of *E.multilocularis* have been hampered by a lack of data. Roberts and Aubert (1995) used a prevalence model to assess the likely success of a treatment programme for foxes in Eastern France. In this region aerial baiting is used to vaccinate foxes against rabies, and it was proposed to add praziquantel to the bait to simultaneously remove tapeworms. The outcome was less an assessment of a control startegy, however, than an assessment of the further data required to complete an understanding of the dynamics of this parasite. Of particular interest is the identification of those mechanisms that regulate parasite abundance. For example, in *E.multilocularis* there is no evidence for acquired immunity in either host, or parasite induced mortality in the definitive host. There is evidence that both *E.granulosus* and *E.multilocularis* debilitate their intermediate hosts, making them easier to catch by predators (Rau and Caron 1979). This, however, is an example of positive feedback and is not a regulatory effect. The factors that regulate wild *Echinococcus* life-cycles have yet to be elucidated.

## 8.2 Trematodes

Trematodes are important parasites of many wildlife species (Ramsden and Presidente 1975). The life cycles of those trematode species of particular interest to man all involve a vertebrate definitive host and a molluscan intermediate host. Beyond that, the life-cycles can be classified according to how the definitive host is infected. Schistosome cercariae penetrate the definitive host directly, other species rely upon the definitive host to deliberately ingest active cercariae or accidentally ingest cercariae encysted in or on a plant or animal paratenic host. Given the complexities of the life-cycle outside the vertebrate host, the simpler models of trematode infections have subsumed the dynamics of larval phases in a single equation or else constrained the applicability of the model so that the larval stages can be ignored altogether. One example of a trematode model which eschewed any consideration of the intermediate host phase is Smith's (1984) model for *Fasciola hepatica.* Smith

applied a simple immigration/death model to *F.hepatica* infections in sheep although the same format could be used for any of the wild hosts species that appear unable to mount an effective immune respone (e.g. Tasmanian marsupials like the red-necked wallaby, the bush tailed possum and red-bellied pademelon (Beveridge 1986)). The model exploited the seasonal nature of the release of ceracariae from the molluscan intermediate host under temperate conditions. It was possible to assume that the majority of metacercariae appeared on the pasture simultaneously and that there was no more recruitment to this population of infective stages for another twelve months. Given also the very poor acquired immune response to *Fasciola* in sheep it was possible to model the course of the infection during autumn and winter with just two equations:

$$\frac{dC}{dt} = -\beta HC - \mu_1 C \tag{50}$$

$$\frac{dP}{dt} = \beta HC - \mu_2 P \tag{51}$$

where $C$ is the density of infective stages, $P$ the total number of parasitic stages, $H$ the host density, $\beta$ the transmission parameter and $\mu_1$ and $\mu_2$ the mortality of the freeliving and parasitic stages respectively. This model has the uninteresting equilibrium solution $C^* = P^* = 0$. Nevertheless, when used in conjunction with a model for parasite deaths due to anthelmintics, analysis of its transient dynamics led to useful conclusions with respect to optimal treatment times.

Detailed work on the dynamics of trematode infections in the intermediate host snails has focused principally on two systems: *F.hepatica* and *Lymnaea truncatula*, and *Schistosoma mansoni* and *Biomphalaria glabrata* (Smith and Grenfell 1984, Smith 1987, Anderson *et al.* 1982, Carter *et al.* 1982, Anderson and Crombie 1984). The schistosome system received the most detailed treament. Of primary interest was to identify mechanisms that might account for the convex age-prevalence curves that are a recurring feature of infected snail populations. The starting point was a simple model for miracidial infections. It was assumed that if $M$ is the density of free swimming miracidia, and $S$ is snail host density, it was reasonable to write

$$\frac{dM}{dt} = -\beta SM \tag{52}$$

Detailed experimental work justified the assumption that the net rate of transmission was directly proportional to the respective densities of hosts and miracidia (Carter *et al.* 1982) and subsequently revealed that the transmission parameter, $\beta$, was an inverse function of miracidial age and snail size. This last was particularly interesting because snail size is a fair index of snail age. The possibility existed therefore that this alone might account

for the declining prevalence of infection in the older age groups of snails. The problem was studied further using free running infection experiments and catalytic models of the infection process (Anderson and Crombie 1984). A straightforward model with constant coefficients was considered first:

$$\begin{aligned} \frac{dX}{dt} &= -(\lambda+\mu)X \\ \frac{dZ}{dt} &= \lambda X - \mu Z - \lambda X(t-\tau)e^{-\mu\tau}\theta(t) \\ \frac{dY}{dt} &= \lambda X(t-\tau)e^{-\mu\tau}\theta(t) - \alpha Y \end{aligned} \tag{53}$$

where $X$, $Y$ and $Z$ were the densities of uninfected snails, unfected but not yet shedding snails, and shedding snails respectively, $\mu$ and $\alpha$ were the mortality of uninfected and infected snails, $\lambda$ was the force of infection and $\theta(t)$ was a step function that permitted the movement of infected snails to the shedding stage after a developmental interval, $\tau$. This simple model could not reproduce the convex time-prevalence curves obtained in the free running experiments. Since the transmission parameter, $\beta$, was an inverse function of snail size it seemed reasonable to assume that the force of infection, $\lambda$, would also decline with snail size. In the event, in order to explain the convex time-prevalence curves, it was necessary to use a partial differential equation model in which the force of infection was a declining function of snail age and the mortality of shedding snails was an exponentially increasing function of the time since shedding began.

Despite the elegant nature of this analysis, and the opportunity for further investigations into the very rich dynamical behaviour of snail-trematode systems, it is important to report that Anderson *et al.* (1982) felt that, in this particular case, the effort was of little value with respect to any understanding we might gain of the dynamics of the overall life-cycle. The conclusion was a consequence of the fact that the intemediate host dynamics operated on a much faster time scale that the dynamics of the infection in the definitive host. The larval schistosome stages are very short lived compared with the sexually mature stages and so have little impact on the overall, long term dynamics of the entire system.

# 9 Models of ectoparasitic infections

## 9.1 Ticks

Usually we are concerned with arthopods as intermediate hosts of more damaging parasite species (Milligan and Baker 1988, Rogers and Randolph 1985). Nevertheless, there are many arthropod parasitisms that are worth studying on their own account (e.g. *Lernaeocera branchialis*, a copepod parasite of

marine fish, and the horn fly, *Haemotobia irritans*, a very damaging ectoparasite of a wide range of animals, including lions) and some which have to be modelled almost entire in order to understand their role in transmitting microparasitic infections (e.g. the lone-star tick, the vector of Rocky mountain spotted fever and *Ixodes spp*, the vectors of Lyme borreliosis). Unfortunately, the usual approach has been to construct a detailed species-specific simulation model. There appears to have been no systematic effort to construct and investigate generic models of arthropod parasitisms. Nevertheless, at least in the case of the tick, *Ixodes scapularis* (previously *dammini*), the lack of detailed knowledge of the biological parameters involved has caused some workers to construct simple models which have some affinity with the generic models discussed in previous sections. For example, Lord (1992) used a simple model to investigate factors controlling the early summer peak in the number of questing *I. scapularis* nymphs in northeastern USA. She framed the model as a general difference equation for nymph abundance at time $t$ ($N_t$).

$$N_{t+1} = R_t - M_t N_t - H_t N_t \tag{54}$$

Various functional forms for recruitment ($R_t$), mortality ($M_t$) and host finding ability ($H_t$) were tested and compared with patterns actually observed in the field. The comparisons indicated that the functional form for recruitment had a profound effect on the nymphal activity pattern. The model fitted best if it was assumed that activity is triggered during a fairly short interval (as if diapause were terminated by a change in photoperiod for example). This finding is important because it directs our attention to the most influential processes.

Models which attempt to mimic the entire *I. scapularis* life-cycle have done so by sacrificing much of the stage specific detail that characterised Lord's model. For example, Porco (1991) described a transition matrix model for *I. scapularis* with a three-month time step. This 'seasonal' view of the life-cycle permitted a number of simplifying assumptions, principally that only one feeding stage of any given cohort of ticks will be active at any one time. Porco further assumed that adult *I. scapularis* feed only in the autumn, that temperature has no effect on tick survival or activity and that host densities are constant, at least within each time step (season). The parameters of the transition matrices were adjusted such that the number of tick eggs laid each year was the same. This device was used to maintain tick numbers at some notional equilibrium in the absence of information about the processes that actually regulate tick density. This simplified model architecture permitted model behavior to be examined analytically for some special cases. Of particular interest was the behaviour of the model when it incorporated the agent responsible for Lyme disease, *Borrelia bergdorferi*. Adult *I. scapularis* feed on white-tailed deer, and it was found that moderate reductions in the density

of white tailed deer may decrease or increase the proportion of infected ticks. The precise outcome depended on the fraction of ticks which feed upon the deer and on the functional dependence of tick population size on the number of deer. This ambiguous result is important since it illustrates the counter-intuitive point that planned reductions in deer density may have exactly the opposite effect to the one desired.

A more detailed transition matrix model was published by Sandberg *et al.* (1992). This model differed from Porco's in that the time step was one month, so there were twelve transition matrices per year instead of four. This permitted a less limited representation of temporal changes in oviposition and questing behavior and the model was able to reproduce the seasonal pattern of abundance of the various stages quite accurately. Nevertheless, even this moderate increase in complexity removed any reasonable possibility of examining model behavior analytically and all subsequent studies of this model and its elaborations will depend on repeated numerical simulations. Since the authors also frankly admit the absence of any good information concerning the processes that regulate tick density, tick numbers increase without bound for every successive year included in the simulation.

## 9.2 Monogeneans

Monogenean trematodes are important ectoparasites of a range of freshwater and marine fish including sharks, skates and rays (Smith and Noga 1993). Monogeneans may be found on the body surface, fins or gills, or in the oral cavity of the host. They feed on host mucous, epithelium or blood and some infestations (particularly in aquaria) are characterised by a substantial parasite-induced host mortality (Figure 2a).

Monogenean infection dynamics have been examined in experimental systems using *Gyrodactylus bullatarudis* and the common guppy, *Poecilia reticulata*. In their attempt to account for changes in the prevalence and intensity of *G. bullatarudis* infections, Scott and Anderson (1984) described a model which included features more usually associated with models of microparasitic infections (Figure 2c). The host dynamics were represented as follows:

$$\begin{aligned} \frac{dS}{dt} &= I - \Lambda SH - bS + dZ \\ \frac{dH}{dt} &= \Lambda SH - (b+\gamma)H - \alpha H \sum ip(i) \\ \frac{dZ}{dt} &= \gamma H - (b+d)Z \end{aligned} \tag{55}$$

This is the typical SIR model framework (see Heesterbeek and Roberts this volume) with two important exceptions. First, susceptible hosts are replaced by immigration ($I$) not births (so as to mimic the conditions of the free-

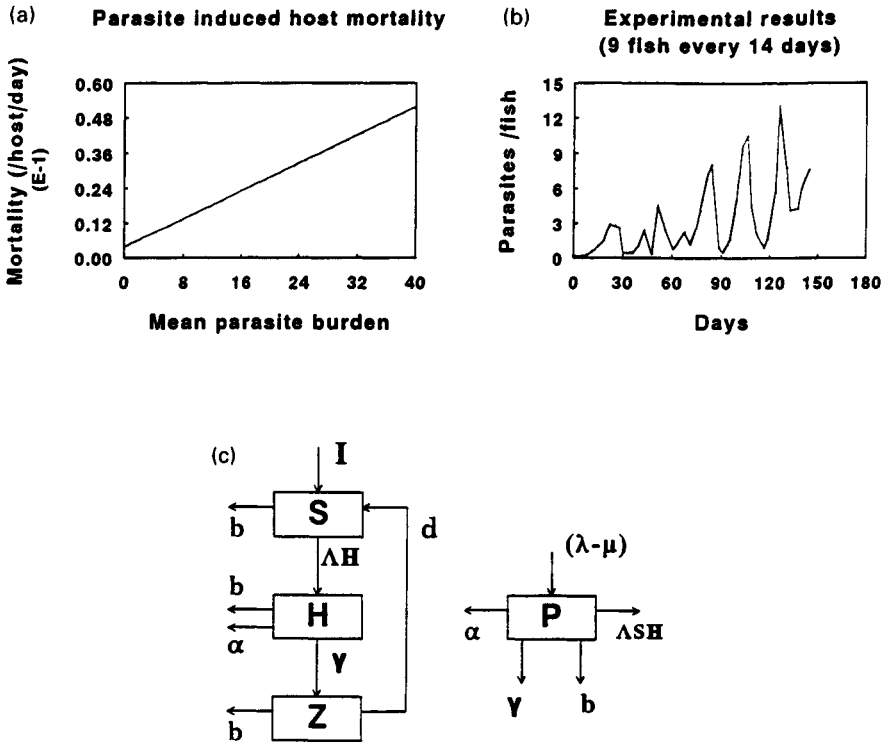


Figure 2: *Gyrodactylus bullatarudis* infection dynamics on the guppy. (a) Parasite induced host mortality, (b) Observed prevalence of infection in a free running system in which susceptible hosts were added at a rate 9 fish/14 days, (c) Flow diagram for the *Gyrodactylus* model (from Scott and Anderson (1984).

running experiments), and, second, host mortality attributable to the infection is a function of the number of parasites on each host ($\alpha H \sum ip(i)$). In this model, hosts are assumed to recover from infection at a rate $\gamma$, and remain refractory to further infection for a period $1/d$. Models of macroparasitic infections, usually describe host resistance in terms of gradual changes in characteristics of the parasite (e.g. mortality or fecundity). Using the typical microparasitic model framework, Scott and Anderson modelled host resistance as an all or none property of the host. Thus parasite losses due to the acquisition of resistance to infection were dealt with in the same way as parasite losses due to hosts deaths. The model for the parasites ($P$) was as

follows:

$$\frac{dp}{dt} = (\lambda - \mu - b - \gamma)P - \alpha H \sum i^2 p(i) - \Lambda Z H \sum ip(i). \tag{56}$$

Gyrodactilid infections are spread by parasite transfer during direct fish to fish contact: there is no intermediate, infective stage. Furthermore, unlike most macroparasites, monogeneans reproduce directly on the host. It follows that transmission is not a prerequisite for increases in parasite abundance and does not figure in the positive term of the parasite equation. Parasites increase at an intrinsic rate $\lambda - \mu$, which is modified by parasite deaths due to natural host deaths ($b$), parasite deaths due to parasite induced host mortality ($\alpha$), and parasite deaths due to transmission to refractory hosts ($\Lambda Z$).

Despite the innovative nature of this model it proved to be a very poor mimic of the dynamics of experimental *G. bullatarudis* infections. In particular, it failed to display the oscillatory behavior that was characteristic of experimental infections in which susceptible fish were replaced at regular intervals (Figure 2b).

# 10 Competition between parasite species

Models often treat the parasite of interest as though it were the only parasite species infecting the host. In fact, hosts are frequently infected simultaneously with several parasite species. (Figure 3). Sometimes the associations between parasite species are such that it can be inferred that there is no adverse effect of one parasite species upon another (Keith, *et al.* 1986). Sometimes though, some associations occur much less frequently that one might expect by chance alone or there is evidence that one parasite survives less well in the presence of the other (Lim and Heyneman 1972, Bates and Kennedy 1990). It is these cases that lead us to believe that there is competition between species for host resources. This can be modelled for the simple situation in which two parasite species share the same host population. The development that follows is based on that by Dobson (1985). Equations (8,13) become

$$\frac{dH}{dt} = (a - b)H - \alpha_1 P_1 - \alpha_2 P_2 \tag{57}$$

$$\frac{dP_1}{dt} = \frac{\lambda_1 P_1 H}{H_0 + H} - (b + \mu_1 + \alpha_1)P_1 - \frac{\alpha_1(1 + k_1)}{k_1}\frac{P_1^2}{H} - \alpha_2(1 + X)\frac{P_1 P_2}{H} \tag{58}$$

and a similar equation for $P_2$. The term $X$ is a measure of the interference between the species, defined by

$$X = \frac{\mathrm{cov}(1,2)H^2}{P_1 P_2} \tag{59}$$

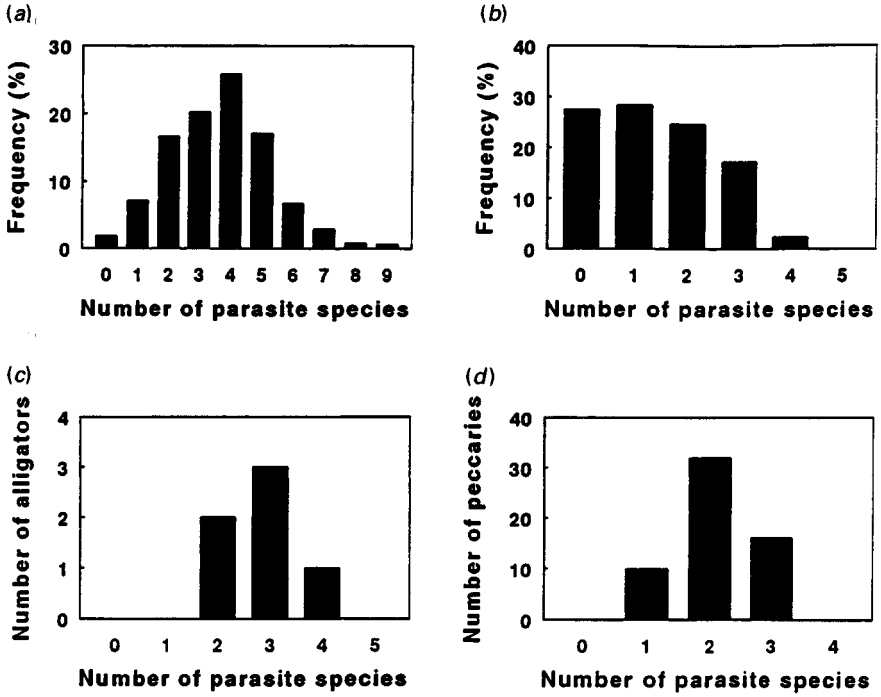


Figure 3: (a) Frequency distribution of helminth species in adult gulls in the UK. A survey of 604 birds revealed 10 trematode species, 11 cestode species and 10 nematode species (Threlfall 1967). (b) Frequency distribution of helminth species in dead manatees recovered throughout Florida. A survey of 215 hosts revealed 4 trematode species, 1 cestode species and 1 nematode species (Beck and Forrester 1988). (c) Number of helminth species recovered from a group of 6 alligators taken from Par Pond, South Carolina. There were 2 species of nematode and 4 species of trematode (Hazen *et al.* 1978). (d) Number of helminth species recovered from 48 collared peccaries in Texas. A survey revealed 4 nematode species and 1 cestode species (Corn *et al.* 1985).

where cov(1,2) is the covariance between the species distributions. Hence if the two species are simply utilising the same host without overt interference then $X = 0$. If one species is antagonistic towards the other then $X < 0$. The non-trivial steady states of (57,58) are solutions of

$$\begin{pmatrix} 0 & \alpha_1 & \alpha_2 \\ \lambda_1 & -\alpha_1/k_1 & -\alpha_2 X \\ \lambda_2 & -\alpha_1 X & -\alpha_2/k_2 \end{pmatrix} \begin{pmatrix} H/(H_0+H) \\ P_1/H \\ P_2/H \end{pmatrix} = \begin{pmatrix} a-b \\ a+\mu_1+\alpha_1 \\ a+\mu_2+\alpha_2 \end{pmatrix} \quad (60)$$

Equation (60) may be explicitly solved to reveal seven different outcomes for the system dynamics. Either the host population may continue to grow with

the two parasite populations becoming extinct, one becomimg extinct and the other establishing, or both establishing; or the host population may be regulated by one or both of the parasite species. This work may easily be extended to an arbitrary number of species (Roberts and Dobson 1995).

Dobson (1985) classified this as *exploitation competition*. The same author listed examples of host-parasite systems where the covariance could be positive, for example where two parasite species share the same intermediate host and conditions favourable for one are also favourable for the other, and of systems where the covariance would be negative, for example due to immune reactions or other biochemical interactions. These mechanisms were classified as examples of *interference competition*. Such mechanisms require more than the inclusion of a nonzero $X$ in (57) however, as this only models one result of the interaction and not the mechanism itself.

# 11 Conclusions

Models for the population dynamics of macroparasites of wildlife, especially those based on the deterministic formulation of Anderson and May (1978) have been reviewed and discussed. This has shown how the model framework has been successful in describing many of the phenomena that are observed in the field, as well as raising some interesting questions. In particular, more emphasis could be placed on developing a mechanistic submodel for the interaction between the parasite and its host that incorporates acquired immunity. New or improved ways of dealing with seasonal fluctuations in host-parasite dynamics could be sought, in order to determine a realistic magnitude for the 'fluctuation about the steady state value'. For some parasite species, notably *Echinococcus*, it is not easy to detect processes that regulate the parasite population in the field, and this hampers the development of an appropriate model. Finally the interaction between one or more parasite species in the same host introduces dynamical compexities, some at first sight paradoxical, even when mechanisms for direct interaction are not included in the model. These systems require further study.

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# Macroparasite Group Report: Problems in Modelling the Dynamics of Macroparasitic Systems

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# 1 Introduction

Macroparasite models take explicit account of superinfection. Hosts may be infected many times and accumulate parasites throughout their lifetime. They are not distinguished according to whether or not they are infected but, rather, according to how many parasites each one contains (Kostizin 1934, Anderson and May 1991). Macroparasitic systems also involve larval or immature phases which entail obligatory development as free-living stages or as parasites of one or more intermediate host. Given these complexities, the discussion group considered the extent to which current models of macroparasitic systems might be deficient. Our conclusion was that the following features of macroparasitic systems have frequently been dealt with in approximate or superficial ways – or else ignored:

1. the aggregated nature of parasite frequency distributions,
2. the complexities introduced by the incorporation of acquired immunity,
3. the development of morbidity
4. arrested development in gastrointestinal nematodes of mammals,
5. the population dynamics of intermediate hosts, transport hosts and vectors,
6. interactions between parasites in communities of parasites.

It was impossible to give each of these topics equal weight in the discussions that followed and there is no pretense that we were able to propose comprehensive solutions or strategies for dealing with the deficits we identified. Nevertheless, we hope that the summary set out below will have cleared away some of the clutter and that we have managed to indicate (however tentatively) which areas are important and what approaches might be useful. We concentrate in the first instance on the problem of modelling parasite frequency distributions and then move on to a discussion of some of the complexities inherent in many macroparasitic life cycles. The chapter finishes with a brief account of the difficulties of investigating the dynamics of communities of parasites.

# 2 Modelling parasite frequency distributions

Most models of macroparasitic systems focus on the number of parasites each host contains. It seems appropriate therefore to consider whether or not it is possible to write models in which parasite frequency distributions arise naturally out of the architecture of the model and, if it is, whether or not

such models might prove tractable methods of addressing questions to do with the influence of the acquired immune response and the distribution of morbidity and mortality in the affected host population. The aim is to construct tractable models of macroparasitic systems that incorporate defensible representations of the natural mechanisms which generate observed parasite distributions. First of all, we consider why we should want to model parasite frequency distributions at all. Next we deal with the problem of measuring and describing parasite frequency distributions in natural populations, and, finally, we survey what is wrong with current methods of representing parasitic frequency distributions in macroparasite models.

## 2.1 The significance of parasite frequency distributions

The importance of parasite frequency distributions in macroparasite models lies in their significance for the regulation of the abundance of host and parasite populations and for the related question of the distribution of infection-related morbidity and mortality. It has been shown in a variety of contexts that parasite induced host mortality, host morbidity, and constraints on parasite survival, development and fecundity are functions of the intensity of infection (Hawkins and Morris 1978, Scott and Anderson 1984, Smith 1984a, Crompton and Stephenson 1990). It follows that the impact of macroparasites upon host populations is critically dependent upon parasite frequency distributions (Gulland this volume, Roberts *et al.* this volume) and an understanding of the nature of parasite frequency distributions enhances our understanding of the patterns we see in the field. For example, the observation that most parasite frequency distributions are highly aggregated (Hudson and Dobson this volume) leads to the counter-intuitive conclusion that the majority of animals we see with clinical signs of infection will have intermediate rather than high parasite burdens (Medley 1993).

We also study parasite frequency distributions for the insight they give us into the nature of the interaction between hosts and parasites and for the questions that arise. Morbidity models provide a good example (Guyatt and Bundy 1991). Although the papers cited above indicate that morbidity is a function of the intensity of the infection, the relationship is by no means clear cut. Are we correct to ascribe morbidity to the current parasite burden, or should we look to some previous burden with a defined time lag, or to the accumulated influence of the entire history of the infection? Although initial considerations seem to suggest that it may be possible to ascribe much of the morbidity in invertebrates and lower vertebrates to current parasite burdens and that morbidity in higher vertebrates is more often a consequence of accumulated experience of the parasite, this remains to be proven. Such considerations lead to questions concerning the host's contribution to mor-

bidity and how this might vary with parasite load. For example, in higher vertebrates, pathogenicity can be a consequence of a misdirected immune response (Rothwell 1989, Lightowlers and Rickard 1988) and it often seems that the host response is constrained in some way. While it is certainly the case that some parasites are capable of immunomodulation (Cross and Klesius 1989), there remains the possibility that the host constrains its own response to effect a balance between parasite control and immunopathogenicity. In addition, it may be that the parasite exploits the host response to modify its own environment (Isseroff*et al.* 1977).

One of the most productive consequences of observed heterogeneities in the number of parasites per host has been the inquiry into how we might account for the observed distributions (Anderson and Gordon 1982, Pacala and Dobson 1988). Explanations for aggregated distributions have tended to focus on differential exposure to infective stages; due to the aggregated dispersal patterns (see below), or differences in the way hosts sample their environment), and differences between hosts with respect to parasite establishment (Herd*et al.* 1992). Interestingly, rather little has been done on the possible consequences of non-random distributions of parasite genotypes (Al Saqur*et al.* 1982). We also need to explain why patterns of aggregation are dynamic entities that may change with season (Spelling and Young 1986) or host age (Hudson and Dobson this volume). Sometimes, for example, the degree of aggregation decreases with host age (Pacala and Dobson 1988). There are a number of possible explanations. The simplest is that there may be age-dependent changes in exposure (Chandiwana and Woolhouse 1991), but it is also possible that lower sample sizes in older hosts will introduce a bias that increases estimates of $k$ in these age groups (Elliot 1977). Simulation studies by Quinnell and Woolhouse (unpublished) show that modelling infection in terms of discrete rather than continuous events can result in older hosts having less aggregated parasite distributions, but the most commonly applied explanation involves some kind of density dependent mechanism (Anderson and Gordon 1982, Pacala and Dobson 1986, Spelling and Young 1986). It is axiomatic that density dependent process are proportionately more severe in hosts with large parasite burdens. If those processes act to reduce the intensity of infection in those hosts, there will, over time, be a reduction in the degree of aggregation in the parasite population. We can use graphical methods to crudely distinguish between the consequences of density dependent processes with memory (e.g. the acquired immune response in vertebrates) and those without (e.g. constraints on the asexual multiplication of trematode larvae in snails); see Figure 1. Although it is true that acquired immune responses seem, in general, to reduce aggregation, the reader should bear in mind that there are some acquired immune responses (e.g. concomitant immunity) that increase aggregation (Medley, Dietz, personal communication).

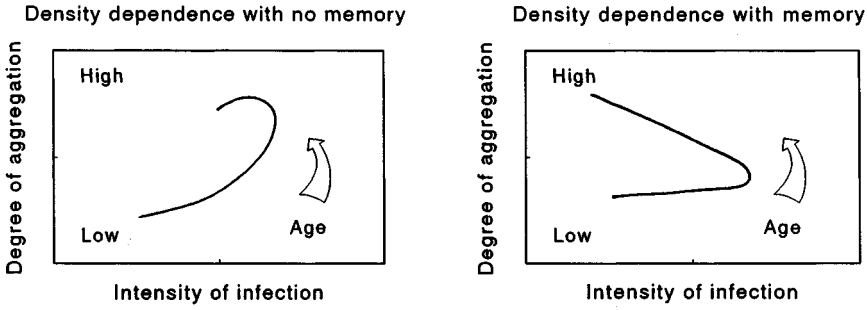


Figure 1. Graphical method of distinguishing between density dependence with and without memory (Woolhouse, personal communication).

## 2.2 Measuring parasite frequency distributions

In order to model parasite frequency distributions we first need reliable methods of measuring the distributions that actually occur in the field. The literature is replete with records of parasite frequency distributions obtained by *post mortem* examination of affected hosts, but there are a number of problems with this approach. Experience with counting endoparasites in domestic species shows that counting errors are common: younger (smaller) parasites are often undetectable (Wilson*et al.* 1982, Smith 1994) and there are large differences in the efficiency of the various methods for extracting parasites from host tissues (Herlich 1956). Even when we have confidence in the parasite counts it may be difficult to obtain a representative sample of hosts. For example, Smith (1984b) counted *Fasciola hepatica* larvae in populations of *Lymnaea truncatula*. While the parasites were relatively easy to find, the hosts were not, and the visual searching methods used by Smith underestimated the densities of younger snails when compared with mechanical methods of host detection (Morphy and Ross 1970). Sometimes, reported distributions depend upon serendipitous access to host tissue rather than upon some systematic sample of the host population. Examples of this include road kills, surveys of parasitism in animals killed by hunters and in animals found dead of disease (Schulze*et al.* 1984, Keith*et al.* 1985, Hoeve and Scott 1988). In each of these cases, certain age groups and sexes of host may be under or over represented either by reason of behaviour differences, hunting restrictions, or susceptibility to infection and subsequent morbidity. The errors are compounded if the likelihood of the host succumbing to any of these causes of death is higher in those animals with most parasites.

Of course, it is not always possible to count parasites directly and a number of surrogate measures have been devised. These methods are subject to most of the errors listed above and incorporate an additional uncertainty with respect to how well they actually represent parasite numbers. Faecal

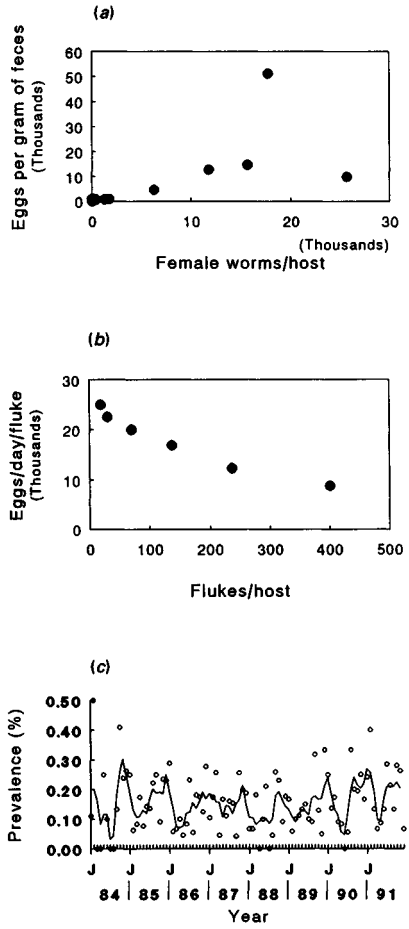


Figure 2. (a) Relationship between the number of mature female *Haemonchus contortus* and the number of strongyle type eggs in the faeces of naturally infected lambs (data from Coyne (1991)); (b) The daily egg production per *Fasciola hepatica* (averaged over 15 weeks) compared with the intensity of infection at the time of slaughter (data from Boray (1967)); (c) Prevalence of ascarid infections in cats in eastern Pennsylvania determined by faecal examination (Nolan, unpublished).

egg counts and plasma pepsinogen levels have been used with some success to measure the mean intensity of infection of gastrointestinal nematode parasites in populations of domestic hosts (Figure 2) (Coyne *et al.* 1991, Kerboeuf *et al.* 1987) but the variance associated with the technical procedures used is so great that the use of either of these methods to estimate parasite burdens

in individual hosts is highly problematic. There are other difficulties: clearly, egg counts cannot be used if fecundity is subject to some severe density dependent constraint (Figure 2), and, even if the only sources of variance are parasite age or size, the distribution of egg counts from hosts to host will not necessarily reflect the underlying distribution of parasites: Tallis and Leyton (1966) showed that aggregated distributions of eggs could just as easily arise from randomly distributed populations of parasites as from aggregated populations. Faecal egg counts may be used with more assurance to estimate the prevalence of infection (Figure 2), but without consistent measures of the specificity and sensitivity of the counts it is hard to estimate the true prevalence of infection from the apparent prevalence that is actually measured.

There are two possible methods of quantifying parasitism using standard immunological measures. Seroepidemiological techniques which measure antibody responses to parasite antigen are widely employed. Unfortunately, such techniques may frequently (Lloyd this volume) measure merely exposure rather than current infection, although the short lived IgA response holds some promise that this difficulty might be overcome for some systems. An alternative method depends upon the detection of parasite antigens. The quantity of antigen found may be related to the intensity of infection provided it is neither immunogenic (and therefore subject to complexing and removal) nor sensitive to host responses that affect the metabolism of the parasite. In all cases, the sensitivity and specificity of these tests must be determined for the target species and target host (Lloyd, personal communication).

## 2.3 Indices of aggregation

Given that some adequate method is found to estimate the intensity of infection for each host in the population, it will often be convenient to summarize the data in a single measure of the degree of aggregation. The best measure of aggregation is one that varies least with the mean intensity of infection and the sample size and which is sensitive to the form of the real underlying frequency distribution. Gregory and Woolhouse (1993) compared various indices with respect to these criteria (Table 1).

Simulation studies indicated that the best single index of aggregation turns out to be the corrected moment estimate for $k$.

## 2.4 Problems in modelling parasite frequency distributions

Over the last fifteen years, many of the advances in modelling the dynamics in macroparasitic systems have come from a class of models in which parasite frequency distributions have been modelled phenomenologically (Crofton 1971, May 1977a, Anderson and May 1978, May and Anderson (1978), Roberts

| Index | Formula ($m$ = mean, $v$ = variance, $n$ = number in sample) |
|---|---|
| Variance to mean ratio | $v/m$ |
| Standardized variance | $v/m^2$ |
| Moment $k$ | $m^2/(v-m)$ |
| Corrected moment $k$ | $(m^2 - \frac{v}{n})/(v-m)$ |

Table 1. Indices of parasite aggregation (from Gregory and Woolhouse (1993)).

*et al.* this volume). These models proved to be extraordinarily useful in many contexts but were cumbersome or inadequate in others (Adler and Kretzschmar 1992, Smith and Guerrero 1993). Most of these phenomenological models assumed that the aggregated distribution that characterizes most parasite populations was best represented by the negative binomial distribution. The first problem that arises is whether the negative binomial distribution is indeed a suitable model for observed patterns. Grafen and Woolhouse (1993) show that if the overall distribution of parasites is correctly described using a negative binomial model then the each of the different subclasses (e.g. development class, genotype or sex) of parasite will be similarly distributed. However, problems arise when dealing with the frequency distributions of parasites in different subclasses of host. For example, if the distribution of parasites in each host category (e.g. young/old, male/female) follows the negative binomial distribution, the overall distribution, though still aggregated, is not best described by the negative binomial model unless the mean and variance of the distribution is identical for each sub-population (Dietz 1982, Pacala and Dobson 1988). Similarly, if different parasite species are negatively binomially distributed in the same host population, the distribution of parasites overall is not a negative binomial unless the variance to mean ratio is the same for all species (although the parasites are still aggregated).

The second problem arises as a result of the assumption that the shape of

the parasite frequency distribution remains the same regardless of the mean number of parasites per host. Using a negative binomial model the shape of the distribution is indexed by the parameter $k$. This distribution model has a number of significant theoretical advantages: among these is that the value of $k$ is invariant under random thinning (Pielou 1977). Unfortunately, aggregation is incorporated in these models precisely because of the need to take account of the non-random thinning that is a consequence of density dependent processes. Thus the models contain an inherent contradiction. They assume that the degree of aggregation remains constant despite the operation of population processes that explicitly affect the number of parasites in each host in a non-random manner. Furthermore, while these models can cope with mechanisms which depend on the current parasite burden or the burden at some previous time (May and Anderson 1978), they founder when the process in question depends upon the hosts' accumulated experience of infection. This reflects the formidable problem of modelling the dynamics of acquired immune responses in higher vertebrates (Anderson and May 1991).

One way out of these difficulties is to write models in which the parasite frequency distributions are an emergent property of the model (Hadeler and Dietz 1983, Kretzschmar 1989, Barbour and Kafetzaki 1991; see also Roberts *et al.* this volume). Advances in bringing together theory and empirical observations in this area have been made by Anderson and Gordon (1982), who focussed on the consequences of parasite induced host mortality, and by Pacala and Dobson (1988) who presented a more generalized treatment. Anderson and May (1985) suggested a method for modelling the acquired immune response to helminth infections in man, which generated aggregated parasite distributions as a consequence of heterogeneities in the strength of the response. Ultimately, such processes may need to be modelled by taking account of how observed parasite frequency distributions arise as a function of the dynamics of infection in different age cohorts of hosts. The explicit form of the resulting distribution is likely to be very complex and more work needs to be done in this area. Grenfell *et al.* (this volume) suggest a possible way forward, via modelling how the variances and covariances of parasite and immunity distribution evolve with host age.

# 3 Arrested development in helminths and diapause in arthropods

Arrested development in gastrointestinal nematode parasites and diapause in ticks are important mechanisms by which the parasite avoids inimical climatic conditions (Armour and Bruce 1974, Yuval and Spielman 1990). Both processes are very influential with respect to the generation of observed patterns of intensity of infection and the temporal distribution of morbidity (Gibbs

1986, Gray 1982). Unfortunately, while there is some notion about the mechanisms that induce diapause in ticks (Belozerov 1967), the mechanisms that give rise to arrested development in helminth endoparasites are unknown (Gibbs 1986). Accordingly, models incorporating arrested development do so phenomenologically without recourse to any mechanistic explanation (Coyne and Smith 1993). This is a serious deficit in our understanding of nematode dynamics.

# 4 Impact of free-living stages, vectors and intermediate hosts on parasite dynamics

## 4.1 Climate and free-living stages

The older medical and veterinary literature on macroparasitic systems is replete with studies dealing with the influence of climate on the risk of infection. This became a neglected and low prestige area over the last two decades as our ability to study the less accessible (and more molecularly glamorous) aspects of the parasite life-cycle increased. However, there are at least two reasons why we should once more become interested in the effect of climate on free living stages. The first is a consequence of global warming (Dobson and Carper 1992), which threatens to cause a dramatic geographical shift of serious parasitisms into regions hitherto unaffected (at least in recent times), and the second is the accelerating spread of resistance to parasiticides (Prichard 1990). In the former case we need to be able to devise probable scenarios for movement of parasitisms into new areas in order that we may implement preemptive control strategies. In the second case, given the paucity of new parasiticides, we shall have to resort to managing resistance with the resources we have to have to hand; this will necessarily include management strategies that exploit our knowledge of the quantitative aspects of the development and mortality of free-living stages (Smith 1990a, 1992). Unfortunately, despite the volume of papers dedicated to the study of free-living stages, there is depressingly little published work that is amenable to comprehensive quantitative analysis (Smith 1990b), although there are some significant exceptions (e.g. Hope-Cawdery *et al.* 1978, Anderson *et al.* 1982, Grenfell *et al.* 1986, Randolph 1993a). Nevertheless, the appropriate analytical tools are to hand and we should be in a better position than previously to properly interpret the significance and relative influence of climatic effects especially given the advances in our understanding of the behaviour of generic models in which seasonal effects are modelled using periodic forcing functions. Such studies oblige us to exercise caution in inferring causal connections between seasonality and periodic parasite dynamics. Analysis of the behaviour of generic models suggests that seasonality in the density and age-structure (or sus-

ceptibility) of the host population may often be as important as seasonal variations in free-living stage survival and development in the causation of seasonal variations in parasite abundance (Roberts and Grenfell 1992).

## 4.2 The dispersion of infective stages and host behaviour

There is a large class of parasites for which transmission to the definitive host depends upon accidental ingestion of the infective stages. When the definitive host is a carnivore, the distribution of the infective stages depends upon the distribution of the infected (and mobile) prey species, and a plethora of mechanisms exist by which the infected prey item is rendered more susceptible to predation by the definitive host (Dobson 1988). The significance of this observation is that it imperils the assumption of homogeneous mixing of parasite and host individuals (the 'mass action' principle) that is at the core of so many models of macroparasitic systems. In addition to those mechanisms which cause hosts to encounter infective stages more frequently that one would expect by chance alone, Dobson (1988) alludes to mechanisms which decrease the chance of parasite-host encounters. This may be of particular relevance when the definitive host is a herbivore.

When the definitive host is a terrestrial herbivore, the dispersal of infective stages is accomplished by a variety of mechanisms (Boswell and Smith 1976, Lawson and Gemmell 1983), but the final distribution is relatively fixed. The question concerning the evolution of host behaviours which may reduce host exposure to infection is of particular significance when the infection stages have highly aggregated distributions such as the larvae of trichostrongylids (Tallis and Donald 1970, Boag *et al.* 1989) and whose presence is readily associated with some detectable marker (i.e. pasture contaminated with faeces). The principal mechanism by which transmission is reduced is that grazing hosts avoid food items contaminated by faeces. This behaviour may or may not be buttressed by distinct defaecation patterns. For example: neither sheep nor cattle have obvious defaecation sites but do not feed near faeces unless stocking densities are high; horses and rhinoceros have distinct latrine areas and do not feed near faeces; and Mangabey Monkey have random defaecation patterns, but will avoid eating in the area where defaecation occurs (Macdiarmid and Watkin 1972, Odberg and Francis-Smith 1976). More complex avoidance behaviours are also observed. Some hosts appear to engage in migratory behaviour that reduces exposure to infective stages. For example, baboons alternate periods of use of a sleeping grove with much longer periods of avoidance. The period of absence from the grove may coincide with the time of peak emergence of nematode larvae from pats deposited a few days earlier (Hausfater and Meade 1982). This kind of behaviour is not limited to the avoidance of nematodes. Some reindeer herds migrate soon after calving

(the time of peak transmission for warble flies) – some do not. Warble fly infestations in those herds that migrate are less than in those herds which do not (Shaw, in preparation).

We do not yet know how important these violations of the principle of homogenous mixing may be with respect to our attempts to accurately represent the macroparasite dynamics and it is possible that there are instances in which they will be of trivial significance because of coevolutionary parasite adaptations. For example, the life span of the infective stages of trichostrongylid larvae is much longer than the period for which most faecal traces persist (Boag and Thomas 1985).

## 4.3 Biting flies and onchocerciasis: density-dependent processes affecting the intensity of infection in the vector

Identifying the processes which regulate parasite numbers is an important step in explaining the dynamics of the infection. The density of macroparasites with a direct life cycle appears to be regulated primarily during the mature parasitic phase. However, this need not be case for those macroparasites with indirect life cycles (Dye this volume). *Fasciola hepatica* infections in sheep, for example, are regulated by processes which occur in both the definitive and intermediate hosts (Smith 1984a). In such circumstances, we are obliged to take particular notice of those phases of the life cycle which occur outside the definitive host.

A particularly compelling example involves *Onchocerca volvulus* which is transmitted to humans by a simulid vector. Recent work by Basañez*et al.*(1994) indicates that there are at least two density dependent processes at work regulating the intensity of infection in the vector. The first of these density dependent processes regulates parasite establishment. As the number of parasites ingested by the flies increases, there is a decrease in the proportion of microfilariae which succeed in passing to the haemocoele and/or thorax of the vector. Thus the number of established microfilariae saturates at some given level irrespective of how many are ingested. The second density dependent process determines vector mortality. It was found that vector survival following a blood meal was inversely related to the mean microfilarial intake per fly. Thus, in addition to the saturation effect alluded to earlier, microfilarial abundance in the vector population as a whole is likely to be regulated also by parasite induced fly mortality (Dye and Williams this volume).

## 4.4 Ixodid ticks as vectors

Although a great deal of progress has been made in modelling macroparasitic systems by keeping the models as simple as possible and by stressing the

similarities between systems rather than their differences, it may be time to explore in more detail the consequences of the different life-cycle strategies that make this group of parasites so interesting. For example, ticks are second only to mosquitos in terms of the number and variety of diseases they transmit but ticks offer a marked contrast to the biting flies in terms of their population biology and the way this impinges on their role as vectors: ticks feed only once in each stage of the life cycle; they are relatively immobile compared with the winged insects; and, there is only a single reproductive event (hundreds or thousands of eggs are laid in a single prolonged egg-laying session). The impact of each of these features warrant further study. For example, tick feeding is prolonged (several days) and ticks have evolved a number of special adaptations of the salivary gland and saliva to overcome the defensive reaction of the host. Pathogens have hijacked these adaptations, exploiting both the volume and chemical (anticoagulant and immunosuppressive) properties of the tick saliva to achieve transmission.

A feature of particular interest in tick biology is that the pathogens for which they act as vectors may be transmitted from one life cycle stage to the next by transstadial or transovarial transmission (Randolph 1993b). The latter may be particularly significant because of the large number of eggs laid by ticks (an amplification phenomenon which effects $R_0$).

The host immune response may be very strong indeed, and, although it may be rather short lived, current evidence indicates that it is the major density dependent regulatory factor acting on ticks. It tends to remove the long tail of the aggregated distribution of ticks on their hosts. This is particularly relevant to *transstadial* transmission, where $R_0$ is determined by the multiple infestation of an infected host by a single tick stage and the subsequent infestation of different susceptible hosts by the next stage. If the tick infestation levels and/or survival are positively correlated with the infectiousness of the host, then the potential for transmission will be enormously enhanced. For example, ticks that feed on rodents infected with *Babesia microti* do indeed feed and survive better than ticks feeding on uninfected rodents (Randolph 1993c).

In common with all vector-borne diseases, estimates of $R_0$ for tick-borne diseases require estimates of tick biting probabilities, transmission coefficients, tick fecundity and tick mortality rates – these are all difficult to measure in the field, not least, because of the effects of behavioural and physiological diapause which lead to considerable generational overlap of tick cohorts in some species (see above)

## 4.5 Snails as intermediate hosts

We can illustrate the progressive exploration of increasing complexity discussed in the previous section by reference to schistosomiasis. The basic

simple model for schistosomiasis is predicated on the idea that there is a very severe density dependent constraint (saturation effect) on the production of cercariae in the snail intermediate host (May 1977b). It is possible to progressively elaborate this simple model to include more complex snail/parasite population dynamics. If $M$ is the mean number of parasites per host and $y$ is the proportion of patent, infected snails the basic model is

$$\begin{aligned} \frac{dM}{dt} &= \alpha N y - \gamma M \\ \frac{dy}{dt} &= \beta H M(1-y) - \mu_2 y \end{aligned}$$

where $N$ and $H$ are the densities of snails and humans respectively, $\alpha$ and $\beta$ are transmission terms, $\mu_2$ is the mortality of infected snails and $\gamma$ is the mortality of the worms. The basic reproduction ratio ($R_0$) for this simple system is

$$R_0 = \frac{\alpha\beta NH}{\mu_2\gamma}$$

If we allow for prepatent snails the basic reproduction ratio becomes

$$R_0 = \frac{\sigma}{\sigma+\mu_1}\frac{\alpha\beta NH}{\mu_2\gamma}$$

where $\sigma$ is the rate of maturation of infection and $\mu_1$ is the mortality of the infected/prepatent snails (Woolhouse 1993). We can progressively introduce further complications such as parasite induced snail mortality, seasonality in snail demography and patchiness in snail distribution and human contact. Each of these elaborations can be examined for the effect it has on the value of the reproduction ratio. It turns out, for example, that patchiness has a significant impact on $R_0$ only in those cases where there is a high covariance between contact rate and the abundance of snails (Dietz, personal communication).

### 4.6 Mammals as intermediate hosts

Mammals are intermediate hosts of the cestode parasites *Echinococcus granulosus* and *Echinococcus multilocularis*. The intriguing problem here is that, unlike other taeniids, field studies suggest there does not seem to be any significant protective immunity to infection in either the intermediate or definitive hosts (Roberts *et al.* 1986). What then is regulating parasite abundance in these systems? In agricultural systems, external constraints, such as limitations on host density may well be influential (Roberts *et al.* this volume).

## 5 Community structure

Although the majority of models of macroparasitic systems appear to make the assumption that parasite species occur in isolation or as single species

populations (see Roberts *et al.* this volume), some considerable progress has been made towards a framework for the quantitative investigation of the dynamics of communities of parasites. It is convenient to consider parasite community structure at three nested hierarchical levels (in order of decreasing richness)

1. The compound community (all the parasites in all the hosts in the habitat)
2. The component community (all the parasite species in a single host species)
3. The infra community (all the parasites species in a given individual host)

Communities can be further classified according to whether they are poor in species number and isolationist or rich in species number and interactive. Field observations in fish communities indicate that although indices of community structure (e.g. mean number of species per host and other measures of diversity) tend to remain fairly constant, the actual composition of the parasite community in a single host species may be very variable indeed. Interactive communities are more predictable but parasites often occur there in association with congeners (Kennedy 1990). How can we deal with communities and make sense of this variability?

One possible approach is to begin with a template (null hypothesis) which assumes that the parasites have no effect on the host or on each other. One can imagine that the proportion of hosts infected by any given parasite species will depend on host density (or some function of host density like contact rate) and that there is a particular host threshold density for each species below which hosts remain free of infection. This leads to a notion of community structure in which poor communities are a consequence of low host densities and rich communities a consequence of high host densities. The species which establish at low host densities will still be present at high host densities and, indeed will be the 'dominant' species in terms of the prevalence of infection. By examining the extent to which simple templates like this can account for the observed patterns it becomes possible to dissect out the patterns that remain to be explained and so simplify the process of analysis (Dobson 1990).

# 6 Agenda for future work

Clearly, there is much still to be done. In particular we look forward to further development of methodologies for the description of the distribution of parasites within wild animal populations and the identification of the factors generating such distributions. A central problem here is the creation of

tractable mathematical methods for generating realistic parasite frequency distributions as an inherent property of the architecture of the model. This should lead to more useful ways of modelling acquired immunity and its consequences particularly in the context of changing environmental inputs (e.g. nutrition). We also think the time has come for a reappraisal of the way in which we represent the free-living parasitic stages in our models (particularly with regard to seasonal and globally changing variables like climate) and a systematic theoretical and empirical exploration of the extent to which it is necessary to incorporate the extra complexities inherent in the life cycles of many macroparasitic systems. Finally we are encouraged by the progress that has already been made in terms of a systematic theoretical and empirical exploration of the extent to which we need to take account of the context (i.e. the parasite community) of hitherto single species models.

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# Critical Evaluation of Wildlife Disease Models

*N.D. Barlow*

## 1 Introduction

This paper briefly reviews existing models then attempts to identify some key remaining questions and challenges in the modelling of wildlife diseases. Both the review and the conclusions reflect a pragmatic viewpoint which emphasises the application and biological relevance of models, and focuses on case studies as opposed to general theory (see Heesterbeek and Roberts this volume, Roberts *et al.* this volume, for a more formal treatment). Moreover the review is by no means exhaustive. Rather I attempted to include sufficient material to cover and allow comment on a range of models and approaches, and to draw some general conclusions on areas of difficulty which deserve future attention.

## 2 The Models

### 2.1 Model scope

The basic structural characteristics of the models considered are summarised and compared in Table 1, then points of note, key results and problems with the models are listed in more detail in Table 2. Of the 35 wildlife disease models reviewed, only two were for macroparasites, the gastro-intestinal nematode *Trichostrongylus tenuis* in red grouse (Model 34, Dobson and Hudson 1992a,b) and the liver parasite *Capillaria hepatica* as a potential biological control agent of house mice in Australia (Model 35, McCallum and Singleton 1988, Singleton and McCallum 1990). Although an enormous literature exists on models for macroparasitic infections, the great majority relate to domestic animals. In contrast, there appear to be few modelling case studies involving macroparasites in wildlife, possibly because of the complex parasite life cycles and the frequent need for population dynamics data on more than one host. For example, Dobson and Keymer (1985) provide a general model structure and list life history parameters for 14 species of Acanthocephala, but model application is constrained by the fact that for no one species is the parameter list complete. Undoubtedly some macroparasite/wildlife modelling case studies have been overlooked, but Models 34 and 35 do at least provide excellent representative studies for the purposes of this review. Partly because this

representation is limited and partly because excellent overviews on general macroparasite models and problems pertaining to them are already available (e.g. reviews by Dobson and Keymer (1985), Dobson and May (1986) and Dobson (1989), see also this volume), the general discussion below focuses primarily on models for microparasitic diseases. Of these, 15 relate to rabies (also reviewed by Pech and Hone (1992)), and the next largest disease category is bovine Tb (8).

Key factors emphasised in the Tables are host biology and disease transmission, while consideration of model objectives and realism reflect the pragmatic context. Realism in Table 1 is defined as the ability to reproduce disease/host dynamics agreeing qualitatively and quantitatively with those observed. This is a necessary but not sufficient condition for model adequacy: it must also be right for the right reasons. Where there is cause to believe that a model may be right for the wrong reasons, this has been addressed in Table 2 and the discussion below.

The scope of the models considered varied considerably, from complete representations of the disease/host system in time and space, through models focusing on the endemic (non-spatial) system or on the velocity of epidemic spread, to those targeting particular processes or relationships, such as transmission dynamics or the evolution of virulence. The macroparasite models (Models 34 and 35) included a free-living parasite stage and (Model 34) predators of the host. Clearly some models contained many more parameters than others, and although the number of parameters is not listed explicitly in Table 1, in general this reflected the number of features the model embodied. Likewise, the number of parameters in a model generally reflected the level of understanding and degree of agreement between model and reality sought by the model-builder. This does not preclude the possibility that a model is either too simple or too complex for the objectives, and some cases are referred to in the discussion and Table 2.

The scope of each model partly depended on its objectives. Thus only 7 models were complete representations of the disease/host system including explicit spatial effects and all essential biology (Table 1, Models 1, 5, 8, 11, 14, 17, 29). Most models of myxomatosis were concerned primarily with accounting for and predicting the evolution and attenuation of the virus. Of the others, 9 had improved disease control as an aim, as well as understanding the dynamics of disease and host. No clear consensus emerges from these models regarding the relative merits of different control strategies, although there were frequent suggestions that vaccination was superior to culling for rabies control and that culling probably disrupted social behaviour and/or caused a vacuum effect enhancing the spread of diseased animals. There were few data or results to support either assertion. Sterilisation was less commonly examined as an option.

Of more concern, half of the papers offered no evidence that the model's

output was realistic. In some cases no such test was possible since the models were predicting a hypothetical event (e.g. the effect of introducing an exotic disease), while in others results were compared with reality and discrepancies noted and acknowledged (e.g. Table 1, Model 24). However, in the remainder no check on the model's realism was described.

## 2.2 Modelling spatial heterogeneity

Extensive reviews of the theory, practice and importance of spatial models are given by Bolker *et al.* (this volume) and Mollison and Levin (this volume). Of the 17 models with a spatial component the preferred approach (11 out of 17 models) was simulation using a grid, or co-ordinates for individuals, and of these all but one (Model 10) were stochastic. The remaining six spatial models were deterministic mathematical ones, using diffusion, a reproduction and dispersal kernel, or transmission as a function of distance to represent the spread of disease.

There was considerable variation in the treatment of the host population, from the simplest in which it was assumed constant (Table 1, Models 6 and 28) to the most detailed and explicit representation of host behaviour (Model 30), including such features as daily den-searching by individuals determined by memory of previously occupied sites. Between these extremes most complete disease/host models included host density-dependence, though the mechanics and consequences for population recovery rates was often inadequately described and unclear. This was particularly true for the spatial stochastic grid models with local density-dependent spacing behaviour. A valuable output from these models would have been the shape of the overall population growth curve (rate of growth versus density). Such intermediate outputs, which would also include values for realised contact rates (new infections per infectious per unit time) as a function of infectious and susceptible densities averaged over the whole area considered, would allow both a better understanding of the models' intrinsic behaviour and direct comparison with their simpler deterministic equivalents.

In terms of disease transmission, most models adopted the standard mass-action approach, applied locally in the case of the spatial grid models and globally otherwise. Except in Models 14, 26 and 29, the transmission coefficient and threshold density for disease elimination were invariablyassumed to be constant with respect to host carrying capacity. On the basis of this possibly invalid assumption (see below), considerable emphasis was given in most cases to effects of different host carrying capacities on disease dynamics and control.

Interestingly, all of the spatial rabies models recreated realistic velocities of spread, but through a wide variety of different mechanisms. For the stochastic grid models these included:

- dispersal of incubating juveniles together with density-dependent spacing behaviour, and assuming that transmission can occur during dispersal (Models 5, 8, 14)
- dispersal of incubating juveniles only, with no transmission during dispersal (Model 10)
- dispersal of incubating juveniles and long-range movement of infectious animals (Model 1)
- long-range movement of infectious animals only (Model 2).

For the mathematical spatial models the mechanisms were:

- random movement of infectious animals (Models 9, 11)
- random movement of infectious animals and latent males (Model 12)
- dispersal of infectious animals from a distribution of dispersal distances (Model 13)

Mollison (1987) provides the simplest mathematical model for the velocity of rabies spread, equal to $R_0\sigma/2\tau$ = 25–50 km/yr, where $R_0$ is the basic disease reproductive rate (5), $\sigma$ is the root mean square dispersal distance (1–2 km) and $\tau$ the mean generation gap of the disease (0.1 yr). The formula does not appear to work for Tb in possums, however, and the value for the root mean square dispersal distance clearly depends on which categories of animals and what proportion of the population is involved. Presumably not all of the above assumptions for mechanisms of spread are correct, yet, since most are effectively tuned to the observed rate of spread, there is no way of telling if the models are right for the wrong reasons. Support for the involvement of juvenile dispersal comes from the major difference in dispersal distances between European and North American foxes (8 km versus 10–30 km), and the corresponding difference in velocity of disease spread (30–50 km/yr versus 90 km/yr), an outcome predicted by models which include juvenile dispersal as an agent of disease spread (e.g. Model 10).

Models 23 and 33, for PDV in seals (Grenfell *et al.* 1992) and anthrax in Kruger National Park game animals (Hahn and Furniss 1983), both describe the course of 'classic' epidemics. These are sufficiently rapid that the host population can be considered otherwise static. The PDV model has the usual classes of susceptibles, infectious and recovered, while the anthrax model has susceptibles, infected carcases and free-living spores (specifically spores ingested per animal per day, as a measure of disease in the environment). Similar formulae apply in both cases for the total size of the epidemic,

measured as the ratio of hosts surviving to hosts initially present ($s$), but with parameters interpreted slightly differently:

$$1 - s = -\alpha\delta \ln(s)/\beta H_0$$

where

$\alpha$ = 1/infectious period (PDV) or 1/spore lifespan (anthrax)
$\beta$ = transmission coefficient from infectious to susceptibles (PDV) or spore production rate from infected carcases (anthrax)
$\delta$ = case mortality = probability that an infectious animal dies of disease (PDV) or decay rate of carcases (anthrax)
$H_0$ = initial host population density (both models)

Such simple models appear well suited to other diseases like RHD (rabbit haemorrhagic disease), currently being considered as a biological control agent for rabbits in Australia and New Zealand. Their only problem is that they almost invariably predict elimination of the disease following a single epidemic, whereas the possibility exists that the virulence of the disease is compensated for by a high rate of spatial spread. In this way, persistence could occur through a kind of spatial 'hide and seek' between host and pathogen. Clearly explicit spatial models are required to address this possibility.

# 3 Discussion and Conclusions

From this brief survey a number of key questions emerge, many of which have been raised before (e.g. Mollison and Kuulasmaa 1985, Mollison 1991). These fall into three broad categories relating respectively to the formulation and structure of endemic models (i.e. those which do not include an explicit treatment of spatial spread of disease), formulation of epidemic models (those that include spatial spread), and model inputs and outputs, including data needs, results and communication:

## 3.1 Endemic Models

(1) How can deterministic endemic models be reconciled with stochastic ones; more specifically, how can spatial heterogeneity of disease be incorporated in deterministic models?

This is a valid and important question, for three reasons. Firstly, patchiness is an emergent property from stochastic spatial models (e.g. Mollison and Kuulasmaa 1985, Efford 1992, Pfeiffer 1993), and the overall number of actual infective contacts per infective per unit time is considerably reduced relative to expectations from a homogeneous mixing model (Mollison and Kuulasmaa 1985, see Table 2). Secondly, disease is observed to be aggregated in space, as is clear in the data for bovine Tb in New Zealand possums (Barlow 1991a, see Figure 1).

Overall key to symbols in Tables.

• **Model:**

**objective** – primary objective(s): **u** understanding; **c** understanding and disease control; **p** prediction (e.g. impact of an exotic disease or biocontrol agent);

**stochastic** – in discrete time (deterministic models all in continuous time unless otherwise stated);

**spatial** – **g** grid, **i** individuals as coordinates in continuous space, **d** diffusion;

**maximum animals per cell** – **m** many, **g** family group, **i** individual;

**latent/infectious classes; recovered class** – all models assumed to have a susceptible class, and the absence of separate latent/infectious classes implies that the model combines both in one infected class.

• **Host:**

**seasonality** – refers to host population parameters and/or disease parameters;

**habitat heterogeneity** – host carrying capacity $K$ varies;

**density-dependence** – **u** present but form or mechanism unspecified, **m** mortality density-dependent, **r** recruitment (reproduction and/or juvenile survival) density-dependent;

**dispersal** – **i** density-independent juvenile dispersal (but some have density-dependent local settlement after dispersing), **d** density-dependent juvenile dispersal, **r** through a reproduction and dispersal kernel (RandD kernel) in continuous time;

**spacing** – local density-dependent movement (adults and/or juveniles);

• **Disease:**

**transmission** – **h** homogenous, calculated globally, **l** heterogeneous, calculated locally;

**density function** – assuming the transmission term is expressed as $\beta I.f(S/N).g(N)$ where $\beta$ is the transmission coefficient, $I$, $S$ and $N$ the densities of infectious, susceptible and total hosts, then $g(N)$ is the density function and $f(S/N)$ the susceptibility function (Getz and Pickering 1983). For $g(N)$, **N** implies $g(N) = N$, **c** implies $g(N)$ = constant (e.g. sexual transmission), **f** indicates some other function (convex-up);

**susceptibility function** – the relationship between the effective or local proportion susceptible (per infectious) and overall proportion susceptible. **S** implies that $f(S/N) = S/N$, **f** indicates some other function (concave-up);

$\beta$ **(transmission coefficient) estimate** – **d** from disease prevalence and/or dynamics, **t** from $K_T$ (threshold for disease elimination), **c** from host behavioural interactions, **m** from other published models, **v** from a variety of sources;

$\beta$ **and** $K_T$ **vary with density and/or** $K$ – $\beta$ negatively and $K_T$ (threshold host density for disease elimination) positively related to $K$ unless otherwise stated;

**disease spread** – disease spread in space through **a** adult movement, **d** diffusion (diseased individuals only unless otherwise stated), **r** the reproduction and dispersal kernel in continuous time (all individuals), **j** juvenile dispersal, **n** transmission between neighbouring individuals or grid cells;

**realism demonstrated** – **y** model output shown to be realistic; **u** testing not feasible (no data, as in predicting the impact of an exotic disease).

**Table 1.** Wildlife disease models. Rabies/foxes:
1 Preston (1973); 2 Berger (1976); 3 Bacon & MacDonald (1980), Bacon (1985); 4 Anderson *et al.* (1981), Smith (1985), Anderson (1986); 5 David *et al.* (1982), David & Andral (1982); 6 Ball (1985); 7 Mollison & Kuulasmaa (1985); 8 Voigt *et al.* (1985), Tinline (1988) (Ontario model).

| Model | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Objective | u[1] | c | c | c | u | c | u | c |
| Stochastic | y | y | –[7] | – | y | y | y | y |
| Spatial | g | g | – | – | g | g | g | g |
| Max animals per cell | m | g | – | – | i | g | i | g |
| Latent/infectious classes | y | y | y | y | y | – | y | y |
| Recovered class | – | y | – | – | – | – | – | – |
| Seasonality | y | – | y | –[6] | y | – | – | y |
| Age-structure | y | – | – | – | y | – | – | y |
| Habitat heterogeneity | – | – | – | – | – | – | – | – |
| Density-dependence | u | – | mr | m | r | –[5] | y | m |
| Dispersal | i | – | – | – | i | – | – | i |
| Spacing behaviour | y | – | – | – | y | – | y | y |
| Transmission (mixing) | l | l | h | h | l | l | l | l |
| Density function | N | N | N | N | N | N | N | N |
| Susceptibility function | S | S | S | S | S | S | S | S |
| $\beta$ estimate | d | d | –[2] | tc | d | –[2] | –[2] | dc |
| $\beta$ and $K_T$ vary with $K$ | – | – | – | – | – | – | – | – |
| Disease spread | a | an | – | – | jn | – | n | jn |
| Cullin | y[1] | – | y[3] | y[4] | – | y | – | – |
| Vaccination | y[1] | y | y | y[4] | – | – | – | y |
| Spatial buffers | – | – | – | – | – | – | – | y |
| Realism demonstrated | y | – | – | y | y | – | – | y |

[1] very approximate estimates given for control policies; [2] effects of different values tested; [3] sterilisation also tested; [4] general formulae given for continuous culling rate and proportion immune necessary to eliminate disease; [5] host population assumed constant; [6] seasonally-varying $\beta$ briefly considered; [7] deterministic but in discrete time.

**Table 1 (cont.).** Wildlife disease models. Rabies/foxes: 9 Källén *et al.* (1985); 10 Garnerin *et al.* (1986); 11 Murray *et al.* (1986); 12 Gardner *et al.* (1989); 13 van den Bosch *et al.* (1990); 14 Smith & Harris (1991) (Bristol model); **Rabies/raccoons:** 15 Coyne *et al.* (1989); **Foot and Mouth/pigs:** 16 Pech and Hone (1988, 17 Pech and McIlroy (1990).

| Model | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
|---|---|---|---|---|---|---|---|---|---|
| Objective | u[1] | u | pc | p | u | pc | c | pc | p |
| Stochastic | – | –[2] | – | – | – | y | – | – | – |
| Spatial | d | g[3] | d | d | d | g | – | – | d |
| Max animals per cell | – | m | – | – | – | g | – | – | – |
| Latent/infectious classes | – | – | y | – | – | y | y | y | y[5] |
| Recovered class | – | – | – | – | – | – | y | y | y |
| Seasonality | – | y | – | – | – | y | – | – | – |
| Age-structure | – | y | – | – | – | y | – | – | – |
| Habitat heterogeneity | – | – | y | – | – | y | – | – | – |
| Density-dependence | – | r | m | – | – | u | m | m | m |
| Dispersal | – | i | – | – | r | d | – | – | – |
| Spacing behaviour | – | – | – | – | – | y | – | – | – |
| Transmission (mixing) | h | l | h | h | h | l | h | h | h |
| Density function | N | N | N | N | N | N | N | N | N |
| Susceptibility function | S | S | S | S | S | S | S | S | S |
| $\beta$ estimate | d | –[4] | m | c | m | v | t | c | c |
| $\beta$ and $K_T$ vary with $K$ | – | – | – | – | – | y[6] | – | – | – |
| Disease spread | d | jn | d | d | r | jn | – | – | d[7] |
| Culling | – | – | – | – | – | y | y | – | – |
| Vaccination | – | – | – | – | – | – | y | – | – |
| Spatial buffers | – | – | y | – | – | – | – | – | – |
| Realism demonstrated | y | y | y | y | y | y | – | y | u |

[1] very approximate estimates given for control buffer zone widths; [2] deterministic but in discrete time; [3] 1-dimensional grid; [4] effects of different values tested; [5] results compared with and without incubating class; [6] $\beta$ varies *positively* with $K$; [7] healthy as well as diseased animals move.

**Table 1** (cont.).Wildlife disease models. Bovine Tb/possums:
27 Roberts (1992); 28 Efford (1992); 29 Barlow (1993a); 30 Pfeiffer (1993); 31 Louie *et al.* (1993). **Immunocontraceptive viral vector/possums:** 32 Barlow (1994). **Anthrax/Kruger game:** 33 Hahn-Furniss (1983). ***Trichostrongylus tenuis*/red grouse:** 34 Dobson-Hudson (1992a,b), Hudson *et al.* (1992a,b). ***Capillaria hepatica*/ house mouse:** 35 McCallum-Singleton (1989), Singleton-McCallum (1990)

| Model | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 |
|---|---|---|---|---|---|---|---|---|---|
| Objective | c | u | c[5] | u | u | p | u | u | p |
| Stochastic | – | y | y | y | – | – | – | – | – |
| Spatial | – | i | g | i | d[6] | – | – | – | – |
| Max animals per cell | – | – | m | – | – | – | – | – | – |
| Latent/infectious classes | y | – | y | y | – | – | –[11] | –[8] | –[12] |
| Recovered class | – | – | – | – | – | – | – | – | – |
| Seasonality | – | – | y | y | – | – | – | – | – |
| Age-structure | – | – | y | y | – | – | – | – | y |
| Habitat heterogeneity | – | – | – | y | – | – | – | – | – |
| Density-dependence | m | –[2] | m | m | – | – | – | mr | m |
| Dispersal | – | i[3] | i | i | i[3] | – | – | – | – |
| Spacing behaviour | – | – | y | y | – | – | – | – | – |
| Transmission (mixing) | h | l | h[4] | l | h[6] | h | h | h | h |
| Density function | N | N | N | N | N | c | N | N[9] | N |
| Susceptibility function | S | S | S | S | S | S | S | S | S |
| $\beta$ estimate | m | d | d | d | m | –[7] | d | t | –[13] |
| $\beta$ and $K_T$ vary with $K$ | – | – | y | – | – | – | – | – | – |
| Disease spread | – | jn[3] | jn | jn | d[6] | – | – | – | – |
| Culling | y[1] | – | – | – | – | – | – | – | – |
| Vaccination | y[1] | – | – | – | – | – | – | – | – |
| Spatial buffers | – | – | y | – | – | – | – | – | – |
| Realism demonstrated | – | – | y | y | – | u | y | y[10] | – |

[1] formulae given for culling, vaccination and sterilisation *rates* needed to eliminate disease; [2] constant host population assumed; [3] juveniles not explicitly distinguished but assumed to be a fixed proportion of the population; [4] implicit treatment of disease aggregation within each cell, through modified transmission term; [5] model also used to predict immigration into controlled areas of different sizes (as an input to Model 26); [6] model includes diffusion and transmission as a function of distance; [7] range of values tested; [8] two alternative 3-equation models for (1) total hosts, total free-living parasites & total adult parasites, (2) total hosts, larvae arrested in hosts & total adult parasites (duration of free-living stage assumed negligible), further model considers predators also; [9] mass action term for new adult parasites as a function of free-living stages and hosts (Model 1) but asymptotic host density function for new arrested larvae as a function of total adult parasites and hosts (Model 2); [10] realism assessed in general terms (period and shape of population cycles); [11] simple epidemic model, classes are susceptibles, infected carcases and free-living spores; [12] classes are total hosts, parasites per host and total free-living parasites; [13] equilibrium population $\propto (1/\beta)$ so host densities all expressed relative to the equilibrium and $\beta$ not estimated.

**Table 2.** Notable attributes, main results and problems associated with the models in Table 1.

**RABIES/FOXES**

| Model | Highlights/results | Problems |
|---|---|---|
| (1) Preston (1983) | High $\beta$ gave local disease hot-spots, increased intensity and decreased frequency of epizootics. Realistic rate of spread (due to dispersal of furious foxes), frequency of epizootics (due to recovery time of the population), and seasonal incidence (due to annual input of susceptibles, not juvenile dispersal or stress of pregnancy as previously suggested). | Unclear how natural mortality and population stabilisation handled. Control policies only superficially evaluated (as reductions in contact rate). |
| (2) Berger (1976) | Realistic rate of spread (due to local movement only). Shows that required levels of vaccination to prevent spread increases with density. | Assumes $\beta$ and $K_T$ constant, hence disease behaviour and control depend on density and $K$; may not be correct. Realism not fully checked. |
| (3) Bacon (1985), Bacon and McDonald (1989) | Main emphasis is sensitivity analysis; Model results sensitive to contact probability. Suggests vaccination preferable to culling. | Realism not checked. Controls not compared on an equal basis (e.g. 6 vaccinations vs 2 kills). Speculation only about disruptive effects of culling. |
| (4) Anderson *et al.* (1981) | First simple but realistic non-spatial model for rabies and its control: a mathematical model but closely linked to the biology, setting the pattern for many subsequent wildlife/disease models. Re-creates realistic outbreak cycles (3–5 yearly) and correct prevalences (3–7%). Gives formulae for culling rate and proportion immunised (but not vaccination *rate*) for disease elimination; suggests vaccination better than culling. Presents most results as functions of host density. | Conclusions relating disease dynamics and control to fox density would be invalid if $\beta$ and $K_T$ vary with density (in which case culling and vaccination rates may be independent of density). |
| (5) David *et al.* (1982) | Predicts correct rate of spread, due to inter-neighbour transmission from Feb to Sept (affected by length of infectious period), and juvenile dispersal from Oct to Jan (affected by density). Re-creates 3-year cycles locally. Highlights problem of control because cubs responsible for most of spread and their mortality is strongly density-dependent. Predicts resurgences behind front due to rearward dispersal of diseased juveniles. | Rather complex rules for dispersal of cubs. |

**Table 2 (cont.).**

| | | |
|---|---|---|
| (6) Ball (1985) | Highlights the danger of assuming homogenous mixing. Allows control affecting group size to also affect between-group transmission probability (i.e. killing foxes increases interactions between surviving foxes). Suggests a threshold control intensity below which culling is counter-effective. Because threshold may be unattainable in the field, suggests vaccination may be better than culling. | Considers only local transmission (no dispersal). |
| (7) Mollison & Kuulasmaa (1985) | Focuses on the transmission process. Clear demonstration of the quantitative difference between homogenous and heterogeneous mixing: for the latter, the infection rate is 70% lower and the reduction in population density 20% instead of 75%. | |
| (8) Voigt *et al.* (1985) (Ontario) | Model reproduced realistic temporal and spatial disease dynamics (3–4 yr cycles, 32 km/yr rate of spread, due to inter-neighbour transmission and juvenile dispersal), and spatially heterogeneous disease with 23–57% of area infected at any one time. | Open system requiring immigration of rabies to stabilise disease. Density-dependent natural mortality fluctuated unrealistically. Results expressed in terms of fox density but assumes $\beta$ and $K_T$ constant. |
| (9) Källén *et al.* (1985) | Simplest spatial rabies model, recreating realistic rate of spread (50 km/yr, due to diffusion of rabid foxes), 3–5 yr local cycles and control buffer width of 15 km to prevent disease spread. Predicts that rate of spread is positively related to $K$, and if $K_T = 1$, rabies front in UK reaches Manchester in 4 years. | Results sensitive to diffusion coefficient (60 $km^2$/yr), which is hard to measure. Results related to fox density but $\beta$ assumed constant. Determination of buffer widths requires arbitrary assumption for prevalence corresponding to extinction (deterministic spatial model does not allow extinction of disease). |
| (10) Garnerin *et al.* (1986) | Realistic rates of spread possible, based on juvenile dispersal, if mean dispersal distance $< 8$ km and mean disease incubation period $>$ 25 days. Predicts successive waves of disease. | |

**Table 2 (cont).**

| | | |
|---|---|---|
| (11) Murray *et al.* (1986) | Expansion of Model 4 to include spatial effects – mathematical model closely linked with biology. Reproduces realistic rate of spread (due to diffusion of rabid foxes), increasing with fox density. Takes 4 years for front in UK to reach Manchester, given actual (heterogeneous) densities (estimated using a supercomputer). High fox densities ahead of a front focus it and cause it to apparently jump. Control break 17 km wide required. | Arbitrary assumption required for disease elimination, to estimate break width (as for Model 9). Results for rate of spread depend on density, because $\beta$ assumed to be constant. Rate of spread very sensitive to diffusion coefficient (200 $km^2/yr$ cf. 60 $km^2/yr$ in Model 9) |
| (12) Gardner *et al.* (1989) | 2-dimensional diffusion model similar to Model 9. Predicts rate and pattern of spread over irregularly-shaped areas (e.g. Isle of Anglesey). Authors argue that deterministic small fractions of infective foxes after epidemics are reasonable; represent very low densities. | In deterministic models, residual infective densities may be too small to represent realistic densities over the areas considered. |
| (13) van den Bosch *et al.* (1990) | Focuses on velocity of spread, mostly theoretical but using rabies as an example. Reproduction and dispersal kernel approach, allowing more realistic patterns of movement than through diffusion. Reproduces realistic rate of spread, *decreasing* with fox density above $K_T$, assuming range of movement inversely related to density but $R_0$ directly proportional to density. | Difficult for most biologists to understand and parameterise. Effect of density on velocity of spread would change if $R_0$ made independent of $K$. |
| (14) Smith & Harris (1991) (Bristol) | Potentially the most realistic spatial rabies model, reproducing observed rates of spread among European low-density foxes, and predicting lower rates (14 km/yr) in high-density urban populations. Examines realistic control policices, predicting that five 40% culls are needed to control a point source infection. High density areas are hardest to control. | Conclusions about the effects of fox density depend on an assumed positive relationship between $\beta$ and $K$ (rather than a negative one, as in Models 24 and 27, or the more usual assumption of no relationship). Positive relationship based on increased overlap of home ranges at high density. Unclear how populations react to culling as density-dependent mechanisms not fully explained. |

**Table 2 (cont).**

| | | |
|---|---|---|
| **RABIES/RACCOONS** | | |
| (15) Coyne *et al.* (1989) | Variant of Anderson *et al.* (1981) (Model 4) including lifelong immunity: effect is to increase $K_T$ and disease persistence, and dampen cycles (3–5 yr cycles of infection do not occur in raccoons). $K_T$ assumed to be 3 $km^{-2}$ which is low relative to $K$ (3–26, ave. 12 $km^{-2}$); as a result, culling and vaccination rates are insensitive to $K$. 32% annual cull or 99% annual vaccination rate required to eliminate disease, so culling better unless vaccination 1/3 the cost of culling or less. | $K_T$ (and $\beta$) assumed independent of $K$, and model relationships between control rates and $K$ depend critically on this assumption (though the conclusion that rates are insensitive to $K$ is reinforced if $K_T$ depends on $K$). Realism of model (e.g. prevalence and host suppression) not explicitly described. |
| **FOOT AND MOUTH/PIGS** | | |
| (16) Pech & Hone (1988) | Similar to Model 15: mathematical but closely linked to the biology and well explained. Model identifies further data required for FMD modelling in pigs, predicts 16% reduction in host density and 4% prevalence. To eliminate disease within 3 weeks requires effective elimination of host. | |
| (17) Pech & McIlroy (1990) | Predicts rate of spread of 3–6 km/day, increasing with pig density, based on diffusion applied separately to all disease classes (cf. Busenberg & Travis 1983). | Dependence of velocity on pig density assumes $\beta$ and $K_T$ independent of $K$. Large difference between $\beta$ value (4.9 $km^2$/yr) and that in earlier model (Model 16, 0.026 $km^2$/yr) reinforces difficulty of estimating contact rates, particularly in the absence of existing disease. |
| **MYXOMATOSIS/RABBITS** | | |
| (18) Saunders (1980) | Model for a single epidemic in a fixed host population. Best fit model has contact rate proportional to square root of density, but reasonable fits also obtained for contact rates independent of or directly proportional to density. | Units for population density and transmission coefficient unclear – makes it difficult to use fitted values in other models. |
| (19) Anderson & May (1982) | Focuses on the relationship between $R_0$ and virulence. Shows $R_0$ maximised at intermediate virulence (Grade IV/V) helping to account for attenuation observed in the field. | $\beta$ assumed constant with respect to virulence. |
| (20) Massad (1987) | Focuses on relationship between $R_0$ and virulence, with $\beta$ varying with virulence and peaking at intermediate values. Maximises $R_0$ at higher virulence (Grade III–IV) than Model 19, closer to the situation observed. | |

**Table 2 (cont).**

| | | |
|---|---|---|
| (20) Massad (1987) | Focuses on relationship between $R_0$ and virulence, with $\beta$ varying with virulence and peaking at intermediate values. Maximises $R_0$ at higher virulence (Grade III–IV) than Model 19, closer to the situation observed. | |
| (21) Dwyer *et al.* (1990) | First complete model for endemic myxomatosis in rabbits, including multiple virus strains. Effect of vector subsumed in a normal (mass action) transmission term. Model shows that dynamics depend on level of disease-free mortality. Interaction of natural periodicity due to maturation, and seasonal forcing (varying reproductive rates) can lead to complex and chaotic behaviour. Most competitive virus strain has highest $\beta$ value, corresponding to Grade IV (intermediate virulence), changing to Grade III (as observed) if host resistance taken into account. Outcome of selection in presence of fleas is not due to different transmission efficiencies between fleas and mosquitos. If resistance continues to develop at the same rate, control should last another 15–20 yrs. Without more data the steady state cannot be predicted. | No host density-dependence; scaling of $\beta$ unclear. Natural mortality should also be seasonal, which would further complicate the dynamics. |
| (22) Seymour (1992) | Local stability analysis of a 4-component model including explicit vector classes. Suggests that epi- zootics act to maintain virulence in the face of a net increase in rabbit resistance. | Conclusions about the interaction between environment and infectious diseases depend on the assumption that $\beta$ is unaffected by density. Conclusions about effects of epizootics on evolution of virulence are not based directly on the model. Equation for infective fleas has new infections proportional to total fleas rather than susceptibles only. |
| (23) Grenfell *et al.* (1993) | Simple 'classic' model of a rapid epidemic, extended to include host population dynamics. Shows that epidemic 'burns out' and size of a new epidemic from reintroduction depends on time since the last. Shows that common seal not threatened by disease but rarer species may be. | |

**Table 2 (cont).**

**BOVINE TB/BADGERS**

| | | |
|---|---|---|
| (24) Anderson & Trewhella (1985) | First model for bovine Tb in wildlife; standard deterministic SI model, suggesting a stable interaction, rapidly damped oscillations, and prevalence increasing with density. Variants to the basic model suggest that stochasticity, seasonality and reservoir of bacteria on pasture have little effect on results. Pseudovertical transmission and presence of carriers enhance disease persistence at low densities; periodic inactivation of disease reduces $R_0$ and increases prevalence. Although $r = 0.2$ for badgers (and $K$ typically = 10 km$^{-2}$), control must be continuous unless applied over very large areas. | Model recreates realistic low prevalence (< 10%) but unrealistic 50% depression of host density. This suggests that classic deterministic models may be unable to mimic endemic behaviour of diseases like Tb, with relatively low pathogenicity (cf. rabies). Model predicts that prevalence varies with density (because $\beta$ is constant), and this may also be unrealistic. |
| (25) Bentil & Murray (1993) | SEIR model of bovine Tb with a recovered class, no disease-induced mortality, and long latent period relative to infectious period. These were necessary to generate observed behaviour (cycles). Stability analysis of the simple SEIR model and a similar model with age-structure. | Emphasis on cycles but data inconclusive – 1 epizootic. Effect on host population density not described, and assumption of no disease mortality conflicts with data: 13% of all deaths due to Tb when prevalence only 5% (Cheeseman *et al.* 1988). Also evidence for significant recovered class unclear, and host density-dependence ignored. So model may have incorrect structure. |
| 26) Barlow (1991a,b) | Simple deterministic model, with modified transmission term to overcome the problem in Model 24 by implicitly accounting for heterogeneous mixing and disease patchiness. Likely parameter values established for Tb and possums ($r = 0.2$, as for badgers), and model re-created realistic behaviour: low prevalence (1–5%), little effect on host density, and relatively rapid disease dynamics. Detailed and approximate formulae (based on $R_0$) provided for culling, sterilisation and vaccination rates to eliminate disease, also optimal realistic control policies over time, including effects of immigration. Interactive version used for communication with field biologists, policy-makers and pest control staff. | Disease aggregation is an input to the model (and an additional parameter), rather than an emergent property; degree of aggregation is also assumed to be constant rather than dynamic. |

**Table 2 (cont).**

| | | |
|---|---|---|
| (27) Roberts (1992) | Stability analysis of similar model to Model 26, but without the heterogeneous transmission term. | Assumption of homogenous mixing means model predicts an unrealistic 50% suppression of host density, but this is unlikely to affect stability conclusions. |
| (28) Efford (1992) | A partial stochastic model (assuming a fixed host population), focusing on epidemic spread and spatial endemic patterns of disease; compare with the deterministic Model 26. Assumes local transmission proportional to distance, and long-range dispersal: stochastic equivalent of the R&D kernel approach. Recreates spatial heterogeneity of disease and realistic low prevalence, but with a smaller $R_0$ than Model 24. | |
| (29) Barlow (1993a) | Deterministic/stochastic model for large-scale spread and control of Tb. Up to 1000 possums/1 $km^2$ grid square and 20 × 50 grid. Model includes age/sex structure, birth and dispersal pulses (cf. Model 23), disease spread locally (between adjacent squares) and by juvenile dispersal. Model predicts immigration rates into areas of different sizes, rate of Tb spread (sensitive to disease parameters), and control control buffer widths. | Model still relies on an implicit treatment of local Tb patchiness (as in Model 23). $K$ may be up to $10^3$ $km^{-2}$ (cf. $K = 10$ for badgers) and dispersal extends up to 12 km, so difficult to implement a full (individual- level) spatial model on a PC. |
| (30) Pfeiffer (1993) | Highly detailed, behavioural stochastic model, first designed to re-create possum/Tb dynamics in an intensively studied site. Model demonstrates how population may be den site limited even with more den sites than possums. It re-creates low overall prevalence, local hot-spots (some fixed in time and associated with den clusters, others wandering), little effect of disease on host density, and no spatial or temporal relationship between host density and prevalence. | Difficult to estimate parameters because model contains so many: extensive tuning required. |
| (31) Louie *et al.* (1993) | Stability analysis of a spatial version of a simplified SI model (2 disease classes and no host density-dependence), allowing either transmiss- ion as a function distance, or for disease spread by diffusion. Shows that simple spatial deterministic models cannot generate spatially heterogeneous steady states (disease patchiness). | Diffusion not applied separately to disease classes (following Busenberg & Travis (1983) and contrary to Pech & McIlroy (1990)); may be unrealistic if dispersal is density-independent (as in possums), in which case diffusion should be a function of the separate density of each class. |

**Table 2 (cont).**

| | | |
|---|---|---|
| **VIRAL-VECTORED IMMUNOCONTRACEPTIVE/POSSUMS** | | |
| (32) Barlow (1994) | Attempt to predict the likely impact of disease as a vertebrate biological control agent, in this case a vector for an immunocontraceptive. Model shows that immunocontraception could give adequate suppression of possums, if vectored by a non-pathogenic, persistent, sexually-transmitted herpes virus, and if > 75% of infected females were successfully sterilised; also immunocontraception gives the engineered virus a selective advantage by increasing mating frequency. | Homogenous mixing assumed because no data available on spatial patchiness of the vector (or of other viruses in similar disease/host systems). |
| **ANTHRAX/GAME SPECIES** | | |
| (33) Hahn & Furniss (1983) | Simple 'classic' model of a rapid epidemic but with explicit treatment of the free-living infectious stage and of infected carcases. Formulae given for overall proportion of hosts surviving the epidemic, similar to that for PDV, Model 23, and for $R_0$ (based on infected carcases) and host threshold density. Previous difference-equation model (Furniss & Hahn 1981) considered infection from both fresh carcases and environmental contamination (spores). | Model mimics epidemic in the whole of Kruger National Park, but all parameters are 'tuned'. Some independent estimates would be desirable to give greater confidence in mechanisms implied by the model. |
| ***TRICHOSTRONGYLUS TENUIS*/RED GROUSE** | | |
| (34) Dobson & Hudson (1992a,b); Hudson *et al.* (1992a,b) | One of two theories for grouse population regulation, the alternative being behavioural (Mountford *et al.* 1990). Excellent case study with strong interaction between modelling and experimentation: stimulus to reasoned debate. If correct, shows wildlife population cycles may be due to parasitic infection. Stable cycles result when impact of parasite on host fecundity greater than on mortality, parasite aggregation between hosts limited, and host self-regulated (by territoriality). Predation reduces tendency to cycle. | Agreement qualitative (cycles of approximately correct period and shape): model results and population data not presented together and model does not reproduce a major crash in 1 year (1982–83) when parasite burdens only moderate and breeding success (1982) high. Model does not include the behavioural effects as in Mountford *et al.* (which can also give cycles), but this model rejected by Dobson & Hudson (1992a) for unrealistic parameter values. |

**Table 2 (cont).**

*CAPILLARIA HEPATICA*/**HOUSE MOUSE**

| | | |
|---|---|---|
| (35) McCallum & Singleton (1989), Singleton & McCallum (1990) | One of very few vertebrate biological control models and disease/host models using time-delayed differential equations. Host death kills parasite larvae but not eggs, and is necessary for transmission. Hence host suppression is independent of pathogenicity (cf. May & Hassell 1988, Anderson 1980) and the rate of parasite increase is slow. The parasite can suppress host population by 80–90% where this is otherwise stable (e.g. urban areas) but would have to be used inundatively where populations are prone to outbreaks (e.g. cereal-growing areas). Once established, the parasite could maintain itself in a population at lower density than required for establishment. | Needs experimental testing, and some estimate of the transmission coefficient (e.g.from observed disease behaviour or prevalence). |

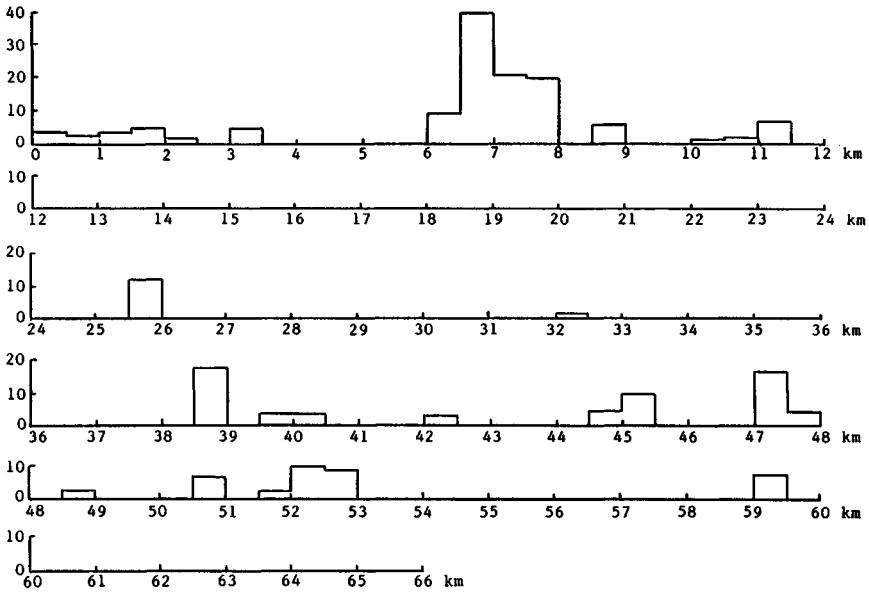


Figure 1: Observed spatial patchiness of bovine Tb in New Zealand possums: prevalences per 0.5 km of a 66 km trap line (from Barlow 1991a).

The data of Cheeseman *et al.* (1981) for Tb in UK badgers show similar aggregation of disease, with the ratio (mean square prevalence)/(mean prevalence squared) = 3; this implies that disease is effectively concentrated in 0.33 of the total area (territories) at a prevalence of 70% rather than the overall mean of 24%. For Tb in possums, disease occupies 1/9 of the total area and effective prevalence is 9 times the average (Barlow 1991a, see below for its

inclusion in endemic models). Finally, it appears that classic SI models, while giving realistic results for pathogenic diseases like rabies, cannot recreate the characteristic behaviour of less virulent diseases like bovine Tb, specifically low prevalence, little effect on host populations and reasonably rapid disease dynamics (e.g. disease recovery rate after culling).

The macroparasite model of Dobson and Hudson (1992a,b; Model 34), in common with most of its genre, includes aggregation of parasites between hosts rather than spatially. The transmission term is therefore unaffected by the aggregation. However, it would be interesting to know whether there is also spatial aggregation of free-living larvae associated with, and possibly accentuating the aggregation of parasites between largely immobile hosts of differing susceptibility. If so, this would affect the overall transmission terms.

(2) What are the shapes of the susceptibility function $f(S/N)$ and density function $g(N)$ in the transmission term $\beta I.f(S/N).g(N)$?

The first part of this question is related to Question 1, since spatial heterogeneity will affect the susceptibility function. In paraticular, if a phenomenological approach is adopted to include the effects of disease patchiness in deterministic models, the question arises as to what form the susceptibility function should take. In the standard mass action transmission term with homogenous mixing $f(s) = s$ (where $s = S/N$). Barlow (1991a,b, 1993a) assumed a piecewise linear form:

$$f(s) = \begin{cases} 1 - (1-s)/q & s > (1-q) \\ 0 & s < (1-q) \end{cases}$$

where $q$ is the effective proportion of the total host-inhabited area infected ($= \sum p_i^2 \,/\, p \sum p_i$ where $p_i$ = prevalence in area/territory $i$, = ratio of mean prevalence squared to mean square prevalence). However, simulation shows that similar disease/host behaviour is obtained with a susceptibility function of the form:

$$f(s) = s^n, \qquad n > 1$$

given exactly the same disease parameters and large $n$ (e.g. $n = 10$). Although this function is continuous and therefore more biologically realistic, it is more difficult to ascribe meaning to $n$ or to measure it, than it is for $q$. Useful starting points would be, firstly, to plot the shapes of the overall susceptibility functions generated by stochastic spatial grid models with mixing locally homogenous but globally heterogeneous, secondly to obtain more data on spatial patchiness or otherwise of disease, and thirdly to test the sensitivity of models to the different functional forms.

Put another way, the second part of Question 2 asks how the contact rate $\beta g(N)$ varies with density (Heesterbeek and Roberts, this volume). Conventionally, and in nearly all the models in Table 1, $g(N) = N$ so contact rate is

proportional to density except for sexually-transmitted diseases when $g(N)$ is generally assumed to be constant (e.g. Model 32, Barlow 1994). However, if social behaviour or movement patterns varied not only with $K$ (as discussed in Question 3) but with changes in density below $K$, for example as a result of culling or other controls, it may be that $g(N)$ is some convex-up function of $N$ (e.g. $\sqrt{N}$ in Model 18, Saunders (1980)). Ball (1985, Model 6) allowed for the possibility that control directly affects the contact probability but it would be useful to have better information on mechanisms. This is particularly true in the light of the numerous rather speculative references to disruptive effects of culling compared with vaccination in the control of rabies. Another approach to the question is to test the sensitivity of model behaviour to assumptions about the shape of the density function. Unfortunately there appears to be no direct experimental or observational evidence for the shapes of either function in the transmission term for wildlife disease models.

(3) Are $\beta$ and $K_T$ independent of $K$?

In other words, does the infection rate ($\beta$) and the lower bound of host population density for parasite persistence scale with the host carrying capacity? (Heesterbeek and Roberts, Roberts *et al.*, both this volume). The significance of this question is that many of the models expressed their conclusions about disease behaviour or intensity of control measures in terms of $K$, on the almost universal assumption that $\beta$ and $K_T$ are independent of $K$. It follows that many of the conclusions of wildlife disease models will be suspect if this assumption is invalid, and there is reason to suppose that it might be.

For example, if the size of home ranges or territories varies inversely with equilibrium host density or carrying capacity (e.g. Trewhella *et al.* (1988) and Figure 2), and coverage of the larger areas by individual animals is as complete as for the smaller ones, then the contact rate ($\beta K$) will be unaffected by $K$ and $\beta$ will increase as $K$ declines (Barlow 1993a). This implies greater mobility when $K$ is low and territories or home ranges are large. Such enhanced mobility could be envisaged as a response to a sparser distribution of essential resources, such as food or shelter, characteristic of the lower habitat carrying capacity, and the need to defend a larger territorial boundary. The same effect would occur if the host is limited by den site availability, as with New Zealand possums (Barlow and Clout 1983). Although dens are not usually shared on any one night, close contacts between animals searching for preferred sites, and the opportunity to acquire Tb from residual infection in the den sites (Pfeiffer 1993) will both relate to the ratio of animals to dens; if this remains constant as $K$ varies then the disease contact rate may also remain constant. It is therefore biologically possible, or even probable, that $\beta$ will vary inversely with $K$, and given the supportive observation that there appeared to be no

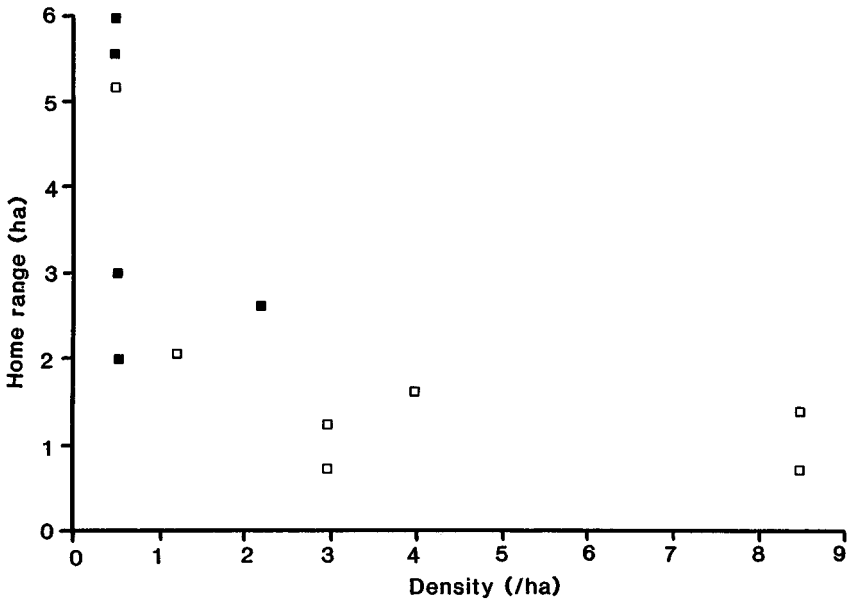


Figure 2: Possum home range sizes in relation to density, averaged over males and females. Open squares are points from New Zealand, closed ones points from Australia (data from Green (1984) and Batcheler and Cowan (1988)).

relationship between disease prevalence and $K$ (which would be expected if $\beta$ were constant), the maximum contact rate $\beta K$ was assumed constant in the possum/Tb models of Barlow (1991a,b, 1993a). The reverse was assumed by Smith and Harris (1991) for rabies in urban fox populations. Here $\beta$ was assumed to increase with $K$ because home range overlap appeared to increase at higher densities (Trewhella *et al.* 1988). Finally, the observation that rabies is endemic in arctic foxes (Crandell 1991) suggests that $\beta$ is greater and the threshold for rabies persistence may be considerably reduced where the natural densities ($K$) are lower.

If contact rate $\beta K$ is independent of $K$ and the threshold $K_T$ is proportional to $K$, then disease prevalence and the likelihood of epizootics are independent of $K$. Under these circumstances, culling and vaccination rates to eliminate disease would also be independent of $K$ (since they depend on the ratio $K_T/K$). If true, this would mean that pest managers would need to achieve not a certain absolute density of hosts, but a density relative to uncontrolled density in order to eliminate disease. Relative densities are much more easily assessed than absolute ones, using indices such as pellet counts. Another implication for modelling is that $\beta$ would need to be estimated from $K_T/K$, not $K_T$ alone. In practice one imagines a non-linear relationship of some kind, possibly asymptotic, between contact rate ($\beta K$) and $K$. The best way of estimating it in the field may be to assess nearest-neighbour distances

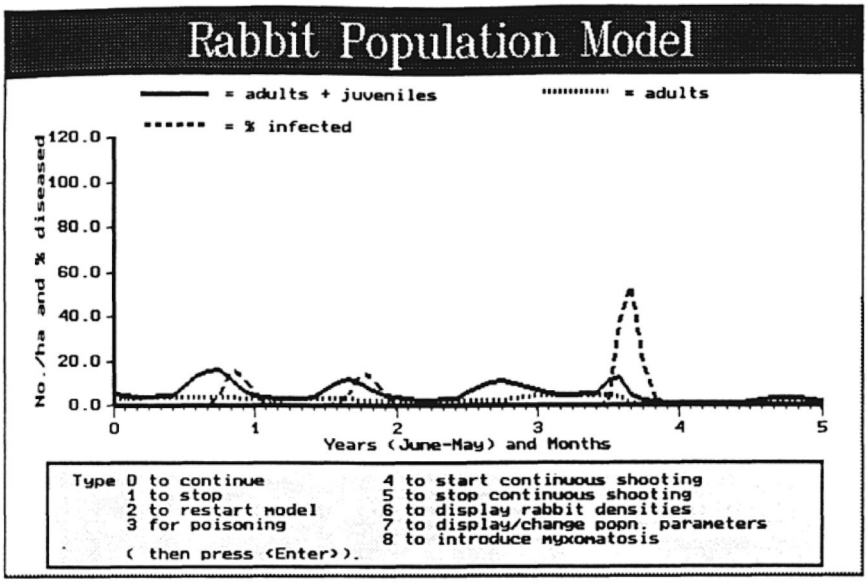


Figure 3: Example of irregular outbreaks of myxomatosis in Otago, New Zealand, generated by a model (Barlow, in preparation), given strong seasonality in rabbit birth and death rates. The Figure also illustrates the type of simple presentation screen used in interactive versions of Models 26, 29 and 32.

at different densities resulting both from natural agencies (i.e. different $K$ values) and from imposed control.

(4) Is it possible to better understand the complex (chaotic) dynamics characteristic of wildlife diseases with seasonal forcing due to variations in disease transmission and mortality and host birth and death rates?

The myxomatosis model of Dwyer *et al.* (1990) gives some indications of complex cyclic behaviour of disease, and we have found (Barlow, in preparation) even more irregular epizootic patterns in a deterministic myxomatosis/rabbit model with seasonally varying host death rates as well as birth rates, and density-dependent mortality but constant disease parameters (e.g. Figure 3). The question is whether there is any alternative to simulation, and any possibility of predicting behaviour as a function of parameter values in seasonally varying systems of this kind.

## 3.2 Epidemic (spatial) Models

(5) Can deterministic epidemic models for the spatial spread of disease be reconciled with stochastic grid ones, particularly given the different types of movement which the latter may embody?

The first question is whether stochastic and deterministic models give similar predictions for rates of spread, and here we have to distinguish between deterministic models which have a similar structure to stochastic ones (e.g. a spatial grid), and those based on diffusion or an RandD kernel in continuous space (Bolker *et al.*, this volume). The second problem with deterministic spatial models involving diffusion is that of atto-foxes (Mollison 1991): disease can never be eliminated, for example by controlled buffer zones. As pointed out by Mollison (1991), a further consequence of this is that diffusion models and stochastic grid models predict entirely different mechanisms for the resurgence of successive waves of rabies following passage of an initial front. In diffusion models (e.g. Models 9, 11, 12, 13) resurgence occurs because the susceptible population recovers to the threshold density for disease persistence, in the presence of extremely small residual densities of infectives (Mollison's atto-foxes). In stochastic grid models, resurgence also depends on the presence of a recovered susceptible population but disease is initiated by rearward dispersal of infected juveniles from the front (e.g. David *et al.* 1982, Model 5). It is likely that only one of these explanations, and models, is incorrect. Thirdly, there is the issue of an appropriate mathematical structure for deterministic models in continuous space and time. This includes both the question of diffusion versus more flexible RandD kernel approaches (e.g. van den Bosch *et al.* 1990, Mollison 1991), and the more well-bounded question of whether diffusion should be a function of the densities of individual host classes (e.g. Pech and McIlroy 1990) or of overall density (Busenberg and Travis 1983, Louie *et al.* 1993). The former would seem the most appropriate if movement is density-independent (i.e. the proportion, not the number moving is independent of density).

## 3.3 Model Inputs and Outputs

(6) How should $\beta$ be measured and scaled?

There are two problems here. Firstly, estimating the transmission coefficient is notoriously difficult and most models leave it as their one unknown parameter, fitted by repeated trials of different values to give realistic disease/host behaviour. This option is unavailable when predicting the effect of an exotic disease (e.g. Pech and Hone 1988, Pech and McIlroy 1990, Barlow 1994). Estimating it from the threshold density $K_T$ requires that this, too, can be measured, and in the light of the above suggestions that $K_T$ may vary with $K$, its estimation in the field may be far from trivial. Alternatively, $\beta$ may be estimated from observations on host behaviour and the frequency of contacts, but this requires both considerable information on detailed host behaviour and a way of estimating how many of the contacts are potentially capable of transmitting disease; this becomes even more difficult if transmission is indirect, through a short-lived infectious stage such as *Mycobacterium*

*bovis* in possum den sites or in scent marks on trees.

The second problem is that of scaling, so that a value for the transmission coefficient, once established, can be used in other models of the same disease/host system. This problem was encountered in modelling myxomatosis in New Zealand rabbits (Barlow, in preparation). Values for the transmission coefficient were derived in Saunders (1980) and Dwyer *et al.* (1990) but could not be readily applied because the units of the coefficient and of population size in these studies were unclear. Moreover, if it is true that $\beta$ may depend on $K$ it may be better to use the contact rate $\beta K$ than $\beta$ to extrapolate between models.

(7) How sensitive are model results to the assumed nature of host density-dependence? What are these mechanisms for wildlife hosts?

The significance of this question can be seen firstly in the 'doomed juvenile surplus' scenario, embodied in the model of David *et al.* (1982). Here culling is relatively ineffective because density-dependence in recruitment is so strong; vacated territories are immediately reoccupied by 'surplus' juveniles which would otherwise die. Classic logistic equations typical of deterministic disease/host models in continuous time do not represent such a scenario, unless the growth curve is highly asymmetric with $(N/K)$ in the logistic term $(1 - N/K)$ raised to a high power $\gg 1$.

Secondly, if dispersal, or more accurately settlement following dispersal, is density-dependent this seriously constrains the effectiveness of spatial buffers to prevent disease spread. Culling simply creates a 'vacuum' effect, drawing in more possibly infected animals.

Thirdly, what is the effect of density-dependent spacing behaviour, embodied in many of the stochastic spatial models, on the overall density-dependence of population growth and the impact of control buffer zones? Tinline (1988) suggests that local density-dependent spacing behaviour causes a vacuum effect in foxes, drawing in both susceptibles and diseased animals to the control zone. Yet in a model for spatial control of Tb in possums (Model 29, Barlow 1993a), this behaviour has no significant effect.

Finally, the nature of host density-dependence critically influences the relative merits of culling and vaccination as disease control strategies (see below).

(8) What are the circumstances under which vaccination is a better control option than culling?

Although many of the rabies models considered both control options, there was no clear consensus about their relative merits. The simplest formulae for rates of vaccination and culling required to eliminate disease are (e.g. Coyne *et al.* 1989):

$$\begin{aligned} c &= r(1 - K_T/K) \\ v &= a(K/K_T - 1) \end{aligned}$$

where $c$ = per capita culling rate, $v$ = per capita vaccination rate, $r$ = intrinsic rate of increase, $a$ = per capita birth rate. Clearly $c$ has $r$ as its upper limit as $K_T$ tends to zero, since eliminating the host by culling at a rate equal to $r$ will surely eliminate the disease. On the other hand, $v$ is essentially unbounded as $K_T$ tends to zero, so the vaccination rate required to eliminate disease can become extremely high (e.g. 99% per year in the model of Coyne *et al.* 1989). Substituting for $K_T/K$ in the above equations gives:

$$v/c = a/(r - c).$$

Since $a > r$, this means that $v > c$: the vaccination rate required to eliminate disease will always be greater than the culling rate required, given this standard SEI model model with host mortality density-dependent. Add to this the problem that vaccination requires that an animal not only ingests a bait but is then successfully immunised, and it would appear that only a substantially lower cost of vaccination compared with culling, or major ecological costs of culling, involving subsequently enhanced contact rates or survival (Question 2), could make vaccination a superior strategy if such a model is valid. More detailed models (Barlow and Smith, in preparation) suggest that culling is more likely to be effective than vaccination when host density-dependence acts through mortality rather than recruitment, population growth is logistic rather than asymmetric (the growth curve relating $dN/dt$ to $N$ is symmetric rather than rightward-peaked) and $R_0$ for the disease is high.

(9) Is it possible to enhance communication of models and their results, and thereby to make them more useful?

This is a general question but I believe a valid one, since there is a clear bottleneck in the capacity of models to influence biological understanding or management, and their capacity to be influenced by it. One component of this bottleneck is the language of mathematics and the existence of parallel but separate streams of literature, representing the biomathematical and the ecological/epidemiological, which few authors or readers transcend. A partial solution may be for authors of mathematical papers to consider publishing syntheses of their results in the more purely biological journals. This would carry the added advantage that the models would thereby be scrutinised on grounds of biological as well as mathematical relevance and novelty. Additionally it would help ensure that the ultimate goals of both theoreticians and field workers are concurrent, namely to understand not the behaviour of models but the behaviour of nature.

The second component is even more basic: the majority of biologists and managers, albeit perhaps a shrinking majority, are unaware of the potential of models of any complexion, and of the usefulness and significance of their results. Yet not only can the communication of model results be improved, but models themselves offer enormous potential to act as media for communication and education, potential which is largely unrealised. All that is

required is for models to be presented with interactive colour graphics which simply and clearly demonstrate the consequences of management actions or variations in the model's assumptions. Certainly such an approach has proved extremely worthwhile in our modelling of Tb and myxomatosis (Models 26 and 29, and Figure 3). It has helped convey biological and management principles, given non-modellers a more favourable impression of what models and modellers can offer, and provided feedback to model development through an ongoing process of interactive 'validation'. Partly for these reasons, the Tb models have been used as the basis for current possum/Tb control policies in New Zealand.

In conclusion, the most important future demands for wildlife disease modelling appear to be: (1) better data on disease transmission and its relationship with density; (2) reconciliation of stochastic and deterministic models, both endemic and spatial; and (3) the creation of models which are simple but more realistic and user-friendly, so that they are more attractive and accessible to field biologists and pest managers. Above all, modellers must be more self-critical and remain firmly in touch with the real world if genuine progress is to be made. As Bradley (1982) remarked in the context of human epidemiological models: 'Hubris seems to be the chief vice of the model-builder without, and even with, field experience. It induces justified scepticism and is counter-productive. It serves only to convince the determinedly non-numerate public health worker that models are a seductive alternative to understanding'.

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# Non-Linearities in the Dynamics of Indirectly-Transmitted Infections (or, Does having a Vector make a Difference?)

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## 1 Introduction

This paper approaches two general questions about the dynamics of indirectly-transmitted infections by looking in the first instance at infections transmitted by bloodsucking flies (diptera). The general questions are: How are the dynamics of indirectly-transmitted infections different from those of directly-transmitted infections? And how are the dynamics of vector-borne diseases distinct from those with other kinds of intermediate hosts? Both questions are to do with identifying non-linearities in the transmission process.

The obvious distinction between models for direct and indirect transmission is that the latter usually have at least one extra equation describing the dynamics of parasitism in the intermediate host. From a theoretical point of view, this paper is about the role this extra equation plays in the overall dynamics of insect-borne parasites. We look at the problem in two ways. The first is in terms of the different timescales upon which parasites, vectors, and vertebrate hosts operate. We bypass the more formal arguments which have been laid out by others (e.g. Nedelman 1984), and aim instead for visual impact. Our second theme explores less familiar ground—the part played by density-dependent processes in regulating the parasite population in its vector host.

A review of the available evidence leads to the proposition that, whilst various non-linear phenomena could in principle lend distinctive features to the dynamics of indirectly-transmitted pathogens, with one or two exceptions they generally do not do so for those transmitted by diptera. We offer an explanation in terms of the life history characteristics of intermediate hosts of this kind: they are relatively short-lived, and their mobility is crucial for transmission. These observations lead implicitly to predictions about which kinds of non-linear processes ought to be associated with other kinds of intermediate hosts—other arthropods included—by contrast with bloodsucking flies.

## 2 Parasitism in vectors and hosts operating on different timescales

Following tradition, we begin with the Ross-Macdonald model for falciparum malaria. In terminology similar to that of Aron and May (1982):

$$\frac{dX}{dt} = abY\left(\frac{N-X}{N}\right) - rX \tag{2.1}$$

$$\frac{dZ}{dt} = (V-Z-Y)ac\frac{X}{N} - (V-\hat{Z}-\hat{Y})ac\frac{\hat{X}}{N}e^{-\mu\tau} - \mu Z \tag{2.2}$$

$$\frac{dY}{dt} = (V-\hat{Z}-\hat{Y})ac\frac{\hat{X}}{N}e^{-\mu\tau} - \mu Y \tag{2.3}$$

$X$ out of $N$ people are infected and infectious. $Z$ and $Y$ out of $V$ mosquitoes are latently infected and infectious, respectively. The latter carry sporozoites which take $\tau$ days to mature to infectiousness (the caret denotes values of variables $\tau$ days ago). As usual, $a$ is the daily biting rate of a female mosquito on people, and $\mu$ is the daily death rate. Parameter $b$ is the proportion of bites by infectious mosquitoes on uninfected people which result in transmission, and $c$ is the efficiency of transmission from people to mosquitoes.

It is commonly assumed that the number of infected mosquitoes changes quickly by comparison with the number of infected people, so that the infected mosquito population is always approximately at equilibrium. Formally, one invokes the pseudoequilibrium approximation which sets $dY/dt = dZ/dt = 0$ (whilst $dX/dt \neq 0$), which leads to the elimination of two of the system's three equations (May and Anderson 1979, Nedelman 1984).

We explore this assumption graphically in Figure 1, with model (2.1)–(2.3) and parameter values appropriate to a highly endemic area of sub-Saharan Africa, the Garki District in N. Nigeria. The parameter values are $a = 0.33\,\text{day}^{-1}$, $bV/N = 13$, $c = 0.4$, $\mu = 0.2\,\text{day}^{-1}$, $\tau = 10\,\text{days}$, $r = 0.013\,\text{day}^{-1}$ $R_0 = 31.28$ (Molineaux and Gramiccia 1980, Nedelman 1984). Figure 1 shows the approach to equilibrium from various points in $(X/N, Y/N)$ space. Because $\mu \gg r$, the trajectories tend to track the vector isocline rather than the human isocline. Notice especially paths 5 and 6 which begin, quite realistically, with low proportions of both infected people and mosquitoes. Figure 1b magnifies trajectories 1, 3 and 7 in the vicinity of equilibrium: 1 and 7 actually cross the human isocline to get to the vector isocline, on an indirect route to the stable point. Setting $dY/dt = dZ/dt = 0$, therefore, yields an approximate expression for $Y$,

$$Y \approx \frac{Vac(X/N)e^{-\mu\tau}}{\mu + ac(X/N)}. \tag{2.4}$$

Cumbersome though it is, this may be substituted into equation (2.1), thereby collapsing the system to one equation in which the only variable is $X$. If

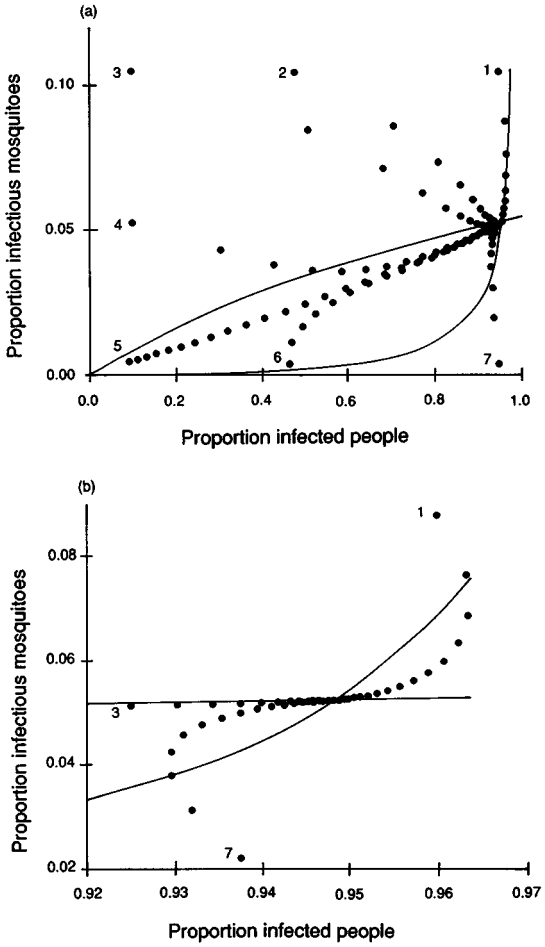


Figure 1: Phase-plane diagram for the malaria model described by equations (2.1)–(2.3). Of the two solid lines, the upper is the isocline for infectious vectors ($dY/dt = 0$) and the lower is the isocline for infected humans ($dX/dt = 0$). Parameter values are given in the text. (a) The trajectories to equilibrium from 7 different starting points, dots marking the daily time steps. (b) Magnification of the trajectories for paths 1, 3 and 7 in the neighbourhood of equilibrium.

the rate at which mosquitoes acquire infection whilst biting ($acX/N$) were much smaller than the rate at which mosquitoes die ($\mu$), we could drop the former from the denominator (Nedelman 1984), and equation (2.1) would have logistic form. In fact, $acX^*/N$ equals 0.126 day$^{-1}$ (see below for a direct estimate of $acX^*/N$ from data) for the parameter values given above, which

is not dissimilar from $\mu$. Under these conditions, equation (2.4) (and hence equation (2.1)) cannot be simplified further.

This example deals with the extreme of holoendemic malaria. For infections which have much lower $R_0$, the rate at which vectors acquire infection is expected to be substantially lower than vector death rate. For example, we can extend model (2.1)–(2.3) to describe the dynamics of another vector-borne disease, leishmaniasis due to *Leishmania tropica*, transmitted in the Middle East by the sandfly *Phlebotomus sergenti*, writing equation (1) as

$$\frac{dX}{dt} = abY\left(\frac{N-W-X}{N}\right) - rX \tag{2.5}$$

and adding a further equation,

$$\frac{dW}{dt} = rX - \delta W. \tag{2.6}$$

Infected individuals now recover at rate $r$ into class $W$, in which they remain immune for the rest of their lives, which are expected to last $\frac{1}{\delta}$ days. Vector equations (2.2) and (2.3) are unchanged. Since the average age of infection is greater than 10 years, $R_0$ for *L. tropica* is much lower than for falciparum malaria (Ashford *et al.* 1993). We set $bV/N = 0.2$, $r = 0.006\,\text{day}^{-1}$, $\tau = 5\,\text{days}$, $\delta = 8x10^{-5}\,\text{day}^{-1}$, and other parameters as above to give $R_0 = 2.94$. Figure 2a reveals that the solution to these equations is a damped oscillation, a point we return to below. Figures 2b and 2c show how the trajectory back to equilibrium in $(X/N, Y/N)$ space, following two different perturbations, exhibits even stronger affinity for the vector isocline than seen in Figure 1. The point $(X/N, Y/N)$ approaches the vector isocline very rapidly and then spirals in to the equilibrium point with large excursions corresponding to the epidemic waves in Figure 2a, but always hugging the vector isocline. Moreover, the proportion of people infected is generally quite low: at equilibrium $acX^*/N = 0.00127\,\text{day}^{-1}$, which is much less than $\mu$. Therefore,

$$Y \approx \frac{VacXe^{-\mu\tau}}{\mu N} \tag{2.7}$$

which leads to the simplified model,

$$\frac{dX}{dt} \approx C(N)X\left(\frac{N-W-X}{N}\right) - rX \tag{2.8}$$

$$\frac{dW}{dt} = rX - \delta W. \tag{2.9}$$

Now we can separate vector and host terms in (2.8). The term $C(N) = Va^2bce^{-\mu\tau}/\mu N$ is called the Vectorial Capacity. It has its origins in malariology and is defined as the number of new cases expected to arise from all

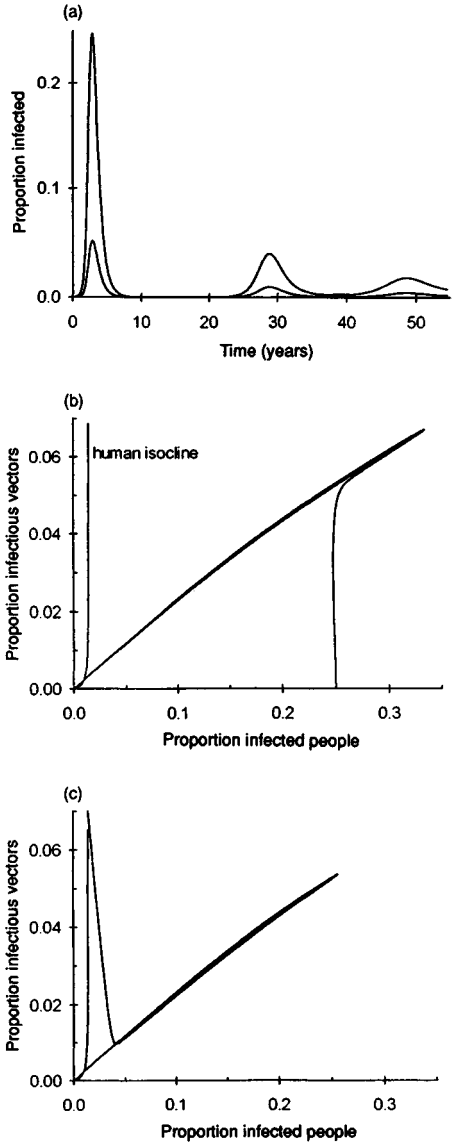


Figure 2: Dynamic behaviour of a model of *Leishmania tropica* (equations (2.2), (2.3), (2.5),(2.6), with parameter values given in the text. (a) The numbers of infected people (upper line) and infectious sandflies through time, after an initial introduction of a small number of infected people. (b) and (c) Phase-plane analysis of the approach to equilibrium from 2 different starting points. For most of its length, the path to equilibrium runs very close to, and conceals, the vector isocline.

the bites taken on one infectious person in one day. The transmission term written as $(C(N)/N)\,X\,(N - W - X)$ is the familiar $\beta SI$ of SIR models for directly-transmitted infections, with $\beta \equiv C(N)/N$. As de Jong *et al.* (1994) have pointed out, it is often not made clear whether and how the $\beta$ of SIR models depends on host density. For the simplified *L. tropica* model, and other vector-borne diseases to which (2.8) and (2.9) apply, $\beta$ is inversely proportional to $N^2$. In the present case of *L. tropica*, the configuration of the transmission term is not so important, since $N$ and $C(N)/N$ are constant. But if $N$ is variable because, for example, the disease is fatal, we may be concerned about whether the vertebrate host population can be regulated by its pathogen. We return to this point in the second part of the paper.

Unusually for vector-borne parasites, *L. tropica* is a non-fatal infection which induces long-lasting immunity. For this reason, its dynamics are expected to resemble qualitatively those of common childhood viral infections like measles, mumps and rubella, whose tendency to oscillate is well-known. Cycles of longer period are predicted because the infectious period is much longer. For small perturbations away from equilibrium, the cycle period, $T$, applicable to model (2.8)–(2.9) equals $2\pi\sqrt{[LD/(R_0 - 1)]}$, where $L$ is the life expectancy $(1/\delta)$ and $D$ is the average duration of the infectious period (Anderson and May 1991). The above parameter values give $T = 17.83$ years (cf $T = 2$ years for measles prior to vaccination in the UK), which is about the same as the second inter-epidemic period (closer to equilibrium than the first) produced by the full model in Figure 2a.

The evidence that *L. tropica* is epidemic and cyclic is slender. However, a recent survey carried out in Aleppo, Syria (Ashford *et al.* 1993), suggests that the average force of infection has been greater upon younger than older children. This means either that younger children are more frequently exposed, or that the force of infection has been increasing through time (compare lines 2 and 3 with line 1 in Figure 3). Since the vector probably bites mainly in houses at night, there seems to be no reason why younger children are bitten more often. We presume, therefore, that the data do reflect a long-term increase in the incidence of leishmaniasis, possibly part of a long-period cycle.

In all of this we have assumed that the transmission rate by the vector population is a constant. In fact, $C(N)$ will often need to be treated as a variable—a more detailed analysis of *L. tropica* and *P. falciparum* dynamics might have to allow for seasonal vector populations. But forcing arising from seasonal fluctuations in the vector population is no different, in principle, from transmission rate varying through the year for other reasons.

To summarize, models of vector-borne diseases usually make explicit the dynamics of infection in the vector population. But if these dynamics operate on a much faster timescale ($\mu \gg r$), and if the rate at which vectors acquire infection is much less than their death rate ($\mu \gg acX/N$, so

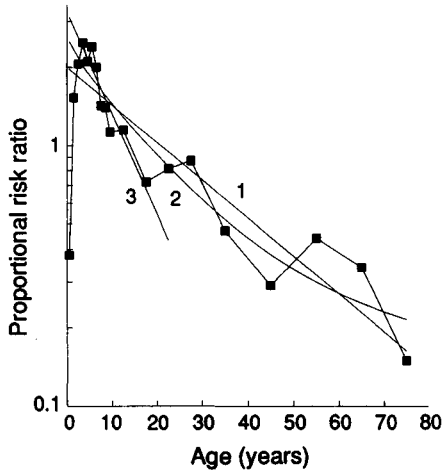


Figure 3: The percentage of cases of *L. tropica* found in different age groups in Aleppo, Syria. The percentage of cases in each age class has been divided by the percentage of the population in that class to create a 'proportional risk ratio'. Line 1 is the best fit least squares linear regression for individuals aged 3 years and over, assuming a constant force of infection. Line 2 is the best fit regression for the same age classes, but assuming that force of infection decreases at a constant rate with age, or has increased at a constant rate in recent history. Line 3 is the best fit linear regression for individuals aged 3–19 years. From Ashford *et al.* (1993).

few vectors live long enough to get infected; Nedelman (1984)), models for vector-transmitted diseases behave in approximately the same way as models for directly-transmitted diseases, in which case the vector equations may be dropped.

# 3 Density-dependent transmission through the vector population

Dietz (1988) has rightly pointed out that the possibility of non-linear parasite transmission through vector populations has been neglected. In this section, we consider the evidence for density-dependent interactions between vectors and parasites, again with a focus on bloodsucking diptera. If density-dependent processes must be included in models, the vector equation will not be easily dismissed. What follows is a brief survey of the theoretical and empirical evidence for seven potentially significant non-linear processes. Our list of categories is not exhaustive: other phenomena not dealt with here are those, as yet poorly-studied, whereby parasites could affect vector fecundity.

## 3.1 Host population regulation by vector-borne infections

Simple models of directly-transmitted infections (for example Diekmann and Kretschmar 1991, Thieme 1992, Heesterbeek *et al.* 1993), and intuition, suggest that regulation requires $\beta$ to be an increasing function of host population size. Since transmission rate varies with $1/N^2$ in equation (2.8), this is a demanding condition under indirect transmission. For a directly-transmitted infection, it is easy to imagine that the contact rate between susceptibles and infectives would increase with population density. However, that condition can be met by equation (2.8) only if $Va^2bce^{-\mu\tau}/\mu$ increases more rapidly than the square of host population size. It is hard to imagine conditions under which this might happen, but mechanical transmission is a possible example. Stable flies (*Stomoxys*) can carry trypanosomes on their mouthparts, but the parasites have a limited life expectancy in such exposed sites. Transmission is only possible if the fly feeds frequently enough. In fact, *Stomoxys* will feed several times per day, and the bloodmeals may be taken from different hosts when these hosts, such as cattle, are stocked at high density. This is a density-dependent effect operating on $a$, which enters the Vectorial Capacity as $a^2$.

## 3.2 Saturation in the prevalence of vector infection

That few individuals live long enough to get infected is very likely a general feature of bloodsucking diptera. Superinfection is expected to be rare. The point can be made with reference to an extreme example. The force of infection on *An. gambiae s.s.* in N.E. Tanzania, $\lambda = 0.21$/bite (Lines *et al.* 1991), is probably the highest ever measured for a bloodsucking fly. Given (from the same source) the survival rate per feeding cycle, $s = 0.5494$, the proportion of mosquitoes which are expected to get infected two or more times during their lives is,

$$P(i \geq 2) = \left(\frac{p\lambda}{1-p+p\lambda}\right)^2 \tag{3.1}$$

which is only 0.042. There are a few examples of very high infection rates in diptera, but these occur under unusual circumstances e.g. 50% or more in the phlebotomine sandfly, *Phlebotomus papatasi*, which lives within burrows of the rodent (*Psammomys obesus*) reservoir of *Leishmania major* (Greenblatt *et al.* 1985).

## 3.3 Vector mortality rate increasing with infection rate

An increase in the vector population will increase transmission rate, which in turn will usually increase vector infection rate. But then parasite-induced

vector mortality would reduce the mean lifetime fecundity per female, and hence the generation reproductive rate. However, if vector infection rates are rarely high, then regulation of this kind can rarely be important.

The case is further weakened by the observation that, whilst effects of parasites on their vectors have often been demonstrated in the laboratory (e.g. references cited in Dye 1990), convincing demonstrations from the field are far less frequent. Returning to the data of Lines *et al.* (1991), parasite-induced mortality operating continuously throughout infection would produce a curvilinear relationship between ln(fraction sporozoite negative) and parous number. Examination of Figure 4 shows not a hint of an effect of *Plasmodium*, even though 77% of the oldest mosquitoes ($\geq$ 7-parous) were sporozoite positive. Lyimo and Koella (1992) presented an indirect argument that *P. falciparum* increases the mortality rate of *An. gambiae* mosquitoes. They showed that larger female mosquitoes take larger blood meals and consequently have higher oocyst (zygote) loads. But they found disproportionately few large females with sporozoites, the oocyst products. The implication is that a proportion of these large females had been killed by their parasites. Reconciliation of the results of Lyimo and Koella (1992) on the one hand, and Lines *et al.* (1991) on the other, might be found in the argument that parasite-induced mortality acts, not continuously through a mosquito's infected life, but is concentrated at one point. Klein *et al.* (1982) found in laboratbory studies that mosquito mortality rate was especially high when mature oocysts ruptured and sporozoites began penetrating the insect's salivary glands. The effect would be to reduce the gradient of the line in Figure 4, without influencing curvature. The weakness of this argument is that the gradient of the line in Figure 4 is already exceptionally high for falciparum malaria (Lines *et al.* 1991). Could it already have been devalued by parasite-induced mortality? The evidence that plasmodia have a significant impact on natural populations of anopheline mosquitoes is equivocal.

A theory that cycles of African trypanosomiasis are driven partly by the pathology of *Trypanosoma* to their tsetse fly vectors (Baker *et al.* 1990) deserves closer scrutiny. Rickettsia-like organisms (RLOs) are said to benefit tsetse by marginally enhancing pupal survival, but impose a cost by increasing susceptibility to trypanosome infection. When very few tsetse in a population harbour RLOs, trypanosomiasis transmission is unsustainable because the vectorial capacity (and hence $R_0$) is below threshold. The slightly elevated pupal survival enjoyed by RLO+ tsetse means that they slowly become more prevalent, and eventually the threshold for an outbreak of sleeping sickness will be exceeded. During the outbreak, the differential parasite-induced mortality of RLO+ flies forces their frequency back below the threshold, and a further time interval must elapse before the next outbreak. What is dynamically interesting here is that the benefits and costs are acting on quite differ-

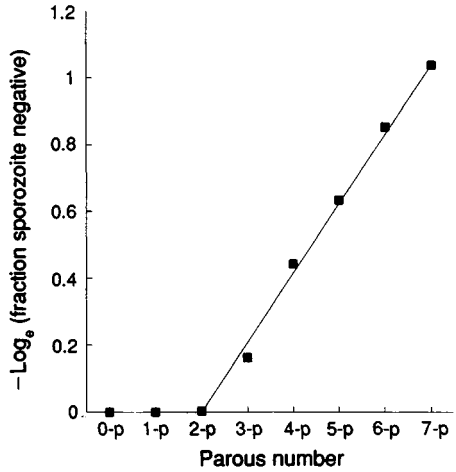


Figure 4: The proportion of female anopheline mosquitoes found not to be infective as a function of physiological age at a site in northern Tanzania. Parous number is the number of times a mosquito has laid eggs. Data from Lines *et al.* (1991).

ent timescales (rather like the production and loss of susceptibles to measles or *L. tropica*), and in a way which generates cycles. Baker and colleagues have shown how this mechanism can generate trypanosomiasis epidemics every 20 years or so, which may explain the pattern seen in Tanzania between 1922–1980 (Figure 5). However, the evidence for pupal advantage in RLO+ tsetse, for *Trypanosoma*-induced tsetse mortality in the field, and that cycles of sleeping sickness really do occur, are all weak. As interesting as the argument is in principle, substantially more evidence will be needed before this story gains wide acceptance.

## 3.4 Vector mortality rate increasing with parasite load

The assertion that evidence for parasite-induced mortality in field populations is rare applies equally to helminth infections. One of the best examples of an effect of filariae was given by Samarawickrema and Laurence (1978). They showed that *Culex quinquefasciatus* mosquitoes naturally infected with *Wuchereria bancrofti* in Sri Lanka do have higher death rates, but the elevated mortality applied only to the 5% of mosquitoes which were most heavily infected. According to these data, there would be just a small range of parasite loads over which density-dependent compensation could occur.

It must also be remembered that a reduction in the parasite load per mosquito should be accompanied by a more or less linear fall in prevalence.

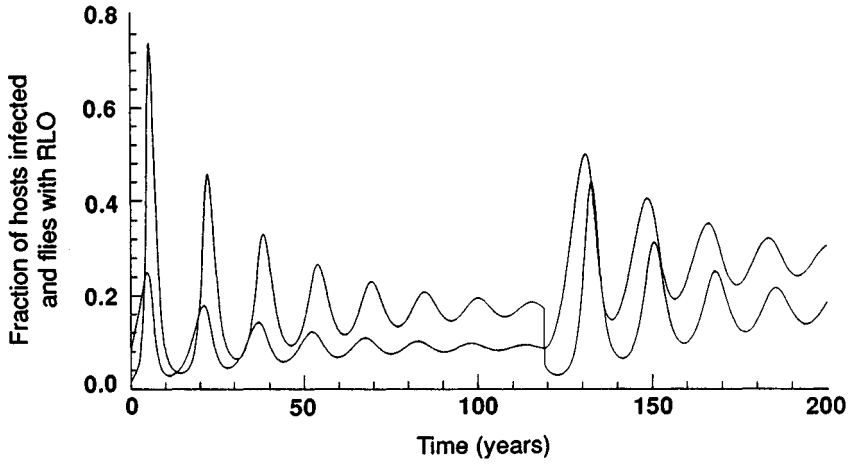


Figure 5: The long-term dynamics of vertebrate hosts infected with trypanosomes (prevalence of infection, upper line in the first half of the series), and of tsetse fly susceptibility to infection (proportion susceptible), according to the model of Baker *et al.* (1990).

If, for example, parasites are distributed among their vectors according to the negative binomial distribution, prevalence and intensity of infection will be almost linearly related at the low mean intensities characteristic of filarial worms in their vectors.

## 3.5 Vectors which prefer to feed on infected hosts

We are especially interested in vectors which display a density-dependent preference for infected hosts; that is, when the inclination or opportunity to choose depends on how many infected hosts there are. Under these circumstances, Vectorial Capacity is bigger when there are more infected hosts, and it is conceivable that threshold $R_0$ might be reached at some finite host infection rate. The result is a system which can have three equilibria rather than two. The lower (the trivial absence of infection at the origin) and upper are like those in Figure 1a. But now there may be an additional, unstable equilibrium separating them. Kingsolver (1987) has explored the problem formally, and one example of his phase-plane analysis is shown in Figure 6, but it is not yet clear how stringent the conditions are for three equilibria in models of density-dependent preference.

We also need to find out how important the effect is in natural populations. As Kingsolver (1987) has pointed out, there is evidence from some field experiments that mosquitoes show a preference for both birds and mammals infected with various arboviruses (Mahon and Gibbs 1982, Turrell *et al.* 1985). By

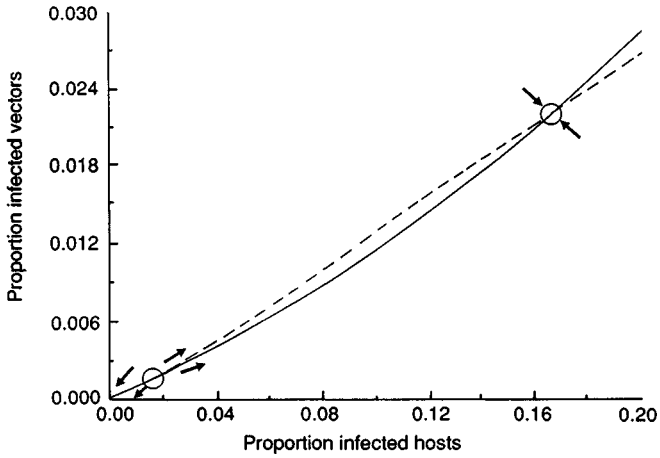


Figure 6: Phase-plane analysis like those in Figures 1 and 2, but for a model in which vectors show greater preference for infected hosts when infected hosts are more common. The continuous line is the human isocline and the dashed line is the vector isocline. Circles mark the positions of unstable (lower) and stable (upper) equilibria. Arrows indicate the direction of change from various points on the phase plane. From Kingsolver (1987).

contrast, Burkot *et al.* (1990) did not find that anopheline mosquitoes feed preferentially on individuals with malarial or filarial infections in an endemic area of Papua New Guinea. It is hard to see how mosquitoes might do so, and what they might gain. Fever could be a cue for mosquito biting, but a high proportion of bloodmeals are taken from sleeping people who are defenceless, whether they have a malaria fever or not. In addition, the point prevalence of malaria fever in a human population is likely to be low, so most mosquitoes will not have a choice. From the parasite's point of view, the asexual stages of *P. falciparum* responsible for fever are not produced synchronously with the transmissible sexual stages. In fact, much of the transmission of *Plasmodium* and *Wuchereria* to mosquitoes comes from infected individuals with no detectable symptoms.

All these investigations have focused on the simplest question of whether preference for infected hosts occurs at all. We know of no studies which have attempted to investigate density-dependent preference. However, any one fly looking for a meal usually attempts to feed from just a small fraction of its host population. Choice is therefore limited. If a bloodsucking fly does prefer to feed on an infected host when given the choice it may have the opportunity when infected hosts are common, but not when they are rare.

Here is a potential but unsubstantiated mechanism for density-dependent expression of preference.

## 3.6 Parasite mortality rate increasing with parasite load (limitation)

The final two density-dependent mechanisms are the related and much-discussed phenomena known as limitation (this section) and facilitation (next section). If $x$ is the number of parasites ingested by a fly and $y$ is the number which survive to become infective, then limitation is the negative feedback process occurring when $y/x$ decreases with $x$. Facilitation is the positive feedback process occurring when $y/x$ increases with $x$. Limitation is most commonly associated with filarial infections of culicine mosquitoes, whilst facilitation is associated with filarial infections of anopheline mosquitoes.

There is some evidence of limitation for the *Simulium* vectors of *Onchocerca*, but the effect is not strong. Basáñez *et al.* (1994; see also Smith *et al.* this volume) have dealt with the process of parasite ingestion from the skin of human hosts. Let $I$ be the number of microfilariae ingested from persons with mean microfilarial skin concentration, $M$. A variety of non-linear models give fits to graphs of $I$ against $M$ which tend to be just significantly better than the linear model (Figure 7). This is true for the important African vector *S. damnosum*, and for the S. American species *S. guianense*. As weak as the density-dependence seems to be, it is the only regulatory mechanism incorporated into a recent microsimulation model for onchocerciasis in West Africa (Plaisier *et al.* 1991). This density-dependence presumably generates a stable model parasite population, but is it really the dominant regulatory mechanism in this system?

There have been more convincing experimental demonstrations of limitation for some culicine mosquito vectors of filariae (Southgate and Bryan 1992; Figure 8). What is lacking, however, in all examples of limitation is a demonstration of the frequency distribution of $x$ in the wild vector population (Figure 9). It is possible that almost all naturally infected mosquitoes lie on that section of the $y-x$ curve which is nearly linear. If so, the opportunity for density-dependent compensation will be limited here too. The frequency distribution of $x$ should be more easily observable for culicine mosquitoes than for simuliid blackflies because the former can be caught resting in houses with fresh bloodmeals.

## 3.7 Parasite mortality rate decreasing with parasite load (facilitation)

The significance of facilitation for parasite population dynamics is even more questionable. Of the four examples recently given in Southgate and Bryan

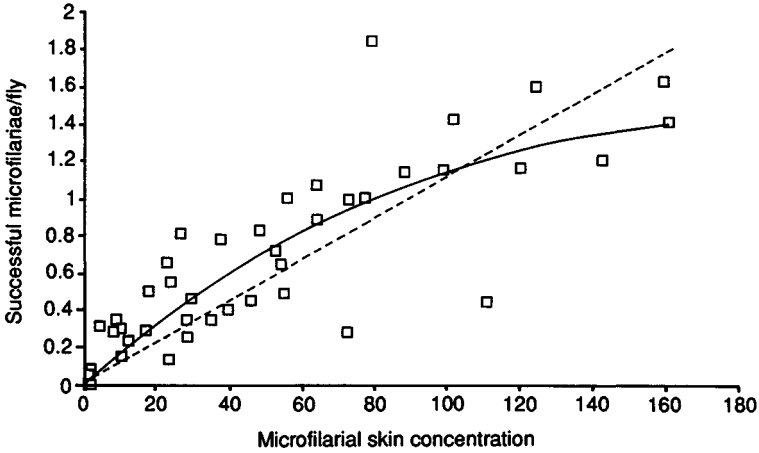


Figure 7: The number of *Onchocerca* microfilariae found passing the haemocoel and in the thorax of *S. damnosum* as a function of microfilarial skin concentration (mff/skin snip). Each point is a mean obtained from 50 flies. Original data come from the West African Onchocerciasis Control Programme, but the analysis shown here is due to M.G. Bassañez *et al.* (1994). The dotted line has slope 0.01, and $r^2$ is 0.61; the solid line is described by $y = 1.71(1 - e^{-0.01x})$, with $r^2$ rising to 0.7.

(1992; Figure 8), only one apparently is statistically significant (*An. gambiae/ Wuchereria bancrofti* in the data of Brengues and Bain 1972). A positive feedback process such as facilitation is dynamically interesting because it could lead to an unstable equilibrium parasite population size, below which the parasite population would be driven unstoppably to extinction (Pichon 1974). Some circumstantial field evidence suggests that this threshold has been crossed in some filariasis control programmes (Southgate and Bryan 1992), but we do not yet have a model of lymphatic filariasis which shows that the unstable equilibrium is relevant, given a weak positive feedback process in mosquitoes and given, moreover, reasonable assumptions about the negative feedback process attributable to human immunity (Dye 1992a).

# Conclusions

Macdonald (1957) suggested that attacking adult mosquitoes with residual insecticides should be relatively effective in controlling malaria, and by implication, vector-borne diseases in general. His argument applies because Vectorial Capacity and $R_0$ depend exponentially on vector death rate, $\mu$, and

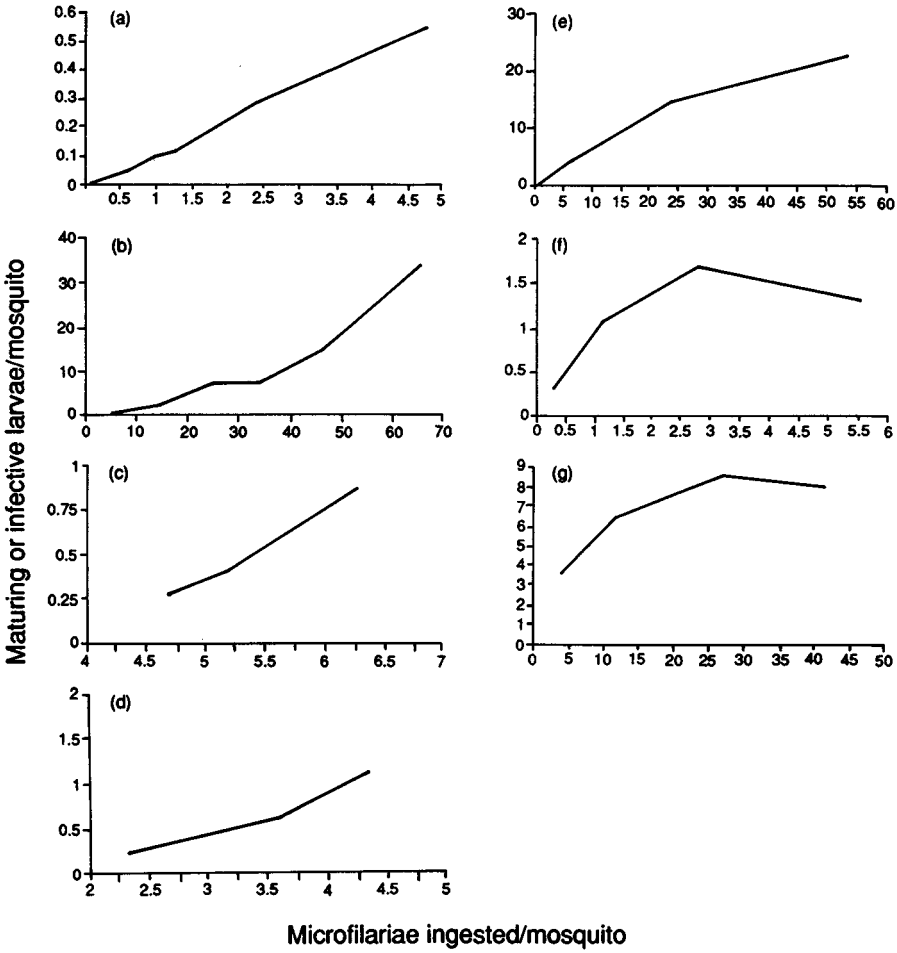


Figure 8: Putative examples of facilitation (left column) and limitation (right column) plotted from data in Southgate and Bryan (1992). The mosquito/parasite combinations are (a)–(c) *Anopheles gambiae/W. bancrofti*, (d) *An. funestus/W. bancrofti*, (e)–(f) *Culex quinquefasciatus/W. bancrofti*, (g) *Aedes togoi/Brugia malayi*.

his explicit consideration of the biology of the vector population provided lasting insights for epidemiology (Dye 1992b). But are there other important non-linearities in the interaction between parasites and their dipteran insect vectors? In this survey we have highlighted the special problem of population regulation by vector-borne infections, but we have not found much other evidence that the dynamics of vector-borne diseases are distinctive.

One reason may be that investigations of many of the topics discussed

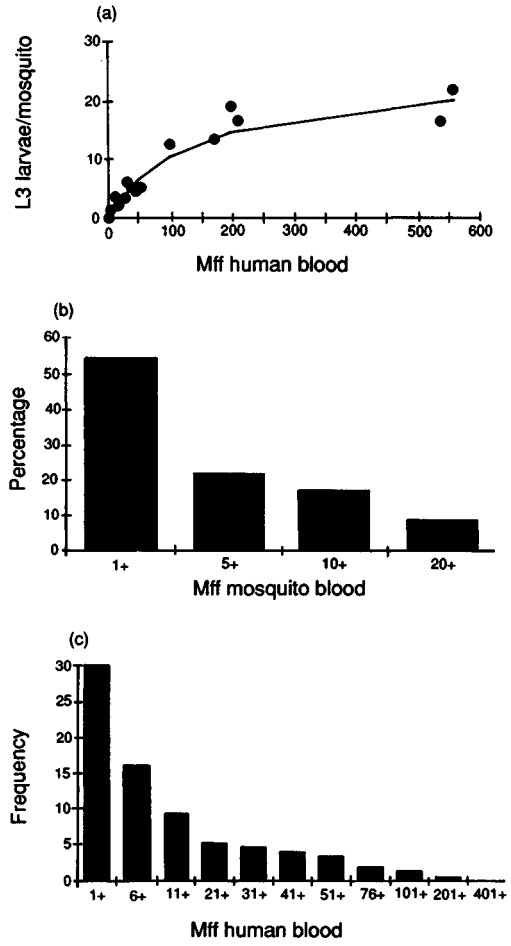


Figure 9: The question of limitation explored with data from Rosen (1955). (a) The number of infective L3 larvae of *W. bancrofti* naturally acquired by *Ae. polynesiensis* in relation to human blood microfilarial (mff) concentration. (b) and (c) The frequency distributions of mff in bloodfed mosquitoes and in human blood. Ideally we would like a plot which has the ordinate of (a) and the abscissa of (b).

above are at an early stage. This applies especially to hard but highly desirable field experiments, more of which might reveal, for example, that vector preference for infected hosts, when it occurs, is indeed density-dependent. But our preferred hypothesis is that, in general, important non-linear effects really are uncommon. This should not be unexpected given two features which make the life histories of bloodsucking insects special: they are rela-

tively short-lived, and their mobility is essential for transmission.

## Brief lives

When the life expectancy of bloodsucking diptera is short compared with the duration of infection in vertebrate hosts, vector infection rate adjusts relatively quickly to any fluctuations in vertebrate infection rate. If, in addition, life expectancy is short compared with the time it takes a vector to acquire infection (low vector infection rate), transmission rate can, to a good approximation, be linearly represented by a constant Vectorial Capacity. These are well-known criteria for collapsing out the vector equation in models of malaria and other indirectly-transmitted infections.

A low prevalence of infection in vectors is an unsaturated prevalence: vector prevalence should fall more or less linearly as the force of infection on the vector population is reduced. Low prevalence also implies that mean vector mortality rate cannot be much elevated by parasitism. From our review of the evidence, we suggest that neither process usually plays a significant part in regulating populations of parasites transmitted by bloodsucking flies.

## Mobility and transmission

There is in any case little evidence for parasite-induced vector mortality (and sub-lethal morbidity) from field studies. Where it does occur, density-dependent compensation may operate only over a narrow range of unusually high parasite densities. Since survival and mobility are imperative for transmission, there will be strong selection pressure on parasites (recall the sensitivity of $C$ to changes in $\mu$) not to impair either.

Even if parasite densities in vectors are rarely high enough to impose significant mortalities on their hosts, they may be high enough to cause significant interactions among the parasites themselves. Limitation and facilitation could, respectively, be important negative and positive feedback processes, but it remains to be shown that they are in nature.

May and Anderson (1979) thought that 'cases where intermediate host populations are unaffected by the prevalence levels of the infection will be the exception rather than the rule.' We have suggested that the short longevity and high mobility of bloodsucking flies are features which make them special. But are vectors of this kind exceptions to a general rule which applies to intermediate hosts? More likely, there will be a spectrum of host-parasite relations of varying intensity, which may be classified in terms of the life history strategies of both parties, considered jointly and independently. What is needed alongside the present review is a survey of the impact of parasites on intermediate hosts with different kinds of life histories. Our predictions for those which are relatively sedentary and long-lived will be clear.

## Acknowledgements

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# Model Frameworks for Plant-Pathogen Interactions

*J. Swinton and R.M. Anderson*

## 1 Introduction

This paper is intended as a contribution to fulfilling the 'need to link theory in plant disease epidemiology with similar theory in other areas of population biology' (Jeger 1986). More particularly we focus on the similarities and differences between the theoretical frameworks that have emerged in plant pathology and animal or human infectious disease epidemiology. Although a number of workers (May 1990, Jeger 1984, Gilligan 1993, Gilligan 1990b, Heesterbeek and Zadoks 1987, Getz and Pickering 1983, Chan and Jeger 1994), have recognised this need and utilised results and methods more often seen in animal epidemiology, and such work is beginning to be incorporated into textbooks (Campbell and Madden 1990, Jeger 1989b), there is still a confusion in parts of the phytopathology literature over questions like the significance of threshold criteria in determining the persistence of an an infection in a defined host population, and the distinctions between epidemic, recurrent epidemic and endemic disease. In this paper we examine a number of these questions and expand on particular cases. We emphasise the construction of a theoretical framework which provides a basis for drawing together a number of different strands of plant epidemiology, and for melding ideas about transmission within a formula that captures the demography of the host and the impact of the pathogen. Some of these issues, like the putative existence of threshold host numbers for the establishment of infection, are common to many areas of epidemiology, but there are a number of distinctive problems faced by plant epidemiologists.

Two of the most distinctive features of plant pathosystems are the importance of spatial and genetic factors in determining disease spread. Spatial factors are significant because the spatial position of hosts typically changes on a very much longer timescale than the spread of infection, so that the pre-existing pattern of host density, and how demographic parameters influence this pattern, have a profound effect on the course of the epidemic. When the pattern of host density is uniform, as in some agricultural monocultures, this may simplify matters since the temporal and spatial spread of an epidemic may be essentially equivalent, as in the problem of focus expansion (van den Bosch *et al.* 1988a). When the host distribution is non-uniform, as typically

encountered in natural populations, problems of spread and persistence pose a tantalising challenge for theoretical and empirical studies.

Genetic effects are important because there are few plant pathosystems which can be understood without reference to the peculiarly intimate coevolutionary relationship between host and pathogen (Frank 1992). For example, gene-for-gene relationships between resistance and virulence have been demonstrated or postulated, predominantly in agricultural systems, across a wide range of host and pathogen genera (Thompson and Burdon 1992, Barrett, 1991). Read *et al.* (this volume) give an up to date survey of work on these problems.

Despite, or because, of the difficulties associated with these issues, we believe that the study of plant epidemiology has a great deal to offer, not least because of the availability of large datasets from agricultural settings and the possibility of experimental manipulations which would be impossible or unethical in animal disease systems. In this paper we outline a mathematical framework general enough for a number of different pathogen types and transmission modes. So as not to be too abstract, however, we describe it in terms of the transmission dynamics of a spore-borne fungal infection such as a cereal rust.

# 2 The Vanderplank model of disease spread

Much early theoretical and experimental work was stimulated by the classic delay-differential equation for plant disease spread introduced by Vanderplank (1963, 1984). One form of this equation is

$$\frac{dy}{dt} = R\,[y(t-p) - y(t-p-i)]\,[1 - y(t)], \tag{2.1}$$

where $y$ is a normalised measure of the intensity of an infection with a latent period $p$ and an infectious period $i$. Despite its utility in analysing and comparing disease progress curves, many workers have recognised the limitations of this model. The incorporation of the logistic density dependence into the equation is essentially phenomonological and obscures the ecological relationship between host and pathogen. Indeed host densities are not accounted for at all although they are crucial in determining plant disease ecology (Burdon *et al.* 1989).

We mention this model here mainly to try and clear up a misunderstanding which has appeared in the literature over the predictions it makes about the asymptotic level of disease. To specify the evolution of the system (2.1) into the future it is necessary to know the extent of spread of infection, not at a single time point, but over an entire time interval of length $i$. This is intuitively clear by seeing that one must know, not only how much infection

is present now, but also how much will emerge from latency in the future. To see this mathematically, divide both sides by $1 - y$ and integrate from $t$ to $t_0$ to obtain:

$$\begin{aligned} \ln \frac{1 - y(t)}{1 - y(t_0)} &= R \int_{t_0}^{t} y(s-p) - y(s-p-i)\, ds \\ &= R \left[ \int_{t_0-i-p}^{t_0-p} y(s)\, ds - \int_{t-i-p}^{t-p} y(s)\, ds \right], \end{aligned}$$

a relationship which holds for any $t$ and $t_0$. If we restrict our attention to solutions which are asymptotically constant, at $y = y^*$ say, we find that

$$y^* = 1 - Q \exp(-iRy^*),$$

where

$$Q = [1 - y(t_0)] \exp R \int_{t_0-i-p}^{t_0-p} y(s)\, ds. \tag{2.2}$$

This $Q$ holds all of the information about the initial state of the epidemic. Vanderplank (1984) postulated that

$$Q = [1 - y(t_0)];$$

we can see that this is indeed the correct value for a disease introduced at time $t_0$ only. However the value

$$Q = [1 - y(t_0)] \exp [y(t_0)]$$

claimed by Jeger (1986) is not a special case of (2.2). For example, an infection maintained at a level of $y_0$ over the entire infectious period alone would lead to

$$Q = \exp iRy_0. \tag{2.3}$$

These results are technical and not very significant in the light of the fact that for small initial inocula they all reduce to the same important basic formula (May 1990),

$$y^* = 1 - \exp(-iRy^*),$$

and indeed that this equilibrium is neutrally stable to small perturbations in disease level. Nevertheless this observation does explain some results of Onstad and Kornkven (1992) on large-scale spatial simulations of a model similar to the one below, who found that when 'uniformly distributed hosts are considered, Van der Plank's formula-based prediction matched our results but Jeger's did not'.

We turn now to a more tractable and transparent representation of disease progress by means of a compartmental differential equation system.

# 3 The basic model

We begin by considering a model for the dynamics of a spore-transmitted pathogen. There are a number of choices for the basic units of the model. Two natural measures of host density are density of plants (that is, number of individual plants per unit area), and density of plant tissue. Natural measures for infection include number of infected hosts, density of infected tissue, or number of infectious lesions. A proper choice of unit depends on the particular characteristics, not only of the infection being modelled, but also of the empirical data available, and will have implications for the structure of the model equations and in particular for the structure of the term representing transmission. Here, for definiteness, we take individual host plants as the basic unit.

Since we shall be particularly interested later on in the spatial diffusion of spores we use a slightly more complicated model than, say, May (1990) by including a variable $W$ for the density of spores as well as the more usual variables $X$ and $Y$ for the density, per unit area, of uninfected and infected hosts respectively. The framework is similar to that employed in the study of insect pathogen systems when transmission is direct via a free living stage such as a bacterial or fungal spore or a viral particle (Anderson and May 1981).

## 3.1 Host growth in the absence of disease

Since both situations in which host densities do not change, like potato late blight which occurs after canopy formation, and those in which host numbers or biomass are growing significantly, like alfalfa leaf spot (Thal and Campbell 1988), are of potential interest, we include both an intrinsic host growth rate and a carrying capacity into our models, a need recognised by Gilligan (1993). In the absence of disease, we assume that host growth is regulated by a simple logistic mechanism with carrying capacity $N_0$:

$$\dot{X} = rX(1 - X/N_0)$$

Of course, this assumption is vulnerable to the same criticism that we levelled at the assumption of logistic growth for disease progress: that it removes attention from the ecological processes controlling host growth in the absence of disease; but here we are focussing specifically on the effects on host growth due to the pathogen. All of our models will possess an equilibrium with $X = N_0$, $Y = W = 0$. Our primary concern is what happens to a system at this equilibrium, representing an uninfected host population at its carrying capacity, when a small amount of infection is introduced. The effect of infection on non-equilibrium host populations, such as exponentially growing ones, can be explored in a similar way (Hadeler and Nagoma 1990).

## 3.2 Disease progress

We assume initially that when a plant is infected, it dies or becomes removed at a net rate $b$, but until removed it is capable of producing new infectious spores at a rate $\lambda$. The loss rate also encapsulates the natural mortality rate of the plant, in the absence of infection and other density dependent constraints, so that the pathogen is assumed to decrease the life expectancy of the plant host. These spores may or may not produce new infections but are in any case removed from the environment, due to natural mortality outside the host at a rate $d$. The key remaining element of the model is the transmission term describing the incidence rate of new infection. The simplest choice for a directly transmitted disease is to assume that infection occurs at a rate $\beta WX$ linearly proportional to the density of free spores and the density of hosts, where by density we mean number per unit area, in contrast to frequency which we use below for the ratio of susceptible hosts to all hosts. Burdon and Chilvers (1982, 1976), for example, found that the presence of non-susceptible plants had very little effect on the rate of mycelial spread of damping-off, suggesting that this transmission term may be correct in this situation. In contrast, a vector-transmitted pathogen is often appropriately modelled by a frequency dependent transmission term of form $\beta WX/N$ more akin to the term often used in vector transmitted or sexually transmitted infections of animals (Anderson and May 1991). There is experimental evidence of such frequency dependent transmission for the pollinator borne anther-smut infection of *Silene alba* (Antonovics and Alexander 1992). This evidence is particularly interesting because it is direct in that it shows an empirical relationship between host frequency and spore deposition in contrast to the indirect evidence of Burdon and Chilvers deduced from infection rates. This provides a good example of the kind of experimental manipulations which are possible in plant systems—the frequency of host plants was manipulated simply by moving plant pots about—but which are rare, though not impossible, in animal systems (Keymer and Anderson 1979, De Jong *et al.* 1995).

Our basic model considers changes in densities of susceptible and infected plant hosts and of free living spores over time. We consider a pathogen that acts to decrease host life expectancy and to totally eliminate the reproductive capabilities of infected plants, so that the birth rate of infected plants is zero.

Here we discuss models incorporating both types of transmission dynamics; we begin with a direct transmission term. Our first system, then, is

$$\begin{aligned} \dot{X} &= rX(1 - X/N_0) - \beta WX \\ \dot{Y} &= \beta WX - bY \\ \dot{W} &= \lambda Y - dW. \end{aligned}$$

A standard linear stability analysis of the disease free equilibrium shows

that the introduction of a small amount of disease will generate an epidemic provided $R_0 > 1$, where

$$R_0 = \frac{\beta\lambda}{bd}N_0.$$

This parameter combination, the basic reproductive number of the pathogen, is the proper generalisation of the idea of Vanderplank's parent/progeny ratio (Vanderplank 1984) to these more general models. The particular form of this combination varies from model to model but its basic meaning is unchanged. It corresponds to the average number of new infections produced by one infection over its lifetime in a population consisting entirely of susceptibles (Anderson and May 1991).

By contrast, the model with a frequency dependent transmission term $\beta WX/N$ leads to a basic reproductive number of

$$R_0 = \frac{\beta\lambda}{bd}.$$

This reproductive number does not depend directly on the number or density of susceptibles. In both models the parameter combination $\beta\lambda/bd$ appears. The $\beta\lambda/b$ combination represents the average number of new infections produced by the spores on one infected host over the mean lifetime of the infection: the '$R$' of Vanderplank. The $1/d$ term represents the mean time that spores are present to cause infection: the '$i$' of Vanderplank. For the direct infection model, there is an additional term $N_0$ representing the number of susceptibles: this term does not appear in the scaled equation (2.1) but is crucial to understanding the difference between epidemic and endemic disease, and the different dynamics of density-dependent and frequency-dependent transmission. For example, for direct transmission, the threshold condition $R_0 > 1$ can be rearranged to give $N_0 > bd/\beta\lambda$ showing a threshold host density before infection can be established. In other words the carrying capacity of the habitat must exceed a given threshold value before a particular pathogen can exist. In the case of indirectly transmitted pathogens in which the transmission term is frequency, as opposed to density, dependent, no such density related threshold exists. The properties of plant disease with frequency dependent transmission of infection, and particularly the conditions which are required to maintain coexistence of host and pathogen, have been explored more fully by Thrall *et al.* (1993). The mathematical formalism for representing different transmission modes, and the implications for the properties of the resulting models, can be rather subtle (De Jong *et al.* 1995).

For both models, the condition $R_0 > 1$ has a double meaning: it is the requirement which must be satisfied for an epidemic of disease to arise, that is for the number infected to rise above the number of infections introduced

initially, and also the requirement which must be satisfied for endemic disease to be maintained. Standard theory (Bailey 1975) distinguishes between the *epi*demic *phase* of an infection: the events occurring on a fast time scale ($\beta\lambda/d$) after the introduction of infection into a largely susceptible population, and the *en*demic *phase* whose level is controlled by the rate of recruitment of new susceptibles into the population. The difference between these two phases is a dynamic one which depends principally on the values of the variables of the system—like the number of susceptibles present—rather than on its parameters, like the value of $R_0$. While some workers have clearly recognised this (Jeger 1986), Vanderplank appeared to come to the conclusion that a basic reproductive number bigger than 5 should be considered as creating an epidemic, while one less than 5 produced endemic disease (Vanderplank 1984). On the other hand he and others have recognised (Zadoks and Schein 1979) that the effective reproductive number must be unity at an endemic disease equilibrium. Recently, Onstad's numerical simulations (Onstad and Kornkven 1992) of a model similar to ours, on a spatially non-uniform environment were used to claim that this is untrue. His results, that infections with an apparent $R_0$ of unity, for the local deterministic system could not necessarily survive on spatially patchy host distributions, serve as a pointer that we should attempt to improve our understanding of threshold behaviour in these situations (Mollison 1991).

## 3.3 Periodic oscillations

One interesting problem that a compartmental differential equation model allows us to explore is the possibility of self-sustaining oscillations in the density of infecteds. For example, for the direct transmission model with a density related transmission term, it can be shown that oscillations are possible when

$$bdR_0^2 - \left[(b+d)^2 + bd\right] R_0 - r(b+d) > 0 :$$

this does not hold when $R_0$ is close to 1 but when it is does hold (Figure 1) there will be a loss of stability to periodic oscillations. Note this only happens for $r$ small relative to the other parameters: vigorous regrowth of host tissue or plant numbers will tend to damp out these oscillations. It is essentially the possibility of a reservoir of free spores which allows these predator-prey type oscillations.

## 3.4 Fitting the models to data

The models above do not in general permit an explicit solution for progress over time. A significant effort has been devoted by plant pathologists to

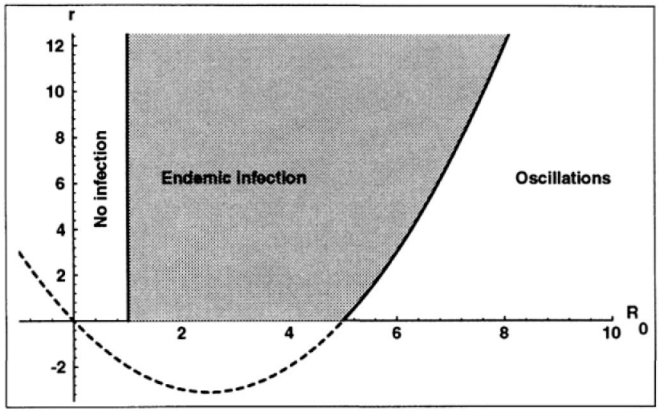


Figure 1: Bifurcation diagram for the model described in section 3.2, showing the two threshold conditions derived there in $r - R_0$ parameter space. When $R_0 < 1$, no disease establishment is possible; when $R_0$ increases through one a stable endemic state is established. If $R_0$ continues to increase, while keeping $r$ fixed, this endemic state will lose stability to periodic oscillations.

fitting mathematical functions, not always derived from specific biological assumptions, to disease progress curves (Campbell and Madden 1990, Gilligan 1990a). We would like to suggest that using the solutions to the simple differential equation models used above, parameterised by the rate constants of the equations may be a useful alternative approach with the advantage of making clearer the biological premises on which a model is based and the significance of the resulting parameters. Although of course some of the parametric models used are derived from simple differential equation models, the extra complexity arising from fitting solutions which may not be analytically known is computational rather than statistical.

# 4 Castrators, killers, and debilitators

Although they served to illustrate our main thesis, the models above could be criticised on a number of grounds. There is a clear necessity to add more biological detail, specifically in the context of variations in the life cycle of the pathogen, the treatment of density dependence, and spatial and genetic effects. A carrying capacity for hosts implemented solely through a density-dependent effect on uninfected hosts is implausible, and for many pathogens infected tissue or individuals may be able to contribute to growth. An exten-

sion to the model which takes account of these complications is

$$\begin{aligned} \dot{X} &= (r_X X + r_Y Y)(1 - (X+Y)/N_0) - \beta W X \\ \dot{Y} &= \beta W X - bY \\ \dot{W} &= \lambda Y - dW \end{aligned}$$

where $r_X$ and $r_Y$ are the rates at which healthy and infected plants respectively produce new healthy offspring, and we assume no vertical transmission of disease. This formulation assumes that the carrying capacity of the environment acts by reducing the birth rate of the population rather than increasing its death rate, similarly to the assumption of Thrall *et al.* (1993) that density-dependent processes act upon juvenile hosts.

One area which can be discussed within this framework is the work of Burdon (1991) who has distinguished between pathogens by introducing the categories of castrator, killer and debilitator. Castrators reduce the fecundity of their hosts without affecting their longevity, while killers directly affect the viability of both juvenile and reproductively active hosts. Debilitators affect both viability and fecundity, but are less pathogenic and may do so over a prolonged periods of time. It is tempting to use the microparasite/macroparasite distinction of Anderson and May (1991) and to assign castrators and killers to the microparasite class and debilitators to the macroparasite class, because in the former case disease is either present or absent while in the second disease depends on the intensity of infection. Nevertheless, in a crude way, all of these types can be included in our, essentially microparasitic, model. Castrators are those which reduce or remove $r_Y$, killers those which increase $b_Y$, and debilitators may affect both. However, merely because these different types can be represented as differently parametrised versions of the same model, does not mean that they will have qualitatively the same dynamics; an exploration of the dynamics resulting from a parameterisation suitable for a particular infection promises to be an interesting area for research.

# 5 Spatial structure

Many researchers have commented that important theoretical questions for plant epidemiologists and ecologists centre on questions of spatial structure (Jeger 1989a). Invasion, spread, and persistence of both hosts and pathogens are deeply spatial in nature and there is a substantial literature on questions of scale (Levin 1992), heterogeneity and diffusion (Okubo 1980). The difficult question of how to deal with epidemics in patchy host environments is addressed in the spatial group report (Bolker *et al.* this volume). Since some plant systems, and in particular agricultural systems, provide some of the best epidemiological examples of habitats which *are* spatially uniform in host

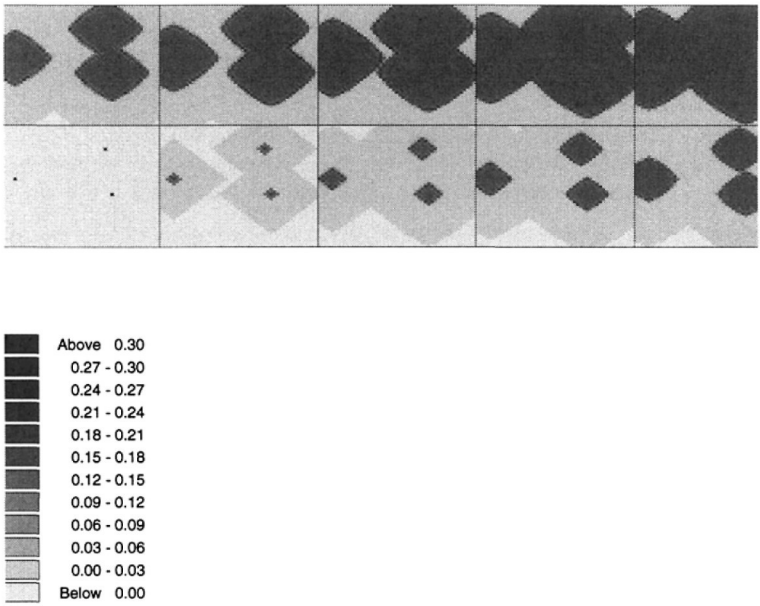


Figure 2: Numerical simulation of the model described in section 5 showing the evolution of a wave of infection from three initial seeds. Parameter values: $\beta = 4$, $r = b = \lambda = d = \kappa = 1$. At the end of each unit time period, a proportion 0.01 of the free spores in each cell are redistributed to the four nearest neighbours. Each square shows the density of infecteds ($Y$) in each part of a 51 × 51 grid, at intervals of 15 time units.

density and genotype, we discuss here two approaches to dealing with such situations.

## 5.1 Travelling waves of infection

In situations where it is known that disease can establish itself, a question perceived important by theoreticians is the speed at which a front of infection spreads through a susceptible population. A numerical simulation of this process is shown in figure 2. As Mollison has pointed out, to a first approximation one would expect the speed to be the ratio of the typical latent period of a single infection to the typical spatial spread of the infection. The best example of a more precise analysis is the work of Van den Bosch and colleagues (van den Bosch *et al.* 1988b, van den Bosch *et al.* 1990, Metz and van den Bosch 1995). They use submodels for the typical contact distribution

of infective spores and for the time distribution of latent and infective periods and use these as parameters for a general spatio-temporal models which produces remarkably good agreement with observed data for later stages of the epidemic, although the initial phases, which cannot be captured by a study of the asymptotic wave-speed, may also be of interest. Whether or not the asymptotic wave speed is of practical relevance to plant pathologists, agricultural specialist, or plant ecologists is another matter. In situations where practically all local host tissue becomes infected quickly relative to the spatial spread of infection, and there are no important subsequent interactions, the intensity of infection within a field is controlled directly by the asymptotic rate of spread of the infectious front. In more complex situations, more important questions may concern the relationship between host density or spatial planting pattern to the likelihood of occurrence of an epidemic of a particular pathogen. In this case an understanding of the biological determinants of $R_0$ or the threshold host density for pathogen spread may be of more practical value.

## 5.2 Thresholds in the presence of diffusion

Another related question which arises in a spatial setting is whether diffusion of spores away from a focus of infection is capable of affecting the threshold criteria. If we assume that spores move by a diffusive mechanism, the simple system above becomes

$$\begin{aligned} \dot{X} &= rX(1 - X/N_0) - \beta WX \\ \dot{Y} &= \beta WX - bY \\ \dot{W} &= \lambda Y - dW + \sigma \nabla^2 W \end{aligned}$$

If we consider the stability of the spatially homogenous equilibrium to small perturbations with spatial structure $e^{i\mathbf{j}\cdot\mathbf{x}}$, it is straightforward to show that both the loss of stability of the disease-free equilibrium, controlled by $R_0$, and, less trivially the loss of stability of the endemic equilibrium to periodic orbits, are unaffected by the diffusion term: in both cases the least stable perturbations have $\mathbf{j} = 0$. This irrelevance of spatial structure is essentially because the basic epidemic threshold controls the number of new spores produced by one spore, and with the basic assumption of spatial homogeneity it does not matter where these new spores are transported to by diffusion since they will have the same effect.

# 6 Host genetics

As discussed in the introduction, any study of plant-pathogen interactions must ultimately take account of the evolutionary pressures on both plant

and pathogen, and although there is a great deal of work in the literature modelling evolutionary dynamics, there is very little which combines this with epidemiologically realistic assumptions. By way of demonstration that the modelling framework described here is indeed capable of capturing this heterogeneity we describe here a simple extension of the model to a diploid plant host with with a parasite resistance controlled by two alleles at a single locus: a dominant susceptibility gene $A$ and a recessive resistance gene $a$. This model is similar to that of Beck *et al.* (1984a,b).

We use the subscript 1 for the population with the $AA$ genotype, 2 for the heterozygous genotype $Aa$, and 3 for the $aa$ genotype. Healthy plants of type $i$ are denoted $X_i$ and infected ones $Y_i$; spore density is represented by $W$. The per-capita rate of reproduction of a healthy plant of type $i$ we denote $a_{iX}$ and that of an infected plant $a_{iY}$. In contrast to the previous sections, we explicitly include the per capita death rate of uninfected and infected hosts, $b_i$ and $b_i + v_i$ respectively. The gross rate at which each genotype produces offspring is given by $h_i = a_{iX}X_i + a_{iY}Y_1$. Allowing for random mating, the rate at which new genotypes are created is then $f_i$ where $f_1 = (h_1 + \frac{1}{2}h_2)/(h_1 + h_2 + h_3)$, $f_2 = 2(h_1 + \frac{1}{2}h_2)(h_3 + \frac{1}{2}h_2)/(h_1 + h_2 + h_3)$, and $f_3 = (h_3 + \frac{1}{2}h_2)(h_1 + h_2 + h_3)$.

Then the equations describing the system as a whole are

$$\begin{aligned}
\frac{dX_i}{dt} &= f_i - \beta_i X_i W - b_i X_i - X_i N/N_0 \\
\frac{dY_i}{dt} &= \beta_i X_i W - (b_i + v_i)Y_i - Y_i N/N_0 \qquad i = 1,2,3 \\
\frac{dW}{dt} &= \lambda_1 Y_1 + \lambda_2 Y_2 + \lambda_3 Y_3 - dW
\end{aligned}$$

In the absence of disease, the model describes an evolution to a Hardy-Weinberg equilibrium. These sets of equations are very difficult to probe analytically in any generality. One approach was taken by Beck *et al.* (1984a,b) in analysing a similar model of genetics coupled to a slightly simpler epidemiological setting. Under the assumption that evolutionary pressure acts slowly compared to epidemiological effects, it is possible to substantially simplify the model via the method of singular perturbations.

Here we content ourselves with an analysis of this system for a 'castrator' type of infection (section 4) in which infected plants cannot reproduce when infected, so that $a_{1Y} = 0$. In this case it is easy to show that this model can possess an endemic state above threshold, stable to perturbations in disease levels. The question we ask here is whether this state can be destabilised by the introduction of the resistance gene—that is whether the resistance gene can establish itself in the already-infected population. The threshold condition can be found and in the case of the simplifying assumption that

$\beta_1 = \beta_2$, takes the form

$$\frac{\beta\lambda_1}{d}N_0 > \frac{(a_{2Y} + r_1 - r_2)(b_1 + r_1 + v_1)}{a_{2Y}r_1 + (v_2 + b_2)(r_2 - r_1)}$$

where $r_i = a_{iX} - b_i$. This expression is independent of the properties of the *aa* genotype, reflecting the fact that in this diploid setting the stability analysis is only concerned with the limiting situation when the population contains a single resistance gene, necessarily contained in a heterozygous host.

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# The Dynamics of Insect-Pathogen Interactions

*C.J. Briggs, R.S. Hails, N.D. Barlow and H.C.J. Godfray*

## 1 Introduction

Insects are abundant members of all terrestrial and freshwater ecosystems and are also of immense economic importance, largely as pests and disease vectors, but occasionally having a more positive influence on human well-being as in the case of silk moths and honey bees. That they are subject to a variety of diseases has been understood for several centuries, but it has only been with the development of modern microbiology in the last sixty or so years that the widespread occurrence and biological diversity of insect diseases has been appreciated. Much of the impetus for the study of insect diseases has come from the possibility that they might be used as biological control agents to combat noxious pests, or from the need to preserve the health of economically valuable species. Thus the potential for insect diseases to control or regulate their host populations has been understood for many years. However, the ecological study of the population dynamics of insect-pathogen interactions is a relatively new field of biology and most work in this area has been carried out in the last fifteen years.

The aim of this chapter is twofold: first, briefly to review the theory of insect-pathogen population dynamics and to try and identify areas that require further study; and second, to examine the most important case studies of insect-pathogen population dynamics and to discuss whether the predictions from theory are concordant with field experiments and observations. There are two broad theoretical approaches to the study of insect-pathogen dynamics. The first begins with simple strategic and normally analytical models that are then elaborated when particular systems are studied. The second approach, with its origins in systems ecology, involves the construction of tactical simulation models (which are often very large and complex) designed to investigate in detail the interaction between a host and its disease. Such models often include a detailed description of the biotic and abiotic environment. Here we consider only the first type of model: good reviews of the second type and an entry into the literature are provided by Brown (1987) and Onstad and Carruthers (1990). We also make no claims that our review of insect-pathogen case studies is exhaustive and have largely chosen studies that illustrate points that we want to make about population dynamics.

The majority of insect pathogens are microparasites although many species are also attacked by macroparasites, in particular nematodes, nematomorphs and mites. The population dynamics of insect macroparasites have received relatively little attention and here we concentrate on microparasites, the most important groups of which are viruses, bacteria, fungi and protozoans.

# 2 The theory of insect-pathogen dynamics

Insect microparasites, like the microparasites of vertebrates, are small, have short generation times, and typically have high rates of reproduction within their hosts. Unlike vertebrates, the insect host also often has a relatively short generation time. Another major difference is that insects do not possess acquired immunity, their risk of succumbing to a pathogen is the same at a second infection as it was at the first. Thus insect-pathogen systems do not have the classical SIR structure (Susceptible-Infected-Recovered) that is typical of vertebrate systems (Anderson 1982a): insects that recover from an infection move straight back into the susceptible class. The majority of insects contract diseases by ingesting pathogen particles in the environment or by contact with infected hosts. There are some cases where insects act as intermediate hosts for pathogens whose definitive host is an insect predator, and a few cases where insect diseases are transmitted by vectors.

The first models of insect-pathogen dynamics assumed that the host population remains constant through time, mortality due to the disease being exactly compensated by an increased birth rate (e.g. Bailey 1975). A simple model of this type, due to Anderson and May (1981), is

$$\frac{dI}{dt} = \beta SI - (\alpha + b + \gamma)I, \tag{2.1}$$

where $S$ and $I$ represent the number or density of susceptible and infected individuals (and hence the total number of hosts is $S + I = H$), $\beta$ is the transmission probability, $\alpha$ the disease-induced and $b$ the background mortality rates, and $\gamma$ the recovery rate. The quantity $(\alpha + b + \gamma)$ represents the rate at which diseased individuals leave the infected class through death or recovery and thus its reciprocal is the average length of infection. Consider a new case of the disease in an otherwise uninfected population: the rate at which the diseased individual causes further infections is $\beta S$ and thus before death or recovery this individual is expected to cause $\beta S/(\alpha+b+\gamma)$ new cases of the disease. This quantity, which is central to all epidemiological studies, is called $R_0$. The disease will establish itself only if, when rare, each infection leads to more than one further infection, in other words $R_0$ must be greater than one. Note that $R_0$ is influenced by the density of susceptible hosts and so the disease spreads only when the density of susceptibles is greater than a

threshold, $H_T = (\alpha + b + \gamma)/\beta$ that ensures $R_0 > 1$. If the infection is able to spread, then the model predicts an equilibruium disease prevalence where the proportion of uninfected hosts is $1/R_0$. This result is again straightforward to explain: at equilibrium, each infection must, on average, lead to exactly one further infection. In the case of a new infection, the diseased individual is able to cause up to $R_0$ further infections; but at equilibrium a large fraction of the possible hosts encountered by the infected animal are themselves infected. If $1/R_0$ of these $R_0$ potential new cases are uninfected then each infection leads to exactly one new case, hence the definition of the equilibrium. Identical or very similar definitions for $R_0$ and $H_T$ arise from the analysis of a wide range of models applicable to many different types of disease (Anderson and May 1979, 1981, May and Anderson 1979, Heesterbeek and Roberts this volume).

While of pedagogical value, models such as the above are of limited value in studying the dynamics of insect pathogens because of the very unrealistic assumption about the constancy of the host population. Anderson and May 1980, 1981) relaxed this assumption and developed a series of models in which the total population density of the host was a dynamic variable influenced by the prevalence of the pathogen. Instead of assuming that recruitment magically balanced death due to disease, the fecundity of infected and uninfected individuals is included explicitly in the model. The simplest model retains (2.1) to describe changes in the number of infected individuals but includes an equation for changes in total population numbers

$$\frac{dH}{dt} = rH - \alpha I, \tag{2.2}$$

where $r$ is the difference between the birth rate $a$ and the background (i.e. non-disease induced) death rate $b$. The conditions for the establishment of the disease ($R_0 > 1$ or $H > H_T$) are identical to the above. It is immediately obvious that in order for the disease to prevent the host population from growing exponentially, the disease must be sufficiently pathogenic to be able to counter the intrinsic propensity of the host to increase ($\alpha > r$). In their original paper, Anderson and May (1981) went on to analyse a number of variants of this model, and since then, further modifications have been studied which we have summarised in Table 1.

The natural interpretation of the transmission mechanism embodied in these models is that infection occurs through contact between infected and uninfected individuals. However, many insect diseases are contracted by the animal eating food contaminated by infectious particles produced by diseased individuals. For example, most viruses of lepidopteran and symphytan larvae are contracted by eating leaves which have been contaminated by dead or dying larvae. To model such systems, it is necessary to include a description of the density of infected particles $W$ in the environment (Anderson and May

| Description | Authors | Predictions |
|---|---|---|
| 1) Transmission through contact between infected and uninfected hosts; disease does not affect fecundity | Anderson & May (1981) (Model A) | a) Disease becomes established if $R_0 > 1$ or, equivalently, if population density $> H_T$.<br>b) Stable equilibrium if $\alpha > r$.<br>c) Greatest host population depression at intermediate levels of $\alpha$. |
| 2) Model 1 but infected individuals have reduced fecundity | Anderson & May (1981) (Model B) | a) Conditions for regulation less stringent; pathogens of lower virulence may regulate.<br>b) Greater host depression at equilibrium. |
| 3) Model 1 with vertical transmission | Anderson & May (1981) (Model C) | a) Conditions for regulation unaffected.<br>b) Greater host depression at equilibrium.<br>c) Persistence condition less stringent ($H_T$ lower). |
| 4) Model 1 with latent periods of infection | Anderson & May (1981) (Model D) | a) Conditions for regulation more restrictive: higher virulence required.<br>b) Equilibrium host densities higher.<br>c) Persistence conditions more stringent ($H_T$ higher). |
| 5) Model 1 but virulence increases with host density | Anderson & May (1981) (Model E) | If virulence increases linearly with host density ($\alpha$ replaced by $\hat{\alpha}H$) then the infection both persists and regulates the host if $\beta > \hat{\alpha}$. |
| 6) Model 1 but background host mortality density dependent | Anderson & May (1981) (Model F) | If mortality increases linearly with host density ($b$ replaced by $b_0 + sH$; $b_0$ and $s$ constants) then the infection persists and regulates the host if $\beta > s$ and $H_T$ is less than the host carrying capacity. |
| 7) Diseased individuals release free-living infective stages into the environment | Anderson & May (1981) (Model G) | a) If virulence moderate, or free-living stages short-lived, then stable equilibria likely.<br>b) If virulence high, and free-living stages long-lived, then cyclic population dynamics occur.<br>c) The authors argued that population cycles in forest insects may be explained by this model. |

Table 1. A survey of tactical models of insect-pathogen dynamics

| Description | Authors | Predictions |
|---|---|---|
| 8) Model 7 with seasonal fecundity ($r$ sinusoidal) | Anderson & May (1981) | a) Regulation requires that $\alpha >$ mean $r$.<br>b) When regulated, host densities and prevalence cyclic. |
| 9) Model 7 with vertical transmission and parasite induced reduction in host reproduction | Anderson (1982b) | As model 7 but<br>a) Conditions for regulation less stringent as infected individuals do not reproduce.<br>b) Lower host equilibrium densities.<br>c) Area of parameter space in which cycles occur larger. |
| 10) Model 9 with density of pathogens artificially increased (designed to investigate biological control) | Anderson (1982b) | a) A threshold exists at which input of pathogens causes host extinction.<br>b) Substantial reduction in host equilibrium density only occurrs near threshold.<br>c) Threshold lowered by<br>i) vertical transmission,<br>ii) no reproduction by infected hosts.<br>d) Pathogen input damps oscillations. |
| 11) Model 1 but transmission non-linear | Getz & Pickering (1983) | If transmission proportional to fraction ($S/H$) rather than absolute number ($S$) of susceptibles then<br>a) the pathogen does not regulate the host but<br>b) is able to persist. |
| 12) Model 6 (i.e. host regulated by other factors) but transmission rate non-linear (as in model 11) | Getz & Pickering (1983) | The disease persists at equilibrium and the host population is suppressed below carrying capacity. |

Table 1 (cont.). A survey of tactical models of insect-pathogen dynamics

| Description | Authors | Predictions |
|---|---|---|
| 13) Model 1 but transmission non-linear | Hochberg (1989a) (see also Liu *et al.* (1986), Andreason (1989)) | If $\beta IS$ is replaced by $\beta I^{p+1}S^{q+1}$ ($p$ and $q$ constants) then a) stability enhanced if transmission increases more than linearly with host density ($p > 0$) and less than linearly with pathogen density ($q < 0$). b) complex dynamic behaviour can occur. |
| 14) Model 7 + a) Age-dependent immunity of host; b) Death rate of infecteds is related to the rate of propagule production | Brown (1984) | a) High virulence ($\alpha$) is now a stabilising influence because it results in faster host death b) Intermediate values of fecundity and the lifespan of free-living infected stages lead to stable limit cycles. |
| 15) Model 13 but fecundity is seasonal (a square wave rather than the sine wave of model 8) | Brown (1984) | a) Stability conditions the same as those for the non-periodic system (model 13). b) When regulated, host populations are periodic. |
| 16) Model 7 but pathogens may enter a reservoir where they cannot infect hosts but where mortality is low | Hochberg (1989b) | a) The presence of the reservoir increases the area of parameter space where a stable equilibrium occurs. b) The reservoir causes a storage effect which mixes the pathogen cohorts and hence tends to damp cycles. |
| 17) Model 7 but host reproduction density dependent | Dwyer (1993); Bowers *et al.* (1993) | The two models include host density-dependence in different ways. Dwyer found that compared to model 7: a) cyclic behaviour occurs over a greater region of parameter space b) cycles tend to have a longer period Bowers *et al.* found that for regions of parameter space that produced cycles in model 7: a) cyclical behaviour was less likely b) cycle period could be shorter or longer, depending on the precise parameter values. |

Table 1 (cont.). A survey of tactical models of insect-pathogen dynamics

| Description | Authors | Predictions |
|---|---|---|
| 18) Model 17 placed in a spatial context as a reaction-diffusion process | Dwyer (1993) | a) If regulation occurs, then the disease will spread through the population as a travelling wave<br>b) The speed of the wave is very sensitive to the transmission coefficient, $\beta$. |
| 19) Model 7 with age-structure: time delays in host development and release of pathogens after infection | Briggs & Godfray (1995) | The two time delays can interact to produce cycles with a period of one, or one half, a host generation. |
| 20) Discrete-time model with vertical transmission | Régnière (1984) | a) Pathogen persistence without regulation, regulation to stable equilibrium or limit cycles, or unstable equilibrium are all possible outcomes<br>b) Regulation is most likely with low virulence and imperfect vertical transmission. |
| 21) Multispecies models: 2 hosts 1 pathogen | Holt & Pickering (1985), Bowers & Begon (1990), Begon *et al.* (1992) | See Begon & Bowers (this volume) |
| 22) Multispecies models: 1 host, 2 pathogens | Hochberg & Holt (1990) | See Begon & Bowers (this volume) |
| 23) Multispecies models: 1 host, 1 pathogen, 1 parasitoid | Hochberg *et al.* (1990) | See Begon & Bowers (this volume) |

Table 1 (cont.). A survey of tactical models of insect-pathogen dynamics

1980, 1981).

$$\frac{dW}{dt} = \lambda I - (\mu - \nu H)W. \tag{2.3}$$

Here, infected hosts produce infectious particles at a rate $\lambda$ which are lost either through natural processes (at rate $\mu$) or because they are consumed by hosts (at rate $\nu H$). (Normally $\mu W$ and $\lambda I \gg \nu HW$ and the second term in parentheses can be ignored). To complete the model, the transmission term in (2.1), $\beta SI$, is replaced by $\nu SW$. The number of infectious particles produced during the lifetime of a diseased host is $\lambda/(\alpha + b + \gamma)$; of these, a fraction $\nu S/(\mu + \nu H)$ successfully infect new hosts so that the basic reproductive rate, $R_0$, is

$$R_0 = \frac{\lambda}{\alpha + b + \gamma} \frac{\nu S}{\mu + \nu H} \approx \frac{\lambda \nu S}{\mu(\alpha + b + \gamma)}. \tag{2.4}$$

Again, Anderson and May (1981) and subsequent authors have examined a number of variants of this basic model which are summarised in Table 1. The model incorporating free-living infective stages (2.1–2.3), generated considerable excitement because in cases of high pathogenicity (high $\alpha$) and long lived free-living stages (low $\mu$), persistent limit cycles in total host density and disease prevalence were predicted. Substituting realistic parameter values into the model led to cycles with periods of the order 3–10 years, exactly the type of cycle observed in a variety of forest insect pests which had hitherto lacked a convincing explanation. Of course, if insect populations cycle for other reasons than disease, prevalence is also likely to be periodic. As is discussed further below, a major goal of empirical host-pathogen studies is to try to discover whether cycles in pathogen abundance cause or are caused by cycles in their host.

What do the simple tactical models described above and in Table 1 tell us about insect-pathogen population dynamics? First, they furnish a condition for the spread of the disease through the host population in terms of the basic life history parameters of the disease and the pathogen, and the population density of the host. Second, they suggest when a disease is able to regulate the host population. The ease with which the models predict host regulation by pathogens has been very influential in making insect ecologists consider the possible importance of disease. Third, at the cost of a little algebra or computer simulation, they can be used to identify the persistent dynamic behaviour of the system; whether the pathogen regulates the host at a stable equilibrium, or whether limit cycles or chaos occur. Fourth, the simple models are easily adapted to include artificial manipulation of the disease by man (Anderson 1982b, Hochberg 1989b, Begon and Bowers this volume) and can thus provide general guidance for the design of biological control programmes. For example, if pathogens are used as biological insecticides then high pathogenicity is at a premium; however, if long-term suppression of host

densities is the goal then intermediate levels of virulence are optimal (Anderson and May 1981). This function of modelling will become more important if genetically manipulated 'designer-viruses' are developed for use against pest insects. Finally, the simple one host-one pathogen models considered so far can be extended to include several hosts or pathogens, as well as other organisms such as parasitoids. These community implications are considered by Begon and Bowers (this volume).

# 3 Case studies

A vast number of pathogens have been isolated from insect species. In the previous section, we discussed how simple models suggest that these pathogens can play a regulatory role in insect systems. However, relatively few have been shown to have a significant effect on the population dynamics of their hosts. In this section we review a number of case studies of the role of pathogens in real insect systems, concentrating on a small number of examples that have been relatively well studied. In the cases where models have been applied to particular interactions, we ask if these models have been useful in understanding the system.

Many of the best-studied examples come from forest insects, in particular from systems in which the insect populations undergo dramatic outbreaks and declines. We start with a discussion of the role that pathogens may play in these outbreaks of forest pests, and then move onto non-forest examples. Much of the study of insect pathogens has been motivated by the desire to use them in the control of pest insects. Because of this, some of the best evidence for the effect that pathogens can have on the dynamics of insect systems has come from attempts to use diseases as biological control agents. In the final section, we discuss approaches to biological control using pathogens, ranging from their use as a biological insecticide to their establishment as long-term classical biological control agents.

## 3.1 Forest Insects

In discussions of the role of pathogens in the dynamics of insect populations, the area that has received the greatest attention is the possible role they play in the multi-year cycles of forest insects (Anderson and May 1980, Anderson and May 1981, Ewald 1987, Myers 1988, Bowers *et al.* 1993). It has long been noted that the populations of a number of forest insects undergo dramatic fluctuations in density (Varley 1949). In many of these species, including *Orgyia pseudotsugata* (Douglas-fir tussock moth), *Acleris variana* (black-headed budworm), *Bupalus piniarius* (pine looper), *Zeiraphera diniana* (larch budmoth), *Diprion hercyniae* (spruce sawfly), and *Malacosoma disstria* (tent caterpillar), the fluctuations are to some degree cyclical, with periods

of 5–15 years (Varley *et al.* 1973). Many of these species cause tremendous economic damage during outbreaks and have been closely studied by forest entomologists.

Cyclic forest insects are often subject to pathogens with the type of natural history – high pathogenicity, long-lived free-living infectious stages – that cause multi-year cycles in simple population models (Anderson and May 1980, 1981). The most important type of pathogen is viruses which rapidly kill their host, producing large numbers of infectious particles which are released either in the faeces or at the death and dissolution of the host. Viral particles can persist for some time in the environment; in the case of nuclear polyhedrosis viruses (NPVs) their survival is enhanced by a polyhedral inclusion body within which the virus is protected.

The cycles predicted by these simple models are not seasonal cycles but have a period of several host generations. They are characterised by a peak in prevalence of the disease shortly after the host abundance has peaked and has started to decline. The models predict that during these cycles host abundance increases gradually followed by a rapid decline. The abundance of infective stages, however, shows a rapid rise in abundance and then declines slowly after the outbreak. During these cycles, the abundance of the host first increases until it breaches the threshold density, $H_T$, at which point the virus can spread through the population. The spread of the virus causes a dramatic decline in host abundance and reduces host density below $H_T$, thus ending the epidemic. The pathogen then persists in long-lived infectious stages, until the host population again rises above $H_T$ and the cycle repeats itself.

### 3.1.1 *Zeiraphera diniana* (Larch Budmoth) – Granulosis Virus

Perhaps the best studied example of cyclical dynamics in forest insects is the 9 to 10 year cycles in larch budmoth (Tortricidae) populations in the Swiss Alps. Four outbreaks of the larch budmoth have been monitored in detail since 1950. Forestry reports reveal an additional 12 outbreaks between 1855 and 1950 (Baltensweiler and Fischlin 1988). Many of the outbreaks have been synchronous between different sites in the Alps (Baltensweiler *et al.* 1977), with fluctuations in budmoth density over 5 orders of magnitude.

Epizootics of a granulosis virus occurred during the declining phases of some larch budmoth cycles. Anderson and May (1980,1981) found that their model with a free-living infective stage, using parameter values independently estimated for the larch budmoth system produced cycles that were similar in form and period to those observed in budmoth populations. They suggested that the host-pathogen interaction was responsible for the observed cycles. Bowers *et al.* (1993) argued that in modelling larch budmoth cycles it is important to include density dependence acting on the host at high densities. They found that incorporating density dependence in host reproduction into

the Anderson and May model made cycles less likely for the range of parameter values estimated for the larch budmoth. When cycles did occur, they were of the correct period, but predicted higher prevalence and lower host abundance than those found in field populations. However, field observations indicate that viruses are not invariably associated with cyclic populations: epizootics of the virus did not occur during all cycles at some sites in the Alps, and at other sites the virus was not found, but cycles still occurred (Baltensweiler *et al.* 1977). Thus, it appears that the host-pathogen dynamics is not a general cause of cycles in larch budmoth. The host may be driving the occurrence of epizootics in the pathogen population, but the pathogen is probably not driving the host dynamics. Other hypotheses for the cause of the larch budmoth cycles are host-induced changes in foliage quality and changes in the genetic composition of the host population (Baltensweiler 1993).

### 3.1.2 *Orgyia pseudotsugata* (Douglas-fir Tussock Moth) – Nuclear Polyhedrosis Virus

The Douglas-fir tussock moth (Lymantriidae) is a defoliator of Douglas fir (*Pseudotsuga menzeisii*) and other economically important tree species in the western United States and Canada. Tussock moth populations display regular outbreaks with a period of 7 to 10 years (Thompson and Scott 1979). The abundance of the moth generally builds slowly over the course of several years, followed by a rapid increase for one or two years. The moth population density typically remains high for 3 or 4 years, and then crashes (Varley *et al.* 1973). Naturally occurring NPV frequently produces epizootics late in these outbreaks, after significant economic damage has already occurred. The role of the virus in the decline of the outbreaks was demonstrated by Shepherd *et al.* (1984) who were able to initiate NPV epizootics earlier in the population cycle, causing the moth outbreak to be terminated more quickly (see also Otvos *et al.* 1987a,b). If the virus is sprayed early in the season on the highly susceptible young larvae, death occurs while there are still healthy larvae in the environment, and this within-generation recycling of the virus helps to reduce host density (Harper 1987). There is also vertical transmission of the virus from infected females to their offspring (Morris 1963). Anderson and May (1981) found that vertical transmission promotes population cycles, when combined with horizontal transmission and the production of large numbers of long-lived infectious stages. Tussock moth NPV survives for a long time in the environment and can be isolated from the soils in areas where no outbreak has occurred in forty years (Thompson *et al.* 1981).

The pattern of host population growth and decline, and the natural history of the interaction, fit Anderson and May's (1980, 1981) model of pathogen-induced cycles. Varley *et al.* (1973) tailored the model to fit the Douglas-fir tussock moth system. They included density-dependent mortality, vertical

transmission, and an incubation period for the virus. The model was parameterised using published data from a number of sources. Their model predicted shorter-period cycles than those found in the field, while the density-dependent mortality tended to dampen the predicted cycles. They concluded that the observed cycles are probably due to factors other than the pathogen-host interaction. However, Dwyer (1994) found that including density-dependent host reproduction in an Anderson-May model with parameter estimates for the Douglas-fir tussock moth increased the likelihood of cycles. However, subtle differences in model structure and parameter estimates make it difficult to exactly compare the two models and to resolve why they give different results. Although these modifications of the model were intended to include many of the realistic features of the interaction, some properties that may be important to the dynamics were still left out. Dwyer (1991) performed a series of field experiments on the tussock moth/NPV system and found that moth density, stage structure, and spatial distribution can all affect the transmission rate of the disease (which is assumed to be a constant, linear function in the Anderson-May type models). Thus it remains an open question whether the cycles in Douglas-fir tussock moth are caused by the NPV virus, or if the NPV is simply responding to high densities of its host.

Dwyer (1992) used a reaction-diffusion model to investigate the spatial spread of the virus through a Douglas-fir tussock moth population within a single generation. The model predicted that the disease would spread as a simple travelling wave. Parameter estimates were obtained using small-scale experiments, and then the model's prediction of the rate of disease spread was tested with an experimental population of tussock moths arranged in a linear array. The model predictions were broadly concordant with the experimental data, suggesting that spatial models may be usefully employed in the design of biological control programmes.

### 3.1.3 *Lymantria dispar* (Gypsy Moth) – Nuclear Polyhedrosis Virus

The gypsy moth (Lymantriidae) is currently found throughout the northern hemisphere as a major defoliator of various tree species in deciduous forests (except in the UK where it unaccountably became extinct around the turn of the century). It originated in Europe, but was introduced into Massachusetts (United States) in the 1860's (Elkinton and Liebhold 1990). The gypsy moth normally remains at low, endemic levels for long periods of time, and then over the course of one or two generations increases in density by several orders of magnitude to epidemic levels. After one or two years, the outbreak collapses and the moth density returns to endemic levels (Elkinton and Liebhold 1990). The reoccurring patterns of outbreak and decline in some gypsy moth populations in Europe appear to be cyclic, with a period

of 8–11 years (Montgomery and Wallner 1988). However, Liebhold and Elkinton (1989) found little evidence for cyclicity in the timing of outbreaks in Massachusetts. The gypsy moth is susceptible to nuclear polyhedrosis virus which is normally fatal and which produces a large number of long-lived infectious stages (polyhedral inclusion bodies). It is believed that epizootics of this virus are responsible for the collapse of outbreaks in gypsy moth populations throughout the world (Elkinton and Liebhold 1990). In Europe and Asia, other types of pathogens including the fungus *Entomophaga maimaiga* and several microsporidia species can also be major mortality agents at high moth densities (Soper *et al.* 1988, Shimazu and Soper 1986, Jeffords *et al.* 1988). However, the explanation for why outbreaks occur appears to be complex. Other density-dependent sources of mortality, including parasitoids and predation by small mammals (and possibly birds), appear to be responsible for regulating the gypsy moth populations at low densities. Outbreaks occur when there are periodic or episodic failures of these regulating factors, the causes of which are as yet unknown (Elkinton and Liebhold 1990). When moth density reaches high levels, an epizootic of NPV occurs, causing high levels of mortality, and driving the moth population back to endemic levels. The disease appears to persist between epizootics because of the long-lived polyhedral inclusion bodies. Thus, even though the cycles in the gypsy moth population may not be caused by the host-pathogen interaction, the virus does have its major effect at high host densities, as predicted by simple theory (Anderson and May 1980, 1981). The NPV has been registered in the United States as a biological pesticide under the name of Gypchek$^{TM}$ (Cunningham 1982).

Within a generation, the NPV causes a bimodal pattern of mortality. There is a small peak in mortality when larvae that hatch from eggs laid on infected substrates develop the infection and are killed after about 2 weeks. The polyhedra released from these dead first or second instar larvae then cause additional rounds of infection in late instar larvae (Woods and Elkington 1987). Most of the mortality due to the disease occurs during this second round of infection. Dwyer and Elkinton (1993) used a delayed-differential equation model to help understand the dynamics of the NPV within a generation of the univoltine gypsy moth. The model describes the decline in an initial cohort of larvae and assumes that infected larvae produce viral particles after a fixed time interval. The model was tested against eight field populations, using independently-obtained estimates of the parameters. The simulations of the model capture the bimodal pattern of mortality due to the disease, and give fairly accurate quantitative predictions for 5 of the 8 field populations. The three populations for which the model poorly described the field results were sites with low moth densities and where the severity of the epizootic was underestimated. Dwyer and Elkinton (1993) speculate that

the transmission efficiency of the virus may be non-linear and relatively more efficient than expected at low densities.

### 3.1.4 *Gilpinia hercyniae* (European Spruce Sawfly) – Nuclear Polyhedrosis Virus

The European spruce sawfly (Diprionidae) is a native of continental Europe, but the best evidence for the role of pathogens in its population dynamics comes from accidental introductions of the sawfly into Canada and Wales, in the 1930s and 1970s respectively. After introduction, the sawfly spread rapidly and caused major economic damage in spruce (*Picea*) plantations. A nuclear polyhedrosis virus which was either accidentally or experimentally released at outbreak sites produced epizootics that spread rapidly through the sawfly populations causing high levels of mortality and leaving few healthy sawflies in its wake (Balch and Bird 1944, Bird and Elgee 1957, Bird and Burk 1961, Entwistle *et al.* 1983). In Canada, the abundance of sawflies has remained low since the introduction of the virus, which can still be recovered at low levels from endemic populations. There was a resurgence of sawflies about 8 years after the first outbreak during which a minor epizootic of the disease occurred, although introduced parasitoids also increased in abundance (Bird and Elgee 1957). The virus is able to persist through periods of low sawfly density by vertical transmission and through long-lived infective stages.

Dwyer (1994) employed diffusion equations to model the spread of the NPV through a spruce sawfly population. Using parameter estimates derived from the literature, he fitted the model to field data from the introduction of NPV into sawfly populations in Wales, and generated reasonable predictions for the rate of spread of the disease.

### 3.1.5 *Neodiprion sertifer* (European Pine Sawfly) – Nuclear Polyhedrosis Virus

Like the European spruce sawfly (Diprionidae), the European pine sawfly is an economic pest of coniferous forests in Europe, and was also accidentally introduced into North America. Epizootics of an introduced NPV lead to a significant reduction in sawfly densities in North America (Bird 1950). The virus was able to persist through vertical transmission and the production of long-lived infective stages (Bird 1961).

The spruce sawfly has also been extensively studied within its native range in Europe, where it commonly exhibits outbreaks (Olofsson 1987, 1988) which are often terminated by an NPV epizootic. The cyclicity of the outbreaks is as yet in doubt: there is some evidence for a 30 year regional cycle, with local outbreaks occurring more frequently and at irregular intervals (Hammes 1978). It is unclear to what extent the pathogen causes the pattern of changes in host density. At low sawfly densities, the virus had no detectable effect on

host population dynamics (Olofsson 1987), although virus could usually be recovered from forest soil in years between outbreaks (Olofsson 1988).

### 3.1.6 *Malacosoma disstria* (Forest Tent Caterpillar) – Nuclear Polyhedrosis Virus

The forest tent caterpillar (Lasiocampidae) in North America undergoes population cycles with a period of 8–12 years. Population cycles in the eastern U.S. are apparently synchronous with those in the central United States and western Canada (Myers 1988). Natural epizootics of a nuclear polyhedrosis virus often occur late in the outbreaks, after the caterpillars have been at high densities for a number of years. The epizootics are associated with a rapid decline in caterpillar densities (Stairs 1965, 1966). Stairs (1965) was able to initiate premature epizootics of the virus in forest tent caterpillar populations by spraying virus particles over a small area. The epizootic spread from the point of introduction and lasted for several generations. The virus persists between epidemics as long-lived infective stages in the soil and through vertical transmission. A parasitoid fly, *Sarcophaga aldrichi* (Sarcophagidae), may also be important in transmitting the virus (Stairs 1965, 1966). The forest tent caterpillar is also susceptible to a number of other pathogens, including the fungi *Beauveria bassiana* and *Entomophthora crustosa* (Carruthers and Soper 1987), which can lead to high levels of mortality in some habitats, especially in relatively moist sites (Stairs 1972).

## 3.2 Non-Forest Insects

The population dynamics of a number of non-forest insects and their pathogens have been studied, again largely by applied entomologists. Here we discuss a pest of tropical plantations, several southern hemisphere pasture pests, and more briefly a variety of insects that attack annual crops.

### 3.2.1 *Oryctes rhinoceros* (Rhinoceros Beetle) – Baculovirus and *Metarhizium anisopliae* Fungus

In India, South-East Asia, and the South Pacific, the Rhinoceros beetle, *Oryctes rhinoceros* (Scarabaeidae), is one of the most serious pests of coconut palms. The beetle damages the palm by chewing the unopened fronds, which reduces the tree's photosynthetic ability, and by damaging the flower stalks: in severe attacks, the palm may be killed (Young 1986). The beetle is endemic to South-East Asia, but was accidentally introduced to several countries in the South Pacific between 1909 and 1942 (Bedford 1986). An unusual non-occluded baculovirus was found in Rhinoceros beetle populations in Malaysia, Indonesia, and the Philippines (Zelanzy 1977).

The beetles lay their eggs in dead palm trunks and in other decomposing vegetation, where the larvae develop, taking approximately five months. The

adults emerge and bore into the hearts of palm trees where they mate and feed, hidden within the unopened fronds. Both the larval and adult stages of the beetle are susceptible to the virus (Zelanzy 1972,1973a). Transmission of the virus occurs through the ingestion of food contaminated by infected faeces at both the breeding and adult feeding sites (Zelanzy 1976). Three to nine days after infection, the adults start to excrete virus in their faeces. They can survive for four to five weeks in an infectious state, excreting virus, and serving as an effective reservoir for the virus (Zelanzy 1973a). The virus, which is not protected in an occlusion body, persists for less than a week outside of the host.

The regulatory effect of the virus on the rhinoceros beetle populations is best illustrated by the success of the release of the virus on South Pacific Islands where neither the beetle or the virus are found naturally. Rhinoceros beetle is a difficult pest to control since all stages of the beetle are protected from contact insecticides, either in the decaying material of the breeding sites, or in the unopened fronds of the feeding sites. In addition, even low densities of beetle can cause economic damage. It was found that the disease could be effectively transmitted by releasing infected adults, which directly carried the virus to the feeding and mating sites (Bedford 1986). The disease was successfully established on a number of islands, and was able to reduce the beetle populations to levels significantly below the pre-introduction densities (Marschall 1970, Young 1974, Bedford 1986). The effect of the virus is most easily measured by the dramatic reduction in coconut frond damage after release. For example, at a number of sites in the Fiji Islands, the percentage of fronds damaged dropped from 35–80% before the introduction of the virus to usually less than 10% after (Bedford 1986). It appears that the virus has been responsible for the regulation of beetle populations at low densities on most of the islands on which it was established, although there have been some instances of local beetle outbreaks (Young 1986). The disease spreads rapidly, since it is dispersed by infected adults, which can fly relatively long distances. In Tongatapu and Fiji, the virus was found to spread at a rate of 2–3 km/month (Young 1974, Bedford 1986).

Hochberg and Waage (1991) developed a mathematical population model to describe the control of the rhinoceros beetle by the virus. Their model divides the beetle population into healthy and infected individuals of three age groups: juveniles, feeders, and breeders. In addition to the mortality due to the virus, the model also assumes density-dependent larval mortality caused by other factors. As many of the model parameters as possible were obtained from the literature but the transmission rates of the disease through six different pathways had to be fit by a least squares procedure using data on the field prevalence of the disease. The model provided a fairly accurate description of disease prevalence and the depression of beetle abundance when

compared with long-term field data. The model predicts that the disease can depress the abundance of juveniles, feeders and breeders to 6.4%, 2.3% and 1.4% of their pre-infection level. Using palm-frond damage to estimate beetle density, a maximum reduction in density of 95% has been recorded (Hammes 1978, Zelanzy and Lolong 1988), but reductions of 50–85% are more common. The model failed to describe observed population patterns in the first six months after the release of the virus, possibly because spatial aspects of the spread of the disease were not incorporated.

Attempts have also been made to control the rhinoceros beetle using the fungus, *Metarhizium anisopliae*, which predominantly infects the larval stage. In contrast to the virus, the fungus is released from infected individuals only upon death. The fungus is not transmitted as effectively within the beetle population, and attempts to control the beetle using the fungus have been relatively unsuccessful. Hochberg and Waage (1991) included *Metarhizium* in their model as a density-independent mortality factor affecting the juveniles and breeding adults. The model predicted that the fungus could reduce the density of juvenile beetles, but that it would not have a major effect on the density of adults, which cause most of the economic damage. If the system is artificially inundated with fungus, it is possible for the virus to be excluded.

### 3.2.2 *Costelytra zealandica* (Grass Grub) – Bacteria and Protozoa

The grass grub, *Costelytra zealandica* (Scarabaeidae), is a major endemic pest of pastures in New Zealand. The larvae kill grasses and clovers by feeding on their roots, thus allowing invasion of the pasture by weeds. Two types of naturally-occurring pathogens have a major impact on grass grub populations: the bacteria, *Serratia entomophila* and *Serratia proteamaculans*, which cause honey (or amber) disease, and the protozoa, *Mattesia* sp. and *Nosema* sp. The diseases provide a measure of natural biological control, augmented in the case of *Serratia entomophila* by its application as a microbial insecticide (Invade$^{TM}$) (Jackson and Pearson 1986, Jackson *et al.* 1992,1993).

Both *Serratia* and the protozoa have been shown to contribute to the regulation of grass grub populations. Disease prevalence (and mortality from disease) shows delayed density dependence, while changes in population density between generations are negatively correlated with disease prevalence (Mendonca 1992, Jackson 1984, Popay 1992, Barlow and Jackson 1993). Milky disease (*Bacillus popilliae*) has been shown to account for otherwise unexplained population declines of grass grubs (East and Wigley 1985) and is likely to act in a similar manner to *S. entomophila* and the protozoa.

Barlow *et al.* (1985) and Barlow and Jackson (1992, 1993) have modelled grass grub population dynamics using both between-generation difference equation models (similar to classic host-parasitoid models, e.g. Hassell 1978) and stochastic matrix models (with matrix elements representing the tran-

sitions between bands of different densities and disease prevalences). They suggest that regulation is due to a combination of diseases and intra-specific density dependence involving larval combat. The models predict that the pathogens depress average grass grub densities by 20–50% and also demonstrate how the disease-host interactions can lead to pest outbreaks following other control measures such as insecticide application or ploughing and reseeding of pasture (Lauren *et al.* 1990, Jackson 1990, Popay 1992). In particular, repeated insecticide use, needed to prevent pest outbreaks, indirectly decreases the level of bacteria in the soil, and so makes a major resurgence more likely to occur when insecticide application is stopped. This simple picture does not seem to apply to the drier eastern areas of the islands where the influence of the climate on disease dynamics is poorly understood (Popay 1992, Barlow *et al.* 1985, Barlow and Jackson 1992, 1993). The models have also been used to study different strategies of augmentative biological control.

### 3.2.3 *Wiseana* spp. (Porina) – Viruses

Larval moths of the genus *Wiseana* (Hepialidae) are native pests of pastures in New Zealand, where they are susceptible to naturally occurring nuclear polyhedrosis, entomopox, and granulosis viruses. There are two theories about the role of disease in this system. The first theory states that *Wiseana* populations are regulated by viruses in old pastures, particularly in the southern South Island, and thus do not cause economic damage (Crawford and Kalmakoff 1977, Fleming *et al.* 1982, Kalmakoff *et al.* 1985). Ploughing removes virus from the soil surface, where it infects the very young surface-dwelling larvae, and this gives rise to the pest outbreaks which are often observed in recently ploughed pastures. Following an outbreak, virus levels build up and pest populations decline. Livestock act to move viral particles from reservoirs in the soil to the surface where they can infect moth larvae. Rotation patterns, where livestock are frequently moved between recently ploughed and mature pastures effectively distribute the virus to the new pastures, preventing *Wiseana* outbreaks (Kalmakoff and Crawford 1982). This theory is supported by the presence of virus epizootics at the end of pest outbreaks where up to 90% of larvae may be infected (Fleming *et al.* 1982), the greater abundance of virus in old rather than young, recently ploughed pastures (Moore *et al.* 1973), and the the fact that mortality due to disease acts in a density-dependent manner (Fleming *et al.* 1986).

The second theory (Barlow *et al.* 1986) holds that the damaging stages (autumn/winter larvae) are regulated by almost perfect density-dependent recruitment. Virus attack occurs in the spring and because of compensating density dependence does not influence population densities in the following generation. This theory is supported by observations that disease prevalence is not correlated with population changes and by the fact that in many other

parts of New Zealand virus levels are too low for this to be a credible agent of population regulation. For example, infection rates over five North Island sites monitored for six years averaged 5% with a peak of 30% (unpublished data of N.D. Barlow). If intra-specific density dependence is the key proximal regulatory factor, then fluctuations in host density may drive rather than be driven by changes in disease prevalence.

Hochberg (1989a) developed a model involving a pathogen population divided into a short-lived transmissible stage (representing the viral particles on the plant foliage that can be directly transmitted to the moth larvae) and a long-lived non-transmissible stage (representing the reservoir of virus particles in the soil) (see Table 1); he argued that it could be applied to the *Wiseana*-virus system, at least on the South Island of New Zealand (the model does not include the strong intra-specific density dependence found in other parts of New Zealand). His model predicts population cycles when rates of translocation from the reservoir to the surface are low, and a stable equilibrium when rates are higher. The types of population behaviour might occur in pastures without and with grazing by livestock, respectively. A stochastic stage-structured simulation model developed for the *Wiseana*/virus interaction by Kalmakoff and Crawford (1982) predicts that the virus can regulate the moth although it also predicts levels of viral infection that are considerably higher than those observed. However, this model also does not incorporate the potentially important influence of density-dependent recruitment.

### 3.2.4 Pests of Crops

Natural disease epizootics occur in a number of pest species that attack annual crops. Many of these diseases can cause high levels of host mortality and exert some degree of natural pest suppression. However, because the environment is periodically disturbed due to harvesting and replanting, it is hard to assess the dynamic importance of the pathogens in more natural environments. Listed below are a few examples of major pathogens afflicting crop pests.

*Spodoptera* **spp. – Viruses** A number of *Spodoptera* spp. (Lepidoptera: Noctuidae) are pests on a variety of crops and many are subject to infection from naturally occurring viruses. For example, populations of the fall armyworm, *Spodoptera frugiperda*, which attacks a number of row crops in the Southern United States, are infected by naturally occurring NPVs and granulosis viruses. which reached prevalences of 60–68% in some fields (Fuxa 1982). Biological pesticides based on naturally occurring viruses have been used to control several *Spodoptera* species (e.g. Klein and Podoler 1978).

*Metapolophium dirhodum* **and** *Sitobion avenae* **(Cereal Aphids) –** *Entomophthora* **Fungus** Because aphids (Aphidae) suck plant juices rather than

feed on foliage, they are not subject to pathogens that require infective particles to be ingested. For this reason, fungi which pass directly through the integument are more important pathogens of aphids than are viruses or bacteria (Carruthers and Soper 1987). Natural epizootics of fungi of the genus *Entomophthora* are often a major source of mortality for the cereal aphids, *Metapolophium dirhodum* and *Sitobion avenae*. In one study, the fungi were found to cause 34–80% of the mortality of aphids in barley fields in England (Dean and Wilding 1971, 1973). They concluded that the fungus was probably more important than parasitoids or predators in controlling the abundance of the aphids. However, the fungus epizootic occurred late in the season, after the aphids had spread to every plant in the field.

*Trichoplusia ni* **(Cabbage Looper) – Nuclear Polyhedrosis Virus** Natural epizootics of a NPV have been found to control outbreaks of the cabbage looper (Noctuidae) which is a pest of cabbage and other crops in Canada and the USA (Jaques 1970, Hofmaster and Ditman 1961). *T. ni* populations on broccoli were thought to be maintained at low levels throughout a season by the high mortality rate imposed by the naturally occurring NPV (Hofmaster and Ditman 1961). The viral particles accumulate in the soil, where they can persist for over 5 years (Jaques 1967).

*Anticarsia gemmatalis* **(Velvetbean Caterpillar) – Nuclear Polyhedrosis Virus** The velvetbean caterpillar (Noctuidae) is a pest of soybeans in North and South America. In South America, epizootics of a native nuclear polyhedrosis virus severely reduce caterpillar population densities (Carner and Turnipseed 1977). Viral particles persist in the soil but the movement of particles from the soil to the pest larvae on the plant foliage is limited, although it can be enhanced by heavy rainfall or tillage of the soil (Beach *et al.* 1984, Young and Yearian 1986).

*Pieris rapae* **(Cabbage Butterfly) – Granulosis Virus** Harcourt (1966) found that a naturally occurring granulosis virus was a key factor in the survival of the cabbage butterfly, *Pieris rapae* (Pieridae), a pest of cabbage in Ontario, Canada. In that study, mortality due to the virus was high, averaging 68%, and density-dependent. Persistence of the virus appears to be due to the accumulation of viral particles in the soil (Jaques and Harcourt 1971).

## 3.3 Biological Control

Pathogens are used in three ways in biological control: as biological insecticides; to augment naturally occurring pathogens; and in the introduction

of novel disease agents where the hope is that a single introduction of a pathogen may provide long-lasting control (classical biological control). The study of all three types of control strategy can provide insights into natural host-pathogen dynamics.

### 3.3.1 Biological insecticides

The best known biological insecticide is the bacterium *Bacillus thuringiensis*, or BT. BT can be found naturally in populations of a number of insect species throughout the world, although it does not appear to have a major effect on insect population dynamics except when it is applied in large doses by humans. There is a large number of strains of the disease, each of which produces a toxin that is pathogenic to a particular range of insect species. Most BT strains are toxic to the larvae of different Lepidoptera species, but others are effective against mosquitoes and blackflies. BT is normally used as a short-term pesticide, having toxic effects that are not dependent on the density of the host insect. In general there is no recycling of BT from insects killed by the disease, and it does not tend to become established in the host population.

A nuclear polyhedrosis virus isolated from the alfalfa looper, *Autographa californica*, is pathogenic to a broad range of pests (Hink 1982) and has been tested against cabbage loopers (*Trichoplusia ni*), beet armyworms (*Spodoptera exigua*), pink bollworm (*Pectinophora gossypiella*), and *Heliothis* spp., achieving varying degrees of success (Vail *et al.* 1971,1972, Bell and Kanavel 1977, Jaques 1977). A commercial product containing NPV of *Heliothis* spp. has been developed, and has been effectively used on cotton in the U.S. (Ignoffo 1973, Ignoffo and Couch 1981). Application of granulosis virus has reduced damage to apple fruits by codling moth (*Cydia pomonella*) in field trials, and a model has been used to investigate the effect of virus concentration on the time taken to kill larvae, and thus the extent of fruit damage (Brain and Glen 1989).

There are a few cases of the successful use of fungi as biological insecticides. For example, the sugarcane froghopper (*Mahanarva posticata*) in Brazil is treated with a commercially produced biological insecticide containing the fungus *Metarhizium anisopliae* (Mendonca 1992). The fungus *Beauveria bassiana* has been used on a large scale in the People's Republic of China for the control of the pine caterpillar (*Dendrolimus punctata*) and in the former Soviet Union for control of the Colorado potato beetle (*Leptinotarsa decemlineata*) (Ferron 1981). A number of projects are currently underway to develop control measures for grasshoppers and locusts using fungi, especially *Metarhizium* spp. and *Beauveria* spp. (Lomer and Prior 1992).

White grubs, larvae of *Melontha* spp. (Scarabaeidae), are highly destructive pests in Europe, feeding on the roots of almost all crops. Outbreaks

last 4–5 years and occur on average every 20–30 years. The fungus, *Beauveria brongniartii*, occurs widely in the populations and has been used as a biocontrol agent since the end of the last century, as conidia or blastospores applied either directly to the soil, or against swarming egg-laying adults which transfer the fungus to the soil. Results are promising, particularly given the unacceptability of alternative chemical control methods (Zimmerman (1992) and references therein).

### 3.3.2 Augmentation

We have already mentioned a number of examples of the use of virus releases to augment naturally occurring pests, for example in the control of Douglas-fir tussock moth, gypsy moth, New Zealand grass grub and *Wiseana* (see above). A further example is the use of the fungus *Metarhizium anisopliae* to control the redheaded cockchafer (*Adoryphorus couloni*), a Tasmanian pasture pest (Rath 1992). Its success depends on a prophylactic suppressive effect over 5–10 years, since its action immediately following application is slow. The best dose rates in different weather conditions, and the design of experiments to determine control efficiency, have been the subject of modelling studies.

### 3.3.3 Classical Biological Control

Perhaps the best known example of the regulation of an insect by an introduced disease is the apparent control of European spruce sawfly (*Gilpinia hercyniae*, Diprionidae) in North America and Wales by an introduced NPV (see above). The success of European spruce sawfly NPV as a classical biological control agent seems due to its ability to survive periods where hosts are absent or very uncommon, either as long-lived infectious stages or through vertical transmission. An NPV has been used with more limited success as a classical biological control agent of European pine sawfly, while clear control of rhinoceros beetle has been achieved by the introduction of a baculovirus. In the last case, infectious particles survive for only a short period of time in the environment (Zelanzy 1972) and the disease persists through sub-lethal infections in long-lived adults.

A final example of a pathogen that can be used as an insecticide or for augmentation, but which can also provide long-term control, is the bacterium *Bacillus popillae* which is used to control Japanese beetle, *Popillia japonica* (Family), a pest of lawn and ornamental plants in the north-eastern United States. *B. popillae* causes the fatal condition in beetle larvae known as 'milky disease' because of the milky appearance of the infected larvae (Dutky 1963). In the 1940s, the United States Department of Agriculture distributed *B. popilliae* spores over more than 100,000 acres throughout 14 states in the north-eastern United States (Hutton and Burbutis 1974). The bacterium is not easily cultured outside of the host, so living Japanese beetle larvae were

used for the production of spores. Thirty years later, an average 49.6% of the larvae at the original colonization sites were infected by the bacteria, and beetle densities at these sites were on average 20% of those found in the 1940s (Hutton and Burbutis 1974). However, the disease did not spread rapidly from the sites of introduction, and there is some evidence that less virulent strains started to become dominant after 1960 (Bulla *et al.* 1978), and that some resistance to the disease may have developed (Dunbar and Beard 1975).

# 4 Conclusions

To conclude, what has the last fifteen years of theoretical and empirical studies told us about the dynamic influence of diseases on their insect hosts? First, there can be little doubt that diseases can be an a strong mortality factor affecting their hosts. The use of pathogens as biological insecticides illustrates the potential killing power of diseases and this is reinforced by observations of natural epizootics, admittedly mostly in agrosystems. Second, there is no doubt that insect pathogens, especially viruses, are often responsible for ending major outbreaks of insect pests, indeed for many species most outbreaks may end in this way. What is far less certain is the degree to which pathogens are responsible for maintaining forest pests and other insects at endemic population levels, and the degree to which pathogens drive, rather than are driven by, cycles in the densities of forest insects. Successes in classical biological control campaigns, for example against spruce sawfly and rhinoceros beetle, do suggest pathogens may alone regulate insect population, although it is always difficult to exclude the alternative explanation that other factors are largely responsible for regulation, with pathogens stepping in when the normal processes of regulation break down.

It is a truism to say that further progress in understanding insect-pathogen population dynamics will require field manipulation experiments, with the results feeding back into new theoretical explorations. The types of large-scale field manipulation experiment required to investigate these questions are expensive, difficult to conduct, and often take a very long time to complete. Recent work on gypsy moth dynamics (Gould *et al.* 1990, Dwyer and Elkington 1993) seem to us paradigmatic examples of this approach. Hopefully more experiments of this scale and ambition will be planned, but considerable insight can also be gained from the study of the use of pathogens in biological control. While biological control programmes are quite rightly seldom designed in a way to maximise their use to ecologists, their geographical scope and replication is often on a scale impossible to achieve by non-applied biologists. It is essential that applied entomologists and population dynamicists work closely together to maximise the information obtained during biological

control releases which will both strengthen our fundamental understanding of insect-pathogen dynamics, and help improve the practice of biological control.

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# Environmental Influences on Host Immunity

*S. Lloyd*

## 1 Introduction

In recent years, scientific understanding of the interactions within the immune system of laboratory animals and humans has advanced considerably. The level and nature of immune responses by wildlife hosts are also likely to be crucial in determining the impact of parasitism, both demographically (Dobson and Hudson this volume, Grenfell *et al.* this volume, Hudson and Dobson this volume) and in terms of host-parasite coevolution (Read *et al.* this volume). Unfortunately, the dynamics and implications of immunity are (largely for logistical reasons) relatively undocumented for most wildlife populations. This review therefore discusses the impact of immunological processes on wildlife diseases by analogy with the mass of information available from studies on humans, laboratory and farm animals. A particular focus will be the likely interaction of immunity with ecological and environmental influences on the host, for example, via nutritional stress, seasonality in reproduction or environmental pollution.

The first part of this review describes the immune mechanisms. These comprise the recognition of foreigness and processing of the antigens of the invading organisms; expansion of clones of lymphocytes; and recruitment and activation of effector systems (a variety of antibodies, macrophages, phagocytes, cytotoxic cells) to eliminate the organisms. A large number of molecules are released or cleaved to provide signals (cytokines, complement components) all of these having different interconnecting functions. Finally, there are regulatory interactions with feedback mechanisms (antibody, cytokines, suppressor cells) for down-regulation of a response. Details of these mechanisms are now becoming available for domestic animals, but only slowly for the very diverse wildlife populations. This review, therefore, draws an analogy for these latter from experimental/agricultural animal immune responses.

The immune system developed to answer the problem of protection of individuals against pathogenic infections of helminths, protozoa, arthropods, bacteria and viruses (Read *et al.* this volume). The complexity of the immune system perhaps reflects the wide dissimilarity of these organisms and their ability to activate or subvert different immune affector, effector or regulatory mechanisms. The diversity in the immune responses generated is generally

greatest for the eukaryotic parasites with their changing life cycle stages and the myriad of antigens they produce. This review, therefore, concentrates on immune responses induced by helminths, but also some by protozoa are discussed. Levels of morbidity and mortality induced by many helminths, arthropods and some protozoa, e.g. intestinal coccidia, can often be related directly to the intensity of infection. Infection intensity with these and some other organisms, e.g. level of viraemia in louping ill, will in turn modulate transmission. The prevalence and intensity of infection will be regulated by a number of host-related factors including anatomy, behaviour and physiology, but a major host constraint determining levels of infection is acquired immunity manifest as immune protection. The level of immunity acquired will vary with host species, strain or individual and also with parasite species.

There are practical problems, however, in measuring immunity, e.g. identifying which one or more of the antigens and corresponding host response(s) should be measured as responsible for protection. Also, there are a number of intrinsic and extrinsic factors which may interact with immune parameter(s) or infections(s) under investigation. The effects on different infections and immune responses of reproduction, age, stress, nutrition, toxicants, concurrent infections, particularly their immunosuppressive effects, are discussed. Finally, the influence that the species of parasite itself and the genotype of the individual host may have on immune protection is described.

## 2 Antigens of the parasites

A parasite entering the host contains and releases a number of materials which are foreign to the host. The proteins, glycoproteins, glycolipids, lipids, etc. which make up the surface of the organism are exposed as antigens to the host. Internal, structural materials will be released when the organism dies. Other materials may be excreted/secreted, e.g. enzymes and surface materials, to aid in feeding or in evasion of the immune response (Titus and Ribeiro 1990, Behnke 1990, Blaxter *et al.* 1992). A complex organism such as a helminth will release a myriad of products, whereas only a limited number of structural proteins are found in a virus.

Of the materials so produced and exposed to the host, some are non-immunogenic. These will remain unrecognised by the host immune system and so will not provoke an immune response. These materials, often mistakenly called 'antigens', could be of use for immunodiagnosis using an antigen detection assay, e.g. antigen capture from serum or faeces. Other materials are immunogenic and therefore antigens or immunogens – by definition 'an antigen (or immunogen) induces an immune response' and 'an antigen reacts with antibody'. If the immune response induced by these antigens has a detrimental effect on the parasite population, then the antigens are functional

and the immune response is protective. However, not all immune responses provoked are protective. Thus, in addition to (i) functional antigens; other antigens may be (ii) diversionary, directing the immune response away from important functional antigens; (iii) immunosuppressive; or (iv) induce immunopathology. Although immunopathology itself may induce a decrease in parasite numbers, e.g. the scratching response to a rash can reduce skin arthropod numbers by 50%, the immunopathology is often detrimental to host welfare and survival affecting nutrient intake, anatomical architecture or permitting secondary infection. Equally, while non-specific immunosuppression might increase parasite survival or numbers, immunosuppression could also increase host susceptibility to concurrent infection and therefore possibly mortality (Anders 1986, Behnke 1987, Lloyd and Soulsby 1988).

# 3 Acquired protective immunity against parasites

In a primary infection, the establishment and early development of parasites are unaffected by an immune response. As the infection develops, and potentially within a few days after infection, the immune response is activated. If protective, immunity may act to limit:

(i) the establishment of parasites;

(ii) the rate of development of parasites;

(iii) the fecundity of parasites;

(iv) the survival of parasites.

Assuming the parasite is affected by and does not evade the immune response, the immune response will detrimentally affect the parasite, but the stage affected and level of the effect will vary from parasite to parasite, host to host, and with the level of immunity achieved.

Once the host has acquired protective immunity, a major effect of the immune response on helminths is rejection of subsequently acquired challenge parasites. Tissue-invading parasites, e.g. schistosomula of *Schistosoma* spp. or oncospheres of *Taenia* spp., can be killed by antibodies and/or cells soon after invasion of the skin, lungs, liver or other tissues (Lloyd 1987a, McLaren 1990). Gastrointestinal nematode larvae, such as those of *Haemonchus contortus* and *Trichostrongylus colubriformis* of ruminants, as well as most of the gastrointestinal nematodes of laboratory animals, are excluded from the mucosa and expelled in the faeces as early as 24–48 hrs after infection (Miller 1984, Lloyd and Soulsby 1987, Moqbel and MacDonald 1990). Generally, the degree to which invading parasites are excluded or killed increases over time and with repeated infections and is dose-dependent. Rapid expulsion of incoming larvae of *T. colubriformis* was induced after 7–14 weeks of continuous

infections of sheep and after an apparent threshold of stimulating infection had occurred (Dobson *et al.*, 1990). Even once the immune response has been generated, there can be a threshold of incoming parasites required to initiate the expulsion response. Thus, a low dose ($10^4$) of *H. contortus* larvae was not expelled from immune sheep although 83 and 93%, respectively, of a challenge of $10^5$ or $10^6$ larvae were excluded (Jackson *et al.* 1988). Induction of rapid expulsion is stage specific, e.g. rapid expulsion of *T. colubriformis* from sheep and *Trichinella spiralis* from rats was more efficiently induced with larval (L3, L4) antigens than with adult antigens (Bell and McGregor 1979, Lloyd and Soulsby 1987, Emery *et al.* 1992a,b).

Separate from and often after the development of exclusion or destruction of larvae, there is rejection of the adult worms established from the early infection(s). This phase of protection is again stage-specific. Expulsion of adult *Trichinella spiralis* and *Trichostrongylus colubriformis* was best induced by immunisation with the adult parasites and not larvae, while *T. colubriformis* parasites were rejected only after they were > 7- to 10-days-old. Presumably it is only at this age that they carry sufficient stage-specific adult antigens (Bell *et al.* 1979, Lloyd and Soulsby 1987, Emery *et al.* 1992a,b).

Immunity may also act to reduce fecundity, the rate of development (time to patency) and growth achieved by female nematodes. Anti-fecundity effects are seen only in certain parasites or hosts. Thus, reduced fecundity, probably serum-mediated, is reported for *Schistosoma haematobium* in man and rodents and the bovine *S. bovis* and *S. mattheei* species. However, it is not normally recorded for *S. mansoni* in man and rodents. Reduced fecundity has been seen also in *Strongyloides ratti*, *Nippostrongylus brasiliensis* and *Trichinella spiralis* in rats and mice and has been reported for sheep nematodes (Lloyd and Soulsby 1987), although Coyne and Smith (1992) did not confirm the presence of reduced parasite fecundity in grazing sheep or sheep previously infected with *Haemonchus contortus.* Reduced fecundity has been recorded repeatedly for other parasite groups, e.g. ticks feeding on immune hosts (Titus and Ribeiro 1990).

Once developed, the persistence of protective immunity (or memory for it) varies with host species, parasite species and the persistence of infection within the host. There are relatively few parasites for which the length of memory against reinfection has been determined; where it has, memory in the absence of reinfection generally has been short-lived. This is in contrast with many viral and bacterial infections where, even in the absence of challenge, immunity following prior infection or vaccination can be prolonged. These differences may be related to antigen structure and route of presentation but also to the stage specificity of the parasite antigens which induce protection or conversely suppression of immune responses. These latter in particular may be important when one considers the time lag inherent in the development

of an anamnestic immune response. Thus, parasites could have lost any antigens liable to attack and expressed new life cycle antigens insusceptible to, or immunosuppressive to, the immune response by the time an anamnestic immune response has developed.

Where length of memory has been deduced, 'concomitant immunity' can have a profound effect on its persistence. 'Concomitant immunity' is where persistent infections, e.g. *Babesia* piroplasms or *Schistosoma* adults, elicit an immune response that prevents new infection. For *S. mansoni* the immunity is possibly induced by a surface glycoprotein gp38, transiently present on early invading schistosomula, and then is maintained by a cross-reacting antigen in a 155kDa molecule released by the adult stages, although the latter are themselves insusceptible to attack against these antigens (Dissous and Capron 1983, Capron and Dessaint 1992). Thus, the persistence of low levels of infection with *S. mansoni* in people may be desirable in endemic areas whether this persistence be from natural infection or after immunisation (Capron and Dessaint 1992). Immunity against reinfection with viable metacestodes of *Taenia hydatigena* in sheep is relatively short-lived, 6–12 months, and concomitant immunity appears to play no role here (Gemmell and Johnstone 1981). Memory for immune exclusion of *H. contortus* seems very short-lived. In two experiments, immune exclusion was present at 3 and 6 weeks after cessation of larval challenge but had been lost by 9–10 weeks (Jackson *et al.* 1988, Coyne and Smith 1992). Rapid expulsion was expressed for weeks to 6–12 months in rats, although not mice, infected with *T. spiralis*. A role for concomitant immunity in gastrointestinal nematode infections has not fully been determined. Nevertheless, as adult stage antigens protect against reinfection with both *T. colubriformis* in sheep and *T. spiralis* in rats (Bell and McGregor 1979, Emery *et al.* 1992b), in the absence of reinfection, low level persistence of adult gastrointestinal nematode infections could possibly be advantageous to the host to maintain immunity in the absence of challenge.

# 4 The immune response

The vertebrate immune response is extremely complex. Even in laboratory mice and humans, much of the fine dynamical detail still needs to be resolved. In the Appendix and Table 1, we present a taxonomy of the various components of the immune response and an indication of the likely dynamic pathways. The almost daily discovery of new molecules and cell types gives any such exercise a short shelf-life. However, the basic features of the immune response can be summarised crudely by the progression in Figure 1.

As described in the Appendix and Table 1, the processes that make up this chain of events are intricate and often ill-understood. In particular, the interaction of t cells and signalling molecules can lead to a variety of responses

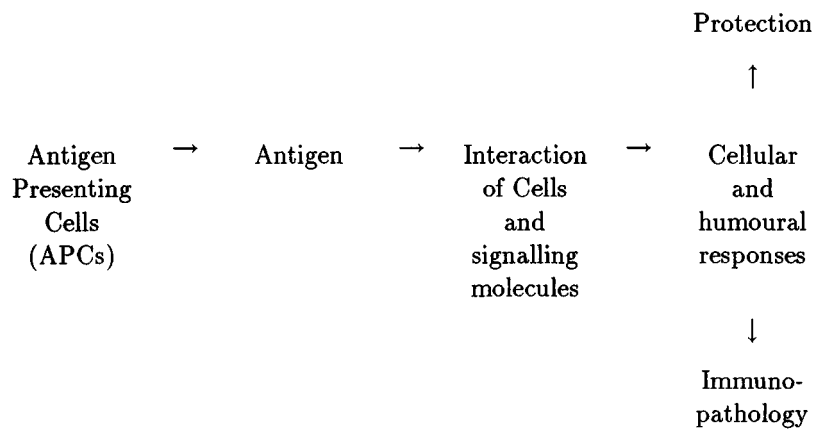



Figure 1. Essential features of the vertebrate immune response.

(protective or immunopathological) depending on the details of the interaction (host and parasite species, the parasite stage, host stage and condition etc.). As indicated in the Appendix, the interaction of t helper cell subsets ($T_h1$ and $T_h2$) and cytokine signalling molecules is especially important in determining the nature and result of the cellular immune response.

# 5 Modulation of immune responses

The development and/or expression of immunity can be modulated by a large number of extrinsic factors including the parasite itself, nutrition, stress, season or reproduction. Recognition of all these factors and their interrelationship(s) is important in any analyses of the immune response and its influence on intensity of infection. This is particularly so for wildlife hosts. Stress, changes in nutrition, presence of concurrent disease, ingestion of chemicals/toxins, reproductive status, can all alter levels of infection with a variety of pathogens – most often through suppression of the immune response. Parasites and other pathogens may take advantage of or indeed exploit this induced weakness in the host immune response. This exploitation of reduced host immune control may be pivotal to the life cycle and transmission of some parasites while, for many, any resultant increased levels of infection could alter the transmission dynamics of the infection in any given year. Intrinsic factors may also alter immune responses. Genotype of the individual host may influence resistance or susceptibility to infection, while the parasites themselves may evade or suppress the immune responses directed against them (Read *et al.* this volume).

## 5.1 Periparturient immunosuppression

Periparturient immunosuppression of pregnant females can create a 'window of susceptibility' when a previously immune and thus resistant female allows activation of infection and/or development to patency of infections often on a synchronous, seasonal basis. For helminths and, to a lesser extent, protozoal infections, this may cause disease in the periparturient animal, but also seems to ensure (e.g. *Toxocara canis*, *Toxocara vitulorum*) or aid (e.g. gastrointestinal nematode infections of sheep) transmission of infection to the next generation of animals. Far less information is available on periparturient increased susceptibility to, and its role in transmission of, bacterial and viral infections. Nevertheless, in man and to a lesser extent other mammals, there is evidence for an increased frequency of occurrence of severe viral infections during pregnancy. The time of suppression and immune parameters affected do vary with host species. Thus, periparturient immunosuppression is most apparent and/or most studied in humans during pregnancy, in laboratory animals and the dog in both pregnancy and lactation, and in ruminants during lactation (Lloyd 1983,1987b, Lloyd and Soulsby 1987).

In pregnancy, reduced lymphocyte reactivity has been ascribed to the direct action of various pregnancy-specific proteins and hormones and to the generation of $T_s$cells acting in various non-specific and antigen-specific pathways (Lloyd 1983). In lactation, a role for hormones, particularly prolactin, in the phenomenon has been suggested as depressed responses parallel endocrinological changes (Connan 1976). Other mechanisms could be important though, as Jeffcoate *et al.* (1990) found that suppression of prolactin in lactating sheep did not prevent their increased susceptibility to infection. In the dog, the marked decrease in lymphocyte reactivity during both pregnancy and lactation would require that equal levels of suppression are induced by different hormones (Lloyd 1987b), although it is possible that different hormones could act indirectly, e.g. trigger suppressor cell populations throughout both pregnancy and lactation (Brierley and Clarke 1987).

Transfer of humoral immunity in the form of IgG and IgA antibodies to the fetus and/or neonate will reduce maternal levels of antibodies and this, plus an immunosuppressed primary humoral immune response, could contribute to the increased susceptibility to infection seen in reproductive animals (Brandon *et al.* 1971, Shubber *et al.* 1981, Jeffcoate *et al.* 1992). The time of transfer of IgG depends on placentation. Placental transfer of IgG is dominant in humans, in laboratory animals and in the dog. Recrudescence of *Plasmodium falciparum* malaria in pregnant women has been ascribed to the maternal transfer of $IgG_1$, to depressed lymphocyte proliferation and to depressed production of IgG antibody in the mother (Bray and Anderson 1979, Riley *et al.* 1989). By contrast, IgG antibodies in ruminants are transferred only via colostrum. The amount of immunoglobulin transferred can be large

– cattle serum $IgG_1$ concentrations decrease by up to 50% in the 2–3 weeks prior to parturition (Brandon *et al.* 1971) and may act in increasing maternal susceptibility to infection. There is also passive transfer in colostrum and milk to the neonate of IgA-induced protection against bacteria, viruses and some helminths (Lloyd 1987a, Roach *et al.* 1991). Shubber *et al.* (1981) and Jeffcoate *et al.* (1992) speculated that reduction in antibody levels in the gastrointestinal mucosa of lactating animals permitted the establishment of nematode infections in the gut of the mother.

The periparturient increase in gastrointestinal nematodes in sheep is well established. Increased susceptibility to nematodes is also seen, but is less marked, in periparturient cattle, horses and pigs. In previously immune sheep, increased susceptibility to infection begins gradually in the last few weeks of pregnancy and reaches maximum in the first few weeks of lactation (Lloyd and Soulsby 1987). The increased burdens of parasites come from (i) newly ingested larvae which are not expelled but develop to patency, and (ii) reactivating hypobiotic larvae which are not expelled but are retained and complete their development in ewes whose periparturient immunosuppression is superimposed on the time of reactivation of these larvae. This increase in egg output from periparturient females supplies a source of eggs and thence infective larvae on pasture at the time when the susceptible new generation of animals begins grazing.

Other parasites, (e.g. *Toxocara vitulorum*, *Toxocara canis*, *Demodex* spp.) have their main, or sole, route of transfer directly from mother to young. It seems possible to suggest a relationship between the migration of *T. canis* and *T. vitulorum* and suppressed maternal periparturient immune response. The ability of *T. canis* to activate and/or migrate to the fetal and neonatal pup over a prolonged period in pregnancy and lactation is associated with a prolonged suppression of lymphocyte reactivity from 5 weeks before to 5 weeks after parturition (Lloyd 1993). In contrast, activation and migration of *T. vitulorum* to the suckled young buffalo occurs only in the immediate periparturient period. This coincides with suppressed lymphocyte reactivity only in the periparturient period plus colostral transfer of $IgG_1$ (Roberts 1990, Rajapakse *et al.* 1994, Amerasinghe *et al.* 1994). Equally, as *D. canis* multiplies in the skin of dogs that are immunosuppressed, it seems likely that periparturient immunosuppression contributes to an increase in these and other ectoparasite numbers on the skin thereby facilitating transmission from mother to young.

## 5.2 Age-related immune unresponsiveness

Age affects the immune response particulaarly in young and old animals. Neonatal unresponsiveness is recognised although mechanisms are largely undetermined. Neonatal rats and mice infected with *N. brasiliensis* or *H.*

*polygyrus*, lambs infected with *H. contortus* and *Ostertogia circumcincta* and calves infected with *Taernia saginata* failed to control infections that were eliminated from or killed in mature animals (Lloyd and Soulsby 1987, Lloyd 1987a). Although these neonatal infections are prolonged or, in the case of *T. saginata*, might be life-long, classical tolerance to new infection did not occur. When reinfected later in life, the neonatally infected animals responded normally to a new infection with *N. brasiliensis* or *T. saginata.*

Various mechanisms for neonatal unresponsiveness have been proposed. Immaturity of the young animal's immune system is proposed with defects in antigen processing, in T cell responses and IL-2 production, and in effector lymphocyte activity and inflammatory responses (Lu *et al.* 1979, Malkovsky and Medawar 1984, Levin and Gershon 1988). This could account for an apparent hierarchy in the effector responses to different antigens/pathogens in fetal and young lambs, or the less efficient responses in young versus adult animals (Fahey and Morris 1978, Watson and Gill 1991).

Deficient lymphocyte responses have been observed. There has been a general lack of lymphocyte or antibody responsiveness to *H. contortus* antigen in lambs from birth to 3- to 6-months-old after neonatal infection or parenteral immunisation (Lloyd and Soulsby 1987, Watson and Gill 1991). Dineen and Kelly (1973) corrected a defect in expulsion of *N. brasiliensis* in young rats by transfer of immune adult lymphocytes. However, Monsell (1985) showed that lymphocytes from fetuses immunised in utero with *H. contortus* antigen did respond to that antigen in utero, but this response was then suppressed after birth for 8–12 weeks.

Ingestion of colostrum is important in neonatal protection against infections, e.g. in many bacterial, viral and some helminth infections, including louping ill, *Taernia ovis*, *T. saginata*, *H. polygyrus* (Lloyd 1987a, Lloyd and Soulsby 1987). Colostrum does not appear to protect against gastrointestinal helminths in sheep and, to the contrary, could perhaps contribute to neonatal unresponsiveness to infection. Lambs which had sucked colostrum from *H. contortus* infected ewes were more susceptible to *H. contortus* than were their unsuckled counterparts or lambs suckled by non-infected ewes (Shubber *et al.* 1984, Losson 1985). In particular, added autologous plasma abrogated responses to *H. contortus* in lymphocytes from naive, colostrum-fed lambs, but not in those from immune adult sheep (Torgerson and Lloyd 1992). However, ingestion of colostrum cannot be a sole source of neonatal unresponsiveness as the phenomenon also occurs in colostrum-deprived lambs.

Alternatively, deficient neonatal immune responses might be related to suppressor cell activity. High activity of suppressor cells has been recorded in new-born mice and humans (Hooper *et al.* 1985, Maier and Holda 1987). These might or might not be triggered by colostrum ingestion.

Systemic immune responses decline in old age. In general, it is T cell

immune function that declines (Goidl 1987) although this does differ with host and with antigen. There can be lower numbers of $CD4^+$ T cells. In some instances, although each remaining cell may have normal function, decreased overall T cell function and reduced synthesis and activity of IL-2 may be seen. Reduced T cell function may in turn down-regulate B cell function. Direct effects of age on B cells have also been described, but less commonly than is the case for T cells. Finally, increased suppressor cell activity has been recorded in aged persons with a potential to down-regulate immune responses. The effect of age on local mucosal immune responses is less well examined and some studies report no down-regulation of local immune responses with age. However, age has been shown to depress hepatobiliary IgA transport in rats and the specific IgA antibody response to oral immunisation with cholera toxoid was depressed in older monkeys (Taylor *et al.* 1992).

Most studies relating age to susceptibility have concentrated on immune surveillance and tumour immunology, but infection intensity or prevalence can also increase in old age. Old mice were more susceptible to *T. spiralis* than 4-month-old animals (Crandall 1975). Old mice also developed more severe infections with *Trypanosoma musculi* than did young adults; the defect correlated with reduced NK cell activity and reduced production of IFN by macrophages (Albright and Albright 1982). Similarly, old mice, when compared with young ones, showed much higher levels of infection with *Toxoplasma gondii*; the larger cyst number correlated with lower antibody responses and reduced macrophage activation (Gardner and Remington 1988).

## 5.3 Stress-induced immunomodulation

Stress-induced immunomodulation has been studied in man and laboratory animal models, and more recently in farm animals for its implications for welfare and production (Cupps and Fauci 1982, Kelley, 1985). Many steroid and neuroendocrine hormones are released upon a stress stimulus – glucocorticoids, encephalins, endorphins, catecholamines, etc. Glucocorticoids seem the most potent of the immunosuppressive agents (Sapolsky 1993). Animals vary in their sensitivity to glucocorticoids but, in a glucocorticoid-sensitive animal, glucocorticoids prevent proliferation of T cells, reduce IL-1 and IL-2 production, depress IL-2 receptor expression, cause a panleukopaenia, depress inflammatory responses and bring about thymus involution. Intestinal mast cells and mucin production are particularly sensitive to dexamethasone therapy (Douch *et al.* 1986, Huntley *et al.* 1992). Antibody formation is suppressed by $\alpha$-endorphin.

Although many experiments have studied only pharmacological level concentrations of these hormones, the concentrations induced by stress are only now being determined. Nevertheless, the physiological concentrations of glucocorticoids produced by natural levels of stress could affect immune re-

sponses and are quite consistent with those observed in the management of wild animal populations (e.g. capture, examination, manipulation, transport) or in unmanaged wild animals, e.g. rut, territory defence, (Kelley and Dantzer 1990). Lambs restrained and isolated for 6 hrs on 3 consecutive days had increased plasma cortisol, decreased lymphocyte proliferation and reduced circulating $CD4^+$ T cells (Minton *et al.* 1992). Simple 2 hour restraint of mice up until the time of injection or challenge suppressed delayed type hypersensitivity (DTHS) responses to sheep red blood cells (SRBC) as antigen (Kelley 1985). Cattle subjected to transport under suboptimal conditions are likely to develop shipping fever (viral/*Pasteurella* pneumonia); transport of horses can induce recrudescence of *Babesia.* Although moderate exercise can boost the immune system, prolonged exercise can decrease phagocytosis, lymphocyte transformation and IgA antibody levels (Fitzgerald 1988). The suppressive effects of corticosteroids on parasitic infections are well characterised. For example, dexamethasone increased the susceptibility of previously resistant sheep to gastrointestinal trichostrongyles while suppressing mast cell and mucin production (Jackson *et al.* 1988, Adams *et al.* 1990, Huntley *et al.* 1992). Similarly, immune mice that were physiologically and psychologically stressed for 14 days through challenge showed depressed protection against *T. spiralis* (Robinson 1961).

The interaction of hormones with the immune system is as complex as is the immune system itself. It differs with the class of hormone induced, the animal species and the immune parameter monitored. Thus, while $\alpha$-endorphin suppressed antibody formation, $\beta$-endorphin enhanced T cell and NK cell activity, and reversed the effects of $\alpha$-endorphin (Tizard 1992). Animal species vary in their response to corticosteroids. For example, much higher doses of exogenous corticosteroids are required to alter cell numbers and responses in pigs than cattle. Individual pigs resonded in a variety of ways to transport in their cortisol and NK cell responses, with alterations in responses greater in the more socially submissive animals (McGlone *et al.* 1993). In lambs, repeated restraint and isolation stress reduced some but not all measures of immune function (Coppinger *et al.* 1991). Indeed, restraint can *enhance* parts of the immune response in mice (Kelley 1985). It should also be noted that immunosuppressive agents such as corticosteroids do not invariably induce immunosuppression, but occasionally permit enhanced immunity against parasites (Lloyd and Soulsby 1987), perhaps by ablating immune suppressor cells rather than helper cells.

Normal environmental changes may also act as stressors. Severe winters and hot, dry summers may induce temperature stress and could also limit food supply, inducing secondary immunosuppression through malnutrition. Seasonal variation in immune responses can be marked. For example, a neuroendocrine-induced corticosteroid suppression of the immune system has

been described in fish exposed to cold winter temperatures. There is involution of the thymus, T cell cytolysis and decreased proliferation and activity of B cells and phagocytes (Zapata *et al.* 1992).

Ultimately, the level of stress-induced immune suppression or enhancement will depend on many factors and these may be uncontrollable in many populations. In particular the temporal relationship in the sequence of application of the stressor and the sampling or challenge can alter responses from immunosuppressed to immune enhanced (Golub and Gershwin 1985). For example, simultaneous application of stress (acute or chronic) (e.g. shipping, capture) and sampling or challenge is likely to result in glucocorticoid-induced immunosuppression, but this may be antigen dependent, e.g. the response to SRBC and DNFB above. Conversely, if relatively prolonged stress is released just before challenge then immune enhancement may occur through a rebound phenomenon. Finally, prolonged and repeated stress all the way through challenge and sampling will modulate immunity, depending on the individual's ability to adapt to the stressor.

## 5.4 Host nutrition and immune responses

There are complex inter-relationships between host nutrition, immune responses, infection intensity and disease prevalence (Gershwin *et al.* 1985). Protein/energy malnutrition is considered a most important cause of secondary immunodeficiency and high prevalence of infection and disease (Gershwin *et al.* 1985, Wakelin 1989). In turn, the infections themselves can induce malnutrition through anorexia, fever, or gastrointestinal pathology.

Protein/energy malnutrition chiefly disrupts cellular immunity. There are thymus atrophy, reduced numbers of lymphoid and circulating T cells and reduced T cell function, all decreasing delayed type hypersensitivity responses. The interaction of malnutrition with the complex immune system can have differential effects. MIF and IL-2 production were described as largely unaffected by malnutrition while IFN, $PGE_2$ and IL-1 production and response of T cells to these are suppressed (Hoffman-Goetz 1988). Malnutrition would appear to decrease T effector cells but was reported to increase T suppressor cell activity (Hoffman-Goetz 1988) although this latter will still have an overall effect to suppress T or B effector cell activity. Thus, McGee and McMurray (1988) suggested that suppressor T cells were activated to suppress IgA responses in protein-deprived mice. Pocino and Malave (1981) however, suggested that restricted protein diet induced a selective depletion of suppressor T cells with resulting enhancement of antibody production.

The numbers of lymphoid and circulating B cells usually remain normal and immunoglobulin levels often are normal or elevated in malnutrition. In a primary response to *T. muris*, protein-malnourished mice not only produced higher amounts of antibody but recognised a greater number of antigens.

Michael and Bundy (1992) suggested three possibilities: that this was an increased threshold of exposure as the infection in the protein-deprived mice was prolonged, or that T suppressor cells were depleted, or that increased intestinal pathology allowed increased systemic absorption of antigens. Similarly, elevated levels of IgA and IgE in malnourished children have been correlated with an increased frequency of gut and helminth infections within the children (Gershwin *et al.* 1985). However, increased humoral immunity responses are not universal. While antibody responses to tetanus and polio virus challenge were normal in malnourished children, responses to diphtheria, typhoid and yellow fever were reduced (Gershwin *et al.* 1985). Antibody was high in the serum of high plane nutrition lambs immunised with *T. colubriformis*, but lower in lambs on a low plane of nutrition (Wagland *et al.* 1984). Furthermore, severely depressed secretory antibody responses to polio and measles virus vaccines were reported in malnourished children whose secretory IgA levels were recorded as normal or high, and whose serum antibody responses were normal (Gershwin *et al.* 1985).

In protein/energy malnutrition there also can be depressed complement levels and impaired chemotaxis, phagocytosis and intracellular killing by cells (Tizard 1992). The immune defect in protein/iron deficient rats, which failed to expel *N. brasiliensis*, appeared to lie in the bone marrow component of the expulsion mechanism with impaired responses of mucosal mast cells and intraepithelial lymphocytes (Cummins *et al.* 1987).

Severe malnutrition might decrease the viability of host cells and therefore could decrease virus growth in these unhealthy cells and so the severity of viral disease (Gershwin *et al.* 1985). Usually however, protein/energy malnutrition will increase the intensity and/or length of infection with an increased survival and multiplication of bacteria and protozoa in the tissues and slower elimination of helminths. The effects of malnutrition can vary with the length and severity of the deficiency, with parasite and host species and age, with current immune status of the host, and even with level of infection. Thus, a low protein diet had no effects on a single dose infection with *H. contortus* in immunised sheep, but such a diet increased susceptibility of lambs to a 'trickle' infection with *H. contortus* (Abbott and Holmes 1990, Roberts and Adams 1990). Low nutrition also reduced the efficacy of immunisation against a challenge infection with *T. colubriformis* in lambs (Wagland *et al.* 1984) and the efficacy of immunisation against challenge with *H. polygyrus* was reduced (Slater and Keymer 1988). While a low plane of nutrition had no effect on establishment and early survival and fecundity of a primary infection with *T. muris* or *H. polygyrus*, the *T. muris* were not expelled from protein-deficient mice resulting in chronic survival of a large infection (Michael and Bundy 1992).

Deficiencies in various minerals and vitamins (e.g. vitamins A and D, se-

lenium, copper, magnesium, zinc, iron) have also been related to alterations in immune responses manifest as decreased T and/or B cell activity or reduced phagocyte function (Reddy and Frey 1990). Deficiencies in some of these occur in grass or diets in different geographic areas and so in animals grazing these deficient areas. Zinc deficiency is most studied and has profound effects on the immune response and parasitism. Zinc deficiency causes thymus involution, atrophy of lymphoid tissue, and decreased proliferative responses of lymphocytes. *Nippostrongylus brasiliensis*, *S. ratti*, *T. spiralis* and *S. mansoni* burdens in laboratory animals were all prolonged through lack of expulsion (Bundy and Golden 1987, Wakelin 1989, Nawar *et al.* 1992). In addition, zinc-deficient people showed higher *Trichuris trichiura* burdens than expected (Bundy and Golden 1987). Cobalt deficiency also enhanced susceptibility of lambs and calves to *O. circumcincta* and *O. ostertagi* – (Downey 1966, MacPherson *et al.* 1987).

A prolongation of infection or increased levels of infection in naive or immune animals could alter transmission dynamics through increased egg/larval output. The relative impact of this will depend on the environmental constraints on the parasite at the time of nutritional modulation and are unlikely to be as profound as the presence of naive animals in a population or the periparturient immunosuppression. Nevertheless, Armour (1989) reported that *Dictyocaulus*, *Ostertagia* and *Cooperia* spp. infections developed in previously immune yearling cattle after a severe mid-summer drought and consequent malnutrition and that this produced an increase in larvae on pasture. Slater (1988) also found that a low protein diet given to a group of mice influenced the experimental population dynamics of *H. polygyrus*. Parasite transmission was examined over 60 weeks in mice successively added to and removed from a cage in which parasite survival and transmission in the environment was possible. The mice were fed either a low protein (2%) diet or a high (16%) protein diet. Infection was transmitted at a faster rate in the cage of mice fed the low protein diet. There was increased prevalence and intensity of infection and higher parasite fecundity in these mice. Parasite-induced host mortality was also considerably higher in the mice fed the low protein diet.

There are other instances where diet can reduce the numbers of parasites present. A sudden change of diet alters gut physiology and may artificially reduce the numbers of parasites present, so masking any effects of immunosuppression caused perhaps by a period of starvation. In one case, a rapid loss or 'self-cure' of *Haemonchus* was observed in sheep grazing fresh, rapidly growing grass (Allonby and Urquhart 1973). Molybdenum supplementation of the diet, as might occur on high molybdenum pastures, also reduced numbers of *H. contortus* and *Trichostrongylus vitrinus* in sheep by a direct effect on the worms (decreased worm growth, viability and proteinase activity) and pos-

sibly through increased immunity against the parasites (either by increasing inflammatory responses for rejection or by decreasing the copper dependent, anti-inflammatory enzymes in the gut mucosa) (Suttle *et al.* 1992).

## 5.5 Toxicants and immune responses

A number of pollutants are environmental contaminants (e.g. polyhalogenated aromatic hydrocarbons, non-halogenated polycyclic aromatic hydrocarbons, heavy metals, ozone, pesticides). While acute exposure may lead to obvious lethal effects (e.g. neurotoxicity), at lower doses these pollutants can accumulate and exert immunosuppressive effects. The mechanisms and long-term consequences of chronic or repeated low dose exposure to toxicants are largely unknown as are synergistic effects between toxicants and other extrinsic factors. However, immunotoxicity and predisposition to infection and disease are important in both aquatic and land environments (Dean and Murray 1991, Zelikoff 1993).

Accumulated metals, especially mercury, lead, cadmium, but also nickel, zinc, copper, alter immunoregulatory functions in fish, birds and mammals. In particular lead is thought to suppress B cell function, possibly through defective macrophage function interfering with macrophage processing of antigen (Koller and Kovacic 1974, Burchiel *et al.* 1987). Cadmium and mercury also appear to act primarily on B cell responses (Koller *et al.* 1975, Dunne *et al.* 1993). However, at low doses all the metals can also interfere with T cell, possibly $T_h$ cell, and NK cell functions (Ilback 1991). Furthermore, several studies have shown metal-induced, increased susceptiblity to infectious agents including *Salmonella*, *Listeria*, *Escherichia*. These results were replicated in mice given lead; *Yersinia* in trout exposed to copper; and viruses in birds and laboratory animals exposed to lead or mercury (Knittel 1981, Dean and Murray 1991).

Several of the family of polyhalogenated aromatics remain in the environment. Polyclorinated biphenyls (PCBs) were manufactured as industrial products worldwide and remain widespread in the environment. Tetrachlorodibenzo-*p*-dioxin (TCDD) has entered soil through trace contamination of herbicides, wood preservatives and chemical wastes. Contamination with polybrominated biphenyls (PBBs) remains confined to areas of Michigan. These pollutants bioaccumulate. There is severe thymic atrophy, particularly with TCDD, atrophy of secondary lymphoid organs and a reduction particularly in DTHS due to a profound effect on T cells (increased $T_s$, decreased $T_h$, decreased $T_c$). B lymphocytes are more resistant but are affected at higher doses. Depressed antibody production could be due to both $T_h$and B cell effects. Decreased NK cell activity has been described (Dean *et al.* 1985, Faisal *et al.* 1991). Humans exposed to these products show chloracne and respiratory infection (Dean and Murray 1991). There is increased susceptibility

to infection and reduced efficacy of immunization in animals. PCB-exposed ducks showed decreased resistance to hepatitis virus. PCB exposure of mice decreased their resistance to viruses and *Plasmodium*, *Listeria*, *Salmonella*. Trout exposed to PCBs accumulated the hydrocarbons and the efficacy of vaccination against *Vibrio anguillarum* was impaired in them. Despite immunisation against *Aeromonas*, 100% of channel catfish died if they were also exposed to PCB. PCBs have been considered important in increased susceptiblity to morbilliviruses. Thus, PCB levels were related to deaths or survival in the 1988 phocine distemper epizootic; and exposure of seals to PCBs and then phocine distemper virus produced clinical signs which mimicked those seen during the epizootic (Cleland *et al.* 1988, Dean and Murray 1991, Harder *et al.* 1992, Hall *et al.* 1992).

Non-halogenated polycyclic hydrocarbons (PAHs), such as dimethylbenz-[a]anthracene from combustion of fossil fuels, particularly affect humoral immune responses through reduced $T_h$cell activity for antibody production; $T_c$ responses may also be affected (House *et al.* 1989). Air-pollution is greatest near industrial areas and even ozone causes irritation of the lung, increased leucocyte and macrophage infiltrate with increased culture of bacteria and susceptibility to pathogenic bacteria (e.g. *Klebsiella pneumoniae*, demonstrated in mice (Lippmann 1989)).

Pesticides were the toxicants that first stimulated wildlife toxicological studies with a need for knowledge on organochlorines, e.g. DDT, dieldrin, chlordane. In general, organochlorines caused thymus atrophy, decreased contact hypersensitivity and depressed serum antibody titres although reduced immune reactivity was not universal in all studies (Dean and Murray 1991). Organophosphate insecticides (malathion, diazinon) at pharmacological levels produce acute and dramatic decreases in cell mediated immune responses with a very rapid suppression in lymphocyte proliferation, decreased antibody production to and increased susceptiblity to *Salmonella* infection (Dean and Murray 1991). The organophosphates do not persist or accumulate in the same manner as the organochlorines did, but the long term effects of repeated or chronic exposure to organophosphates have not been determined (Newcombe and Esa 1992).

## 5.6 Concurrent infections

One infection or disease can have profound effects on another concurrent infection (Christensen *et al.* 1987, Behnke 1990), and this may have considerable implications for host-parasite population dynamics (Roberts *et al.* this volume). The inter-relationship between two infections may be direct, e.g. competition for space; however, commonly the interaction is indirect. The physical or physiological damage induced by a first infection might render the host environment unsuitable for the establishment of the second parasite.

Alternatively, interaction can be mediated via the immune system where one infection may either increase or depress the immune response against a second. Thus, one parasite could debilitate the host through anorexia, malabsorption and protein catabolism, so inducing a secondary malnutrition and subsequent immunosuppression and increased susceptibility to a second infection.

An important interaction is that one parasite may induce immune enhancement and reduced survival of the second infecting parasite through cross immunisation by shared, common functional antigens. There are many instances where even closely related parasites induce little or no cross protection, e.g. *Eimeria* spp. in poultry. Examples where cross protection after infection or immunisation is apparent between closely related or even taxonomically diverse parasites include *Taenia hydatigena* and *Taenia ovis* in sheep, *Taenia saginata* and *T. taeniaeformis* in cattle and mice, *Trichinella spiralis* and *Trichuris muris* in mice (Lloyd 1979, Lee *et al.* 1982, Rose 1985, Gemmell *et al.* 1986). As a result of this, control of one parasite could have important effects on the prevalence of a second (Gemmell *et al.* 1986).

Alternately, while actual induction of the immune response may be antigen specific, one infection may be affected detrimentally and non-specifically by the immune effector mechanisms produced by the first, e.g. by activated macrophages, IFN, TNF, degranulation of inflammatory cells, etc. Thus, the effector mechanisms that induced immune elimination of *Babesia microti* from the blood of mice eliminated a concurrent *Plasmodium vinckei* infection (Cox 1978). Similarly, a concurrent *Babesia* infection was suppressed in mice that were infected with the larval stages of *H. polygyrus* (Mzembe *et al.* 1984). Also, the effector mechanisms for the 'self-cure' reaction against gastrointestinal nematodes in sheep will remove the initiating parasite, e.g. *H. contortus*, but also will non-specifically remove other nematodes whose habitat is in the same location or posterior in the gut, e.g. *Ostertagia*, *Trichostrongylus* (Lloyd and Soulsby 1987). Immune enhancement may not always be beneficial to the host, in that enhanced immmunopathology could be induced.

Other parasites can enhance survival of a second infecting organism via immunosuppression. Experimentally, many, if not all organisms, depress one or more parameters of the immune response at least temporarily and commonly in a non-specific manner. Mechanisms whereby parasite antigens interact with the immune response have been shown to include complement consumption, blocking antigen presentation, reducing T cell proliferation and reactivity, depressing antibody production and inhibiting inflammatory cells and their enzymes. The exact relationship of this immunosuppression and survival of the homologous parasite or a concurrent heterologous parasite remains largely speculative. For helminths, the classic example where one parasite enhances the survival of others is *H. polygyrus* in mice. Adult *H. polygyrus* immunosuppress the host and so allow prolonged survival of themselves and

*N. brasiliensis*, *T. muris*, *Hymenolepsis diminuta* and *T. spiralis* within the gut (Behnke 1990). Other interactions are less well characterised. Nevertheless, dual infections with *O. ostertagi* and *O. leptospicularis* in calves, *T. colubriformis* and *H. contortus* in sheep, and *O. ostertagi* and *Dictyocaulus viviparus* in cattle resulted in enhanced infections with both parasite species (Armour 1989, Adams *et al.* 1990). Such interactions are not confined to helminth or protozoal infections. Depression of T cell responses, e.g. by distemper virus in dogs or immunodeficiency virus in cats, can permit overgrowth of *Demodex* (Chalmers *et al.* 1989). Enhanced prevalence of Burkitt's lymphoma occurs in malaria patients (Behnke 1990). Distemper and feline or human immunodeficiency virus infections are associated with reactivation of *Toxoplasma gondii* (Velimirovic 1984, Witt *et al.* 1989).

## 5.7 Parasite-induced immunomodulation

In addition to such parasite variables as dosage and dose rate and their threshold effects, the species of parasite itself, is very influential on whether immune protection develops and on its rate of development. Infections must therefore be identified by species rather than taxonomic groups. Extremes have been shown in laboratory animal parasites where there is rapid expulsion of a primary infection and strong immunity to reinfection with *N. brasiliensis* compared with a prolonged survival by *H. polygyrus* induced by the worms' own modulation of the hosts' immune response (Behnke 1987). Similar variation in induction and suppression of immune responses and length of survival of the parasites now is known for parasites of domestic animal species. In cattle and sheep there can be fairly rapid development of and expression of a protective immune response to *Cooperia* and *Nematodirus* spp. In the field this is evident by a fairly rapid decline in egg production after a few weeks to 3–4 months and strong immunity to reinfection. In contrast, the development of immunity to some *Ostertagia*, *Trichostrongylus* and *Haemonchus* species is much slower (Armour 1989, Adams *et al.* 1990). This has been related to immunomodulatory effects by, for example, *O. ostertagi* ES molecules (Klessius 1993). Parasite manipulation of the immune response therefore influences epidemiology and disease. Prolonged survival can increase levels of contamination and potentially levels of infection in that same or the next generation of hosts. Also, the lack of absolute immunity to certain nematode species, e.g. *Ostertagia*, *Trichostrongylus*, in ruminants, means that older animals contribute to contamination and transmission whereas adult animals will have little influence on transmission of *Nematodirus* and *Cooperia* (Armour 1989).

## 5.8 Genetic variation in host resistance

In addition to a regulatory role for genetically-mediated, physical, physiological and behavioural differences between hosts, there are clear genetic differ-

ences between breeds and differences within breeds (individuals) in resistance to infection (Barger 1989, Grencis 1990, Wakelin 1992, Read *et al.* this volume). Within populations of domestic animals this difference in resistance has been particularly apparent with trypanosome-infected N'dama cattle and tick-infected Zebu breeds, more recently it is being studied in gastrointestinal nematode infections in sheep, and it was exploited commercially with coccidia in chickens.

Immunological reactions play a dominant role in this heritable, genetically-mediated resistance. The superior inherited resistance to *H. contortus* in sheep was abolished by immunosuppression with dexamethasone (Presson *et al.* 1988). $CD4^+$ T cells play a pivotal role in resistance, as sheep genetically resistant to *H. contortus* when treated with anti-$CD4^+$ antibody showed levels of infection comparable with randomly bred sheep (Gill *et al.* 1993a). Positive lymphocyte responses before infection correlated directly with the resistance achieved on subsequent infection with *H. contortus* in sheep (Lloyd and Soulsby 1987). After infection with *H. contortus* elevated levels of inflammatory cells, serum $IgG_1$ and faecal IgA correlated with resistance to *H. contortus* (Gill *et al.* 1993b) as did serum antibody, lymphocyte responses and particularly levels of leukotrienes with resistance to *T. colubriformis* (Windon and Dineen 1981, Gray *et al.* 1992).

Within populations of animals this inheritance of genetic resistance or susceptibility could influence the epidemiology of infections quite readily. Populations of tick-resistant cattle showed reduced amplitudes of cycles of tick numbers over several years compared with the susceptible cattle also grazing infested pastures (Sutherst *et al.* 1979). Albers and Gray (1987) predicted that sheep that were resistant to gastrointestinal trichostrongyles would cause an exponential decline in pasture contamination and thus infectivity over the years of grazing. Also, a reduced periparturient rise in resistant sheep could reduce larval availability for the lambs grazing later in that season (Woolaston 1992). Gulland *et al.* (1993) (see also Read *et al.* this volume, Box 3) present evidence of parasite-associated polymorphism in the resistence of feral Soay sheep against infection by *Teladorsagia circumcincta.*

# 6 Conclusions

## 6.1 Measuring the immune response in wildlife host populations

This review illustrates the complex range of extrinsic and intrinsic factors that can alter levels of immunity, and hence susceptiblity or resistance to infection in an individual animal or in a group of animals. It suggests that great care must be taken when individuals or groups of animals in a population are

examined to clarify the effects of immunity.

Intrinsic factors, e.g. genetic resistance with the resulting increase in aggregation of the parasites in individuals (Smith *et al.* this volume), must be considered if only a small number of animals can be examined. It is important to bear in mind that a single, dominant male, that is unusually resistant or unusually susceptible to infection could rapidly alter the levels of resistance in the next generation/cohort offspring and thus the population. Equally, knowledge of the epidemiology of the parasite is important so that animals can be sampled for levels of infection/protection when the population of parasites is within the host rather than the environment.

The presence of extrinsic factors which might affect the infection must be monitored. In an experimental animal population at least some, although probably not all, extrinsic factors can be controlled or monitored to evaluate their effects on either the infection or immune parameters under investigation. However, when an individual or even a group of animals are sampled in a domestic field or wildlife situation, the environmental pressures may not be immediately apparent. It will be important to elucidate as much information as possible about the population and its environment at the time of and immediately prior to sampling in order to interpret results.

## 6.2 Interactions between factors

Inevitably, within populations, two or more factors which affect either the immune response and/or the development of the parasites may be operating at any one time with cumulative or synergistic effects. An example might be the relationship between periparturient immunosuppression, climate and nutrition, plus the impact of the climate in one year on the levels of parasitism in the next year. Many of these factors were relevant for Soay sheep on St Kilda (Gulland and Fox 1992).

In many climates, the intensity and prevalence of infection with gastrointestinal nematodes in the current year related to the history of the host/parasite/climate relationships in the previous year or season. Thus, in a temperate climate, a fairly dry summer followed by a wet autumn can permit survival and cold-conditioning for hypobiosis of large numbers of larvae in the autumn. These could then affect the magnitude of the periparturient/spring rise in the following season. If parturition were superimposed on the reactivation of this unexpectedly large population of larvae in the spring, then this will increase the periparturient rise in faecal egg counts. If the winter were mild, permitting large numbers of larvae to persist on pasture over the winter, the magnitude of the rise will then be increased further as the grazing, immunosuppressed, periparturient animals ingest this new infection. Conversely, if the winter weather is severe, or stocking levels are particularly high, while over-wintering larvae may be destroyed, malnutrition and

its immunosuppressive effects will influence parasite levels instead. Thus, again, the magnitude of the periparturient immunosuppression may be increased substantially. In addition, malnutrition in the winter may result in immunosuppression in non-reproductive animals. Owing to the breakdown of resistance in these animals, any reactivating hypobiotic larvae, instead of being expelled, will persist. As a consequence a large spring/periparturient rise in worm numbers in both parturient and non-reproductive animals could exacerbate the effects of food limitation on wildlife hosts (Gulland and Fox 1992) and/or influence the numbers of larvae present on pastures later in that grazing season.

Porter *et al.* (1984) tested a model which suggested important links between available food and water, climate and infection/toxicant interactions. The results did show that, if malnourished, white mice or deer mice were more sensitive to an encephalitis virus challenge and environmental elements (a plant growth regulator, itself immunosuppressive, or PCBs). With unlimited food and water mice compensated to survive the insults. Animals in the wild therefore could be affected by an infectious/toxicant insult only at certain times of year when subjected to food or water stress.

The potential interaction of other immunosuppressive factors, e.g. stress from cold, multiple infections, etc., remains undetermined.

## 6.3 Integrated studies

Acquired immunity is an important constraint on the development of epidemics of disease and it influences the eventual steady state of the infection. Most studies which have examined the immune system have analysed responses to defined antigens and in populations of animals that are genetically similar (e.g. inbred strains of mice) within a physically defined environment (e.g. constant climate, unlimited nutrition). However, in many, especially wild, populations, the various extrinsic and intrinsic determinants associated with the host, the parasite and the environment do not exert their effects in isolation. Instead the determinants interact to produce disease. Furthermore, this interaction may be cumulative or even synergistic. Recently the importance of population genetics on the prevalence and intensity of infection are becoming apparent. Predictions by Albers and Grey (1987) and Woolaston (1992) relate the influence of genetic resistance in domestic sheep to future transmission of infection and levels of disease within the population, while Gulland *et al.* (1993) have shown an association between parasite, parasite-induced host polymorphism and host condition and survival. It is important that such integrated studies relating the effects of different variables continue and are extended to include the host-induced immune constraints on the parasite population.

# Appendix. Details of the immune response

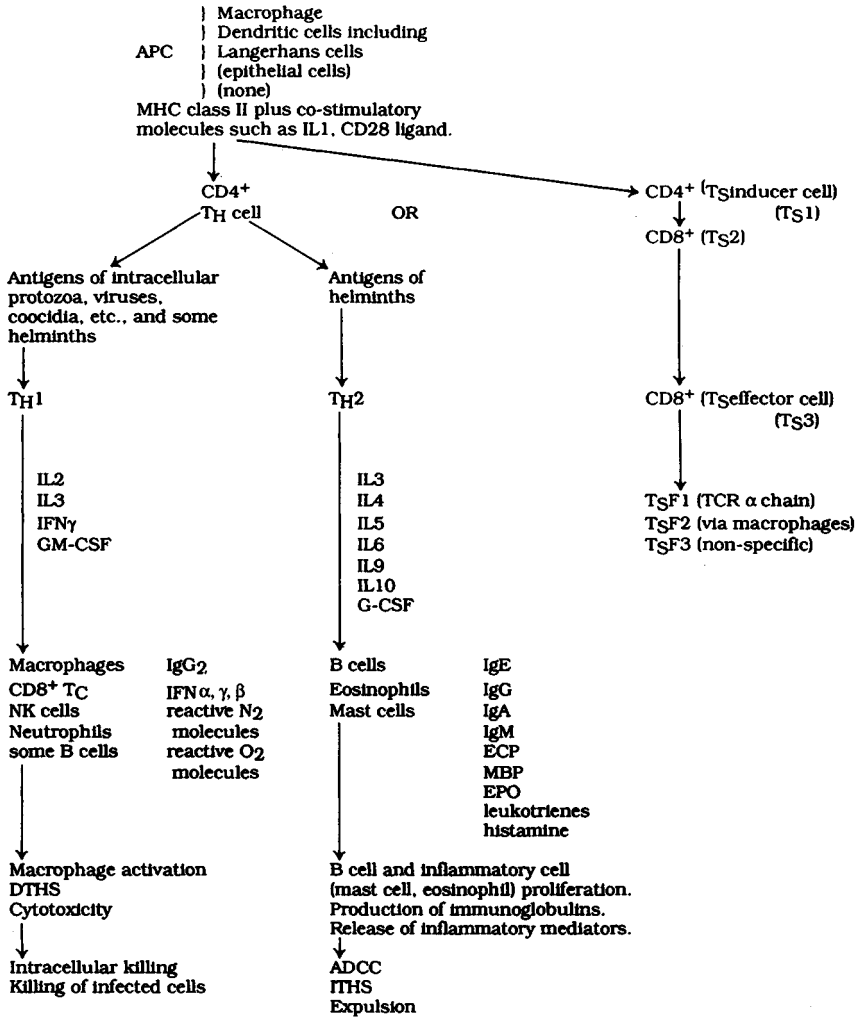
The mechanisms which mediate immune protection (or conversely survival of the parasite) vary with host species but particularly with parasite species (Table 1; Cox and Liew 1992, Bloom *et al.* 1992a,b).

Initially, there is processing and presentation of antigen by antigen presenting cells (APCs), particularly macrophages and dendritic cells, including Langerhans cells, but also cells such as B cells and epithelial cells (Unanue and Allen 1987, Steinman 1991, Mamula and Janeway 1993). This antigen presentation is controlled by the Ir (immune response) genes which are MHC Class II genes. These ensure that successful APCs express on their surface MHC Class II molecules that have affinity for the antigen and ability to transport the processed antigen to the surface and express it thereon.

$CD4^+$ helper T cells are stimulated only by antigen in association with MHC Class II plus other appropriate co-stimulatory molecules produced by the APCs (and perhaps T-T cell interactions) (Steinman 1991, Bretscher 1992). Within $CD4^+$ helper cells are two subsets – $T_h1$ and $T_h2$, divided by the cytokines they produce. These two subsets were defined in mice, but are increasingly recognised in humans and the existence of the two subsets is now being recognised, through cytokine production of the cell populations, in domestic animals. It seems the parasites themselves are a major factor in determining which T helper subset is activated. Intracellular protozoa seem to stimulate particularly $T_h1$ responses and helminths stimulate particularly, but not exclusively, $T_h2$ responses. Reasons for this polarisation are not understood. Antigens and their route of presentation may be important. Presentation of worm antigens in the context of proteases plus their presentation at a mucosal site perhaps preferentially stimulate $T_h2$ (Finkelman and Urban 1992). Also, dose levels and class of APCs can influence results. Stimulation of the $T_h1$ or $T_h2$ subset produces a 'cascade' culminating in different effector mechanisms (Table 1).

$T_h1$ cells produce IL2 and IFN$\gamma$in particular; these are important in activation of macrophages, $CD8^+$ $T_c$ cells and NK cells. Activated macrophages, through production of TNF$\alpha$, reactive $N_2$ and $O_2$ molecules and enzymes, are involved in protection against intracellular protozoa such as: *Leishmania major*; some intracellular viruses; and schistosomula of *S. mansoni* in mice; (James *et al.* 1990, Sher and Coffman 1992). Activated $CD8^+$ $T_c$ cells and NK cells recognise virus-infected cells by virus antigen expressed with MHC class I molecules on the surface, and kill; the 'lethal hit', is through cytolysis by the granzymes, perforins, cytotoxins (Tizard 1992).

$T_h2$ cells are important in antibody-mediated and mucosal immunity. They produce interleukins and granulocyte-colony stimulating factor important in B cell proliferation and antibody production and in proliferation and acti-




APC - antigen-presenting cell, CD4 - receptor recognizes MHC class II; CD8 - receptor recognizes MHC class I; DTHS -delayed type hypersensitivity; ECP/MBP/EPO - eosinophil cationic protein, major basic protein, peroxidase; G-CSF/GM-CSF - granulocye/granulocyte, macrophage - colony stimulating factor; Ig - immunoglobulin; IFN - interferon; IL - interleukin; NK - natrual killer cell; $T_H$ -helper cell, $T_S$ -suppressor cell; $T_C$ -cytotoxic cell; $T_S$F (TCR)-suppressor factor (T cell receptor); TNF -tumour necrosis factor.

Table 1. Schematic overview of the affector and effector arms of the immune response. (Adapted from Cox and Liew 1992)

vation of mast cells, eosinophils and anaphylactic responses. $T_h2$-mediated responses, e.g. IgE, mastocytosis, eosinophilia, can be obvious in helminth-infected hosts (Cox and Liew 1992, Finkelman and Urban 1992). Antibodies, through such mechanisms as direct lysis and opsonisation for phagocytosis,

are important in protection against bacteria and some parasites. IgG and IgA antibodies are the main immune defence mechanism against the metacestodes of taeniids, e.g. *Taenia taeniaeformis* in mice and rats (Lloyd 1987a). IgA passively protected mice against *Trichuris muris* (Roach *et al.* 1991). IgE, IgGs and even IgA all participate in antibody-dependent, cell-mediated cytotoxicity by eosinophils, mast cells and macrophages against *S. mansoni* in man and rats (Capron and Dessaint 1992, Dunne *et al.* 1993). IgE, mast cells and eosinophils all have been associated with rapid expulsion and self cure of gastrointestinal nematodes (Huntley *et al.* 1992), and $T_h2$ responses correlated with protection against *Heligmosomoides polygyrus* and *T. muris* in mice (Urban *et al.* 1991, Else *et al.* 1992a).

Stimulation of an inappropriate response may lead to prolongation of infection. In *L. major* infection, $T_h1$ responses lead to healing and protection while $T_h2$ responses lead to non-healing and exacerbation of disease (Sher and Coffman 1992). The opposite might be true for gastrointestinal nematodes; there is evidence that $T_h2$ responses correlated with protection against *T. muris* and *H. polygyrus* and that $T_h1$ responses prolonged infections (Urban *et al.* 1991, Else *et al.* 1992a). However, information for *T. spiralis* is less clear cut. In one experiment, $T_h2$ responses dominated in both NIH (resistant) and B10.G (susceptible) mice while, in another, $T_h1$ responses correlated with resistance in AKR mice and $T_h2$ with susceptibility in B10.BR mice (Pond *et al.* 1989, Grencis *et al.* 1991) Other factors, such as the pattern of and the spectrum of cytokines produced in each infection plus the kinetics of a response, could be important (Lezama-Davilla *et al.* 1992, Else *et al.* 1992b, Svetic *et al.* 1993). Thus, an earlier $T_h1$ response in resistant, compared with susceptible, strains of mice seemed important in protection against the coccidian, *Eimeria vermiformis* (Wakelin *et al.* 1993). Also, with the multiplicity of parasite life cycle stages and antigens and immune mechanisms, different cell subsets may function in mediating protection at different times. For example, protective $T_h1$ cells were present early in the course of infection with *Plasmodium chabaudi* in mice while, on reinfection, the cells isolated were protective $T_h2$ cells that mediated antibody production (Taylor-Robinson and Phillips 1993).

Antigen presentation does not invariably lead to a helper, protective immune response and $CD4^+$ and $CD8^+$ T cells are not always effector cells. Instead there may be anergy or suppression of immune responses. This may be useful when there is suppression of immunopathology, e.g. suppression of *Schistosoma* egg granulomata (Phillips and Lammie 1986). While antigen presentation for help requires APCs and co-stimulatory second signals, the absence of these latter can lead to anergy or suppression (Bretscher 1992). Macrophages are efficient APCs for help, but they also seem to be efficient APCs for suppression, possibly with altered requirements for numbers and

altered co-stimulatory molecules (Dorf *et al.* 1992). B cells in particular may function as APCs to induce suppression as they present antigen in the absence of IL1, etc. (Bloom *et al.* 1992a,b). Antigen presentation by B cells also, in certain circumstances, preferentially induces a $T_h2$ response (Gajewski *et al.* 1991). There is interaction and cross regulation, particularly cytokine-induced down regulation between the $T_h1$ and $T_h2$ cascades. For example, IFN$\gamma$is a potent inhibitor of $T_h2$, and IL4 and IL10 from $T_h2$ will inhibit $T_h1$ responses. Thus, an activated non-protective $T_h2$ response then could inhibit a protective $T_h1$ response and vice versa. Also, a cascade of T suppression exists involving $CD4^+$ and $CD8^+$ cells (Table 1). Bloom *et al.* (1992a,b) have described this as activation of antigen-specific $CD4^+$ suppressor–inducer cells and antigen-idiotype-specific $CD8^+$ suppressor cells followed by $CD8^+$ antigen specific effector cells which are MHC unrestricted and a number of soluble suppressor factors. Bloom *et al.* (1992a,b) have further divided the $CD8^+$ cells into Type 1 which suppress B cell responses and Type 2 which suppress DTHS.

In addition to the effector $T_h$lymphocytes and the $T_s$cells which inhibit the effector cells, a third distinct cell group is described, namely T contra-suppressor ($T_{cs}$) cells, with effects apposed to $T_s$cells. The $T_{cs}$cell circuits have been described and studied particularly in relation to contact hypersensitivity responses and in the maintenance of local mucosal immunity despite systemic oral tolerance. These $T_{cs}$cells are recorded to aid $T_h$cell function even in the presence of $T_s$cells and to inhibit suppressor factors (Friedman *et al.* 1990).

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# Modelling the Immuno-Epidemiology of Macroparasites in Naturally-Fluctuating Host Populations

*B.T. Grenfell, K. Dietz and M.G. Roberts*

## 1 Introduction

Quantitative approaches to parasite population biology can be broadly classified into two research areas. The first body of work is essentially epidemiological, concentrating mainly on infections of humans (Anderson and May 1991) and managed farm animals. A major focus here is the role of host immunity in determining patterns of infection, particularly in the case of long-lived helminth parasites (Quinnell and Keymer 1990). This area has recently received considerable theoretical attention, particularly in the derivation of immuno-epidemiological models, which seek to account for parasite age-intensity profiles in terms of simple phenomenological models for immunity (Anderson and May 1985a, Grenfell and Michael 1992, Woolhouse 1992).

The second area (and the subject of this volume) is essentially an ecological examination of the interaction of parasites with their (naturally-fluctuating) host populations (Anderson and May 1978, May and Anderson 1978). Unlike many human infections, where host dynamics can often be neglected, the focus here is on the dynamics of the host-parasite interaction (Roberts *et al.* this volume) and, increasingly, with questions of coevolution (Lively and Apanius, this volume). In terms of host-macroparasite population dynamics, a crucial issue is the balance between parasite induced host mortality and reproductive limitations due to parasitism (which tend respectively to stabilize and destabilize host dynamics (Anderson and May 1978, May and Anderson 1978).

The statistical distribution of parasites among hosts has a major impact on both the above areas. Parasites are characteristically aggregated in their host populations and (as reviewed in detail by Smith *et al.* this volume) this pattern can generally be characterised empirically by the negative binomial distribution (Dietz 1982). Epidemiological work on human parasites indicates that parasite aggregation has important implications, both for the population impact of host immunity (Anderson and May 1985b, Anderson and May 1991) and the performance of anthelmintic strategies (Anderson and Medley 1985). The degree of aggregation of parasites in naturally fluctuating host populations also plays an important role in the dynamics of these

systems. Essentially, aggregation of parasites increases the stabilising effects of parasite-induced host mortality (Anderson and May 1979, Roberts *et al.* this volume).

The dynamics of immunity are also likely to be a crucial influence on the ecology of macroparasites in naturally fluctuating populations of verterbrate hosts (Lloyd this volume). In particular, the time delays implicit in immunological memory and the interaction between parasitism, immunocompetence and various ecological variables (notably nutrition) could have complex and nonlinear effects on host dynamics. These potential complexities are also likely to be increased by variability, both in the infection process and arising from differences in host immunocompetence or parasite pathogenicity. Although the interaction between immunity and between-host variability has been modelled for human helminths (Anderson and May 1991, Woolhouse 1992), it has been much less examined in the case of wild animal host populations. Previous studies have explored the issue indirectly, for example, representing immunity-nutrition interactions in terms of host (Anderson 1979) or plant density (Grenfell 1992), however, they do not explicitly consider the effects of immunity.

In this paper, we use simple models to explore these issues. Specifically, we examine how the interaction between host immunity and variability in infection rates influences observed parasitism in naturally fluctuating vertebrate host populations.

## 1.1 Modelling variability and the impact of immunity

Producing a 'complete' model of both these processes presents the following significant technical problems.

*(a) Variability* As discussed by Roberts *et al.*, (this volume), published models of parasite variability have adopted one of two methodologies. The first is to use a phenomenological approach, based on the fit of observed parasite distributions to the negative binomial distribution (Crofton 1971a,b, Anderson and May 1978, May and Anderson 1978, Dietz 1982, Pacala and Dobson 1988, Anderson and May 1991). This strategy has been highly successful in exploring the effects of parasite aggregation, however, it does not focus on the mechanisms underlying observed worm burden distributions. The second approach attacks this problem by constructing explicit stochastic models of the demographic processes which generate parasite distributions (Kretzschmar 1989, Hadeler and Dietz 1983, Kretzschmar and Adler 1983). The resulting age- and time-specific stochastic models are, in general, too intractable to yield biologically useful results, although Monte Carlo simulations can yield insights, particularly when based on simplified cases (Anderson and Medley 1985).

*(b) Immunity* Modelling the dynamics of variability in immunity potentially adds another layer of complexity to the stochastic models described above. In particular, immunity involves the accumulation of experience of previous infection by individual hosts (Lloyd this volume), and the resulting time delays can generate complex behaviour even in models for immunodynamics in single hosts (Anderson and May 1985a, Crombie and Anderson 1985, Schweitzer and Anderson 1992). Though the dynamic implications of between-host variations in immunity have been modelled for human helminths (Woolhouse 1992), the general stochastic case has been largely unexplored. More broadly, though models are now being formulated with explicit immunological assumptions (Schweitzer and Anderson 1992), much still needs to be learned about immunodynamics, both empirically and theoretically (Lloyd this volume).

Given the above uncertainties, we focus our discussion using a simple theoretical framework for the immuno-epidemiology of directly-transmitted helminth infections in wildlife host populations. In this preliminary version, we concentrate on a temporal equilibrium model. Specifically, we examine how the interaction between immunity, stochasticity in the infection process and the demographic impact of parasitism (specifically on host survival) determine the mean and second moments of parasite age-intensity curves. A significant complication here is that the second moments, which determine the variances and covariances of parasite numbers, depend on the third moments; the third on the fourth, and so on. We approach this problem by using a normal approximation for the third moments in the manner of Whittle (1987) and Isham (1991).

The rest of the paper is divided into three sections. In the first, we derive a basic model, setting out the technical details in an appendix. Since the resulting framework is potentially very complex, we focus on the epidemiology of ungulate-gastrointestinal nematode interactions (one of the best documented systems empirically). The second section uses simulations and analytical work to outline the model's behaviour and we conclude with a discussion of these results and of directions for future work.

# 2 The Model

## 2.1 Helminth immuno-epidemiology

Excellent reviews of the empirical and theoretical background to this area are given by Anderson and May (1991), Quinnell and Keymer (1990) and Woolhouse (1992). The essential conceptual framework has been used in various contexts, in both human and veterinary epidemiology. It relies on the assumption (borne out by a number of empirical observations on experimental systems) that the epidemiological effects of immunity can be represented by

tracking a host's previous experience of infection, as an index of potential immune responsiveness, and then using this variable to determine immunological limitations on parasite demographic rates. Depending on the system to be modelled, there are a number of options for the most suitable model. In particular, experience of infection could depend on accumulating infection rates, larval burdens, adult burdens or the reproductive rate of the latter, while the effects of immunity can be manifested by reductions in larval establishment and adult survival and fecundity. This leads to a complex family of models (Woolhouse 1992).

## 2.2 Model structure

### 2.2.1 General structure and biological assumptions

Host age is an essential component of models which seek to incorporate the impact of immunological memory. The following is a standard formulation for the dynamics of the mean worm burden, $m_M(a,t)$ as a function of age, $a$, and time, $t$

$$\frac{\partial m_M(a,t)}{\partial a} + \frac{\partial m_M(a,t)}{\partial t} = \Lambda(a,t) - \mu_M(a,t)m_M(a,t). \tag{1}$$

Here, $\Lambda(a)$ and $\mu_M(a)$ are respectively the age-specific net establishment rate of new infections and the death rate of adult worms. Either or both these parasite demographic rates may be modulated by host immunity. The resulting dynamic model is rather intractable so, as a first step, we consider the age distribution of infection and immunity at the temporal equilibrium. Again by analogy with previous models, this leads to the following model for the age distribution of infection, $m_M(a)$:

$$\frac{dm_M(a)}{dt} = \Lambda(a,m_I) - \mu(a,m_I)m_M(a) \tag{2}$$

where $m_I$, the accumulated immunological experience, obeys

$$\frac{dm_I}{dt} = X - \mu_I m_I. \tag{3}$$

Here, $X$ represents parasite abundance which, depending on the system modelled, could be taken as larval challenge ($\Lambda$), adult burden, or net reproductive rate. The parameter $\mu_I$ allows for a finite immunological memory of previous infection, of average duration $1/\mu_I$.

In order to assess the impact on this picture of parasite-induced host mortality and variability in input, we focus on a particular case: the epidemiology of directly transmitted gastrointestinal nematode parasites of ungulates. The ecology of these parasites is particularly well documented in sheep and cattle,

a general epidemiological review is given by Grenfell, Smith and Anderson (1987a,b). Essentially, we can divide the population into free-living egg and larval stages and parasitic adults, which develop from ingested infective larvae. The basic biological assumptions of the model are summarized in Figure 1a; in particular,

- (a) **Variability in input** is modelled explicitly by using a compound Poisson process. Thus we assume that, for any individual host, encounters with parasite transmission stages occur in an inhomogeneous Poisson process with rate $\varphi(a)$, depending on the age $a$ of the individual. During an encounter, the number of parasites ingested, $C$, is a random variable with mean $m_C$ and variance $\sigma_C^2$. By taking $m_C = 1$ and $\sigma_C^2 = 0$, this model for the infection process reduces to an ordinary (inhomogeneous) Poisson process. Here, we assume that $m_C$ is the mean daily infection rate, though the model is flexible enough to deal with other scenarios (for example, the distribution of infections per bite). In order to trace how this variability in infection rate affects subsequent parasite stages, we track the abundance of larvae (L4 worms, denoted by the symbol $L$) as well as adult parasites ($M$). In this initial version of the model, intrinsic variability between host infection rates or responses to parasitism are not considered. As derived below, the model is easily modified to allow for this heterogeneity.

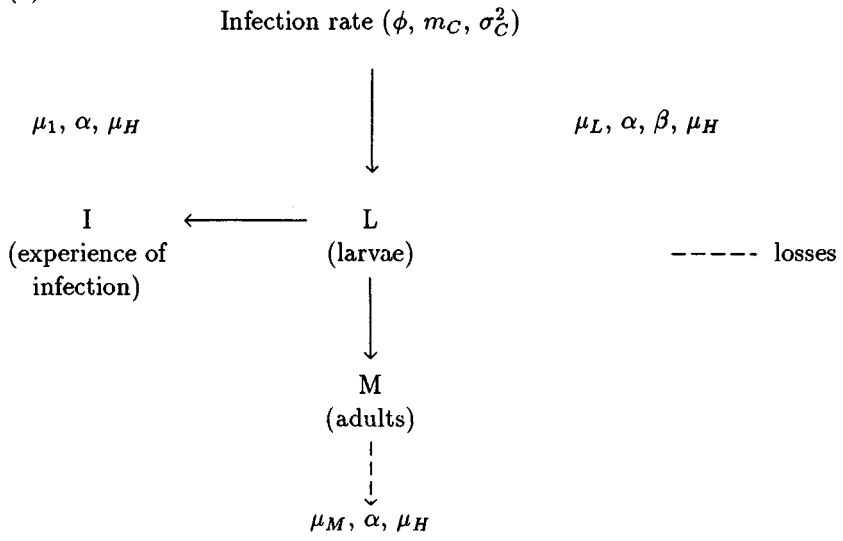
- (b) **Nonlinear effects: immunity and parasite-induced host mortality.** The general consensus is that host immunity in ungulate-gut nematode interactions accumulates with the accretion of new infections (Grenfell *et al.* 1987a,b). In principle, this could be modelled in terms of a specific point in the establishment of larvae (for example, the entry of L3 larvae), or the average larval burden. For mathematical simplicity, we use the average larval density here, the effects of this assumption are discussed below. Previous experience of infection ($I$) is assumed to increase the mortality of larvae by a rate $\beta I$. Parasite induced host mortality is taken to be proportional to the adult burden, with rate parameter $\alpha$ per adult worm. Host mortality then, of course, kills both larvae and adults and experience of infection.

Given this background, we can now derive a model for the mean age distribution of infection and immunity, as well as the corresponding second moments (variances and covariances).

### 2.2.2 Model derivation

The rate parameters used in the following formulation are defined in Figure 1(b). Let $M(a)$ be the number of mature parasites, $L(a)$ be the number of

(a)




(b)

| | DEFINITION | DEFAULT VALUES |
|---|---|---|
| Loss rates: $\mu_I$, $\mu_L$, $\mu_M$ | | |
| $1/\mu_I$ | Duration of immunological memory | 10 years |
| $1/\mu_L$ | Life expectancy of larvae in the host | 7.5 weeks |
| $1/\mu_M$ | Life expectancy of adult worms | 5 weeks |
| $1/\mu_H$ | Life expectancy of hosts without parasites | 10 years (arbitrary) |
| $\alpha$ | Death rate of hosts induced by 1 adult parasite | Various |
| $\beta$ | Death rate of larvae due to 1 unit of infection experience | Various |
| Infection and developmental rates | | |
| $\varphi(a)$ | Encounter rate with infective larvae constant with age | Daily (365/year) |
| $\mu_C$, $\sigma_C^2$ | Mean and variance of larvae ingested per encounter | Various |
| $\gamma_L$ | Developmental rate of larvae | $1/\gamma_L = 2.5$ weeks |
| $\nu$ | rate of increase of immunity level due to larvae | 0.1 |

Figure 1. (a) Schematic diagram of the model infection process and (b) definitions of and defaults for parameters

larvae, $I(a)$ be the (discrete, integer-valued) level of immunity as functions of age, $a$.

Then $n_{i,l,m}(a)$ is the probability that a host survives to age a and has immunity level $I = i$, number of larvae $L = l$ and number of mature parasites $M = m$ at age $a$. Hosts get into contact with infective larvae at the age-dependent rate $\varphi(a)$. On each contact a random number $C$ of infective larvae is ingested with p.g.f. $h$:

$$h(y) = E(y^C) = \sum_{c=0}^{\infty} P(C = c)y^c = \sum_{c=0}^{\infty} p_c y^c \tag{4}$$

with mean

$$m_C = h'(1) \tag{5}$$

and variance

$$\sigma_C^2 = h''(1) + h'(1) - (h'(1))^2. \tag{6}$$

In the absence of immunity in the host these larvae would either die at rate $\mu_L$ or develop into mature parasites at rate $\gamma_L$. In the presence of $L = l$ larvae, the immunity level increases by one unit at rate $\gamma_L l$ and decreases by one unit at rate $\mu_I i$. Mature parasites die at rate $\mu_M$ and hosts die at rate $\mu_H(a) + \alpha m$ if $M = m$. The immunity level increases the death rate of larvae by the additional term $\beta il$.

In the Appendix, we derive a model for the equilibrium age structure of $I$, $L$ and $M$, framed in terms of their first two moments (determining the means, and variances and covariances respectively). This formulation is based on a normal approximation for the higher moments (Isham 1991, Kurtz 1971, Whittle 1957), which is asymptotically exact for the linear case ($\alpha, \beta = 0$) and robust for the nonlinear case (Isham, in preparation). This leads to the following set of differential equations for the dynamics of the moments with age, in which we adopt the notation, for example for adult parasite abundance: mean $m_M$, variance $\sigma_M^2$, covariances with $I$ and $L$ $\sigma_{IM}$ and $\sigma_{LM}$ respectively.

$$\begin{aligned}
\frac{dm_I}{da} &= \nu m_L - \alpha\sigma_{IM} - \mu_I m_I; \\
\frac{dm_L}{da} &= \varphi(a)m_C - \alpha\sigma_{LM} - \beta\sigma_{IL} - (\mu_L + \gamma_L + \beta m_I)m_L; \\
\frac{dm_M}{da} &= \gamma_L m_L - \alpha\sigma_M^2 - \mu_M m_M; \\
\frac{d\sigma_I^2}{da} &= \nu m_L + \mu_I m_I + 2\nu\sigma_{IL} - 2\mu_I\sigma_I^2; \\
\frac{d\sigma_L^2}{da} &= \varphi(a)(\sigma_C^2 + m_C^2) + (\mu_L + \gamma_L + \beta m_I)m_L - \beta(2m_L - 1)\sigma_{IL} \\
&\quad -2(\mu_L + \gamma_L + \beta m_I)\sigma_L^2;
\end{aligned} \tag{7}$$

$$\begin{aligned}
\frac{d\sigma_M^2}{da} &= \gamma_L m_L + \mu_M m_M + 2\gamma_L \sigma_{ML} - 2\mu_M \sigma_M^2; \\
\frac{d\sigma_{IL}}{da} &= \nu\sigma_L^2 - \beta m_L \sigma_I^2 - (\mu_I + \mu_L + \gamma_L + \beta m_I)\sigma_{IL}; \\
\frac{d\sigma_{IM}}{da} &= \nu\sigma_{LM} + \gamma_L \sigma_{IL} - (\mu_I + \mu_M)\sigma_{IM}; \\
\frac{d\sigma_{LM}}{da} &= \gamma_L(\sigma_L^2 - m_L) - \beta m_L \sigma_{IM} - (\mu_L + \gamma_L + \beta m_I + \mu_M)\sigma_{LM}.
\end{aligned}$$

This is a complex and highly coupled set of nonlinear equations. For example, the rate of change of mean larval abundance with age ($dm_L/da$) increases with infection rate ($\varphi(a)m_C$) and decreases in proportion to $m_L$ due to natural mortality, development and immunity (at *per capita* rates $\mu_L$, $\gamma_L$ and $\beta m_I$ respectively). In terms of second moments, $m_L$ also declines in proportion to its covariance with the level of immunity ($\sigma_{IL}$) and with the burden of adult parasites ($\sigma_{LM}$). The latter effect is due to host mortality induced by adult parasites, which manifests itself in the adult equation ($dm_M/da$) via the adult variance, $\sigma_M^2$ (Roberts *et al.* this volume).

The next section uses numerical simulations and simple analytic arguments to explore the biological implications of this model. A recurrent theme will be the mechanisms that generate variability in parasite loads and how these interact with nonlinearitites such as immunity and parasite-induced host mortality. We assess parasite aggregation by a simple variance/mean ratio, as well as by the moment estimate of the negative binomial parameter, $k$. For example, $k$ for adult parasites is given by $k_M = m_M^2/(\sigma_M^2 - m_M)$.

# 3 Biological implications

We begin by exploring the basic properties of the model and then examine the issues relating to parasite variability, immunity and parasite-induced host mortality raised in the Introduction.

## 3.1 Basic patterns of parasitism

Figure 2 shows predicted patterns of infection, immunity and aggregation by age, in the absence of parasite-induced host mortality and immunity ($\alpha = \beta = 0$). Note that, in this case, the system is linear, so that the normal approximation for the third and higher moments of the system is exact. Parameter values (which are adapted from Grenfell *et al.* (1987a)) are summarized in Figures 1b and 2. In particular, we assume that the infection distribution, $C$, has a mean of $m_C = 500$ L3 larvae per encounter and variance $\sigma_C^2 = m_C + m_C^2$, as would be appropriate if $C$ were negative binomial with dispersion parameter, $k = 1$. As expected from equations (7), the basic

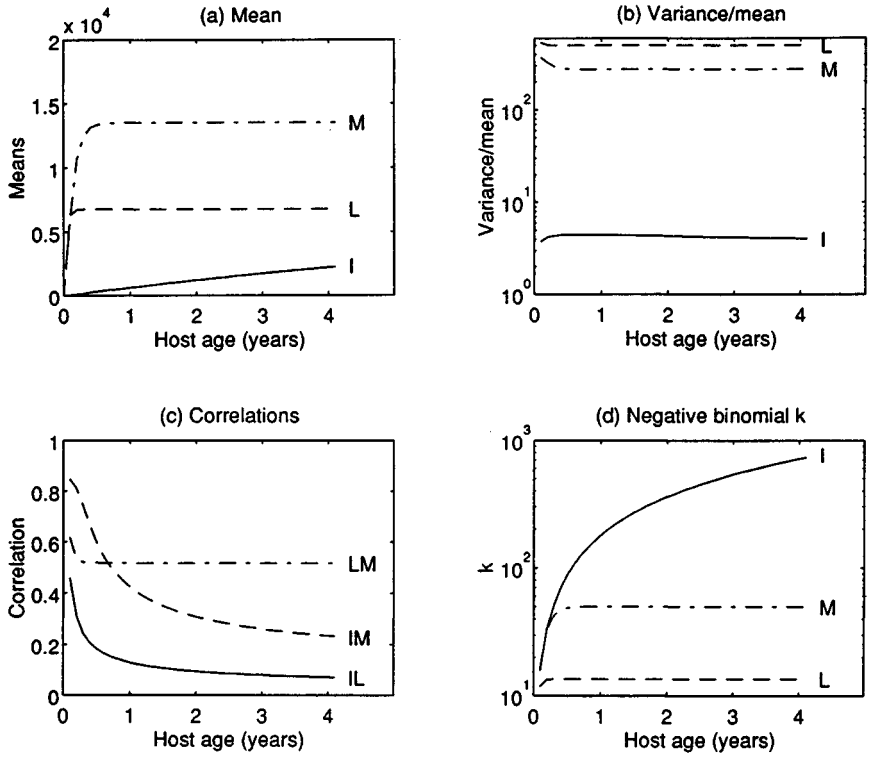



Figure 2. Simulation of equations (7), based on the parameter values defined in Figure 1 and the text. The equations were simulated numerically by standard methods to calculate age profiles of first and second moments of $I$ (previous experience of infection), $L$ (larvae) and $M$ (adults) as defined in the text. The results show means of these variables and various functions of their second moments (variance/mean ratios, moment estimates of negative binomial $k$ and correlations between variables). This is the linear case, without parasite-induced host mortality or immunity ($\alpha, \beta = 0$).

mean age-intensity pattern (Figure 2a) reflects a series of immigration/death processes, with $I$, $L$ and $M$ rising to an upper asymptote with age. The initial rise in adult intensity and average infection level are reasonable reflections of what is observed for these systems (Grenfell *et al.* 1987a,b).

The degree of variability in parasite counts (as measured by variance/mean ratios, Figure 2b and moment estimates of the negative binomial $k$ parameter, Figure 2d) is high at very young ages (reflecting the variability in initial infection), then declines to a steady level. The degree of aggregation (essentially $1/k$) is much lower than that observed in the field (where $k$ for adult worms is close to 1, compared to an asymptotic value of 50 in Figure 2);

explanations for this anomaly are discussed in the next section.

The previous experience of infection ($I$) is even less variable (Figure 2c) – the degree of aggregation decreases progressively towards a Poisson distribution with age. This arises partly from our assumption that $I$ is accumulated from the average larval burden, $L$; generating $I$ directly from the current infection rate produces a slightly higher variance, though the qualitative pattern is similar to that in Figure 2. Because of this low and decreasing variability, the correlation between $I$ and the parasites burdens ($L$ and $M$) falls with host age (Figure 2c), compared with the high and relatively constant correlation between $L$ and $M$.

## 3.2 Determinants of heterogeneity

The patterns of parasite heterogeneity shown in Figure 2 can be elucidated by an equilibrium analysis of the basic model. Consider the asymptotic equilibrium of equations (7) ($a \to \infty$), with the further simplification that $\alpha = \beta = 0$. Some elementary algebra then leads to the following expressions for the means and variance to mean ratios of $L$ and $M$.

$$\begin{aligned} m_L &= \frac{\varphi m_C}{\mu_L + \gamma_L}; \quad m_M = \frac{\gamma_L m_L}{\mu_M}, \\ \sigma_L^2/m_L &= (1/2)[\sigma_C^2/m_C + m_C + 1], \\ \sigma_M^2/m_M &= 1 + \gamma_L(\sigma_L^2/m_L - 1)\mu_L + \gamma_L + \mu_M \ < \sigma_L^2/m_L. \end{aligned} \tag{8}$$

They indicate that asymptotic parasite variability in the linear system can be explained entirely in terms of variability in the infection process. These results also allow us to calculate the following asymptotic moment estimates of the negative binomial parameter, $k$, for larvae and adults. Defining $k_C = m_C^2/(\sigma_C^2 - m_C)$ as the moment estimate of $k$ for the infection process, we obtain

$$\begin{aligned} k_L &= \frac{2m_L k_C}{(k_C + 1)m_C}; \\ k_M &= \frac{2m_L m_M(\mu_L + \gamma_L + \mu_M)(k_C + 1)}{m_l \gamma_L m_C k_C}. \end{aligned} \tag{9}$$

The lack of variability in Figure 2 can now be explained. Given the negative binomial form for the variance of infection rate (with $k_C = 1$), the variance to mean ratio, $(\sigma_C^2/m_C) = m_C + 1$. Substituting this into equations (8) gives the same variance to mean ratio for $L$: $(\sigma_L^2/m_L) = m_C + 1$. Since $m_C$ ( = 500) is much less than the equilibrium value of $m_L$ (= 7000), the resulting moment estimate of $k$ for larvae, $k_L = m_L/m_C$ is substantially greater than unity.

Figure 3 uses equations (9) to explore the relationship between $k$ for the infection process ($k_C$) and the resulting asymptotic $k$ for adult parasites ($k_M$).

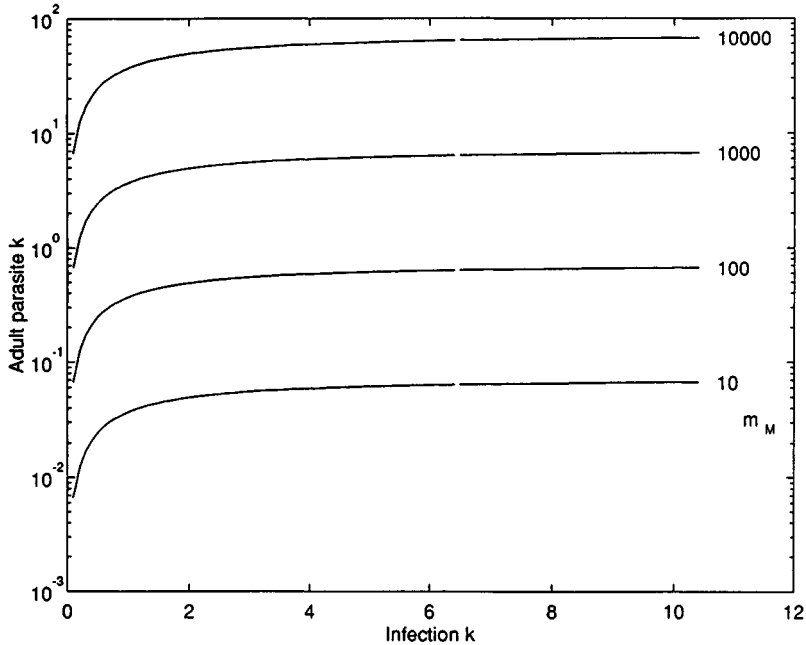



Figure 3. Effect of variability in infection rate on variability of adult worm burden, as described in the main text. Equations (9) are used to calculate the moment estimate of $k_M$ (inversely measuring adult worm variability) as a function of $k_C$; different curves show the effect of varying infection rates ($\varphi = 0.27, 2.7, 27, 270\text{year}^{-1}$) to produce the asymptotic adult worm burdens (10,100,1000,10000 respectively) as shown.

The relationship is shown for a range of mean adult burdens, generated by varying the encounter rate ($\varphi$). For a given encounter rate, $k_M$ at first increases with $k_C$ and then saturates as the input distribution approaches a Poisson distribution ($k_C \to \infty$); the finite asymptotic value of $k_M$ reflects the extra-Poisson variability introduced by the random encounter rate, $\varphi$. Comparing the curves for different encounter rates (and hence mean adult burdens) indicates a decrease in aggregation as levels of parasitism increase. This occurs because the asymptotic variance/mean ratios for $L$ and $M$ are independent of the mean. Scaling down the mean burden therefore significantly increases the degree of aggregation. Further simulations of the full nonlinear system indicate that these variance/mean results also work almost exactly for $\alpha, \beta > 0$. Essentially, since the variance/mean ratio stays approximately constant, scaling down the mean burden, by immunity or other processes, also increases the degree of aggregation.

These effects are also apparent in the relationship between the age profiles

of mean worm burden and the degree of variability. In essence (Figure 2), the model predicts that larval and adult $k$ values essentially track their respective means; i.e., aggregation varies inversely with the mean. We discuss the realism of this relationship in the context of variations between hosts after considering the effects of immunity and parasite-induced host mortality on a homogeneous host population.

## 3.3 The impact of host immunity

Figures 4 and 5 superimpose increasing levels of immunological limitations on larval survival ($\beta = 0.02$ and 2 respectively) onto the basic picture of Figure 2. As expected from previous empirical and theoretical work (Anderson and May 1985a, 1991), immunological limitations on establishment cause the mean parasite burden (Figures 4a, 5a) to decline with age, after an initial peak. For relatively small immunological effects (Figure 4), other features of the simulation are similar to the zero immunity case. However, for higher levels of immunity, the correlation of $I$ with parasite burden (Figure 5c) quickly becomes *negative* with age. The explanation for this change is as follows. For $\beta = 0$, the system is linear, and heterogeneity in $I$ depends on $L$, generating a positive covariance, $\sigma_{IL}$. By contrast, for larger $\beta$, $I$ feeds back to reduce the level of $L$ (via larval mortality), generating a negative covariance.

As described above, this picture is generated by assuming that immunity accumulates with new infections. We have also explored a model assuming concomitant immunity (Anderson and May 1991, Lloyd this volume) – i.e., $I$ and hence the immunity level against new infections increases with adult burden. This generates qualitatively similar patterns to Figures 4 and 5, though oscillations in worm burden are possible for appropriate parameter values (Anderson and May 1985a). The stage-specificity of immunity is likely to be particularly important in the context of host-parasite dynamics; these issues will be explored in more detail elsewhere.

## 3.4 Parasite-induced host mortality

Figure 6 shows the effect of parasite-induced host mortality on the basic linear model of Figure 2. We examine the impact of mortality at two transmission levels: relatively 'low' transmission ($\varphi = 3.65\text{year}^{-1}$) and a 'high' transmission rate ($\varphi = 365\text{year}^{-1}$, the same as for Figure 2). Parasite–induced host mortality has relatively little effect on mean adult burdens (Figure 6a), reducing them by a few percent. On the other hand, the effect on host survivorship (Figure 6d), and in consequence on the total adult parasite burden in the host population (Figure 6b), is significant. In general, increasing the degree of parasite aggregation should increase the mortality due to parasitism, by increasing the proportion of individuals with large burdens (Anderson and

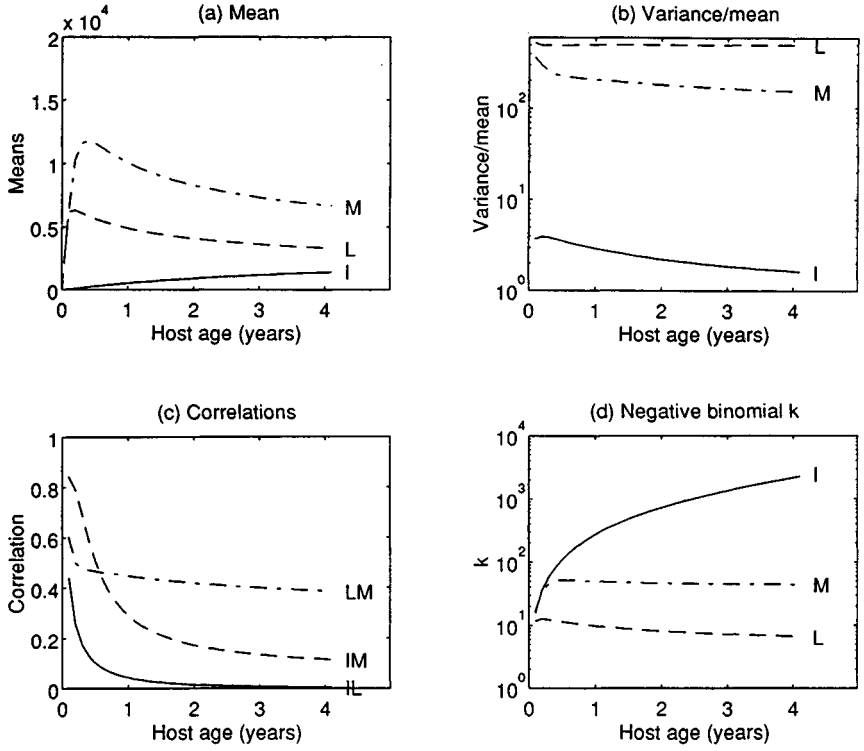



Figure 4. The effect of a low level of immunity ($\beta = 0.02$ larvae$^{-1}$ year$^{-1}$) on the results of Figure 2.

Gordon 1982, Pacala and Dobson 1988). In the present case, the impact on host survivorship is much greater at the higher infection rate, even though parasite burdens are much less aggregated than at the lower infection pressure (as shown by the age profiles of $k_M$ in Figure 6c). Here, the high infection rate swamps any distributional effect, causing high host (and therefore parasite) mortality.

Overall, Figure 6 reflects standard theoretical predictions about the impact of parasite-induced host mortality (Anderson and Gordon 1982), although, in this essentially homogeneous host population, such mortality cannot generate a peak in mean parasite burden with age (see next section). The present approach also gives an explicit idea (expressed in Figure 6c) of how parasite aggregation varies with host age; the parasite negative binomial parameter essentially tracks the mean level of parasitism. The effects on these results of allowing hosts to differ in their response to parasitism are discussed below.

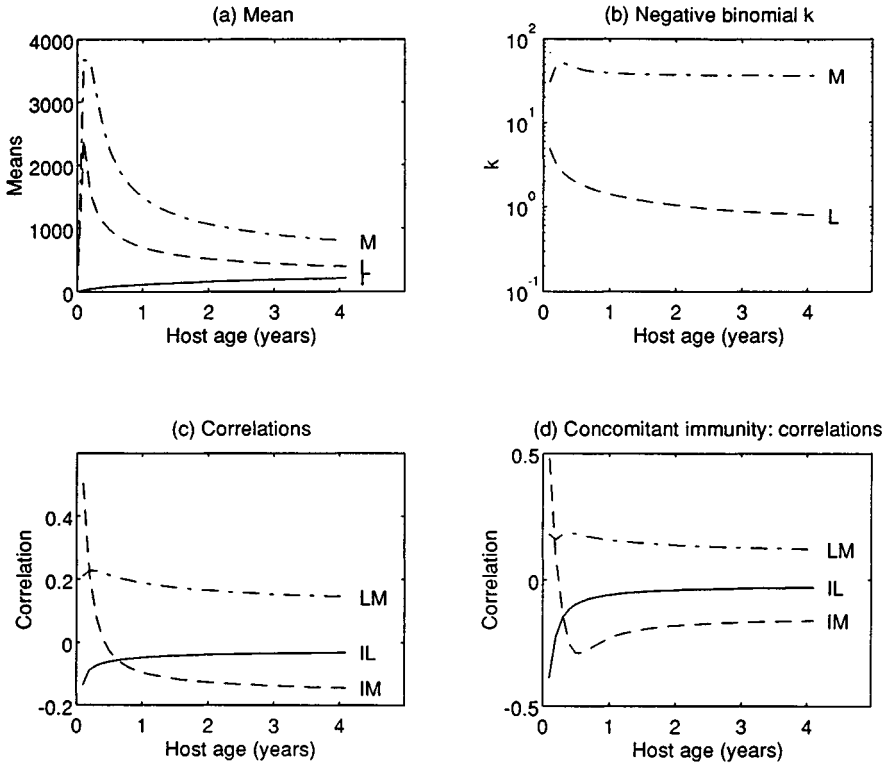



Figure 5(a)-(c); the effect on the results of Figure 4 of increasing the level of immunity ($\beta = 2$ larvae$^{-1}$ year$^{-1}$). Figure 5(d): correlations as in (c), but assuming concomitant immunity (i.e., immunity to new infections accumulates with adult rather than larval burden: details of this model will be given in a subsequent paper).

## 3.5 The impact of between-host heterogeneity

Environmentally- or genetically-determined heterogeneities in host responses to parasitism are known to be of considerable importance to the epidemiology of human and animal parasites (Anderson and Medley 1985, Pacala and Dobson 1988, Anderson and May, 1991). For example, in the context of the present work, Anderson and Gordon (1982) used Monte Carlo simulations to show that differences between hosts in the ability to survive parasitism can generate a peaked age profile for mean worm burden. They also show that the decline in mean burden at older ages is accompanied by an *increase* in $k$, as hosts in the upper tail of the parasite distribution are differentially killed.

Similar patterns can also potentially be generated by host immunity (Pacala and Dobson 1988). We illustrate this in the context of the present model by

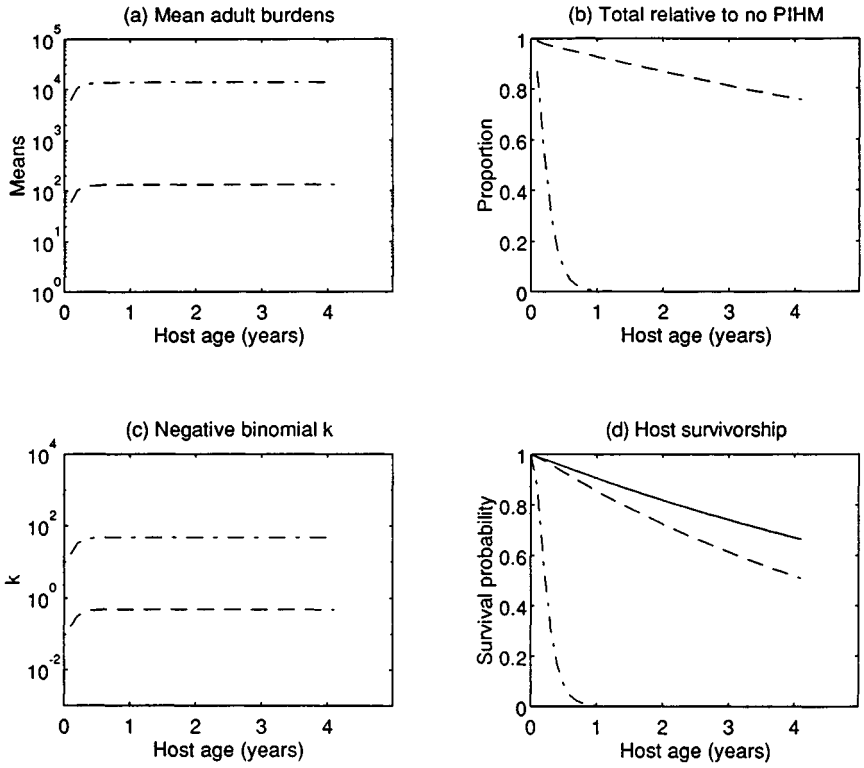



Figure 6. The impact of parasite-induced host mortality ($\alpha = 0.001$ parasites$^{-1}$ year$^{-1}$, $\beta = 0$) at low and high infection levels ($\varphi = 3.65$ year$^{-1}$: dashed lines; $\varphi = 365$ year$^{-1}$: dash dotted lines respectively). (a),(c) Means and $k$ as previously; (b) total worm burdens, (d) host survivorship — the solid line is the survival curve in the absence of parasitism.

assuming that the host population is divided equally into individuals with low and high levels of immunity (corresponding to the low and high levels of $\beta$ used in Figures 4 and 5 respectively). The resulting simulation is illustrated in Figure 7, which shows age profiles for the mean (Figure 7a) and $k$ (Figure 7b) for the adult parasite distributions of the two sub-populations, as well as the corresponding average mean and $k$ age profiles for the total population (Figures 7c and d respectively).

This simple heterogeneity has a marked effect on the age-distribution of parasite aggregation. For the individual sub-populations, $k$ tracks the unimodal profile of the respective means (see Figures 7a,b). By contrast, the total population shows a unimodal mean parasite load with age (Figure 7c), whereas the overall $k$ increases monotonically. These patterns reflect the progressive 'homogenisation' of the host population, as the overall proportion

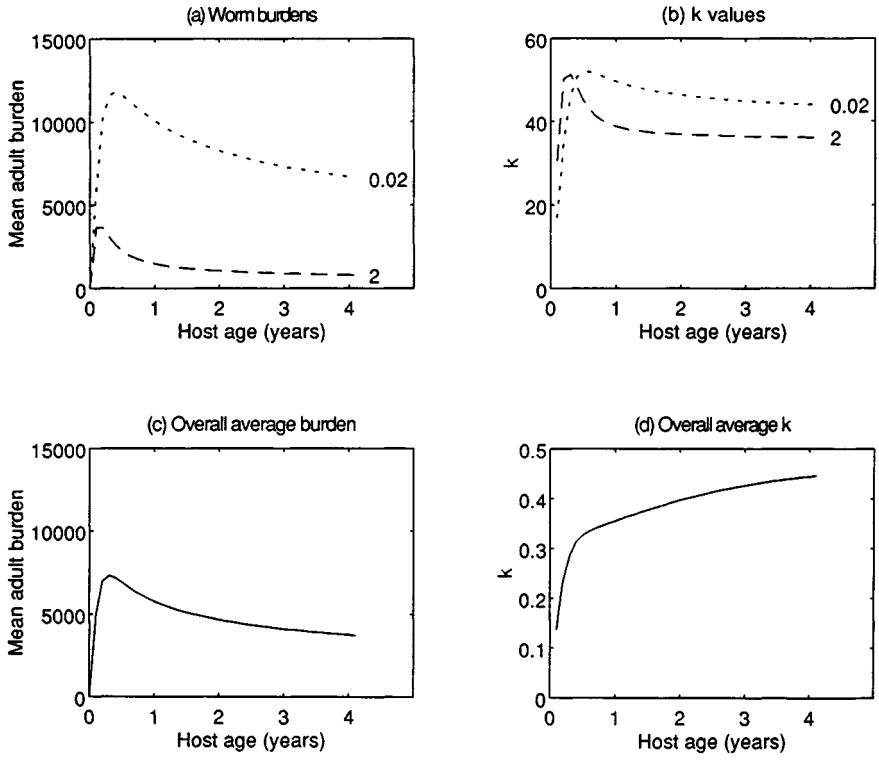



Figure 7. The effect of simple heterogenities in host immunocompetence, as described in the main text. The population is divided into two equal groups, with low ($\beta = 0.02$ larvae$^{-1}$ year$^{-1}$) and high ($\beta = 2$ larvae$^{-1}$ year$^{-1}$) immunity (other parameters are as in Figure 2). (a),(b) mean and adult parasite $k$ for the two sub-populations; (c),(d) population averages of mean and $k$.

of parasites in less immune hosts increases. Similar effects can be induced by parasite-induced host mortality and these patterns are not qualitatively affected by more complex choices of the distribution of heterogeneity between hosts.

A recent extensive analysis of published data (Dobson and Shaw, in preparation) indicates that age distributions of parasite aggregation show a variety of patterns. Depending on the system examined, the observed age distribution of $k$ may track the mean burden (Halvorsen and Andersen 1984, Pacala and Dobson 1988), or increase with age as the mean plateaus or declines. Previous theoretical work has laid the basis for understanding these patterns (Anderson and Gordon 1982, Pacala and Dobson 1988). The main focus here has been on the interaction of host heterogeneity and the stochasticity of infection with nonlinear effects, such as host immunity and parasite-induced host mor-

tality. The present model is a preliminary attempt to provide a framework for modelling these interactions explicitly, without the use of Monte Carlo simulations.

# 4 Conclusions

Two recurring themes in this volume are the potential complexity in the dynamics of infectious diseases in natural populations and, in many instances, the lack of empirical information available to clarify these processes. These problems are especially acute in terms of the ecological role of host immunity (Lloyd this volume). We have therefore framed our review around a new immuno-epidemiological formulation. This now allows us to focus on what further theoretical and empirical work required to clarify these questions. They fall under three broad headings.

## 4.1 Determinants of aggregation

Our model indicates the general point that the variability in parasite burdens induced by stochasticity in infection of a homogeneous host population will tend to decline with infection level (and hence worm burden). In these cases, a Poisson infection rate will lead to a Poisson distribution for adult worms (Anderson and Gordon 1982). Here, we also examine the impact on the variance of larval and adult worm burdens of extra-Poisson variability in the infection rate. The principal result is that this extra variation in the infection process is transferred less to the adult worms as infection levels increase. More specifically, these results also indicate that models based on a homogeneous host population cannot account for the observed level of aggregation in trichostrongylid nematode-ruminant interactions. Observed parasite aggregation in these systems ($k \approx 1$; see Grenfell *et al.* (1987b)) is much greater than that predicted by our model, which sugg• sts $k \gg 1$ at the high worm burdens observed for trichostrongylids. This emphasizes the need to consider heterogeneities in host response (Anderson and May 1991), which also appear to be required to explain the decrease in parasite aggregation with host age sometimes observed in host macroparasite system (Pacala and Dobson 1988). By contrast our homogeneous host model predicts that the negative binomial $k$ for adult parasites should 'track' the mean burden. However, inclusion of simple host population heterogeneities (such as in immunocompetence) allows inverse relationships between the mean burden and $k$ to develop. The development of analytical models of the balance between infection and host heterogeneity in determining parasite variability is a fruitful direction for future research (Isham, in preparation).

## 4.2 Immuno-epidemiological patterns

The main thrust of previous work in this areas has been to establish the age profile of average levels of immunity and worm burdens. Here, we examine the higher moments of the underlying distribution and, in particular, the correlation between previous experience of infection (as a measure of potential immunity) and larval and adult burdens. The results reveal an intricate picture, with positive correlations between larval burdens and immunity at low levels of immuno-competence, giving way to negative associations at high levels of immunity. This is a prediction that could be tested in experimental infections or the field as the appropriate molecular technology develops. However, we suspect that variation between hosts in immuno-competence is likely to be a better area for matching theory and observation (Behnke and Wahid 1991).

## 4.3 Modelling the temporal dynamics of macroparasites in wildlife host populations

As discussed above, this is a formidable problem. Host and immunological dynamics could, in principle be added to existing stochastic simulations (Anderson and Gordon 1982, Anderson and Medley 1985). However, producing more analytically tractable models, which trace the dynamics of parasite distribution through age and time, will generate an even more complex set of equations and interactions that the relatively simple equilibrium analysis presented here. Another major problem is that we also ideally need to track the prevalence of infection as well as the mean and other moments. Preliminary work in the area shows promise (Isham, in preparation), though analytical approximations are likely to founder for relatively small parasite populations (Anderson and Gordon 1982).

As ever, however, the crucial need is for well designed (and preferably long term) field immuno-epidemiological, studies in order to focus new theoretical developments. Finally, though we have concentrated here on helminth infections, much also needs to be done in clarifying how the interaction between acquired immunity, host genetics and environmental influences the dynamics of host-microparasite interactions (Lloyd this volume).

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# Appendix

The biological assumptions set out in the main text imply the following system of equations:

$$\begin{aligned}\frac{dn_{i,l,m}}{da} = & \\ -[\mu_H(a) + \alpha m + \mu_I i + \varphi(a)(1-p_0) + \nu l + \mu_L l + \beta i l + \gamma_L l + \mu_M m]\, n_{i,l,m} & \\ +\varphi(a)\sum_{c=1}^{l} n_{i,l-c,m} p_c + \nu l n_{i-1,l,m} + \mu_I(i+1)n_{i+1,l,m} + \mu_L(l+1)n_{i,l+1,m} & \\ +\beta i(l+1)n_{i,l+1,m} + \gamma_L(l+1)n_{i,l+1,m-1} + \mu_M(m+1)n_{i,l,m+1}\,. & \end{aligned} \tag{A1}$$

Denoting the probability generating function with respect to $I$, $L$ and $M$ by

$$P(a,x,y,z) = \sum_{i=0}^{\infty}\sum_{l=0}^{\infty}\sum_{m=0}^{\infty} n_{i,l,m}(a) x^i y^l z^m \tag{A2}$$

one can derive the following partial differential equation:

$$\begin{aligned}\tfrac{\partial P}{\partial a} \quad & +\mu_I(x-1)\frac{\partial P}{\partial x} + [\nu(1-x)y + \mu_L(y-1) + \gamma_L(y-z)]\frac{\partial P}{\partial y} \\ & + [(\alpha+\mu_M)z - \mu_M]\frac{\partial P}{\partial z} + \beta x(y-1)\frac{\partial^2 P}{\partial x \partial y} \\ & = \varphi(a)[h(y)-1]P - \mu_H(a)P. \end{aligned} \tag{A3}$$

The host survivor function $S(a) = P(a,1,1,1)$ (measuring the probability of survival of hosts as a function of age) is given by the following differential equation:

$$\frac{dS}{da} = -[\mu_H(a) + \alpha m_M(a)]S \tag{A4}$$

where $m_M(a)$ is the mean number of mature parasites per host conditioned on survival up to age $a$. Let $Q(a,x,y,z) = P(a,x,y,z)/S(a)$; then

$$\begin{aligned}\tfrac{\partial Q}{\partial a} \quad & +\mu_I(x-1)\frac{\partial Q}{\partial x} + [\nu(1-x)y + \mu_L(y-1) + \gamma_L(y-z)]\frac{\partial Q}{\partial y} \\ & + [(\alpha+\mu_M)z - \mu_M]\frac{\partial Q}{\partial z} + \beta x(y-1)\frac{\partial^2 Q}{\partial x \partial y} \\ & = \varphi(a)[h(y)-1]Q + \alpha m_M Q. \end{aligned} \tag{A5}$$

For this equation, one can derive a system of equations for the moments of the variables $I$, $L$ and $M$ by calculating partial derivatives and setting $x = y = z = 1$ appropriately. For example, the dynamics of the mean level of immunity with age is given by

$$\frac{dm_I}{da} = \nu m_L - \alpha \sigma_{IM} - \mu_I m_I \tag{A6}$$

where we use the following notation

$$E(I) = m_I;\ E(M) = m_M;\ \mathrm{cov}(I, M) = E(IM) - m_I \cdot m_M = \sigma_{IM} \quad \text{(A7)}$$

Variance terms are calculated in an equivalent manner, e.g.

$$\mathrm{var}(I) = E(I^2) - m_I^2 = \sigma_I^2, \quad \text{(A8)}$$

and we note that all such moments are functions of host age, $a$. Similar notation is used for the other variables, leading to the following system of equations for the means, variances and covariances of $I$, $L$ and $M$:

$$\begin{aligned}
\frac{dm_I}{da} &= \nu m_l - \alpha\sigma_{IM} - \mu_I m_I;\\
\frac{dm_L}{da} &= \varphi(a)m_C - \alpha\sigma_{LM} - \beta\sigma_{IL} - (\mu_L + \gamma_L + \beta m_I)m_L;\\
\frac{dm_M}{da} &= \gamma_L m_L - \alpha\sigma_M^2 - \mu_M m_M;\\
\frac{d\sigma_I^2}{da} &= \nu m_L + \mu_I m_I + 2\nu\sigma_{IL} - 2\mu_I\sigma_I^2 + \alpha[2m_I\sigma_{IM} - \mathrm{cov}(I^2, M)];\\
\frac{d\sigma_L^2}{da} &= \varphi(a)(\sigma_C^2 + m_C^2) + (\mu_L + \gamma_L + \beta m_I)m_L - \beta(2m_L - 1)\sigma_{IL}\\
&\quad -2(\mu_L + \gamma_L + \beta m_I)\sigma_L^2 - \alpha[m_M\sigma_L^2 + m_L\sigma_{LM} - \mathrm{cov}(LM, L)]\\
&\quad +2\beta[m_I\sigma_L^2 + m_L\sigma_{IL} - \mathrm{cov}(IL, L)];\\
\frac{d\sigma_M^2}{da} &= \gamma_L m_L + \mu_M m_M + 2\gamma_L\sigma_{LM} - 2\mu_M\sigma_M^2 + \alpha[3m_M\sigma_M^2\\
&\quad +m_M^3 - E(m_M^3)];\\
\frac{d\sigma_{IL}}{da} &= \nu\sigma_L^2 - \beta m_L\sigma_I^2 - (\mu_I + \mu_L + \gamma_L + \beta m_I)\sigma_{IL}\\
&\quad +\alpha[\sigma_{IL}m_M + \sigma_{LM}m_I + \sigma_{LM}m_L + m_I m_L m_M - E(ILM)]\\
&\quad \beta[m_I\sigma_{IL} + m_L\sigma_I^2 - \mathrm{cov}(I, IL)];\\
\frac{d\sigma_{IM}}{da} &= \nu\sigma_{LM} + \gamma_L\sigma_{IL} - (\mu_I + \mu_M)\sigma_{IM}\\
&\quad +\alpha[m_I\sigma_M^2 + 2m_M\sigma_{IM} + m_M^2 m_I - E(IM^2)];\\
\frac{d\sigma_{LM}}{da} &= \gamma_L(\sigma_L^2 - m_L) - \beta m_L\sigma_{IM} - (\mu_L + \gamma_L + \beta m_I + \mu_M)\sigma_{LM}\\
&\quad +\alpha[m_L\sigma_M^2 + 2m_M\sigma_{LM} + m_L m_M^2 - E(LM^2)]\\
&\quad +\beta[m_M\sigma_{IL} + m_L\sigma_{IM} + m_I\sigma_{LM} + m_I m_L m_M - E(ILM)]. \quad \text{(A9)}
\end{aligned}$$

Assuming a normal approximation for the third and higher moments (Whittle 1957, Isham 1991), the terms in square brackets in equation (8) are zero, leading to the basic model: equation (7) in the main text.

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# Spatial Dynamics of Parasitism

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## 1 Introduction

We consider the establishment, spread and persistence of parasitic infections in wildlife populations. In all of these, the spatial structure of the populations and their dynamics play a crucial part.

The contact structure of infections in wildlife populations is usually spatially very localised. This small scale process, where the potential interactions of an individual are often restricted to a very small number of neighbours, affects all stages of the large scale disease dynamics that we observe. We therefore need careful modelling of space, whether we are interested in the transient phenomena of establishment and spread or in steady-state phenomena such as persistence, coexistence and patterns of abundance; and whether our aim is prediction, control, or simply understanding.

We review the present state of mathematical models appropriate for parasitic diseases of wildlife, emphasizing the importance of simple models incorporating key aspects of the process in an *identifiable* way. Some of the issues we raise are discussed further in the group report on spatial models (Bolker *et al.* this volume); see also the papers by Cliff, Metz and van den Bosch, and Durrett in Mollison (1995), and, for a review from a somewhat different standpoint, Kareiva (1990).

Challenges to our present understanding include (1) The dependence of thresholds and velocities on population density, and on the spatial distribution of the contacts of an individual, and (2) Endemic patterns and related problems, such as the critical community size required to sustain a disease and its dependence on temporal and spatial scales, and the effectiveness (or otherwise) of barriers or control zones. Endemic patterns, especially, seem to require models with discrete individuals (stochastic *or* deterministic) rather than continuous populations as in traditional differential equation models.

We discuss these problems and what further kinds of information are needed to resolve them. Available data can in many cases support the development of models giving qualitative understanding, but are usually insufficient for reliable prediction. In view of the inevitable 'softness' of much data on wildlife populations, there should be more emphasis on predictions susceptible to falsification from data, than on the all-too-easy business of 'fitting' models to data.

## 1.1 Establishment and spread

If a disease is to become established in a population, conditions must be such that an initial focus of infection can grow; in a mathematical model this may be expressed in terms of a 'threshold theorem', typically requiring the *reproductive ratio* of the disease, $R_0$, which represents the mean number of potential infections per infectious individual, to be above a certain critical value. In the simple case of a homogeneously mixing population, classic theorems (e.g. Kermack and McKendrick 1927, Whittle 1955) show that the threshold value of $R_0$ is 1; but for local spatial mixing it can be significantly higher (see Section 3).

Once the disease has becomes established in the population, if infection is a sufficiently local process the epizootic can be expected to spread in a fairly steady manner with a characteristic velocity (see Section 4), provided that the environment is spatially reasonably homogeneous – major variations in the environment or in population density will naturally have an effect on spread.

Calculating the velocity of spread is, within certain limitations, a straightforward matter: it depends only on the mean number of infections made by an individual, and on the distribution of an individual infectious contact in time and space; and not (for instance) on the form of density-dependence, or on the interdependence between different contacts. [See §4.1 – and for the limitations §4.2.]

## 1.2 Persistence

For a disease to persist in a population in the long term, it is not enough that it should be above the epidemic threshold for establishment. There is a further 'persistence threshold' condition, that the population should keep on producing enough susceptibles to sustain the disease. This condition is often framed in terms of the 'critical community size' required for disease persistence, though features other than sheer numbers, particularly the spatial distribution of the population, may also be important.

Patterns of persistence – assuming the disease does persist – may be considerably more complex than patterns of spread. Because of disease dynamics, the set of infected will typically show strong 'clumping', and it will not always be easy to distinguish this from clumping due to environmental heterogeneity. Both spatial and temporal scales of enzootic disease, and their relation to the scales of the infectious process and of population regrowth, are crucial for an understanding of disease persistence.

It is therefore especially important to consider the individual and local character of the infection process when trying to understand patterns of persistence (see Section 6). This leads to emphasis on discrete, usually stochastic

models. Models which treat populations as continuous, and by implication divisible into infinitesimal sub-units, may be useful for certain aspects, especially for analysing velocities of spread (see Section 4), but even then need to be treated with caution.

More generally, if we are to get anything reliable out of a model we need to choose it very carefully; this is the topic of our next section.

## 1.3 Model choice

Widely spatially distributed populations vary from those of territorial animals, among whom interactions may be only with a very limited number of neighbours, to populations which form large groups or, through mobility either of the host or parasite, make contacts over considerable distances. Given the complexity of the host-parasite relation, it is not surprising that most attempts at modelling have begun with 'mean-field' models in which spatial structure is ignored; nor that when spatial structure is incorporated, we often find qualitatively different population dynamics.

While spatial structure is thus crucial, the complexities of the biological relationships make it important to incorporate spatial interaction in our models in as simple a manner as possible, relying on the 'principle of universality' to imply that they should hold for more detailed models, provided that proper care is taken in interpreting time and space scales.

The simplest models for a spatially distributed population of discrete individuals are lattice (or grid) models. In these space is represented by a regular array of sites, with one individual or population sub-group based at each. We need parameters to describe the life-histories of individuals, such as the mean of a natural life-span $L$ and the net population growth rate $r$; and parameters for the disease: its mean generation gap ($\tau$) and mean reproductive ratio $R_0$, and the spatial distribution of an infectious individual's contacts.

Most research effort has been devoted to the basic case where infectious contacts are chosen at random from among an individual's nearest neighbours. There has been some work on the effect of larger neighbourhoods and of long distance contacts on model behaviour (Bramson *et al.* 1989, Mollison 1972), see Section 4).

The earliest attempts to go beyond 'mean-field' models for spatial modelling in ecology and epidemiology were the classic papers of Kolmogoroff *et al.* (1937), Fisher (1937), and Skellam (1951) using reaction-diffusion equations; for a recent review see Holmes *et al.* (1994).

Although relatively tractable, these classic models have a number of drawbacks, including restrictive implicit assumptions about the distribution of the infectious period. The more general *reproduction and dispersal kernel* method of Diekmann (1978) and van den Bosch *et al.* (1990) is also more natural, in

that it is formulated directly in terms of the distribution of an individual's contacts in time and space, giving a suitable framework for analysing the dependence of the velocity of spread on that distribution (Mollison (1991), see Section 4).

However, the kernel method does not avoid a major problem of differential equation models for populations, namely that they treat the population as continuous, rather than composed of individuals; this can lead to grossly unrealistic results where the establishment and persistence of the endemic state are concerned (see Section 6).

Models based on discrete individuals have advantages of clarity as well as realism. Stochastic discrete models have thus often been used, explicitly or implicitly, at the model formulation stage, though they have usually then quickly been dropped in favour of an approximating continuous model. [For a discussion of the different ways in which Fisher (1937) and Kolmogoroff *et al.* (1937) derived the same reaction-diffusion equation see §1.1 of Mollison (1977).]

In recent years, however, study of the more realistic discrete models, both stochastic and deterministic, has received more attention (Mollison 1977, Cox and Durrett 1988, Durrett and Levin 1994a, Fisch *et al.* 1991, Rand *et al.* 1995). This is not only through appreciation of the shortcomings of continuous models noted above, but also because of the improved methodology for the study of discrete models, including simulation techniques for the more powerful computers that have become available and new approaches to the analysis of stochastic processes (see, e.g., Durrett 1988, Durrett and Levin 1994a, Ball 1995).

# 2 Consequences of clumping

It is one thing to recognize that mean-field models miss relevant detail; it is quite another to determine how much detail is relevant to understand observed phenomena. The strength of modelling is that increasing levels of detail can be studied by proceeding through a hierarchy of abstractions, from mean-field to individualistic, thereby exposing which aspects of detail affect which features of system dynamics.

Clumping can be modelled by explicit spatial representation, or simply by characterizing the spatial distribution through a few macroscopic parameters. A case in point involves the Nicholson-Bailey host-parasitoid equations, mean-field descriptions whose solutions undergo undamped oscillations (Nicholson and Bailey 1935, Nisbet and Gurney 1982). But the mean-field approach is not appropriate to the biology, and incorporation of a clumping parameter that represents the fact that parasitoids are aggregated on hosts stabilizes the interaction (Hassell *et al.* 1991). Is such a model better or worse than a more

detailed model that accounts as well for the dynamics of clumping, rather than taking clumping as a given, with fixed parameters? The answer depends on the purpose. The strength of the above approach is that it demonstrates the key feature in more complicated models that accounts for stabilization – the fact that parasitoids are not uniformly distributed over their hosts. This simple and essential fact would be lost in the detail of a more complicated model, which might however elucidate other features of system dynamics (see, e.g., Hassell *et al.* 1991).

The introduction of clumping parameters into mean-field models makes a number of assumptions. Not only does it ignore dynamics; it also assumes that the degree of clumping is homogeneous in space. This feature can be relaxed in several ways: spatial gradients can be treated explicitly, through the assumption that parameters change in some regular way.

In such an approach, simply allowing the parameters of the clumping distribution to vary in space might introduce the appropriate complexity. In other cases, inter-site variation may show no secular trend, but may be thought of as the result of sampling from some distribution. In this case, one has the option of constructing models that imitate that sampling, or models that explicitly reproduce particular landscapes. Once again, which best serves the goal of the modelling exercise will depend on the context and the purposes of the investigation. Cases in point involve the modelling of myxoma in Australia, in which interregional variation reflects different climatic conditions (Fenner and Myers 1978, Dwyer *et al.* 1990); of measles worldwide, in which different communities of different population sizes will support different disease dynamics (Olsen and Schaffer 1990); and fox rabies, in which explicit spatial variation can be introduced in various different ways (Bacon 1985, Murray *et al.* 1986, van den Bosch *et al.* 1990, Mollison 1991; see also Bolker *et al.* (this volume)).

The problem of nonhomogeneous mixing, as represented in situations described above, is one of the central problems in the theory of infectious diseases, and the key issue introduced above – should clumping (grouping) be introduced phenomenonologically or emerge from detailed individual-based models – is the subject of continual debate and catalyzes much productive research. The issues raised here fit into that general context.

# 3 Thresholds for disease outbreaks

A fundamental feature of disease dynamics is the existence of thresholds, of population or ecosystem conditions, below which epidemic outbreaks will not occur. The corresponding fundamental feature of models of disease dynamics is the existence of a key parameter, $R_0$, defined as the potential number of secondary infections per infectious individual, which must exceed a given

threshold value if the initial population of infectives is to show sustained growth, thus starting an epidemic. Therefore, computation of $R_0$ is one of the most important, if not the most important, activities for theoretical investigation. In the simplest mean-field models, this is straightforward, almost trivial; but in models of nonhomogeneous mixing, the calculation of $R_0$ represents a substantial challenge.

In mean-field models, the typical criterion for establishment to be possible is that $R_0 > 1$, and establishment is characterized by exponential growth in the number infected (at a rate depending on $R_0$ and $\tau$).

For spatial models, $R_0$ has to be greater than a critical value $R_c$ which is significantly greater than 1, because there is now a non-negligible chance of 'wasted' infections, where a potential contact has already been infected. The exact value of $R_c$ appears to depend mainly on the number with whom an individual interacts. Where this is small, $R_c$ can be appreciably greater than unity: for example, in the epidemic with removal (SIR model) with nearest-neighbour contacts on the square lattice $R_c$ is $> 2$ (Kuulasmaa (1982): $> 4$ if you count repeated attempts to contact the same neighbour in the calculation of $R_0$ – see Mollison (1991), §1.5). On the other hand, Bramson *et al.* (1989) showed that for similar models, $R_c$ tends to unity as the radius over which contacts are spread increases.

For most diseases, $R_0$ can only be estimated indirectly from data, and usually the only quantitative conclusion we can draw is whether $R_0$ is greater than $R_c$. It may be possible to go beyond this when comparing data from populations with different parameter values, e.g. different population densities, but only if we make assumptions about the dependence of $R_0$ on the parameter concerned – and it may be more approprate to view the nature of that dependence as a question rather than an answer (Mollison 1984, de Jong *et al.* 1995). Understanding the dependence of $R_0$ on population parameters will be vital if we are to predict how it may change under various control measures: for instance, the effect of culling on $R_0$ requires ecological as much as mathematical insight (Mollison 1984). Inference about establishment in a new environment may be even more fraught with difficulties.

# 4 Dynamics of spread

A wide variety of populations, including infectious disease agents, have been observed to advance with a fairly steady characteristic velocity (Skellam 1951, Bacon 1985, Hengeveld 1989, Metz and van den Bosch 1995). The earliest model with such spatial dynamics to be studied was the KPP/Fisher reaction-diffusion equation for the advance of an advantageous gene (Fisher 1937, Kolmogoroff *et al.* 1937), which has proved to be just the first example of a wide class of deterministic, continuous population models, which all predict

spread at a steady velocity.

## 4.1 Calculation of velocities: the kernel method

The calculation of velocities is mathematically quite straightforward if we ignore density-dependence. For such 'linear' models, whether deterministic or stochastic, the velocity ($c$) depends only on the mean number of infectious contacts made by an individual ($R_0$), and on their position in space ($X$) and time ($T$) relative to the time at which the individual was itself infected. The joint distribution of $X$ and $T$ is called the *reproduction and dispersal* kernel (van den Bosch *et al.* 1990). The velocity can be calculated as the smallest positive value of $c$ for which $R_0\mathbf{E}[\exp(\theta X - \theta cT)] = 1$ has a solution (van den Bosch *et al.* 1990, Mollison 1991).

Further, and crucially, for a wide class of models the velocity is not affected by the introduction of density-dependence. Van den Bosch *et al.* (1990) call this the 'linear conjecture', and explain why it may be expected to hold widely.

The immediate consequence of this is to simplify greatly the calculation of velocities, and to explain why families of theoretically distinct models should have the same velocity; for instance, the velocity found by Goldwasser *et al.* (1994) for a mixed population of 'slow' and 'fast' dispersers is actually the same as if each individual had a corresponding mixture of 'slow' and 'fast' contacts.

The much simpler calculation of velocities also has the great practical advantages of (1) clarifying that many population parameters do not affect the velocity, and (2) allowing consideration of the dependence of the velocity on the remaining parameters.

The velocity of spread can be written as $c_0 d/\tau$, where $d$ and $\tau$ are characteristic space and time scales of the process (respectively the standard deviation of the dispersal distance $X$, and the mean of the generation gap $T$. The dimensionless velocity $c_0$ depends on $R_0$ – spread is only possible if $R_0 > 1$ – and on the shape of the reproduction and dispersal distributions. Broadly speaking, the velocity is more sensitive to the effect of long distance contacts if $T$ is nearly constant, and more sensitive to the value of $R_0$ if $T$ is variable (for more details, see Mollison (1991)).

## 4.2 Limitations of the kernel method

While it is exact for linear models, and for many nonlinear deterministic models, the kernel method is only an approximation for more realistic individual-based models. However, simulations, and results for simpler models, have long suggested that similar qualitative behaviour applies to individual-based

models, provided that the dispersal distribution is sufficiently local in character. A recent breakthrough in theory was the proof by Cox and Durrett (1988) of such regularity of spread for the basic SIR epidemic, where contacts in a homogeneous (2-D) environment are with nearest neighbours only. This process, whenever it does become established, spreads out in a ring at a steady velocity. Values of its velocity for varying $R_0$ have been estimated from simulations (Mollison 1991), and turn out to be at most about half those of the corresponding continuous-population model, as found by the kernel method.

Nevertheless, the qualitative behaviour – spread at a steady velocity – is the same as that of the deterministic, continuous models for which the kernel method works. Also, the contrast between discrete and continuous models in this example is rather extreme, with individuals interacting only with their four nearest neighbours; better quantitative agreement may be expected for a wide range of realistic parameters.

However, there is a greater, qualitative divergence between continuous and individual-based models when long range dispersal is important. If the probability of dispersal falls off with distance more slowly than exponentially, continuous population models predict infinite velocity, whereas such limited results as are available suggest that individual-based models have bounded velocity, but may advance in a mixture of steady progress and irregular 'great leaps forward' (Mollison 1972); see Figure 1.

A simple form of individual-based model, which may be appropriate to cases where very long range dispersals are common, and data imprecise, combines local spread with a small mean-field contribution, of contacts distributed uniformly over the whole population (such contacts will be important even if their probability *per capita* is only of order $1/N$, where $N$ is the total population).

## 4.3 Estimation of velocities from data

Van den Bosch *et al.* (1990) and Mollison (1991, §4) use the kernel framework to discuss various attempts in the literature to fit continuous population models to data. Because the relevant parameters, especially the r.m.s. dispersal distance $d$, can seldom be estimated with any precision, it is generally difficult to come to clear conclusions. There will also often be appreciable effects of environmental heterogeneity, important at least on a local scale, as revealed in Ball's (1983) analysis of the dependence of the rate of spread of rabies on habitat type (Figure 2).

Further, it is not clear what scientific purpose is served by simply fitting a model; more may be learnt in cases where a model can be *falsified* (as in Skellam's (1951) example of the return of oaks to Britain after the last Ice Age – see §4.4 of Mollison (1991)).

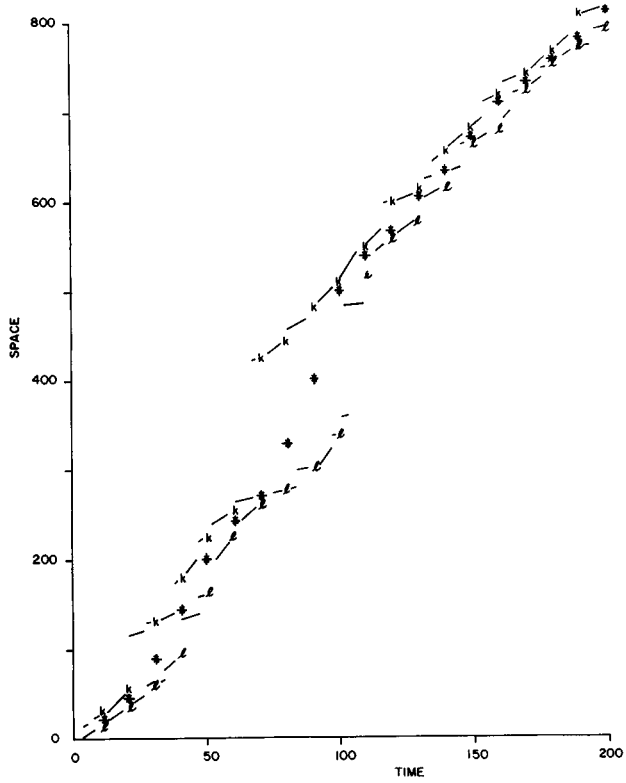


Figure 1: Spatial spread of an epidemic where the probability of dispersal to distance falls off more slowly than exponentially (here $\sim s^{-4}$). $-k-$ shows the position of the furthest forward infected, $-\ell-$ the position of the furthest back susceptible. *(From Mollison 1972)*

Although steady velocities are commonly observed in the spread of biological populations, they are by no means universal, as for instance in the case of the North Sea seal distemper outbreak of 1988 (see Bolker *et al.* this volume). As mentioned in the previous section, such cases of irregular advance, with 'great leaps forward' alternating or combined with more regular local spread, are hard to reconcile with continuous-population models, but are just what we would expect from individual-based models with sufficiently long-tailed dispersal distributions.

'Great leaps forward' are clearly also significant in human diseases such as influenza (Cliff *et al.* 1986), but the overall contact structure seems generally more complex than a straightforward spatial model can handle.

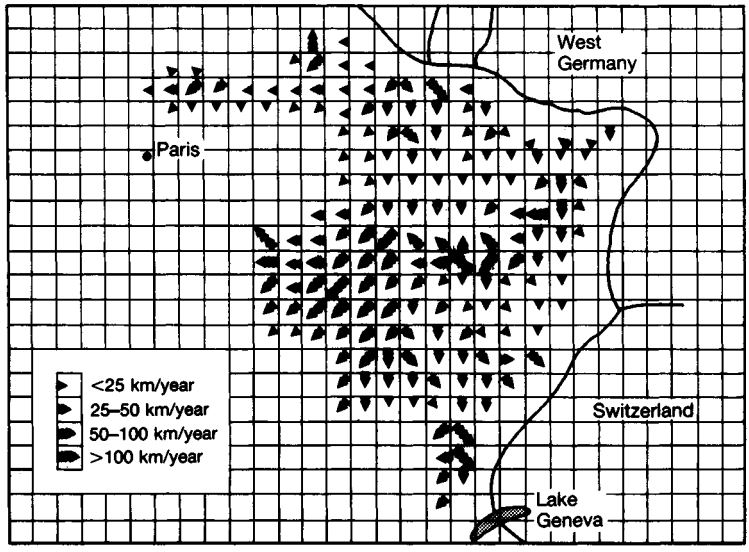


Figure 2: Estimated front-wave velocities for French fox rabies (grid squares are 20 × 20 km). *(From Ball (1985))*

# 5 Thresholds for persistence

That an infection can become established and spread within a population does not guarantee that it can persist, as is illustrated by classic studies of epidemics in Iceland and elsewhere by Cliff *et al.* (1981) (see also Cliff (1995)).

Bartlett (1957) introduced the concept of *critical community size*, i.e. the minimum population required for a disease to persist. However, as discussed in detail by Dye *et al.* (this volume), critical community size is not easy to evaluate theoretically, still less to measure in practice.

This notion of a critical community size is similar to that of a critical patch size for plankton dynamics (Kierstead and Slobodkin 1953). In each case, the idea is that a population too small cannot generate enough daughters to compensate for loss, whether loss through death or acquisition of immunity. In the case of plankton patches, once one ventures beyond the simplest models, the determination of thresholds becomes problematical. The situation is exacerbated in heterogeneous enviroments.

The critical community size will, in particular, depend on the difference between the time scales of demographic turnover and disease transmission; it may be increased – and become difficult to define – in the presence of cyclic or possibly more complex stochastic fluctuations; it may be decreased by spatial and age structures acting as buffers. To understand the role of spatial structure in determining critical community size we need to consider

patterns of persistence.

# 6 Patterns of persistence

A subject of considerable interest in ecology is that of how grouping can be understood in terms of the actions of individuals. Such considerations extend full force to understanding grouping within the context of epidemiological models.

Ecological groups range in size from pairs to millions of individuals, and models that describe grouping span a comparable spectrum (Levin 1995).

At one extreme, models of clumping are special cases of models of pattern formation, for which the classical approach is through reaction-diffusion equations. Through multiple stable states in nonconvex domains, differential diffusion in arbitrary domains, or other mechanisms, pattern can form autonomously in homogeneous environments. But such models are not truly individual-based, in that they deal with infinitesimals. Durrett and Levin (1994b) contrast and compare reaction-diffusion equations, mean-field models, metapopulation models, and interacting particle models, and show that each has unique dynamics. Obviously spatial pattern cannot emerge in mean-field models, but different patterns of clumping, including spatio-temporal ones, can result in each of the other three versions.

Continuous population models, such as reaction-diffusion equations, correct the fact that space is ignored in mean-field models, but do not treat individuals as individuals, and do not lend themselves easily to the introduction of local stochasticity. They may wrongly allow endemic patterns that rely on small fractions of individuals for their persistence (see §4.6 of Mollison (1991)), or disallow them because such fractions make for very local disequilibrium (as in the hawk-dove competition model of Durrett and Levin (1994b)). We name such impossible subdivisions of individuals 'atto-foxes', 'nano-hawks', *etc.*, where the prefix gives their order of magnitude (here $10^{-18}$, $10^{-9}$). The effectiveness of barriers in controlling spread is another problem area where realistic choice of population units is crucial (Mollison 1987).

Metapopulation models remedy both shortcomings, but do not consider the complex geometric relationships among individuals. For host-parasite systems, they may address the most critical features; for example, individual hosts may be treated as patches, aggregations of individuals that interact weakly with other aggregations. Introduction of this formalism allows explicit consideration of the evolution of reduced virulence, as in the *myxoma-Oryctolagus* system (Levin and Pimentel 1981, Dwyer *et al.* 1990).

The study of the dynamics of clumping itself is perhaps best done within the framework of interacting particle systems, which does not have to pre-

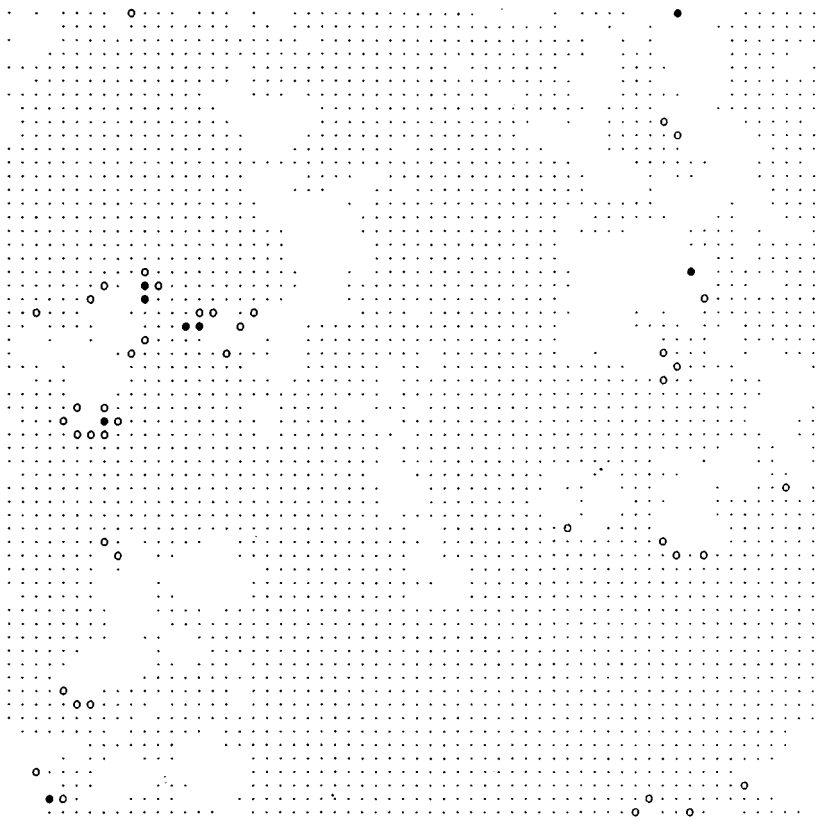

Figure 3: Endemic pattern from a spatial model for rabies with only nearest-neighbour interactions
• infectious site, o incubating site, · susceptible site, vacant. *(From Mollison and Kuulasmaa (1985))*

suppose an initial clustering into local demes. In the interacting particle approach, unlike the reaction-diffusion equation case, initially homogeneous distributions can be seen to evolve into patterns of clumping that can be traced back to individuals. Interacting particle models therefore represent an active area of research, with profound implications for the modelling of disease dynamics.

For models with discrete individuals, stochastic *or* deterministic models (cellular automata) show patterns of wandering patches. (For stochastic examples see Mollison and Kuulasmaa (1985), Durrett and Levin (1994a); for deterministic ones see Fisch *et al.* (1991), Hassell *et al.* (1991)). The deterministic models have the more beautiful patterns, such as spirals and 'persian carpets'; but quite such a level of coherence is implausible in ecology, though

Fisch *et al.* argue that stochastic models can display more large scale coherence than one would suspect from small-scale simulations. It is interesting to note that the spatial scale of patterns depends on both spatial and temporal scales of the process: even if spatial interactions are only between nearest neighbours, the difference between the time scales of population growth and infection can give rise to spatial patches on a large scale (Mollison and Kuulasmaa (1985), see Figure 3).

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# Group report: Spatial Dynamics of Infectious Diseases in Natural Populations

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# 1 Introduction

## 1.1 Overview

This chapter reviews some current issues in the construction and use of spatial models for disease in natural populations. Since many of the problems that arise in spatial modelling are highly system-dependent, and since the subject is so broad, we chose to approach the subject through specific examples. The chapter presents five brief case studies of modelling in disease systems where spatial processes are important; fox rabies, phocid distemper virus (PDV) in common seals, bovine tuberculosis in possums, a grouse-nematode system, and a plant-pathogen system (*Silene–Ustilago*). The case studies all tackle the central questions of *spatial scale* and *hierarchical models* in one way or another, but the methods used in each are as different as the questions they attempt to answer. The chapter concludes with some general conclusions drawn from the case studies, and an explicit agenda for future research in spatial models. Our hope is that this chapter, and the case studies in particular, will provide a portfolio of current methods in spatial modelling of wildlife disease, and suggest entry points into the literature and possible strategies for future modelling efforts. Detailed spatial modelling issues are also dealt with by Mollison and Levin (this volume), whilst non-spatial aspects of the case studies are addressed by Dye *et al.* (PDV, rabies) and Hudson and Dobson (grouse/*T. tenuis*).

## 1.2 Why use spatial models, and what are they?

Like all disease models, spatial models of disease in natural populations contribute either to understanding the processes generating observed disease patterns, or to effective control of the disease. 'Space' in this context usually means the way in which aggregation or heterogeneities in geographic distribution affect contacts between hosts and parasites or other hosts, but measures of effective distance can vary drastically among systems, for example among social animals where the effective epidemiological distance between animals in different groups could be much greater than their spatial separation. As there are so many potential definitions of space, the definition of a spatial model is necessarily wide-ranging and somewhat blurry; spatial models range from simple two-patch models to network models, reaction-diffusion equations, and interacting particle models (Mollison and Levin this volume). This workshop has concentrated on the applications of spatial models for understanding rather than control, but understanding is invaluable when the time comes to consider control strategies (Anderson and May 1984); most of the case studies presented below are actually fundamentally motivated by questions of disease control.

## 1.3 When are they necessary?

Spatial models are nearly always more complicated than their non-spatial analogues, so they should be used only where they offer new insight into systems sufficient to justify the costs; in addition, unnecessary spatial detail can obscure the important mechanisms of spatial processes (Mollison and Levin this volume). The broad categories where spatial disease models are useful can be divided into explicit spatial problems, for example analyzing the spatial spread of diseases or understanding observed patterns of aggregation in disease occurrence; and implicit spatial problems, for example understanding persistence or coexistence of disease strains in scattered populations (Dye *et al.* this volume), where the spatial localization of interactions may explain broad scale persistence or coexistence.

Explicit spatial problems are the classic field of application of spatial models. For such problems, there is no question that spatial models are necessary, and as a result there is a large body of literature covering various aspects, from early theoretical work on wavefronts and velocities of spread in continuous models to later work comparing these results, and similar results from models with discrete individuals, to data on spatial spread (Mollison 1991, Anderson *et al.* 1981, Andow *et al.* 1990b, Mollison and Kuulasmaa 1985, Cliff 1995, Metz and van den Bosch 1995, Hengeveld 1989). Many researchers have also studied the problems of spatial pattern formation, in both continuous and discrete formulations (Murray 1990, Hassell *et al.* 1991, Levin 1978).

Implicit spatial problems occur in systems where non-spatial models fail to capture an important characteristic of the disease process. Persistence of pests in otherwise untenable situations by transient persistence in a large number of patches (Huffaker 1958, Huffaker *et al.* 1963) is a famous example of an implicitly spatial problem. A related problem is where spatial aggregation of hosts leads to different levels of effective contact than would be expected assuming homogeneous distributions of hosts and parasites (see Section 4.3, Anderson and May (1978), Mollison and Kuulasmaa (1985)). There are many other possible applications, for example in explaining the details of equilibrium incidence levels or cyclic population fluctuations.

Spatially explicit models can lead to qualitatively different outcomes from non-spatial models, and may address their failures. This chapter emphasizes systems involving implicit spatial problems, not because they are inherently more interesting or difficult than explicit problems, but because they represent a newer and hence less thoroughly studied class of problems, where new techniques are particularly useful.

Whenever possible, spatial models should be used to generate clear, testable qualitative predictions about the average behaviour of the system (Mollison 1991), or to make quantitative statistical comparisons with spatial data using well-defined null models (Section 3.2). Otherwise it may be difficult to

distinguish spatial effects from other possible generating mechanisms.

Spatial models can serve to point out hidden weaknesses or assumptions in non-spatial models, and ideally to remedy them. For example, the assumptions of homogeneous mixing and identical mixing behaviour after an epidemic, built into many non-spatial fox rabies models, become clear and may be modified in stochastic grid models of fox rabies. Spatial models often appear complex because they take hidden, troublesome assumptions about mixing and spatial distributions and make them explicit.

Finally, as too much detail can obscure the essential nature of an interaction, another goal of modelling must be to find the *minimum* level of spatial detail needed to account for observed phenomena; collapsing smaller spatial scales in a sophisticated way may sometimes be possible (see Section 4.1).

# 2 Biological issues

## 2.1 Sources of spatial structure

As mentioned above, 'space' can describe any of a broad class of heterogeneities in population structure, which may or may not correspond directly to geographic structure (the more usual meaning of space).

In particular, spatial or pseudo-spatial population structure divides into three broad classes, which can be arranged roughly in order of the spatial scale on which they operate, from large to small (Box 1).

The mode of transmission of pathogens changes the effective distances between hosts caused by the heterogeneities listed in Box 1. Since distance in disease models is equivalent to the relative difficulty of transmission between hosts, transmission mode can drastically modify the distance between hosts. In directly transmitted diseases, host movement and frequency of contact between hosts determines effective distance. Indirectly transmitted diseases can involve much more complicated patterns of movement of primary and intermediate hosts (and important spatiotemporal correlations between these movements). Two hosts both preferred by a particular individual of a vector species, for example, can be epidemiological neighbours even while they are geographically widely separated (see Section 4.5). Finally, for wind- and water-borne diseases, aerodynamic and hydrologic patterns govern the effective distances between individuals.

## 2.2 Scale and hierarchy

In any host-pathogen system, various types of heterogeneities will affect the system at different spatial scales. While the list of heterogeneities in Box 1 (environmental, contact, host/pathogen) is roughly ordered by spatial scale,

1. *Environmental heterogeneity:* this category covers most of the structures typically associated with geography and space, including climatic and hydrologic factors and the field of medical geography generally.
2. *Contact heterogeneity:* this category includes all structure relating to contact patterns between hosts and parasites, including the majority of the questions of current research interest: the spatial distribution of hosts and parasites, movement of hosts, etc.
3. *Host/pathogen heterogeneity:* this category includes differences among primary and secondary hosts (including vectors) and pathogens that affect the transmission and course of disease; for example, genetic and behavioural predisposition or resistance to disease. This category relates only loosely to space in the usual sense, but the structure of populations with respect to these heterogeneities is often closely analogous to more familiar spatial structures. In addition, these heterogeneities often interact with the heterogeneities in environment and contact structure mentioned above (see also Section 4.5).

Box 1: Generators of epidemiological heterogeneity

it is easy to imagine exceptions within the broad range of possible spatial models. For example, genetic differences in susceptibility might apply to geographically separated demes of hosts (host/pathogen heterogeneity at a large spatial scale) or microclimatic differences might apply to small patches containing only a few hosts each (environmental heterogeneity at a small scale).

Spatial structure occurs not only at different scales in different systems, but at multiple scales within a single system. Individuals generally represent discrete patches in space from the perspective of a parasite; these individuals in turn have heterogeneous densities in space, varying more or less continuously; larger areas can contain patches or gradients of environmental conditions, or the density of groups or clusters of individuals can vary at a larger scale. Spatial structures at different scales often have different causes.

Since spatial models cover such a broad range of possibilities, it is extremely easy—but not necessarily useful—to construct plausible examples of almost any combination of different types of heterogeneities at different scales. Instead, several case studies of host-pathogen systems given below give useful examples of different types and scales of spatial structure (see Section 4).

# 3 Analytic issues

## 3.1 Model selection

Much of the focus of a particular study will often be dictated by the choice of model structure (and ideally *vice versa*); for example, using metapopulation models will suggest hypotheses about patterns of parasite density in different sub-populations, but preclude questions about local host-pathogen interactions. Unfortunately, there seem to be no firm rules for choosing appropriate spatial models. Arguments about appropriate levels of detail in spatial models, as with any biological models, are often acrimonious, in part because different schools of modelling practice emphasize either 'tactical' or 'strategic' models (Nisbet and Gurney 1982). Tactical models tend to be relatively complex, with relatively more parameters, and attempt to describe a particular system fairly exactly; strategic models are simpler, have fewer parameters, and concentrate on the qualitative mechanisms driving diseases in natural populations. Within either of these categories common sense, knowledge of the ecology and epidemiology of the host-pathogen system, and reasonably broad knowledge of the spatial modelling literature (Mollison and Levin this volume) seem to be the only guides. There is always room for more comparative work using several different models at varying levels of detail on a single system to compare the strengths and weaknesses of different approaches, and to see what additional questions can be asked or information gathered with different levels of detail and effort.

*Reaction-diffusion models* are a classic approach to spatial modelling in ecology and epidemiology (Murray 1990). In this approach, a set of spatially homogeneous population differential equations is extended by adding diffusion terms. Because they usually assume a homogeneous or regular spatial arena underlying spatially heterogeneous population dynamics, reaction-diffusion models are more generally used in strategic than tactical modelling, although they have been very useful in determining some of the fundamental properties of spatial spread (Murray 1990, Mollison 1991, Anderson *et al.* 1981, Andow *et al.* 1990b).

Many spatial problems fall under the heading of *metapopulation* problems (Gilpin and Hanski 1991, Dwyer 1991). Metapopulations generally represent a special case of host contact structure, where a large population divides naturally into a grouping of weakly-coupled smaller populations; while the division into patches itself represents spatial heterogeneity, there may be additional heterogeneity between patches (Anderson and May 1984). In a metapopulation system, the problem of spatial relationships reduces to the simpler problem of relationships between a finite number of patches. Many wildlife disease problems, particularly where the host organism lives in discrete herds or groups, can be thought of as examples of metapopulation dynamics (see

Section 4.2).

Metapopulation models are in some respects the simplest class of spatial models. They allow the consideration of local interactions and localized stochastic events, while permitting individuals to be treated as discrete. Reaction-diffusion approaches, on the other hand, have the advantage of explicit spatial representation, while losing the capability for dealing easily with local stochasticity and individuality; these models have in the past proved useful for studying the explicit spatial problem of spatial spread, but they may be harder to apply to implicit spatial problems because of their lack of local structure and the necessity of dealing with infinitesimals. Interacting particle systems (Durrett and Levin 1994a,b), with more detail, may provide a way to incorporate several of these features into a single model structure. At present these models are something of a novelty in epidemiological contexts, and few examples of tactical models of this type exist yet, but they appear to be a useful addition to the strategic arsenal.

When spatial distributions at a particular scale are discontinuous enough to be lumped into discrete units with simple dynamics on a short time scale (i.e., they have short-range spatial and spatiotemporal correlations), and when spatial structure at different scales can easily be separated, then simplifying spatial models is relatively straightforward (Sections 4.1, 4.2). Sometimes, however, there is less clear separation between patches or between spatial scales (Section 4.4), or interaction between different kinds of heterogeneity on one or more scales (Section 4.5); in this case, any analysis of the system must include both scales or kinds of heterogeneity explicitly.

## 3.2 Spatial data and spatial statistics

A critical factor in choosing a spatial model is the data set itself. Collecting spatial data is inherently more difficult than collecting aggregate data, and spatiotemporal data are harder still to obtain. Field data on wildlife disease are often gathered at inappropriate scales, either through over-aggregation or under-sampling (for example, if one wants to test unequivocally whether host metapopulation structure causes parasite persistence). Nevertheless, modelling decisions should be made with attention to potential sources of verifying data, using what seem (from ecological knowledge) to be appropriate scales. Ideally, data collection and modelling will be two parts of an iterative process, with additional data collected to test particular new predictions or refine potentially interesting parts of spatial models (Section 4.4). As mentioned above (Section 1.3), there are cases where spatial models generate sufficiently clear predictions of the average behaviour of a system to test them against non-spatial data, but in general spatial models should if at all possible be tested against spatial data.

Spatial data, and the output of spatial models, tend to be complex and

to lead to qualitative rather than quantitative interpretation. While robust, qualitative predictions from models are invaluable for understanding the effects of simple spatial mechanisms (Mollison and Levin this volume), these may be too difficult to derive for a particular problem; in this case, careful quantitative comparisons of models and data should be made to test whether the mechanisms incorporated in the models are really capable of reproducing patterns observed in the data.

In particular, tactical models may not provide results suitable for tests of qualitative predictions. In order to prevent the modelling exercise from degenerating into a complicated curve-fitting process (since the variety of spatial models allows so much freedom in fitting models to data), complex models should be tested carefully. The testing process includes not only sensitivity analysis and basic attempts to understand what underlying qualitative mechanisms are driving the patterns generated by the model, but also rigorous, quantitative tests of model results against biologically significant spatial patterns. Both traditional spatial statistics such as spatial autocorrelations and semivariograms (Diggle 1983, Cliff and Ord 1981) and novel methods such as join-count statistics or fractal dimension (Cliff and Ord 1981, Sugihara and May 1990, Johnson *et al.* 1992), are underutilized in epidemiology. They not only identify significant spatial patterns during exploratory data analysis, but also provide a quantitative basis for comparing these patterns with the output of spatial models.

# 4 Case studies

The case studies presented below cover a range of problems with different spatial scales and different kinds of spatial heterogeneity, and are meant to give a feel for some different approaches to analysis of spatial disease systems (Box 2).

The case studies are arranged roughly in order of complexity. They start with a purely explicit spatial problem with heterogeneity on only one spatial scale (spread of fox rabies). The next two systems (seal/PDV, possum/Tb) have both an implicit component, where the authors invoke small-scale spatial heterogeneity of host movement and distribution to explain discrepancies in estimates of contact rates and dynamics, and an explicit component, where the authors attempt to understand larger-scale spread of disease based on the foundations of small-scale spatial models. The final two case studies present somewhat more complicated cases, where either spatial structure exists on a number of scales that are harder to separate (grouse/*T. tenuis*), or several different kinds of spatial heterogeneities interact (*Silene*/*Ustilago*).

| Host | Parasite | Heterogeneity | scale | Methods |
|---|---|---|---|---|
| fox | rabies | contact | 100–1000 m | grid model |
| seal | PDV | contact | 1–100 m | probability model for meetings |
| | | | 1–100 km | ?? |
| possum | Tb | contact | 1–100 m | implicit spatial model |
| | | | 1 km | grid model |
| grouse | *T. tenuis* | environmental contact, host/path. | 10–100 km | implicit spatial model |
| | | | 100 m–1 km | probability models/ spatial statistics |
| *S. alba* | *U. violacea* | contact, host/path. | 1 m–100 m | probabilistic nearest-neighbour model |

Box 2: Summary of case studies

## 4.1 Fox rabies

The spread of fox rabies represents an explicitly spatial wildlife disease problem where control is the major objective. Fox rabies is an intensively-studied spatial wildlife disease problem, with extensive literature on host ecology, pathogen etiology, observed disease spread, and modelling approaches (Bacon 1985, Källén *et al.* 1985, Murray *et al.* 1986, Anderson *et al.* 1981, Smith and Harris 1991). The spatial question of most interest here is the inhomogeneous mixing of infected and susceptible foxes because of territorial behaviour. The model described here uses a hierarchical approach, collapsing territories into discrete units.

The British government's contingency plans in the event of a fox rabies outbreak in Britain include the killing of foxes in a region surrounding the initial reported case, and spatial modelling has attempted to evaluate the efficacy of such control measures (Bacon 1985).

In many habitats, foxes live in groups occupying well defined territories, with little overlap between neighbouring territories. Also, there is some ev-

idence that during most of its active infectious period, a rabid fox does not behave too dissimilarly from a normal fox. Thus we are interested in modelling the early stages of a nearest-neighbour epidemic spreading away from a point source (although long-distance dispersal, particularly by juveniles, will also be important for some aspects of epidemic spread). A homogeneous mixing model will not suffice since (a) it does not provide a close approximation to nearest-neighbour spread and (b) it will not tell us where to apply control. A model needs to be stochastic since the appropriate population unit is a fox group and group sizes are small, rarely exceeding five. Also, by using a stochastic model we can estimate the probability that a given control measure is successful. A model needs to be as simple as possible, consistent with adequate biological realism, since simulations will be required to estimate the probability that a given control measure is successful, and the more simulations performed the greater the precision of the estimates. A model meeting the above criteria is one in which fox groups are located at the points of a two-dimensional lattice and a rabid fox can only infect foxes in its own and neighbouring groups. Realistic values for the within-group infection probability imply that once one fox in a group is infected then it is very likely that the whole group will become infected. Thus a good approximation is obtained by using a group, rather than an individual fox, as the basic unit (Ball 1985). Hence, we end up with a model having just one parameter, namely the probability that one rabid group infects a given neighbouring group. This model can be used to estimate the success probability for various control strategies. It is also straightforward to modify it to incorporate possible effects of a control policy on the surviving susceptible population.

## 4.2 Phocid distemper virus in seals

Spread of phocid distemper virus among common seals in the North Sea is both an implicit and an explicit spatial problem, at different temporal and spatial scales. The implicit problem is explaining observed transmission rates within small groups, where (as with fox rabies, discussed in the previous section) the assumption of homogeneous mixing breaks down. The explicit problem is explaining the spread of the epidemic between spatially separated groups. Again as with fox rabies, a hierarchical approach to the problem—using a simple model to collapse the within-group dynamics in the model of spatial spread—is possible, but in this case analyzing the behaviour of the disease at the smaller spatial scale has more inherent epidemiological interest. Nevertheless, the hope is that the two important scales in the problem can be separated.

The 1988 outbreak of phocid distemper (PDV) in Northern Europe, largely among common or harbour seals (*Phoca vitulina*) in Northern Europe, was among the most dramatic and well documented wildlife disease epidemics of

recent years. It began in April on the Danish island of Anholt in the Kattegat where unusually high numbers of aborted foetuses were found. Adult seals with symptoms of respiratory distress were soon reported in the same area and washed up carcasses followed. The disease spread rapidly to populations in the Skagerrak, Norway and the Wadden Sea. By July the first dead common seals were reported in the Wash on the east coast of England and by September sick and dead seals were being found in all populations around the British Isles (Dietz *et al.* 1989, Hall *et al.* 1992). Aerial surveys carried out after the outbreak estimated mortality rates of between approximately 60% in the Wadden Sea to 10–20% on the east coast of Scotland, with undetectable mortality in Orkney (Heide-Jorgensen *et al.* 1992).

The underlying cause of death was found to be a newly recognised morbillivirus genetically distinct from, but causing similar pathological effects to, canine distemper in dogs (Cosby *et al.* 1988, Osterhaus and Vedder 1988). Common seals suffered much higher mortality than grey seals (*Halichoerus grypus*) although both seem to have been equally exposed (Harwood *et al.* 1989).

A simple mathematical model to examine the long-term dynamic consequences of the infection in the North Sea was used to estimate feasible ranges for the transmission and mortality rates (Grenfell *et al.* 1992). However, the underlying model assumes that encounters between infective and susceptible animals occur at random. This is probably not the case with seals because susceptible animals are more likely to be infected through contact with infectives while both groups are hauled out together on rocks or sandbanks. Haul-out behaviour varies seasonally, geographically and with weather conditions (Thompson 1989). Common seals also appear to be less tolerant of their neighbours whilst on land, maintaining a minimum inter-individual distance whereas grey seals may be very densely packed together, particularly during the annual moult. Patterns of haul-out behaviour may vary topographically and on some sandbanks in the Wadden Sea seals appear to haul-out in a linear manner, with animals moving adjacent to those already on the sandbank. As a result the probability of virus transmission will not be related to total population size in any simple way, and density, during periods on land at least, may be constant for common seals. The threshold population of susceptibles is thus likely to be different to that in a randomly mixing population. This is further complicated by the evidence from telemetry studies that some grey seals can travel very long distances, visiting various haul-out sites *en route* (McConnell *et al.* 1992).

Another question about PDV is how the epidemic wave progressed from colony to colony around the coast of Britain. Since epidemics within colonies were typically on short time scales compared with the spread between colonies, and since PDV is infectious enough that a single infective seal has a large

probability of starting a major epidemic in a colony, it may be possible to treat colony epidemics as discrete events in a stochastic model. Condensing an epidemic in a colony into an event is a matter of encapsulating the within-colony dynamics, either by sensible approximations from the analytic results of the SIR or micro-spatial models, or by generating probability profiles of percent infected, dead, and immune, and elapsed time, by repeated stochastic simulation of within-colony disease models. These events could then be coupled in some way in a grid or network model to explore the spatial spread of the disease under different conditions.

The exact mechanisms of spread on this larger scale are also uncertain. Although the observed pattern of between-colony spread appears to be driven mostly by nearest-neighbour (colony) contact, 'great leaps forward' (Mollison 1972) do also occur, for instance when the disease jumped across the North Sea to East Anglia. However, because of the inherent rarity of these events, characterizing their distribution in time and space is difficult; the degree to which this distribution can actually be determined from the available data depends in part on the sensitivity of the spatial model.

## 4.3 Bovine tuberculosis and possums

The next case study deals again with a problem that is both implicitly and explicitly spatial, considering the time-scale of dynamics in an endemic area and the speed of epidemic spread respectively. As with the case studies above, the problem seems to require a hierarchical approach to deal with different spatial scales. In this case, however, the lower level of the hierarchy is too continuous, and the dynamics too complicated, to collapse simply into discrete units. Instead, the method below implicitly includes local heterogeneity by adding an extra, observationally determined, aggregation parameter. The case study uses this aggregation parameter both in a non-spatial model addressing the implicit problem of contact rates in an endemic area, and in an explicitly spatial model addressing the explicit problem of epidemic spread.

The objective in modelling bovine tuberculosis (Tb) in possums was to evaluate control options in the face of urgent need, namely the threat to a NZ$2 billion/year cattle export market. The objective fell into two parts: modelling control in endemic areas, and modelling ways of preventing spread of the disease beyond these areas. The spread problem required a model with an explicit spatial model; for endemicity, Barlow (1991) proposed an implicitly spatial model (see below and Box 3).

In terms of the endemic situation, the problem with modelling bovine Tb in possums is that the disease exists at low prevalence, exhibits relatively rapid dynamics (e.g. recovery rate after control of the host), and has little effect on host density. Standard SIR deterministic models cannot reproduce all three characteristics; typically they predict significant suppression of the

Standard homogeneous-mixing models can be modified to take aggregation into account by replacing the mean density of diseased animals per infective within the area (patch) covered by the contact probability by the ratio of the mean square to the mean: the transmission term becomes $\beta Y(H - (\sum D^2 / \sum D)$ instead of $\beta Y(H - \overline{D})$, where $H$ = total/unit area, $Y$ = infectious, $D$ = infectious plus latent, and summation is over all patches. $(\sum D^2 / \sum D - 1)$ is equivalent to mean crowding, and $\sum D^2 / \sum D$ is equal to $(\sigma_D^2 / \overline{D} + \overline{D})$ but for simplicity is assumed proportional to the mean: $\sum D^2 / \sum D = \overline{D}/q$. This modification gives a transmission term $\beta Y(H - D/q)$ instead of $\beta Y(H - D)$, where $q$ measures the proportion of the habitat effectively occupied by disease at $1/q$ times the overall average prevalence. $q$ can be estimated from field data on disease or prevalence among patches (= mean prevalence squared/mean square prevalence), and is an indication of the degree of spatial aggregation: $q = 1$ denotes no aggregation and low $q$ implies small patches with local prevalences greatly exceeding the overall average.

Box 3: An implicit model of epidemiological aggregation

host, in the order of 50%. This was the outcome of a model for bovine Tb in badgers Anderson and Trewhella (1985), yet no such reduction in host population was observed (e.g. data of Cheeseman *et al.* (1981)).

Homogeneous-mixing models do not work because the disease is highly aggregated in space (Barlow 1991). Therefore, each infectious animal is surrounded by more infectives - and hence fewer susceptibles - than expected from random mixing. The effective contact rate is therefore lower for a given total prevalence of disease; this effect can be observed in fully spatial models (Mollison and Kuulasmaa 1985), but an alternate modelling strategy is to modify the standard mass-action transmission term (Box 3) (Barlow 1991).

A similar transmission term can also be arrived at by a different route, considering the habitat to consist of two patches, one with disease and one without, and with the total host density equilibrated between both by density-dependent immigration into the diseased patch (Barlow 1991). This modified SIR model appeared to capture realistic disease dynamics, essentially by confining the classic model form to part of the total area but averaging prevalence over the whole area.

Examining spatial spread required an explicitly spatial model, in this case a grid (interacting particle system) model. A large grid cell (1 km$^2$) encompassing up to 1000 possums was occasioned by the long dispersal distances of the juveniles (up to 12 km), and because of the high densities of possums this

necessarily implied many animals per cell. Each cell used the modified (aggregated) SIR model, although in this case with a slightly altered framework including continuous mortality and disease transmission but a more realistic yearly birth pulse, together with a yearly juvenile dispersal pulse. Modelling individual possums in space, over the scale required by juvenile dispersal and the need to show movement of a front, would require over 1 million animals to be tracked by the computer. Modelling a home-range scale was pointless because home ranges overlap. The spatial model was made partly stochastic to avoid problems with unrealistically low densities corresponding to less than one individual host (Mollison 1991), by interpreting rates affecting less than 5 possums as probabilities; all densities were stored as integers. Spatial disease transmission was between neighbouring cells, by density-dependent movement between neighbouring cells, and by long-range juvenile dispersal. This model could predict rates of disease spread, immigration rates of diseased animals into controlled areas of different sizes, and effects of different spatial control programmes. However, it still included the rather unsatisfactory simplification of implicit rather than explicit spatial heterogeneity within grid squares. The challenge is to derive an explicit spatial model for possums at individual or small-group levels which is manageable on a computer.

## 4.4 Red grouse and *Trichostrongylus tenuis*

This case study continues the trend toward more complex spatial problems. Here the explicit spatial problem is of distribution rather than spread, and includes both environmental (climatic) and contact (host movement) heterogeneity. The problem deals with a fairly large spatial scale, so there are at least three levels of spatial hierarchy to consider: regional climatic differences, interactions between neighbouring moors within a region, and dynamics on an individual moor. The largest scale is probably separable, but dynamics on the two lower levels of the hierarchy may be hard to collapse in any of the ways discussed so far. The red grouse-*T. tenuis* system is also the first macroparasite system considered thus far, introducing a possibly important level of spatial structure at the level of individual hosts. This case study points to the usefulness of additional, focused data collection after an initial modelling effort, and of innovative spatial statistics, to address spatial disease problems.

The long-term game records for red grouse in Scotland and the north of England provide empirical insights into the spatial dynamics of parasite host demography. The primary determinant of changes in grouse population numbers in most of Northern Britain are interactions between the grouse and the parasitic nematode *Trichostrongylus tenuis* (Dobson and Hudson 1992, Hudson *et al.* 1992). Time series data have been collected for up to 100 years for 400 grouse estates throughout the region; intensive population studies

have also been undertaken for up to 10 years on 40 of these sites. These data suggest that data from estates within 5 to 10 miles of each other are fairly tightly coupled, but correlations drop to statistical insignificance at distances in excess of 40 or 50 miles.

The broader geographical patterns in these data have been examined with a range of techniques. The major trend to emerge from the data is that population cycle length tends to increase from around five years in the north of England to eight to ten years in the north of Scotland (Hudson 1992). A hierarchical similarity analysis of these data suggests that sites that are in the same geographical area tend to be fairly closely synchronized, in contrast, sites from different upland regions tend not to be synchronized. This synchrony of population cycles within a region could reflect either similar meteorological conditions in sites that are in relative proximity to each other, or synchronization of population numbers through dispersal of birds (and their parasites). A combination of spatial modelling, molecular ecology and radiotracking of birds is currently being used to elucidate this issue.

## 4.5 Plant-pathogen systems

The final case study opens up a much wider class of interesting spatial heterogeneities. There is less difficulty with hierarchical spatial patterns in this experimental system, but there are genetic and behavioural heterogeneities among hosts and pathogens. There are many non-spatial models of host and pathogen genetic and behavioural heterogeneity in disease systems (Onstad and Kornkven 1992), but the possibility that these heterogeneities interact with pre-existing spatial structure in the host population suggests that we investigate new mechanisms of disease spread and dynamics.

The stationary distribution of plants provides a unique opportunity for examining the consequences of spatial heterogeneity in disease dynamics. Plants and their pathogens are often aggregated in space and transmission intensities are often spatially dependent and variable. Plants can also be experimentally manipulated to generate specific degrees of spatial contagion that are not easily accomplished in animal systems.

The *Silene alba–Ustilago violacea* system represents a model natural plant-pathogen system for analysis of disease dynamics. *S. alba* (the white campion) is a common herb infected by a host-specific anther smut fungus. Upon infection flowers produce fungal spores rather than pollen; infection is spread by pollinators. Infected flowers are distinguishable by their purplish cast, due to the shed of purple fungal spores. Healthy flowers are white.

The spatial distribution of disease within the plant population is significantly more aggregated than the population as a whole over a range of spatial scales (Real *et al.* 1992). Thus we can use empirically determined spatial distributions from natural populations to examine the consequences of different

biological modes of transmission and the effects of spatial aggregation on disease spread. Comparing rates of disease spread as proportion of the population infected under different vector preference behaviours suggests that vector preference for movements among diseased plants will slow the rate of spread relative to random foraging under most densities of disease within the plant population. (Preference is here defined as the likelihood of visiting flowers of different disease status when encountered.) Preference for healthy plants will similarly slow the rate of spread but not as dramatically as preference for diseased plants. Vector preferences act to contain the disease (Marschall *et al.* 1994).

Simulations of aphid spread of the barley yellow dwarf virus in agricultural systems (McElhany *et al.* 1994) suggest that the dependence of rates of disease spread on vector behavioural preference is a function of initial disease proportion. When disease is randomly assigned in space and initial density of disease is low ($< 10\%$) then preference for disease increases the rate of spread relative to random movement and vector behaviour does not contain the disease. When aggregated distributions of disease are used as the underlying pattern, however, preference for diseased plants by vectors leads again to the containment of the disease at all initial disease proportions and a reduction in the rate of spread relative to random movement. Aggregation increases the local density of disease, thereby altering the local probabilities of transmission under different vector preferences.

The general consequences of aggregation in plant systems can be effectively explored by constructing two-dimensional arrays of plants generating different degrees of spatial aggregation. Biological processes may then be superimposed on these different spatial patterns to see if some processes are more sensitive to spatial heterogeneity than others. For example, vector-borne diseases may be more sensitive to patterns of aggregation than wind- or water-borne diseases. Ideally, the effects of spatial distribution implied by simulation can be tested using planted arrays corresponding to different spatial patterns and subject to different modes of disease transmission.

# 5 Discussion

What general strategies or conclusions do this set of case studies suggest?

The studies address a range of different kinds of spatial heterogeneity, from the usual local patterns of host movement and contact in the fox, possum, and seal case studies to larger-scale climatic differences in the grouse case study. The interactions between genetic or behavioural and spatial heterogenities suggested in the *Silene* case study are less well-represented in the literature, and may represent a new class of important spatial structures for analysis.

As mentioned in the introduction, the studies mostly emphasize implicit

spatial problems, characteristics of the system that are not themselves spatially structured but may be caused by spatial structure. Some, such as the fox rabies and bovine Tb studies, are primarily concerned with solving implicit problems in order to construct better explicit (spatial spread and control) models. Those studies that examine implicit problems for their own sake, especially the grouse and *Silene* systems, suggest that field study and experiment are invaluable for detailed examination of local spatial structures.

Most of the case studies support the idea that multiple spatial scales are important in wildlife diseases. Because explicitly hierarchical models are so difficult to analyze, the studies try to separate the scales of interest. Wherever possible (fox rabies, seals, bovine Tb) the first step is to simplify the lower level of the hierarchy. Different system-specific methods apply in each case, from simple collapse to an implicit model incorporating local heterogeneities in density, depending on the source and characteristics of the spatial structure on the lower level. Following the collapse of the latter, the upper level could be modelled by any of the general model types given above, although several authors opted for interacting particle systems. The latter lend themselves to computer simulation, and retain relatively realistic local dynamics; they may, however, be difficult to connect directly to quantitative data on observed local dynamics in specific cases (Durrett and Levin 1994a).

In the last two case studies, collapsing levels of the hierarchy proves more difficult. In the grouse case, some levels of the hierarchy (climatic heterogeneity) can be dealt with separately from the rest of the problem, but within- and between-moor heterogeneities are less separable; this difficulty partly explains the emphasis of this study on spatial statistics and additional data collection, but ideally these efforts should not be a last resort.

Finally, the *Silene* case study uses individual-based models to simulate an *experimental* system, which allows more thorough comparison of model and data than is usual in observational systems. The range of important spatial scales is narrower because an experimental system can be homogenized, or randomized, on small scales and shielded from fluctuations on large scales.

The case studies broadly support a particular approach to spatial modelling, using knowledge of local interactions and any large-scale heterogeneities to build models of each hierarchical level separately, and linking them where possible. They do not, however, suggest any cut-and-dried procedure for building the models on each level. The variety of models presented here is a small subset of the immense variety of possible spatial models; this diversity in models must be maintained in order to cover the even larger variety of spatial disease systems that occur in the natural world.

# 6 Agenda for future research

1. **Scale**

   Since creating an exact representation of the physical and biological world is impossible, all disease models must pick one or a few important scales on which to analyze the behaviour of a disease system. In some cases, as with directly-transmitted disease (Tb) in strongly territorial animals (badgers), these scales may be clear from the ecology of the host and parasite, but in other cases determining scale will require careful model analysis and intelligent sampling in the field. Neither model analysis nor data alone can identify scale; misguided sampling and misguided modelling can both usually be relied upon to come up with a misleading answer. Often the data initially available are not aggregated at the appropriate epidemiological scale, as in bag records of grouse by moor. Modelling using the known ecology and epidemiology of the system and comparing it with the available data, followed by additional sampling, is the only way out.

2. **Multiple scales (hierarchy)**

   Most epidemiological systems have more than one appropriate scale. Some degree of heterogeneity exists in all processes from the biochemical to the landscape level, and all of the heterogeneity driving a system is unlikely to be concentrated in a single process acting at one temporal and spatial scale; some kind of hierarchical approach is usually necessary. If the time scales of two strata are sufficiently different, as with between- and within-colony dynamics in grey seals during the PDV epidemic, then the smaller-scale stratum can be collapsed (after appropriate analysis) in modelling larger scales. This process of relating phenomena across scales, and particularly of simplifying some scales in order to focus on others, is a part of many biological models but comes out strongly in disease systems because there are processes at so many scales (genetics, animal behaviour, topography, climate, etc.) that can potentially affect the behaviour of the system. Because modelling the whole system explicitly is rarely feasible, determining whether simplifications are appropriate, and how exactly to simplify lower strata of the hierarchy, is an important part of spatial modelling.

3. **Appropriate non-spatial models**

   As mentioned above, one of the virtues of spatial models is that they force us to make our assumptions explicit. Spatial models can both reveal where the standard assumptions, for example of homogeneous mixing, break down (for example in the spread of fox rabies), and clarify

the assumptions inherent in standard forms such as density-dependent contact, where the transmission term equals $\beta SI$.

One possible avenue (as described in Section 4.3) is the development of implicitly spatial models, which incorporate a correction term for non-homogeneous mixing into the transmission term. Such correction terms have been proposed, but they will have to be used with sensitivity and tested, both in models and in measurements in the field at different host densities and infection densities, to see whether they are viable. This process will benefit not only modellers, providing them with a quick but slightly less dirty solution than homogeneous mixing, but also epidemiologists in general, who will gain valuable information about the density-dependence of the mixing and contact processes.

4. **Modelling practice, design and sampling, spatial statistics**

A variety of issues relevant to modelling in general come out acutely in the area of complex spatial models. As with all complex models, the parameters of complex spatial model systems should ideally be (1) estimable from data and (2) interpretable in empirical terms. In addition, the problems of sampling in spatial systems argue for a close correspondence between models and experimental and sampling designs; this correspondence is always important, but becomes particularly critical for spatial problems. Sampling at too-small scales can obscure the interesting dynamics, while sampling at too-large scales can aggregate the interesting dynamics out of existence. Finally, the use of statistical methods for parameter estimation and model validation (again, a general point but one that becomes especially important for complex spatial models) is vital; while statistical methods do not generate information about underlying mechanisms, they can tease out information about the scale and pattern of spatial processes that may not be directly apparent from the data. In addition, combined use of spatial models and spatial statistics to find differences between different potential mechanisms for spatial disease patterns is a powerful and under-used tool.

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# Genetic Diversity in Host-Parasite Interactions

*C.M. Lively and V. Apanius*

## 1 Introduction

> Probably a very small biochemical change will give a host species a substantial degree of resistance to a highly adapted microorganism. This has an important evolutionary effect. It means that it is an advantage to the individual to possess a rare biochemical phenotype. For just because of its rarity it will be resistant to diseases which attack the majority of its fellows. (Haldane 1949)

As is clear from this passage, Haldane recognized that the temporary resistance conferred by rarity could lead to the maintenance of alleles involved in antagonistic coevolution. He then set out to explain the 'surprising diversity revealed by serological tests,' and suggested that some of the proteins uncovered in these tests 'may play a part in disease resistance.'

Our purpose here is to review some of the more important theoretical and empirical advances since Haldane's time. We begin by considering simple genetic models of host-parasite interactions, with a particular interest in whether such interactions are expected to result in (1) stable equilibria for allele frequencies, (2) stable limit cycles of small amplitude, (3) stable limit cycles of large amplitude, or (4) unstable oscillations (see Fig. 1). We suggest that unstable oscillations, as well as stable oscillations having large amplitudes, can lead to the loss of genetic diversity, and discuss ways in which diversity could be protected, or at least re-supplied, if lost.

We then extend the discussion to consider the polygenic basis of resistance, and discuss the molecular evidence for the accrual of resistance genes in vertebrate genomes. It is clear that a profound revolution has taken place in our understanding of the genetic basis of disease resistance. The molecular mechanisms for accelerating the genetic evolution of parasites and for expressing genetic variation during the lifetime of an individual host could not have been anticipated in Haldane's time. We then consider the role that parasitism might play in the maintenance of sexual reproduction and the evolution of recombination rates in host populations. Finally, the evolution of inducible phenotypic responses to parasitism are considered. Because of the primacy of disease resistance in biomedical research, most of the discussion focuses on the vertebrate immune system. Nonetheless, advances in that arena

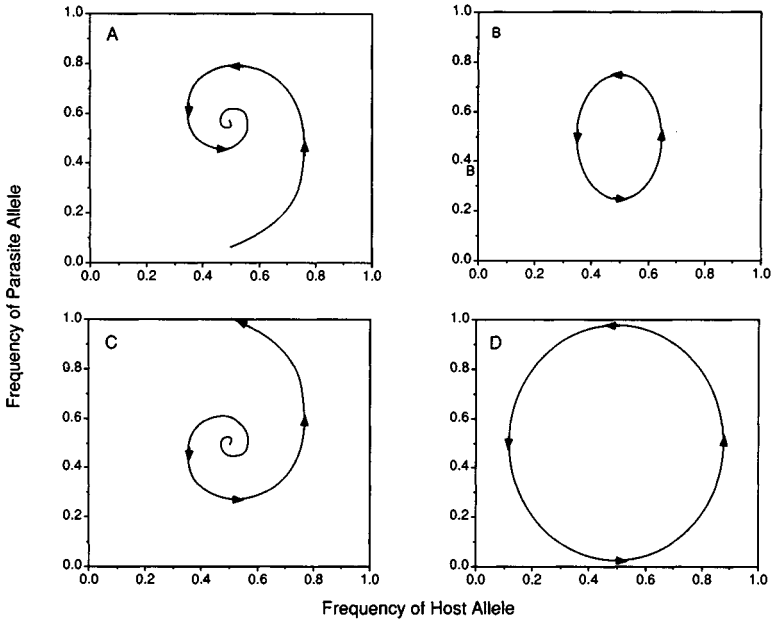


Figure 1. Phase planes showing the frequency of a host allele against the frequency of a matching parasite allele which result in infection: (A) stable equilibrium, as observed in the model by Mode (1958), and under very strict conditions in the model by Clarke (1976); (B) stable limit cycle having a small 'orbit', as observed under high mutation rates in the two-locus model by Seger (1988); (C) outward spiraling cycles, leading to fixation of alleles in either the host or the parasite, as observed in the one-locus model of Jayakar (1976); and (D) stable limit cycle having a large orbit as observed under low mutation rates in the model by Seger (1988), and under strong fitness effects and no migration in the model by Clarke (1976). The situations for either C or D lead to the loss of diversity either through deterministic (C) or stochastic processes (D).

have provided unexpected insights into the design and operating principles of resistance traits that can be applied more broadly.

## 2 Instability of host-parasite interactions

One of the first genetic models of antagonistic coevolution was contributed by Mode (1958). In an analysis of single 'gene-for-gene' interactions between flax and a rust described by Flor (1942), Mode found that a stable genetic polymorphism could readily exist.

Mode's model was followed by Jayakar's (1970) model, which made different assumptions concerning the genetic basis of the interaction and reached very different conclusions. Jayakar assumed first that both parasite and host

were haploid, and that parasites with allele **B** could infect hosts with allele **A**, but not allele **a**. However, parasites with allele **b** could infect both host types equally. Starting with different initial frequencies of **A** and **B**, he found that parasite allele **b** would usually fix before host allele **A** was lost from the population; and that host alleles **A** and **a** would persist in the frequencies they were at when allele **B** was lost from the parasite population.

Jayakar then introduced fitness differences. Hosts with allele **a** were less fit than hosts with allele **A** (as if there were a cost to **a**-bearing hosts for being resistant to **B**-bearing parasites), and parasites with allele **b** were less fit than parasites with allele **B** (as if there were a cost to **b**-bearing parasites for being infective to both host types). Under these biologically realistic conditions, there were oscillations around an internal equilibrium point. But in plots of successive recursions of host allele frequency against parasite allele frequency, the oscillations were seen to spiral out until one of the alleles fixed (as in Fig. 1C). Hence, in the first indication of genetic cycling, there was a loss of genetic diversity in either the host or the parasite (see Figs 10 and 11 in Jayakar 1970).

Following these models, Clarke (1976) examined two separate single-locus models: one of specific resistance, as in the flax-rust interaction examined by Mode (1958), and one of general resistance, analogous to Jayakar's model of general virulence just discussed. However, whereas Mode (1958) found a stable polymorphism in his model of specific resistance, Clarke reported a stable polymorphism for only a very restricted range of parameter values. Regarding these conditions he stated that (his italics):

> These conditions can be specified, but they need not concern us because *under all other conditions, ... the system moves into a stable limit cycle which will also maintain joint polymorphisms in hosts and parasites.*

It is the cycles that interest us here. Such cycles had been recognized as important in ecological models (May 1972), but they had been under appreciated in theoretical population genetics (Clarke 1976). Clarke then added that when the conditions are set at their most extreme (meaning here that when parasites match their hosts, the host dies; and that when parasites do not match, the parasite dies):

> ... the system goes into a peculiar sort of cycle, in which the frequencies of the genotypes and phenotypes move round the outside edge of the diagram (plotting host gene frequency against parasite gene frequency). Thus hosts and parasites are alternatively polymorphic, presumably with some waiting at the corners for new mutations to occur.

Hence, Clarke's analysis of specific resistance renders two key insights: first, and most important, is the idea that genetic diversity can be maintained in the absence of stable equilibria; and second is the idea that diversity can be lost when the fitness effects are dire. Bell's (1982) two-locus model of time-lagged, frequency-dependent selection later makes clear a problem that is hinted at in Clarke's analysis of strong fitness effects. The problem is that host-parasite interactions may lead to (1) stable limit cycles of large amplitude, allowing the possibility of stochastic loss of alleles, or (2) large undamped oscillations that will lead to the loss of alleles (Fig. 1C). In general, oscillations of these potentially diversity-purging types are caused by both strong fitness effects and time lags (see Bell's Fig. 2.17), and it is exactly these kinds of effects that favor recombination (Hutson and Law 1981, Bell 1982). May and Anderson (1983) obtained similar results in their models of frequency-dependent selection, but added that making parasite transmission dependent on host density made the fluctuations even more extreme (see Fig. 5 in May and Anderson 1983). Since time lags, strong fitness effects, and density-dependent transmission are expected to be common features of host-parasite interactions, some mechanism is needed to prevent the extinction of rare alleles. In the absence of such a mechanism, it is hard to see how antagonistic coevolution alone could lead to the long-term maintenance of genetic variation. In what follows we discuss some ways that variation could be protected.

# 3 Diversity protection

## 3.1 Mutation

It is possible that variation could be continuously re-supplied by mutation. Using deterministic computer simulations, Seger (1988) found that high rates of mutation ($m = 10^{-3}$) resulted in oscillations of relatively low amplitude. Reducing the mutation rate, however, increased the amplitude of the oscillations until the orbits became dangerously close to the boundaries (Figs 3–5 in Seger 1988). For reasonable rates of mutation ($m = 10^{-7}$), alleles could be lost by drift, resulting in the kind of mutation-selection oscillation envisioned by Clarke (1976). Seger (1988) also found that intermediate rates of recombination tended to greatly reduce the amplitude of the oscillations, but made no claim that such rates of recombination should be expected to be evolutionarily stable.

Mutation-driven antigenic variation of influenza A virus promotes genetic diversity in the virus population within a cyclic epidemiological pattern. Point mutations alter the amino acids of the virus coat protein called hemagglutinin which allows variant viruses to escape immunological clearance (Wilson and Cox 1990). Mutation rates can be as high as $10^{-3}$ per nucleotide site per year

(Saitou and Nei 1986) due to the viral RNA polymerase being polymorphic with respect to fidelity of replication (Steinhauer and Holland 1987). Thus, the viral mutation rate can be selected to counteract the development of host resistance.

One mechanism used by long-lived vertebrate hosts to counter rapidly evolving parasites is the mutational fine tuning of antibody specificity. Point mutations are targeted to the nucleotide sequences that code the antigen-combining site of antibodies (Wilson and Cox 1990). The process is termed somatic hypermutation because it occurs throughout the life of an individual host at an accelerated rate, $10^{-3}$ to $10^{-4}$ per nucleotide site per 18–24 hr cell cycle (French *et al.* 1989). Empirical and theoretical evidence suggests that this particular mutation rate is matched to the kinetics of lymphocyte proliferation to permit rapid convergence to sequences that code for high affinity antigen-binding sites (Agur *et al.* 1991). These high affinity antibodies can persist for the lifetime of the individual and confer immunological memory.

Mutation of hemagglutinin proteins permits new variants to overcome immunity to prior infections and leads to recurring waves of influenza infection in one host generation. The host response tracks each wave of viral variants by an epigenetic immune response. This scenario resembles the single allele models whereby mutation is sufficient for producing entrained cyclical variation in virulence and resistance traits. In this case, resistance is an acquired trait that persists for the lifetime of an individual and leads to an additional level of cyclical behavior.

Figure 2 shows the prevalence of antibodies against a particular influenza variant that circulated widely between 1947 and 1957. Individuals exposed to this variant retained immunological memory as evidenced by the high prevalence of antibodies in surveys conducted in 1961, 1971 and 1977. This influenza variant was found circulating again in 1977 (Nakajima *et al.* 1978), presumably because individuals born after 1957 provided a suitably large cohort of susceptibles to support endemic transmission. Therefore mutation allows influenza A to evade immune recognition and persist in host populations. In addition, host demographic processes appear to permit persistence on a global scale. Where was the variant virus during this gap in transmission? Perhaps in another part of the world or in an alternate host species, such as aquatic birds (Gorman *et al.* 1992).

## 3.2 Movement

Another way to protect genetic variation may be through movement between structured populations (Hamilton 1986). Hamilton's idea is that if there are multiple subpopulations, they would be expected to oscillate out of phase with each other. If this is true, as seems reasonable, then migrants for one population are very likely to restore alleles in adjacent populations that have

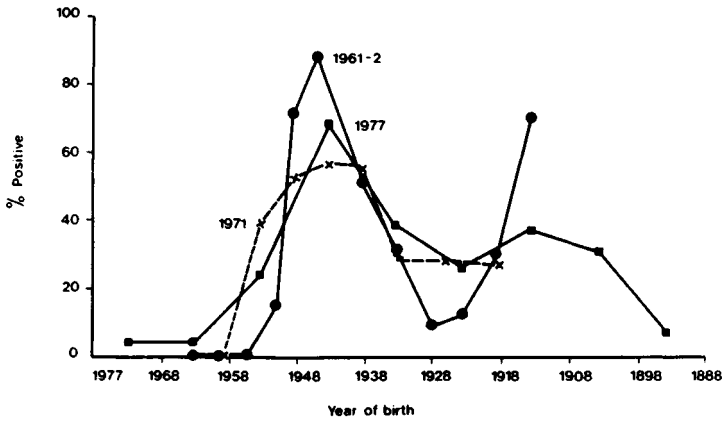


Figure 2. The prevalence of antibodies directed against a particular influenza A variant (A/FM/1/47) as a function of age in the human population of Sheffield. The three lines represent the age-distributions at three successive sampling times. Notice that all individuals born before or during the period of endemic transmission of the variant have a high probability of retaining antibodies for a long period of time. Individuals born after 1957 failed to develop antibodies as the variant was no longer in circulation in that community (after Stuart-Harris 1981).

been lost, and vice versa. Such replacement, of course, depends on the rate of migration and the likelihood that two populations do not ever become in phase long enough for there to be a simultaneous loss of alleles in both populations. The latter problem is certainly diminished as the number of populations exchanging individuals increases.

The movement of hosts is certainly important in the epidemiology of influenza A virus, where broad host specificity allows long-distance transport by a variety of vertebrate hosts (Hinshaw and Webster 1982). Our current understanding of the epizootiology of wildlife rabies provides another example of how geographic subdivision and movement can maintain genetic diversity.

On a continental scale, host-adapted variants of the rabies virus are geographically localized in North America (Fig. 3). The variants are characterized by a single antigenic profile which predominates in a single host species, with occasional spillover into alternate host species (Smith 1989). Movement of infected individuals between sub-populations permits the virus to invade new populations and leads to a disjunct distribution when observed at one point in time. A rabies variant associated with raccoons (*Procyon lotor*) spread across the state of Florida in a matter of decades then leaped to the middle Atlantic states in the mid 1970s. An antigenic profile typical of fox (*Vulpes* spp.) rabies is found in the northwest part of North America

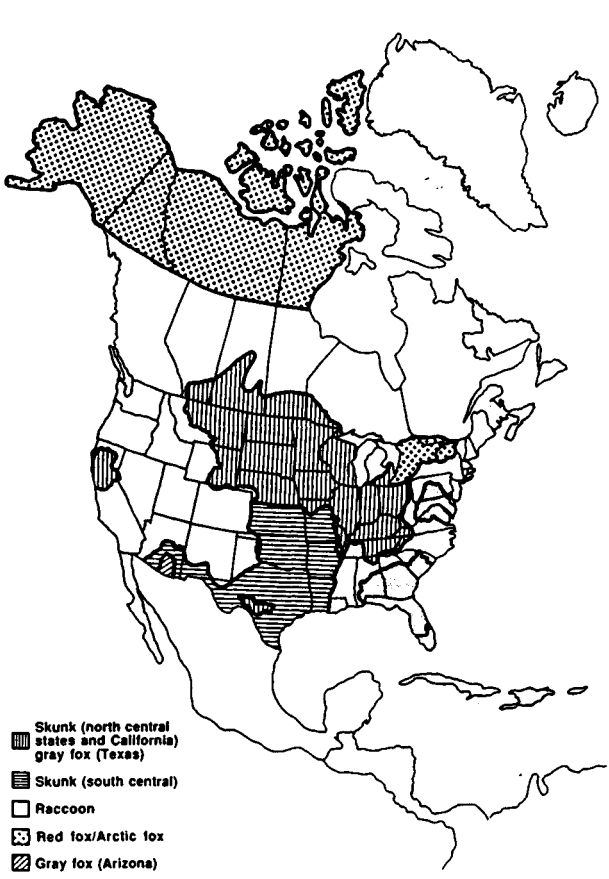


Figure 3. Geographic distribution of rabies virus variants based on antigenic profiles (from Smith and Baer 1988). A particular host species is predominately associated with each variant in the various geographic compartments and is denoted in the legend.

and also in southern Ontario and Quebec, presumably as a result of an epidemic wave that spread southward across Canada between 1946 and 1962. In striped skunks (*Mephitis mephitis*), two rabies antigenic profiles are found in the center of the continent. One group appears to represent an endemic focus in the upper Mississippi valley. The same profile can be observed in skunk isolates from California. A different antigenic profile can be found in skunks in the lower Mississippi valley and westward through Texas. This distinct variant of skunk rabies is thought to represent the expansion of an epidemic focus centered in Texas. The occurrence of both skunk variants in Missouri and Arkansas in the central Mississippi valley is considered to be the result of the confluence of the two expanding rabies populations.

These disjunct and melding distributions are consistent with Hamilton's

hypothesis (1986) that movement between non-synchronized host-parasite cycles can maintain global genetic diversity. However, contrary to the expected oscillations, antigenic profiles appear to be relatively stable within geographic compartments (Smith and Baer 1988).

On a finer scale, cyclic behavior of rabies prevalence can be observed in an endemic focus of fox rabies in southern Ontario. In the central core, the number of rabies cases shows a periodic pattern (Figure 4a). In areas surrounding the core population, the epidemiological pattern appears irregular (Figure 4b). It is thought that the virus persists in the core population due to recurring invasion from marginal zones (Tinline 1988). At present, it is unclear whether this pattern is due to purely demographic processes (Coyne *et al.* 1989) or whether genetic turnover is occurring in host or parasite populations. The recent application of polymerase chain reaction methodology to genetically characterize rabies isolates has confirmed that syntopic host species share the same rabies variant and that geographic differentiation does occur within compartments (Sacramento *et al.* 1992, Nadin-Davis *et al.* 1993). If this mode of analysis is extended to a longer time frame, then it should be possible to directly test Hamilton's assertion of the importance of population subdivision and movement between compartments.

The interaction between freshwater snails and digenetic trematodes provides another setting where Hamilton's idea can be directly investigated. The larval stages of these helminths commonly sterilize their snail hosts, and therefore impose a strong selective effect. Where it has been investigated, freshwater snails also have highly structured populations (e.g. Mulvey and Vrijenhoek 1982, Phillips and Lambert 1987, review in Jarne and Delay 1991), and the associated trematodes have become adapted to infecting their local snail populations (Lively 1989). This pattern is consistent with movement between isolated host populations serving to foster genetic diversity. What is needed is an estimate of the rate of migration among locally adapted populations. Hamilton's idea would be strengthened by intermediate amounts of migration: enough to restore lost alleles, without homogenizing the locally adapted demes.

# 4 Complex genetic interactions

All of the models discussed above were concerned with very simple genetic interactions: one locus with two alleles, or two loci, each with two alleles. It seems possible that more complex genetic systems might show less extreme oscillations. For example, Hamilton *et al.* (1990) found that increasing the number of parasite species as well as the number of loci involved in combating these parasites had the effect of reducing the amplitudes for host gene frequencies. In fact, after 7,000 generations in a computer simulation of the model,

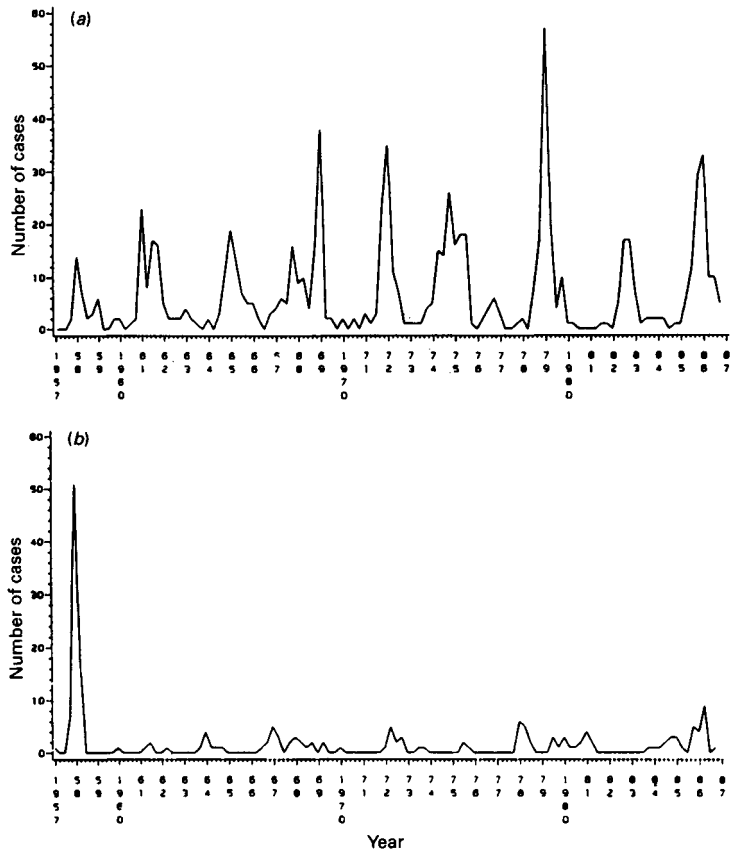


Figure 4. The number of cases of fox rabies cases in A) Renfrew County and B) Prescott County, Ontario, Canada. Renfrew County is located in the core of an endemic rabies focus, while Prescott is at the periphery (from Tinline 1988).

the original variation at host resistance loci had not been reduced. However, the parasites were asexual and their variation was continuously supplied by mutation ($m = 0.005$). Hence it is not clear that the antagonistic coevolution was sufficient to maintain genetic variation in both the host and its parasites.

Cohen and Newman (1989) used a game theoretic approach that disregarded mode of inheritance but only considered the evolutionarily stable strategy for antagonistic relationships. They suggested that continual diversification of tactics was the inevitable outcome of these interactions. This theoretical insight may help explain why gene-for-gene tactics might be overlaid with more complex virulence and resistance traits. Comparative immunological analysis reveals an evolutionary accrual of defense mechanisms. As innovative biochemical and cellular resistance traits evolve they are inte-

grated with rather than supplant ancestral resistance mechanisms (Marchalonis 1977, Cooper 1976, Herzenberg *et al.* 1992).

Mice selectively bred for resistance against a single nematode species (*Heligmosomoides polygyrus*) showed quantitative inheritance of that trait (Brindley *et al.* 1986). Although there are numerous examples of resistance associated with a single locus, resistance traits are typically polygenic (Wakelin and Blackwell 1988). Given that each individual host harbors a community of viral, prokaryotic, protozoan and metazoan parasites and that resistance to each parasite species may have a polygenic basis, then multilocus models should be more intuitively appealing. Furthermore Hamilton's approach of using multiple parasites portends greater realism of natural systems.

# 5 Multilocus genetics and meta-populations

Frank (1993) presented a model of antagonistic coevolution that evaluated population dynamics as well as gene-frequency dynamics. In addition (as in the model by Hamilton *et al.* 1990) he also allowed for multiple loci. Finally, Frank's model included the possibility of extinction and recolonization of demes.

Frank's results show that the intrinsic rate of increase for the parasite is the primary determinant of population dynamics in both the host and the parasite. Slow growing parasites lead to endemic disease and relatively stable population sizes. Fast growing parasites, by contrast, lead to epidemics, larger fluctuations in population sizes, and local extinctions. For rapidly growing parasite populations, the probability of extinction was also affected by the movement rate. Low rates of immigration and emigration increased the likelihood of local extinction, especially for the parasite (Frank's Fig. 4), by increasing the waiting times for the introduction of currently advantageous genotypes. Finally, and curiously, the effect of infection on individual hosts did not affect the dynamics.

Similar results were found for the gene-frequency dynamics. Relatively slow intrinsic growth by the parasite resulted in moderate fluctuations in gene frequency, whereas explosively growing parasites led to the loss of diversity during the crashes of local populations. Gene flow among demes tended to stabilize the meta-population. Hence, it would appear that greater complexity of genetic systems is not by itself enough to guarantee the maintenance of resistance and virulence alleles, at least where parasites are capable of rapid population growth.

# 6 Do parasites 'track' common genotypes?

The entrained cycling of host and parasite genotypes requires that parasites differentially respond to, or track, host genotypes as they become common. However, whereas population cycles are well known (e.g. Hudson and Dobson 1991; also this volume), reciprocal entrainment of genetic cycles is yet to be documented in the field. Nonetheless, recent studies have provided information consistent with the crucial idea that parasites do evolve to infect the most common local genotypes.

*Ophiostoma ulmi* is the fungal pathogen responsible for Dutch elm disease. Genetic analysis of a recent outbreak of a virulent subgroup indicated that fungal populations at the front of the epidemic were clonal and that genetic diversity increased toward the center of the outbreak. This parasite is itself infected by a virus-like cytoplasmic factor. The prevalence of this factor is greatest in genetically homogenous fungus populations and decreases in more diversified populations (Brasier 1988), which is a pattern consistent with parasite tracking.

Lively *et al.* (1990) compared the levels of infection by trematode larvae in natural populations of coexisting sexual and parthenogenetic fish (*Poeciliopsis* spp.). The parthenogens are triploid, and their eggs require activation by sperm to initiate development; hence, the parthenogens become sperm limited as they become common, and they cannot replace their sexual counterparts. The resulting coexistence of sexual and clonal fish means that a single clonal (but highly heterozygous) genotype can become and remain very common. Hence, one would expect to find that the parasites of these fish are better at infecting the most common clone. An analysis of encysted trematode larvae (*Uvulifer* sp.) was consistent with this basic prediction: clonal fish had more parasites per unit length (and a significantly lower residual variance) than did coexisting outcrossed fish. However, the result did not hold for a highly inbred founder population of sexual fish in another area. In fact, the inbred sexual fish had more parasites per unit length than the clones (perhaps due to the greater homozygosity of the inbred sexual subpopulation). But, two years after sexual fish were reintroduced by Vrijenhoek into the inbred founder population, the trend reversed, and clonal fish had more parasites and a lower variance than sexual fish (see also Vrijenhoek 1993). This rapid change by the parasite is evidence that they can rapidly track the changes in genotype frequency in natural host populations.

Jaenike (1993) recently showed similar tracking of a host by its parasite to an extreme degree. One strain of nematode, which was originally capable of infecting four different species of *Drosophila*, lost the ability to infect one of these species in less than three years. During this time the parasite was only exposed to one of the host species, which it could still infect. Hence, this study and the results of Boots and Begon (see Read *et al.* this volume,

Box 4) provides evidence for the evolution of host specificity, and the genetic trade-offs that are necessary to cause the cycling of genotypes.

Additional indirect evidence of genetic tracking by parasites comes from reciprocal cross-infection experiments. These experiments test the idea that parasites have become locally adapted to their host populations, which is suggestive of tracking. Recent studies of natural trypanosome-insect (Shykoff and Schmid-Hempel 1991), aphid-pea (Via 1991), fungi-plant (Parker 1985), thrips-composite (Karban 1989), trematode-fish (Ballabeni and Ward 1993), trematode-snail (Lively 1989), and nematode-mouse (Quinell *et al.* 1992) associations have been consistent with the expectation of local adaptation in structured coevolving populations, and add support for the assertion that negative-frequency dependent selection from parasites maintains genetic diversity. In addition, the concept of host-tracking is critical for the arguments pertaining to the advantages of sexual reproduction in the face of parasite selective pressure.

# 7 Parasitism and modes of host reproduction

If host-parasite interactions do in fact provide an explanation for the maintenance of genetic diversity, then they might also be a factor in the maintenance of diversity-generating phenomena such as sex and recombination (Hamilton 1975,1980,1982,1990, Levin 1975, Jaenike 1978, Glesener and Tilman 1978, Bremermann 1980, Lloyd 1980, Bell 1982). In its simplest form, the idea here is that if a sexual population is invaded by a rare mutant that reproduces solely by clonal means, it should be able to increase in frequency due to the advantage of not producing sons (Maynard Smith 1971). But as the mutant becomes common, it will also have the most common phenotype at resistance loci; parasites would rapidly counter the resistance trait and disproportionately exploit the common genotype. This kind of parasite-mediated selection against common clones could prevent them from fixing. One of three possibilities then exist: (1) the clone comes into a stable equilibrium with the sexual population (2) the clone is eliminated from the population, which would be expected if the parasite 'overshoots' (due to a time lag) and continues to infect the clone even after it is driven to extreme rarity, or (3) the clone is driven to rarity, but does not go extinct.

## 7.1 Difficulties for theory

Regarding the last possibility, a clone could be driven to a single individual and still recover (because of its ability to reproduce without a mate). The clone would then be expected to engage in the same initial spread as that

initiated by the original ameiotic mutant, resulting in a parasite-mediated oscillation in the frequency of the clone. This kind of result might cause a problem for the parasite theory of sex, because selection would favor the accumulation of clones. The advantage of sex would be eroded in direct proportion to the number of clones with different resistance phenotypes. This is true unless there is some additional mechanism that functions to eliminate clones as fast or faster than they are generated. Mutation accumulation by Muller's ratchet (Muller 1964, Bell 1988, Lynch and Gabriel 1990, Chao 1990) may provide such a mechanism. The idea here is that each time a host clone is driven to rarity (but not extinction) by the parasite, the mutational load in the least-loaded clone should increase. Hence, parasites could prevent the fixation of clones, and Muller's ratchet could function to eliminate them (Lively 1992, Howard and Lively 1994).

Along the same lines, there may be another problem for parasites, at least as they apply to the maintenance of biparental sex in hosts. In contrast to the situation of invasion by a invariant clonal lineage, consider the effect of an allele for selfing. In the absence of fairly severe inbreeding depression, the selfing allele should spread (Lloyd 1979). The problem here is that there is no single genotype associated with uniparental reproduction (as there is for the situation involving obligately apomictic reproduction). Nonetheless, parasite pressure could prevent the allele from fixing, leading to a stable level of mixed reproduction within individuals. Aggregation of sibs (as seems reasonable in plants) combined with density-dependent transmission of disease might be expected to push the equilibrium (or point of attraction) towards more outcrossing. Conversely, the intermixing of families might be expected to push the equilibrium more towards complete selfing.

One final concern for the idea that parasites maintain sex is that, for sex to be favored, the effect of parasites have to be severe (May and Anderson 1983). One possible solution to this problem is truncation selection (Hamilton *et al.* 1990). The idea is that the most intensely infected individuals will be less able to compete for some limiting and discrete resource, and as a consequence they will be unable to survive. Hence, parasites need not kill or sterilize their host to be effective in maintaining sex. In addition, as they point out, the elimination of individuals under this kind of truncation selection is independent of the intensity of parasitism. Thus some intensely infected individuals could still reproduce, which might act to protect genetic variation. Recent experimental evidence for possible truncation selection in the wild comes from the study of red grouse (*Lagopus lagopus*) infected by a nematode (*Trichostrongylus tenuis*). These parasites made the grouse more susceptible to predation; worm burdens for depredated animals were intermediate compared to randomly collected (shot) birds and those killed by the parasite (Hudson *et al.* 1992, Hudson and Dobson this volume).

## 7.2 Empirical support

These difficulties aside, the parasite theory is the best supported of the ecological theories for the maintenance of outcrossing. In an elegant experimental study, Antonovics and Ellstrand (1984) tested for frequency-dependent selection, and whether it was generated by density-dependent or density-independent factors. A density-dependent advantage to being rare would be evidence for the competition-based 'tangled bank' hypothesis (Bell 1982), provided the competitive advantage was not associated with a light parasite load. A density-independent advantage to being rare would be evidence for the parasite hypothesis. By manipulating densities of plant tillers (*Anthoxanthum odoratum*), they found that rare genotypes had an advantage that was independent of density, but the exact mechanism underlying the advantage was not determined. In a later study, an unexpected invasion by aphids suggested that attack by this insect may either directly or indirectly favor rare genotypes, due to the transmission of viruses (Schmitt and Antonovics 1986).

The biogeographic distribution of parthenogenesis has also been found to be consistent with the parasite hypothesis for sex. For example, the dioecious freshwater snail, *Potamopyrgus antipodarum*, contains both biparental and uniparental populations, as well as populations that are mixtures of both sexual and parthenogenetic individuals. Hence, the opportunity exists for rapid replacement of sexual females by parthenogenetic females. The frequency of sexual females in this species was found to be correlated with the prevalence of infection by digenetic trematodes, which suggests that males and crossfertilization have been lost from populations where the parasite is rare or absent, and have persisted where the parasite is common (Lively 1987, 1992). It is not known whether infected snails are more likely to be removed by truncation selection, but because the parasites consume the reproductive organs of infected individuals, the strong fitness effects required by theory (May and Anderson 1983) would seem to be met.

Schrag *et al.* (1994a) found strikingly similar results in their study of a simultaneously hermaphroditic snail from Nigeria. Two morphs of this snail exist in natural populations: an aphallic morph, which can either self fertilize or cross fertilize its eggs, but cannot donate sperm; and a euphallic morph, which can donate sperm to either aphallic or euphallic individuals. As they point out, the frequency of cross fertilization in the population must be positively related to the proportion of euphallic individuals it contains, which is highly variable (Brown and Wright 1972). In a thorough examination of the biotic and abiotic correlates of euphally in this snail, Schrag *et al.* found that parasites were the best predictor of the frequency of the euphallic type. Specifically, the most common trematode taxon explained most of the variance in the frequency of euphallics, even after the effects of season and snail

age were statistically removed. Moreover, euphally is environmentally determined (Schrag and Read 1992), and in those populations that develop the euphallic morph, the induction of this condition seems closely timed so that broods exposed to the highly seasonal parasites are cross fertilized (Schrag *et al.* 1994b).

These correlational studies on snails tend to suggest that parasites influence the level of uniparental reproduction such that, across populations, biparental reproduction is favored where there is a high risk of parasitism, and uniparental reproduction is favored where there is a low risk of parasitism. Within populations, however, the parasite theory predicts that uniparental reproduction should be associated with greater parasite loads. Moritz *et al.* (1991) in a study of parasite (mite) loads of sexual and parthenogenetic geckos found that, where both reproductive modes were represented, parthenogenetic geckos were significantly more likely to be infected, and they had significantly higher mite burdens. Moreover, in the 6 locations they sampled where mites were found on at least 25% of the geckos, parthenogens were 150 times more likely to be infected than sexuals. This result held for multiple clonal types. Hence, as in the study of parasite loads in coexisting sexual and clonal fish (Lively *et al.* 1990) described above, parasites do seem to disproportionately attack clones where both clonal and sexual types coexist.

Similarly, Burt and Bell (1991) compared parasite-induced leaf damage for 106 pairs of vegetatively produced suckers and sexually produced seedlings of American Beech (*Fagus grandifolia*). For trees 0.5 m tall, suckers had significantly (1.7 times) more damage than seedlings. This asymmetry decreased with increasing tree height, until at 2 m there was no difference in the degree of damage between the two types. Hence there was a transient advantage to the sexually produced seedlings.

## 7.3 Parasitism and recombination

There are viable alternatives to the parasite theory of biparental sex, particularly those that deal with the irreversible accumulation of mutations in obligately uniparental populations (see Kondrashov 1988, Lynch and Gabriel 1990). But, however sex is maintained, parasites could still be the primary force selecting for rates of recombination (Levin 1975). The most striking evidence of this comes from a study of excess chiasma frequency by Burt and Bell (1987a,b). They reasoned that longer lived species should be selected to have higher rates of recombination to partially compensate for the disadvantage of long life in the face of rapidly evolving pathogens. For non-domesticated mammals, they found that a highly significant fraction (75%) of the variance in excess chiasma frequency was explained by age at maturity.

As recombination shuffles genes within the genome between generations, gene re-arrangements perform the same function during the lifetime of an

individual. This process is best understood in the ontogeny of the vertebrate immune system. In fact, the permutational assortment of immunoglobulin genes can be observed twice in the lifetime of a metamorphosing amphibian as it switches from aquatic to terrestrial habitats (Flajnik *et al.* 1987). By analogy to somatic hypermutation, it may be convenient to consider this process as somatic hyperrecombination because it occurs at an accelerated rate during an individual's lifetime. Like somatic hypermutation, it is targeted to specific parts of the genome, namely those that code for the antigen receptors of lymphocytes.

Gene re-arrangements generate approximately $10^8$ to $10^{10}$ specific antigen receptors from a limited number, on the order of $10^3$, germline genes. This array of antigen receptors, one specific type per lymphocyte clone, constitutes an individual's primary immune repertoire, which becomes available for clonal expansion and somatic hypermutation following exposure to parasite antigens (Rajewsky *et al.* 1987). It is believed that this primary immune receptor repertoire is sufficient for initially recognizing any biochemical identity posed by parasites (Klein 1990).

Mutation-driven variation of parasite antigens provides only a temporary respite from negative selection by the vertebrate immune system. Typically this window of vulnerability lasts for only several days as accelerated lymphocyte proliferation, mutational refinement and competition for antigen between cellular clones leads to a population of lymphocytes bearing high affinity receptors that efficiently seek and destroy invading parasites (Klein 1990). Although parasites are considered to have rapid generation times permitting rapid genetic evolution, this appears to be countered by somatic recombination and mutation in long-lived vertebrate hosts.

Parasites have also capitalized on gene re-arrangements for the somatic evolution of virulence. Major epidemics of influenza A are associated with reassortment of the 8 RNA molecules that constitutes its genome (Webster *et al.* 1982). In addition to recombination through sexual reproduction, some trypanosomes (e.g. *Trypanosoma brucei*) have an extensive library of genes that code for surface coat proteins that are sequentially expressed via a gene rearrangement mechanism (Barbet and Kamper 1993). Although textbooks depict trypanosome population dynamics within the host as negative-frequency dependent cycles produced by the lag in immune clearance, the true picture is more complex (Barry and Turner 1991). The initial progeny from a clonal infection are less virulent and show pronounced cycles. Successive waves of progeny become more virulent and coexist with other previous progeny leading to non-cyclic chronic infections illustrated in Figure 5. Nonetheless, the behavior of these interactions based on gene re-arrangements superficially resembles the cyclical genetic changes predicted by simple gene-for-gene models.

In vertebrates, the set of germline genes coding for antigen-binding recep-

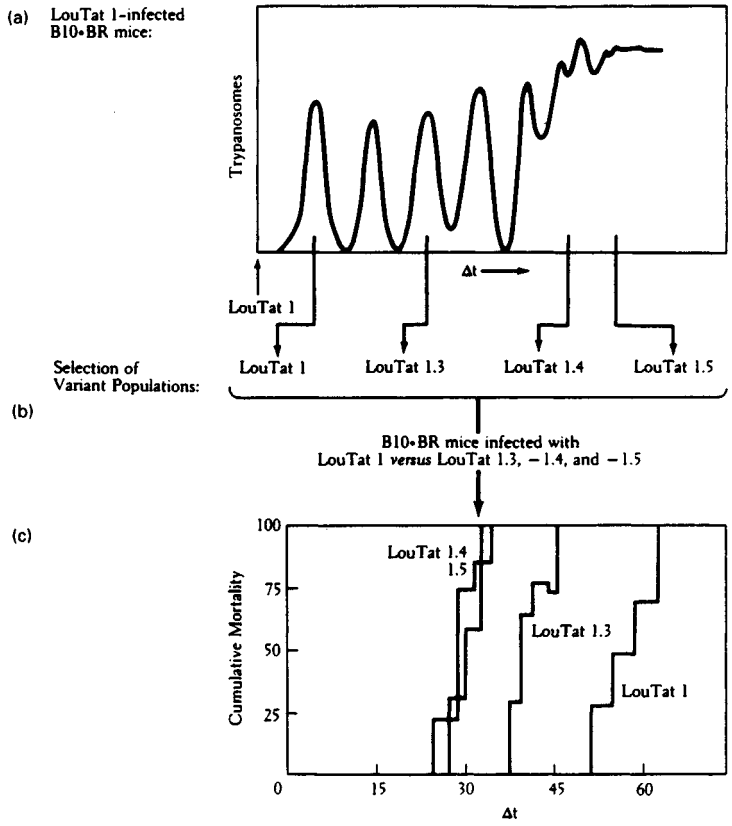


Figure 5. (A) The number of *Trypanosoma rhodesiense* trypomastigotes in the circulation of infected mice after infection by a single parasite clone (LouTAT 1). (B) Designation of daughter clones collected at different time points during the infection. (C) Virulence of the daughter clones as indicated by the survival time of mice of the same strain as the original infection (from Mansfield 1990).

tors genes appears to have diversified over geologic time through gene duplication via unequal crossing-over events (Warr and Dover 1991). In the murine and human genomes, approximately $10^3$ variable (V) region immunoglobulin genes are available for re-arrangement and incorporation into the primary immune repertoire. These V-region genes can be grouped into a limited number of families based on nucleotide sequence similarity. In a comparative analysis, V-region gene complexity increases with the divergence of each chordate lineage. Elasmobranchs have a limited diversity of V-region genes and are also characterized as having a more primitive genomic architecture (Hinds and Litman 1986). Higher vertebrates, except birds, possess a greater

number of V-region families and a greater number of members per family. The pattern suggests that immunoglobulin gene diversity increases with each derived vertebrate class. Curiously, birds use 25 pseudo-genes as donors of sequence motifs which are expressed in the single functional reading frame via a gene conversion mechanism to generate antibody diversity (McCormack *et al.* 1991).

Within a vertebrate clade, the complexity of V-region families can be dynamic over evolutionary time. In rodents, family complexity can increase in one family while decrease in another family over an interval of 1 to 30 million years (Tutter and Riblet 1988). It remains to be seen whether these changes in genetic diversity correspond to shifts in the immune repertoire and if these shifts are a counterploy to parasite tracking. It would be especially illuminating to evaluate immunoglobulin gene diversity in sexually and parthenogenetically reproducing sister taxa.

These molecular observations provide generality for the role of recombinational processes in mediating antagonistic interactions. As with mutation, current theoretical models use a single recombination rate to express the lability of genetic variation in parasite and host interactions. Our present understanding of the genetic basis of virulence and resistance, especially in vertebrates, shows that these genes are subject to rates and processes that differ from other regions of the genome. Accounting for this intragenomic heterogeneity of rates and incorporating the dynamics of somatic responses provide daunting challenges for future theoretical analysis of genetic coevolution.

# 8 Evolution of phenotypically plastic responses

The central tenet of Haldane's principle of parasites driving host genetic diversity is the importance of individuality. Modern agriculture and some natural systems discussed above (see Parasite Tracking and Modes of Reproduction) provide examples of how parasites successfully exploit genetically uniform host populations. We have discussed how, in genetic terms, individuality is generated by mutation and sexual reproduction and why parasites may be important in these processes. The interaction between the genome and environment further differentiates individuals within a population. Genotype by environment interactions figure prominently in the development of the resistant phenotype because of the predominance of inducible defenses.

As exposure to natural enemies, or intensity of exposure, becomes unpredictable and the fitness consequences severe, then the benefit of inducible defenses increases (Lloyd 1984, Lively 1986, Harvell 1990, Clark and Harvell 1992). Host-parasite interactions are characterized by features that promote

inducible defenses: (1) mutations which produce novel virulence traits appear sporadically; (2) movement of parasite infectious stages or infected individuals may be haphazard; (3) climatic or local environment conditions may favor transmission on an irregular basis; and (4) reservoir or intermediate host population dynamics may alter transmission independent of the focal host. Most importantly, the suite of potential parasite species that can infect a host species is greater than the number of species an individual host encounters during its lifespan. All of these aspects favor the evolution of inducible resistance traits.

Germ-free animals have a paucity of immunocytes compared to healthy animals reared in even the relatively sanitary conditions of the laboratory (Gordon and Pesti 1971). This indicates a significant inductive effect of 'benign' microbial flora on the development of the lymphoid compartment. In chronic parasitic infections, host responses are closely modulated to track the intensity of infection. Demographic models of unicellular parasites and lymphocytes within a single host show that the number of lymphocytes at the onset of infection is an important determinant of the outcome of infection (Schweitzer and Anderson 1992). Yet the vertebrate immune system generates immune effector cells on demand rather than maintaining a large reserve. Taken together, these divergent sources of evidence suggest that inducible resistance traits are costly and are carefully regulated to minimize the physiological cost to the host. Direct evidence for the cost of immune function is scarce but can be seen in the retardation of growth rates of chickens undergoing induced immune and inflammatory responses (Klasing *et al.* 1987).

The resource-dependent expression of the resistance traits is considered more fully in the chapter by Lloyd (this volume). Here, we wish to point out that the interrelationship between parasitism, resistance and nutritional resources poses serious challenges for future genetic research. The covariances between resource availability and effectiveness of host resistance will confound the relationship between the intensity of parasitism and host fitness. Thus, genetic variation in foraging performance or nutrient acquisition could be mistakenly attributed to the genetic component of parasite resistance. This underscores the difficulty of assessing the role of parasitism in natural wildlife populations as discussed by Gulland (this volume). Furthermore, the nutritional-dependence of resistance will render some questions unanswerable, such as genetic predisposition to geohelminth infections (Woolhouse 1992).

In addition to inducibility, the host immune system has two other critical design features: specificity and memory. As discussed previously (see Recombination), an elaborate genetic mechanism generates a practically limitless set of exquisitely specific antigen-binding sites. The antigen-driven expansion and focusing of this antigen-receptor repertoire is not only a form of

genotype by environment interaction but also has the hallmarks of cognitive process (Cohen 1992). There is positive and negative selection of the receptor repertoire as the lymphocytes 'learn' to discriminate between self tissues and foreign antigens (Boehmer and Kisielow 1990, Goodnow *et al.* 1990). Quantitative information about exposure to parasite antigens forms the basis for short-term immunoregulatory feedback loops (Schweitzer and Anderson 1992). In this way, proximate immune responses are scaled to the dose of the parasite antigen. Long-term retention of antigenic exposure is preserved in the memory cell compartment (Gray 1993). The fact that immune responses display dose-dependency and memory can impart complex dynamics in host-parasite relationships when these factors are taken into account (see chapters by Grenfell *et al.* (this volume)).

A model that incorporates immunological memory as a driving force in parasite evolution has been developed and analyzed by Pease (1978). It is based on the immunoselection of influenza A variants in a host population capable of resisting the previous epidemic variants. It assumes that the parasite's ability to invade the host population is linearly related to the time- (not replication) dependent mutation rate of the parasite genome. A provocative outcome of the analysis is the suggestion that a transmission threshold for the host population does not exist. This is because the virus can persist in small host populations because susceptibles are not introduced by a host birth process but rather by the ability to evade previous immunity by a mutation/selection process of the parasite that can match the host demographic characteristics. The model treats immunological memory and parasite mutation rate as converse yet identical processes, i.e. a higher mutation rate of the parasite implies that immunity is transient rather than phenotypically stable. This appears to be a tenuous assumption as it would allow cycling of parasite genotypes within one host generation. At least for the case of influenza A, immunological memory appears to be long-term (Figure 2).

The benefit of immunological discrimination between self and nonself comes at the cost of molecular mimicry by parasites. By resembling host self antigens, either through conservation or convergence, the parasite can evade immunological detection and destruction (Damian 1987). In a study where 14 human organs were screened with 635 monoclonal antibodies against 11 viruses, cross-reactivity between human host and viral antigens was observed in 3.5% of the combinations (Srinivasappa *et al.* 1986). Thus, all but the most critical functional sites of enzymes and structural proteins would be expected to be polymorphic in host populations in order to prevent parasites from fixing on common self-antigens. The fact that immunological non-responsiveness to self or tolerance is a phenotypically acquired trait assures biochemical individuality. The joint processes of molecular mimicry by parasites, genetic drift and the host's ability to discriminate between self and nonself on an individ-

ual basis may be epistemologically sufficient to account for the serological polymorphism that Haldane sought to explain.

The major histocompatibility complex (MHC) is a genetic locus of vertebrates that is remarkable for its extreme polymorphism and its retention of alleles across speciation events (reviewed in Nei and Hughes 1991). Coded within this locus are cell-surface receptors that present non-self antigens to reactive lymphocytes, thereby initiating specific immune responses (Klein 1986). A number of hypotheses have been advanced to explain the extreme degree of polymorphism and all rely, to some extent, on diversification from parasite selection pressure (Potts and Wakeland 1990, Hughes and Nei 1988,1989, Jones *et al.* 1990, Ohta 1991).

Recent evidence suggests that specific alleles are associated with resistance to specific parasites, cerebral malaria from *Plamodium falciparum* for example (Hill *et al.* 1991). The non-equilibrial frequencies of MHC haplotypes in Africans with severe clinical signs of parasite-induced disease and the geographic concordance between haplotypes and endemic malaria serve as evidence. Yet additional processes such as negative frequency-dependent selection cycling or population subdivision and movement need to be invoked to explain the persistence of alleles over time.

It is possible that the MHC is so polymorphic precisely because it is constrained by its functional role. Outside the immune system, biochemical individuality can increase through mutation-selection balance. The process of tolerance induction assures that each individual can recognize self from nonself tissue so that parasites can be recognized and controlled by highly specific immune responses. This discrimination is acquired through a single gateway—the MHC molecule. MHC molecules are constrained in one significant feature. There needs to be a conserved functional site for cell-cell contact and communication during antigen presentation. This crucial role for initiating specific immune responses will constrain variation and make this site predictable and exploitable to parasites. The recent discovery that *Theileria parva* sporozoites use MHC molecules to gain entry into host cells (Shaw *et al.* 1991) and the manipulation of immunity via binding of bacterial enterotoxins to a conserved site of the MHC protein (Johnson *et al.* 1991) are just two examples that illustrate this threat . Thus, the extreme degree of MHC polymorphism may arise from the mutation-selection processes typical of other loci, except that selection is exceptionally strong because of its central role in generating phenotypically plastic immune responses that are otherwise unpredictable and, hence, non-exploitable by parasites.

# 9 Conclusion

Models of host-parasite coevolution have confirmed Haldane's (1949) insight that the advantage enjoyed by rare alleles can lead to the maintenance of genetic variation. However, at least in models of very simple genetic systems (one or two loci with two alleles), there are several factors that could lead to the fixation of alleles, rather than their protection. These include long time lags, strong fitness effects, and parasite transmission that is determined by host density. More complicated genetic systems (several loci with two or more alleles) may help to reduce the gene frequency 'orbits', but even these could be insufficient for protecting variation when the population dynamics are strongly oscillatory (Frank 1993). This potential for loss of diversity provides a subtle challenge for Haldane's idea. Empirical validation of these theoretical studies is limited. There is evidence of cyclical genetic variation in influenza A epidemiology, but host genetic changes are unknown since immunity depends on epigenetic mechanisms. Trypanosomes and the vertebrate response is also posited to show cyclical genetic interaction, but again within the lifetime of an individual host. Studies based on simple allelic determinants of parasite virulence and host resistance have not examined cyclical dynamics of these genes. Studies that combine a molecular genetic understanding of virulence and resistance with a population genetic analysis are critically needed.

Current theoretical models and existing empirical information challenges (perhaps more stridently) the parasite theory for sexual reproduction. This is because strong negative effects of parasites on their hosts are required if outcrossing is to overcome its reproductive and genetic disadvantages. Yet, these conditions lead to large orbits in gene frequency phase planes. Clearly if diversity is lost, there is no advantage to outcrossing, and uniparental forms of reproduction should replace cross fertilization. Movement between subdivided populations could be a viable mechanism for restoring lost alleles to local populations, and maintaining diversity (Hamilton 1986, Seger 1988, Frank 1991). Studies of local genetic differentiation in natural populations in concert with estimates of gene flow are needed to resolve the question.

Truncation selection as envisioned by Hamilton *et al.* (1990) could be a potent force maintaining variation in the face of large selective differentials and time lagged frequency-dependent selection. It also obviates the need for the parasites themselves to cause host mortality or infertility in order for antagonistic interactions to favor sex. The available evidence for the parasite theory of sex, recombination, and genetic diversity is supportive, but not definitive.

Our current understanding of the genetic processes determining virulence and resistance traits imposes conceptual difficulties for unifying the genetic effects of parasitism into a single framework. Recently documented processes such as gene capture, gene re-arrangements, gene conversion and somatic

hypermutation confer resistance for hosts and some cases, provide for accelerated evolution of virulence genes of parasites. These discoveries blur the conventional distinction between genotype and phenotype and new models incorporating these biological innovations are needed.

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# Group Report: Genetics and Evolution of Infectious Diseases in Natural Populations

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## 1 Introduction

At a meeting dominated by population dynamicists, it was perhaps inevitable that much of the discussion in the evolution sessions centred on what impact

genetic considerations might have on epidemiology in natural populations. The emergent view was that we simply don't know: there is relatively little epidemiological theory with explicit genetics and even less data. This is perhaps because theorists fear over parameterisation of already complex models, and empiricists are put off by the expense and need for even wider collaboration: counting individuals is easier than assaying genotypes. Nevertheless, there is great potential for those willing to try, and in the first part of this report, we attempt to summarise some of the possibilities.

In the second part, we focus on issues of interest to evolutionary biologists (and, we trust, others). Necessarily, the list is incomplete: discussing the evolutionary *et al.* over half the world's organisms in two days necessitates the odd oversight. We conclude with a tentative agenda, developed very much at the editors' prompting. This is at best a partial list of possibilities: current theoretical and empirical ignorance is so great that almost any detailed analysis of the evolutionary genetics of host-parasite interactions in natural populations would be an advance.

# 2 Genetics and epidemiology

## 2.1 Does genetic heterogeneity matter?

Initially conceived in the original Newton meeting programme as 'Other host population heterogeneities, particularly age structure and host immunity', our session had by the second circular attracted the word genetics to its title, but only in the final programme did 'Genetics and Evolution' emerge. Such treatment inevitably emphasised that explicit evolutionary genetics has largely been absent from the successful development of epidemiology over the past two decades. As Anderson and May (1991, p. 208) pointed out in the context of human disease '... there has been, in recent years, a growing amount of work on age-related, social and other heterogeneities in host populations, [but] the possibility of genetic heterogeneity continues to be neglected in most epidemiological studies... This is understandable, because there is not much concrete evidence on which to base such studies'. We note that this lamentable state of affairs is, if anything, more acute for wild populations. Variation in disease resistance in domesticated and laboratory animals is well documented (e.g. Wakelin and Blackwell 1988, Kloosterman *et al.* 1992), as is genetic variation in resistance to pathogens within crop plants (e.g. Burdon and Jarosz 1990). Those studies that have attempted to look in natural populations of pathogen and hosts have documented genetic variation in interactions (Parker 1985, 1986, Burdon 1987, de Nooij and van Damme 1988, Alexander 1989, Burdon and Jarosz 1991, Fritz and Simms 1992, Alexander *et al.* 1993, Alexander and Antonovics, submitted); as an example, interactions between aphids and two of their natural enemies are described in Box 1. The

**Box 1.** Genetic variability in resistance and virulence in a natural system.

Experimental studies of the genetics of interactions between pea aphid and their most common parasitoids and fungal pathogens provides evidence of genetic variation within an insect species in resistance to its natural enemies. Within a single population, susceptibility to the parasitoid wasp *Aphidius ervi* ranged from 0–90% among different clones (Figure 1a; Henter and Via submitted). Within the same set of aphid clones, susceptibility to the dominant fungal pathogen (*Pandora neoaphidus*) ranged from 22–79% among different aphid genotypes (Hural 1994, Hural and Via in preparation). This genetic variability provides the raw material in this aphid population for the evolution of resistance to both of these natural enemies. Moreover, experiments have also revealed significant genetic variability within both the fungal population (Hural 1994) and the wasp in the same field (Figure 1b; see also Henter submitted). Therefore, genetic variation is locally available in all the participants in a potential three-species coevolutionary interaction.

absence of data is especially acute for wild vertebrates; indeed the greater emphasis on genetics in plant compared with animal epidemiology is perhaps in part due to the greater empirical base, presumably as a consequence of the relative ease of genetic analyses.

In what sense might genetic variability be unique relative to other heterogeneities considered by epidemiologists? How might the results of models differ if realistic estimates of genetic variability were included? When pressed, none of the group could come up with a convincing example of the failure of an epidemiological model that was definitely attributable to an absence of explicit genetics. Nevertheless, the general view was that this reflects the absence of genetic data as much as (or even more than!) the success of epidemiological models. The following areas emerged in discussion as potentially of interest to epidemiologists.

*Epidemiological dynamics can depend on genotype*

Numerous theoretical studies have demonstrated that heterogeneity of any sort can have major implications for population dynamics (e.g. Anderson and May 1991). However, relatively few data are available which combine population and genetical data. One such study is summarised in Box 2; here genetic composition of experimental populations had both qualitative and quantitative effects on the population dynamics observed.

An unexplored possibility is the role that genetic heterogeneity may play in stabilising host-pathogen dynamics in the wild. From a recent model which in-

**Box 2.** Silene-Ustilago: an example of the impact of host genetics on epidemiology of disease in natural populations.

*Silene alba* is a short-lived dioecious perennial found in ruderal habitats. The anther-smut *Ustilago violacea* parasites some populations of *S. alba*, such that diploid teliospores are produced in the anthers of infected flowers. These spores are transmitted to new hosts via insect pollinators. Newly diseased flowers appear between three weeks and two months after infection, when the fungus has grown through the plant and into developing buds. Plants often become systematically infected, so that by the following year all flowers are diseased resulting in complete sterility. There is no evidence that infected plants recover, and on average, disease-induced plant mortality is negligible.

The basic model for host-pathogen dynamics with frequency-dependent disease transmission applied to this system can be written as (Thrall and Jarosz submitted):

$$X_{t+1} = \frac{b_0}{b_1 N_{t+1}} + (1-d)\left(1 - \frac{BY_t}{N_t}\right) \quad (2.1)$$

$$Y_{t+1} = Y_t(1-d)\left(1 - \frac{BX_t}{N_t}\right) \quad (2.2)$$

where $d$ is the host death rate; $b_0/(b_1 N_{t+1})$, the density dependent per capita rate of reproduction, with $b_0$ the maximum host reproductive rate, and $b_1$ a constant; $X_t$, $Y_t$, and $N_t$ are respectively the number of susceptible hosts, infected hosts and total population size at time $t$; $\beta Y_t/N_t$ the frequency dependent rate at which individuals become infected, with $\beta$ as a measure of the effectiveness of transmission. Parameter values were estimated from data other than that used to test the model.

When natural host mortality was low, the model predicted coexistence of host and pathogen in susceptible populations, but in resistant populations the pathogen was lost (Figure 2). When natural host mortality was high, the pathogen was lost from the host population with little effect of host genotype.

These predictions were tested as follows (Thrall and Jarosz submitted). Experimental populations were established in pots on an abandoned golf course. A proportion of the pots were planted with diseased or healthy plants, with the remainder left available for seed colonisation. Following establishment of the pots, seedling establishment and disease transmission was allowed to occur naturally. Populations were established from crosses between parents of known susceptibility (determined from greenhouse inoculations and independent field trials). Data from two years are now available (Figure 3). The initial dynamics of susceptible populations was qualitatively different from those of resistant populations, consistent with the model predictions.

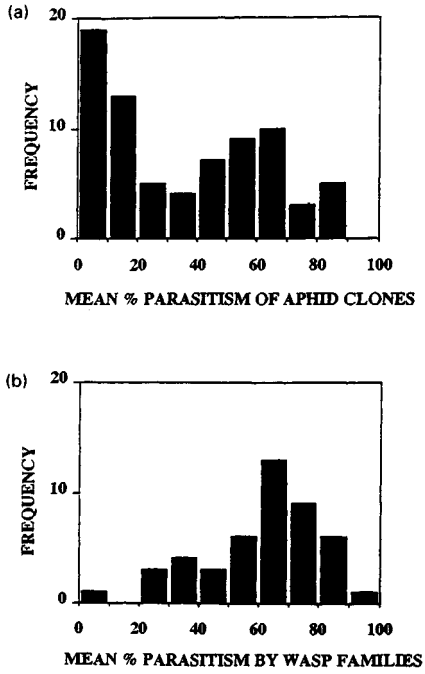


Figure 1. Genetic variation in a natural host-parasite system. (a) Aphid susceptibility to parasitism. Data are parasitism rates for each of 64 aphid clones, as the averages of five trials for each clone. Each trial consisted of exposing 20 juvenile aphids of each clone to a single wasp that had been chosen at random from a laboratory colony established from wasps collected in the same field as the aphids. After 24 hours of exposure, each wasp was removed, and parasitised individuals were scored eight days later. (b) Parasitism by wasp parasitoid families. Female progeny from a half-sib mating design of field collected wasps were allowed to parasitise groups of aphid nymphs of single moderately resistant clone, using the exposure protocol of (a) (both figures redrawn from Henter and Via submitted).

corporates quantitative genetic variation in a predator-prey model, Saloniemi (1993) derives stability criteria which are a function of the magnitudes of genetic variation in phenotypic characters that mediate the interaction between predator and prey. Stability was enhanced as genetic variation in these characters increases in both predator and prey. Other model produce a qualitatively similar picture in host-pathogen systems (Antononvics in press). This is in interesting contrast to the view of several theoreticians that incorporating demographic factors into coevolutionary models can make complex dynamical behaviours more likely (Anderson and May 1991 p. 643, Frank 1993).

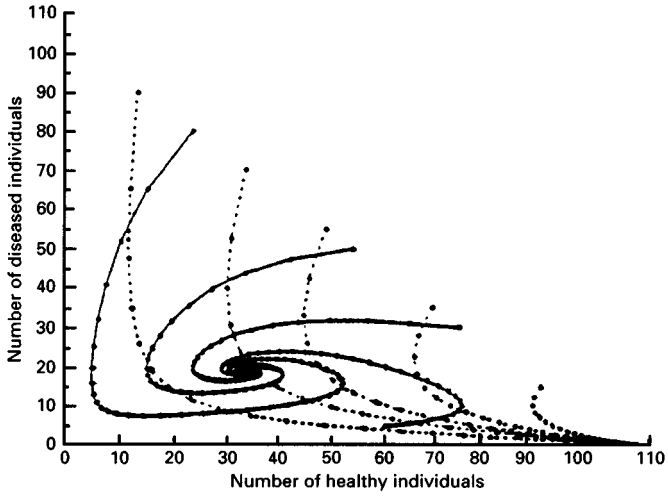


Figure 2. Dynamics of hosts and parasites from equations (1) and (2). Dashed lines, resistant hosts; solid lines susceptible hosts (from Thrall and Jarosz (submitted), who give parameter estimates).

*Genetic heterogeneity may generate epidemiological patterns presumed to have other causes*

Age dependence in the force of infection (rate that a susceptible of age $a$ will acquire an infection at that age), typical of many human diseases such as measles, is usually viewed as a consequence of age-specific changes in the degree of mixing and contact within and among age classes (e.g. school attendance). However, as Anderson and May (1991, Chapter 10) have emphasised, genetic heterogeneity in response to infection is capable of generating the same pattern. More susceptible individuals would, on average, become infected at younger ages than less infectable individuals who might suffer disease at later stages. Genetic differences are clearly not the only heterogeneity which might generate such a pattern, but the general point is clear: they might. If such heterogeneities are relevant, estimates of the level of herd immunity required to eradicate the disease are affected, with implications for the design of vaccination programs (Anderson and May 1991). It would be interesting to know whether similar age dependencies exist in natural populations with very different social structures, and if so, whether there was any genetic basis. More generally, investigations of the role of host genetic diversity in generating epidemiological phenomena in wildlife populations is likely to be fruitful. Invasive or destructive investigations of the causes of aggregation in macroparasite populations, for example, may be more tractable in natural populations.

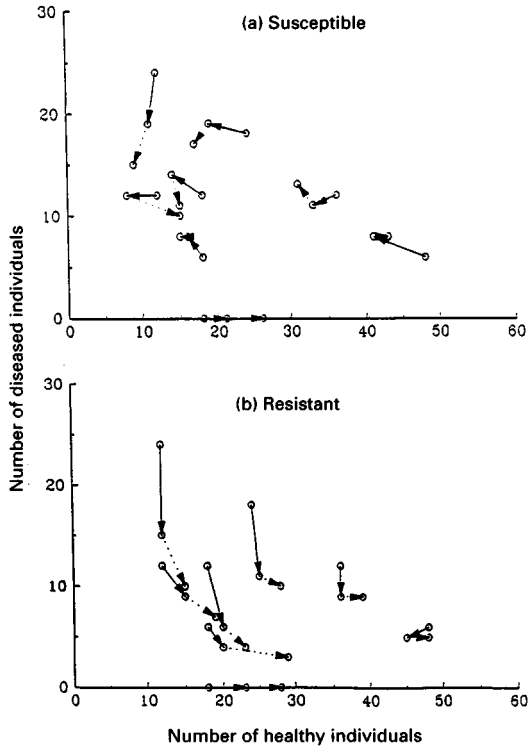


Figure 3. Year to year transitions in numbers of healthy and diseased individuals for population cages (1990–1992) (from Thrall and Jarosz, submitted).

*Pathogenicity can be influenced by pathogen genotype*

It is well known that for many human diseases there is often a poor correlation between the presence or level of infection and the severity of disease (e.g. Marsh 1992). The extent to which this is due to differences in parasite genotype is in some cases controversial (e.g. Marsh 1992, Day *et al.* 1992), but in other cases there seems little doubt. For example, *Toxoplasma gondii*, an important human pathogen particularly in AIDS patients, is found in many vertebrates and strains can be characterised as either virulent or avirulent by their effects on susceptible mice. A recent genetic analysis of 28 strains taken from humans (both with and without AIDS) and various domestic animals found that virulent strains ($n = 10$) had essentially the same genotype, whereas nonvirulent strains were polymorphic (Sibley and Boothroyd 1992). As population genetic analyses of parasites become more common, we expect the influence of parasite genetics on the outcome of parasitic infections to be more obvious.

*Parameters of epidemiological models can evolve rapidly if they are genetically variable*

Most characters examined in quantitative genetic analyses have been found to be genetically variable. Genetic variation in behaviours and physiological traits influencing transmission thus affords the potential for evolutionary change in key parameters of epidemiological models.For example, both the virulence of the myxomatosis virus and the resistance of the rabbit to the virus have evolved during the relatively short time in which the two species have been interacting in Australia. To what extent a knowledge of the genetic variability in both virulence and resistance in this system would make accurate predictions about the future ability of the virus to control the rabbit remain to be seen (Dwyer *et al.* 1990, and see below). Nonetheless, the general point is uncontroversial: genetic variation (in hosts and parasites) allows evolution (and coevolution). The role of genetic diversity in shifting host-parasite relationships is relevant to inbred domestic animal populations as well as dwindling natural populations, such as black-footed ferrets or large felids (e.g. Antonovics 1990).

*The outcome of biological control measures might be affected by host-parasite coadaptation*

Genetic variability in host-parasite or host-pathogen interactions may be relevant to biological control. It is known, for example, that the source of material used in biological control programs can influence the outcome of an introduction (Hopper *et al.* 1993). A dramatic example of the importance of considering the source of an introduced natural enemy is provided by the introduction to Australia of an herbivore to consume the floating weed *Salvinia molesta* (Room *et al.* 1981). After failing to control the weed with herbicides, considerable effort was initially made to release a beetle species collected from northern South America and Trinidad where it was known to consume a closely related species (*S. auriculata*). These introductions were completely unsuccessful. However, collections of the same beetle species from a site in Brazil where *S. molesta* was used as a host were successful. Thus, attention to the fact that parasites are likely to be locally adapted to their hosts (Lively and Apanius, this volume, Burdon and Jarosz 1991) can dramatically improve the chances of a successful introduction. Local genetic adaptation of species to various aspects of their environment may also be important with respect to conservation issues and maintenance of biodiversity given small and fragmented populations (e.g. Antonovics 1990).

## 2.2 The relationship between evolutionary genetics and epidemiology

In many ways, the genetical problem of characterising conditions for the persistence of alternative alleles at a single locus in a closed population closely

parallels the ecological problem of understanding the coexistence of interacting species in a community, and selectively maintained genetic monomorphism is akin to interspecific dominance and exclusion. For simplicity, genetical models are often cast as single-locus haploid systems: these are, in effect, models for interacting species. For example, McLean and Nowak's (1992) model of the evolution of AZT-resistance in HIV populations within a single individual is effectively a two-species competition model, with sensitive and drug resistant genotypes competing for CD4+ cells, fitnesses defined in terms of population growth rates of the two types, and with each type maintained by mutation from the other state. Such models suggest the idea that incorporating evolutionary genetics into epidemiology need not involve much new theoretical baggage: ideas developed more or less independently from evolutionary and ecological models might be mutually illuminating.

For instance, consider the following. Genetic explanations for polymorphism in haploid systems usually invoke frequency-dependent selection. Ecological explanations for coexistence instead concentrate on the relative strengths of intraspecific and interspecific density-dependent interactions (which can lead to frequency-dependence). These interaction strengths in turn often reflect the interplay of niche differentiation (in a very broad sense) with environmental heterogeneity and patchiness. In the pathogen-pathogen-host model of Hochberg and Holt (1990), for example (see Begon and Bowers, this volume), where individuals infected with one strain cannot be infected by the other, there is basically exploitative competition for a single limiting resource, so that the species able to persist at the lower resource (= susceptible host) density excludes the other species. What factors, then, could promote the coexistence of pathogen genotypes? Community ecologists have compiled a lengthy laundry list of possibilities, appropriate to different ecological situations. A few of these, tailored to the multi-pathogen-host system, are as follows: (i) One species could use the other as a resource. In the Hochberg-Holt system, coexistence can occur if the inferior exploitative competitor is able to invade hosts already occupied by the superior exploitative competitor, and supplant the latter; (ii) The host population may be heterogeneous, so that pathogen demes differ in their ability to utilise subsets of hosts. Anderson and May (1991, pp. 622–624) present an interesting model in which the host has a strain-specific immune response which fully protects it in the future against that strain, but not against the other strain. This permits two pathogen strains to coexist on one host, essentially because each has an exclusive resource not available to its competitor. On the flip side, use of immunosuppressive adaptations by a parasite strain to infect a host may allow unrelated parasites to colonise the host population. The recent outbreak of pneumocystis pneumonia in HIV-infected people is a poignant example. Other possibilities for coexistence of two strains due to host heterogeneity

include localised dispersal coupled with local superiority in particular habitat patches; differential attacks as a function of age; and, of course, appropriate genetic variation in the host. The aggregated distributions typical of parasitic helminths are crucial in determining coexistence and may allow two or more species to coexist in the same host population (Dobson 1985).

Thus considerable value can probably be gained from more explicit attempts to interpret the dynamics of evolving host-parasite systems using the perspectives of community ecology. There are, however, some obvious differences in the scope of the two classes of models. The main difference is in the details (albeit often crucial) of the transmission dynamics: species breed true, whereas genotypes beget unlike genotypes. Indeed, evolutionary models are perhaps best viewed as ecological models with the addition of complex mating dynamics. Consider for instance the host-host-pathogen model of Begon and Bowers with host self-regulation. This is perfectly reasonable as a community model, for different species often do have largely non-overlapping resource requirements. It is not likely that this model structure will apply directly to very many examples of within-host genetic variation: most genetic variants differ in a few respects from their conspecifics, but not so much as to be regulated completely independently. Moreover, genetic models in which one tracks the fates of a few competing host and/or parasite strains are literally only appropriate for major genes, and as a kind of scaffolding needed when using ESS approaches. Thus, while a simple one-locus approach provides a convenient way to begin to explore the role of genetics in epidemiology, the analogy with ecological models blurs when considering systems with multilocus or quantitative genetic variation, or where inheritance of traits and associated relative fitness' is not just the mid-point of parental values (e.g. where there are sex differences in reproductive success [fecundity selection], heterozygote advantage etc.).

The extent to which one or two locus models are too restrictive to provide an accurate description of either dynamics or equilibria in host-pathogen systems remains an open question, again principally because of the paucity of data. We note, however, that in models of evolution in spatially patchy environments, classical one-locus genetic models (e.g., Levene 1953) are a special case of more general quantitative genetic models (Via and Lande 1985). The one-locus model predicts the maintenance of genetic variation in a spatial patchwork, while the quantitative genetic model does not. This is because the one-locus case cannot produce the wide range of genetic and phenotypic values (and consequently the range of parameter values) that can be utilised in a quantitative genetic model (see also Dickinson and Antonovics (1973) p. 260). This means that there is a limitation on the degrees of freedom for evolutionary change in the simpler models. Thus, the results of the one-locus models in this case are actually constrained by the simplicity of the genetic

assumptions (other assumptions are the same as in the quantitative genetic models of Via and Lande 1985). This is a possibility that should also be considered as genetics are incorporated into epidemiological models, though which approach is the preferable is unclear (and contentious!). Nevertheless, where evolutionary studies of parasites have been attempted (e.g. the evolution of virulence), models have been largely devoid of explicit genetics. It is not yet obvious whether this matters much, again, because nobody has tried to find out.

## 2.3 Genetical theory devoid of epidemiological considerations

Although discussion was focused on what genetical considerations might bring to epidemiology, a recurring theme was that an explicit consideration of the ecological dynamics of host-parasite systems may sharpen one's understanding of evolution in these systems, and for several distinct reasons.

First, the dynamic stability – or instability – of a host-parasite interaction can constrain the potential for selection to act. As an extreme example, the American chestnut tree was devastated by a blight early in this century. The chestnut's numbers were reduced to such low densities that the tree went extinct (at least as breeding adults) over large areas, and is now found only in scattered pockets, mainly near the edge of its previous range. Any genetic variation initially present that could potentially have fostered an increase in resistance was simply not given the opportunity to become expressed, given the speed and severity of the epidemic. The ecological conditions that permit a lineage to persist define the arena within which evolution can occur. In the case of the chestnut, one could easily imagine that the rate of transmission of the blight might have been less, had the chestnut been more patchily distributed in the forest; this might have permitted enough individuals to remain for natural selection to operate.

Population dynamics might also indirectly govern the rate or direction of evolution in less extreme cases. The effective size of a population scales the standing crop of variation that can be maintained in the face of drift, and governs the rate at which new variation is generated via mutation. Given population fluctuations, effective population size is approximately the harmonic mean population size, which is dominated by population lows. Unstable host-pathogen interactions leading to recurrent population crashes may thus influence the amount of variation available for selection.

Second, formulations of fitness in terms of epidemiological and ecological parameters allow simultaneous analysis of frequency- and density-dependence in selection. In particular, Anderson and May (1991, p. 643) emphasise that epidemiological models can be used to develop fitness functions explicitly reflecting the ecology of the populations. They present an example of how

incorporating density effects into a coevolutionary model makes complex dynamical behaviours (cycles/chaos) more likely. This general protocol permits a richer interpretation of the selective forces impinging on the interacting populations (relative to the somewhat abstract relative fitness coefficients of 'gene-for-gene' models). The parameters of a well-specified model comprise those traits among which one might seek trade-offs (e.g., in developing an ESS model) or genetic covariances (in formulating a quantitative genetic evolutionary model).

### 2.4 Putting it all together

Perhaps the most striking feature of efforts to model evolution in host-pathogen systems is the tendency to add genetics and/or fitness functions to an existing ecological framework, or to add epidemiology to existing genetical models. There may be value in attempting to develop models incorporating both population and evolutionary dynamics from the start (e.g. Anderson and May 1991, Frank 1993, Nee and May 1993).

## 3 Evolutionary issues

### 3.1 Can parasites maintain genetic diversity?

The idea that coevolution of hosts and parasites is responsible for the maintenance of host genetic diversity (e.g. reviewed by Lively and Apanius in this volume) has received little direct empirical support for disease-associated direct selection in natural populations of vertebrates, though there is some evidence from human populations (e.g. Allison 1954, Hill *et al.* 1991) and laboratory-maintained populations derived from wild-caught animals (e.g. Wassom *et al.* 1973). The paucity of examples from wild populations may arise because there are still comparatively few studies with good measures of fitness components for large numbers of individuals (Clutton-Brock 1988), and even fewer involving both genetical and parasitological screening. The only non-human animal example of which we are aware is that of Soay sheep on St Kilda (Box 3), and there is a clear need for similar detailed studies in other wild animal populations. Furthermore, even in the case of the relatively well studied Soay sheep, the population dynamical consequences of parasite-induced genetic polymorphism are poorly understood. In plants, there is abundant circumstantial evidence that such polymorphism exists (e.g. Burdon 1987, Fritz and Simms 1992), although precise quantification of forces acting on resistance (or virulence) genes in any particular system is lacking. There is a need for studies that assess whether such polymorphisms are transient or stable (either locally or, when pathogens are widely dispersed, on a larger scale), and whether they are present because of selection on correlated features of the organism.

**Box 3.** Parasite-associated genetic polymorphism in wild sheep.

A feral population of Soay sheep has existed on the island of St Kilda, Scotland, for over 1000 years. The population follows an apparently stable limit cycle (Grenfell *et al.* 1992), where differences in mortality during over-winter population crashes (Clutton-Brock *et al.* 1991, Grenfell *et al.* 1992) was associated with gastro-intestinal nematode parasitism (Gulland 1992, Gulland *et al.* 1993). Extensive genetic screening has been carried out using polymorphic protein loci and polymorphic microsatellite loci. At the adenosine deaminase protein locus (a biallelic protein screened from leucocyte lysates), significant differences in survival in three consecutive population crashes (1986, 1989, 1992) were associated with significant differences in gastrointestinal worm burdens (as measured by faecal egg counts). Homozygous individuals suffered higher mortality (Figure 4) and had higher faecal egg counts. The explanation of these correlations remains speculative. However, ADA-associated immunocompetence has been reported in a number of domestic animals, and adenosine deaminase deficient genotypes in humans have abnormal T and B lymphocyte production and hence abnormal immune responses. Indeed, the Newton meeting coincided with press reports of the first use of human gene therapy in the UK, which was targeted at the ADA locus and immune deficiencies.

It remains to be seen if there are any population dynamical consequences of the ADA heterozygote advantage.

## 3.2 Can parasites maintain diversity-generating strategies?

A related issue is the role of parasite-mediated selection in the maintenance of sex, recombination and outcrossing (Lively and Apanius this volume). There is a clear need to distinguish these strategies in empirical and theoretical tests. In particular, the latter may be most challenging for the parasite view, as selfing can generate variable offspring, especially initially.

Several lines of theoretical work were suggested (see also Lively and Apanius this volume). First, even if parasites are involved, other environmental features may also play a role and the effects of any interactions is unclear in the absence of crowding or resource limitation. For example, parasites may not always apply significant selection pressures. Second, we have little theory about what sort of parasites should be involved (e.g. their life cycles, generation length, virulence, reproductive mode, endemic or epidemic etc). Third, under what conditions would parasite imposed selection actually act to increase levels of clonal diversity, rather than favour sex or outcrossing.

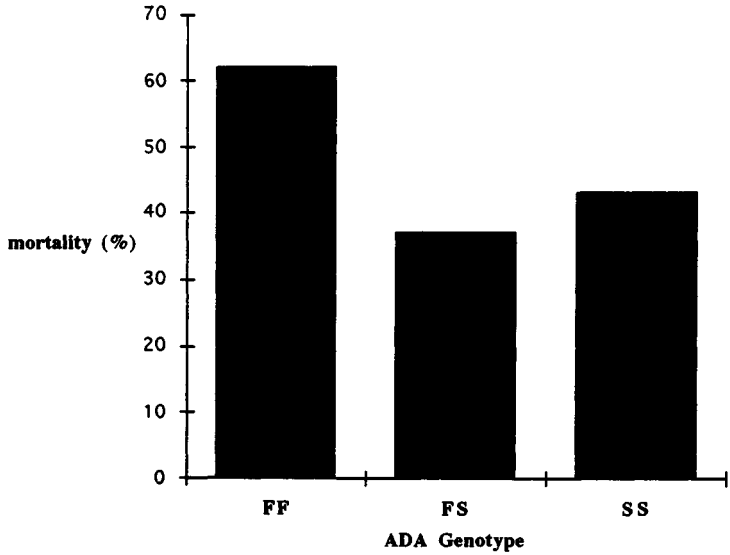


Figure 4. Percentage mortality of Soay sheep of different ADA genotypes average across three consecutive population crashes. $X^2 = 9.58$, $p < 0.01$. (Redrawn from Gulland *et al.* 1993).

Finally, what factors should influence parasite sexual strategies?

In addition to the types of empirical tests reviewed by Lively and Apanius (this volume), other, possibly stronger tests should be possible. For example, parasites may act to increase recombination in the genome in general, but the costs of recombining other, well-adapted gene complexes must be quite high. Thus, parasites may act to increase recombination in 'hot spots'. These would be areas of the genome that are relevant to parasite defence, such as the MHC complex. Other areas should remain relatively untouched. The somatic 'recombination' seen in some vertebrate immune systems might be a pinnacle of such 'hot spots'. As a caveat, though, recombination in specific areas may not be related to parasites; rather, other areas of the genome might be conserved, as for example, in mimicry patterns.

Selection experiments should offer powerful tests. Artificial selection can alter recombination rates (Brooks 1988), but whether parasites could exert such pressures remains to be shown. Parasites may also act to increase outcrossing rates in sexual organisms. In general, there might be a relationship between mechanisms that ensure outcrossing and risk of parasitism. This might be an explanation for outcrossing beyond the avoidance of inbreeding depression; in fact, inbreeding depression may be a consequence of the genetic load imposed by parasites selecting for outcrossing.

Parasites may play a role in the evolution of breeding systems (e.g. Read

1991). Mate choice may be a way to confer parasite resistance on offspring. For example, mate choice in mice generates larger than expected frequencies of heterozygotes at the MHC locus (Potts *et al.* 1991). This may well be a mechanism of conferring parasite resistance if heterozygotes express enhanced resistance. Also, multiple mating in polyandrous systems may increase the genetic diversity of offspring. An interesting case is provided where offspring stay to form social groups, such as in colonial invertebrates, social insects or social mammals (Hamilton 1987, Sherman *et al.* 1988). Increased genetic variation within such groups has demonstrable effects on trypanosome infections in colonies of social insects (Shykoff and Schmidt-Hempel 1991). These castes also provide examples of populations where spatial structure is closely related to genetic structure. This should profoundly affect the dynamics and evolution of the host-parasite system and may provide good examples to test ideas about the interaction of genetics, space and selective pressures. Clone experiments and field studies would allow investigation of the extent to which parasites influence the evolution of sociality (Freeland 1976, Hamilton 1987).

## 3.3 Host resistance

Our understanding of the mechanistic basis of host resistance – defined broadly to include any trait likely to mitigate the effects of parasitic infection – is inversely related to taxonomic diversity. The genetic and physiological basis of resistance is best understood in mammals and a few crop plants, less well characterised in other chordate classes and only dimly understood in the speciose invertebrate and dicot plant phyla. Certain modes of resistance are clearly widespread, such as phagocytosis and self-nonself recognition, while other modes, like somatic evolution, are probably restricted to particular phylogenetic lineages. Traditionally, the field of comparative immunology has focused on identifying homologous components of the mammalian immune system in other taxa, primarily analysis of nucleotide sequence similarity of cognate genes (e.g. Lambert *et al.* 1989). As a consequence, our functional understanding of parasite resistance modes in the majority of host organisms has suffered. Notable exceptions include the molluscan (Noda and Loker 1989), acarine (Burgdorfer *et al.* 1991) and arthropod (Schaub 1992) vectors of human parasites where resistance mechanisms receive the same vigor of investigation devoted to mammalian immunity. The artificial barrier between 'biomedical' and 'basic biological' investigations erected by funding agencies inhibits cross-fertilization between evolutionary ecology and invertebrate and vertebrate immunology.

Currently, there is no synthetic theory of resistance which has the potential to explain, much less predict, which particular resistance mechanisms are likely to evolve in any particular circumstance. For example, when are specific immune responses favoured over non-specific responses, or why do

particular modes of resistance overlap in a seemingly extravagant duplicity of effort? Such a theory would be a major step towards understanding the natural history of resistances mechanisms, about which we currently know a great amount of detail but have few ultimate explanations. It would also have tremendous practical significance: enormous redundancy in mechanisms is apparently a feature of host resistance, with a plethora of fixed and facultative responses involved. Determining which of these are actually important in controlling a particular infection, and which are epiphenomena perhaps important in other infections, might be easier if we had an adaptive theory of resistance. In contrast to cellular and molecular studies of host responses, evolutionary understanding requires an emphasis on function and process rather than structural detail. The inroads made by other disciplines attempting to understand the design principles of an immune system are illustrated by models of immunoregulation which attempt to distil the wealth of detail into simple functions (e.g. Schweitzer *et al.* 1993), and the appreciation that self-nonself recognition is a cognition problem (Cohen 1992).

Developing ideas about the evolution of resistance is likely to require some notion of the conditions under which non-specific responses are inadequate, and of the costs and benefits of particular resistance mechanisms. Data on the fitness costs of resistance are also are likely to be relevant to ecological dynamics (e.g. Frank 1993), evolutionary dynamics (e.g. the rate and magnitude of evolving resistance, as well as other traits affected by the costs of parasitism), and the evolution of pathogen virulence (see below).

Relevant data are scanty. It seems likely that resistance to parasitic infection will be associated with reductions in other components of fitness, but supporting evidence is largely indirect. One argument is that it is difficult to see why else hosts susceptible to extant pathogen genotypes would exist in a population. Indeed, this is probably why susceptible *Escherichia coli* are maintained in phage-infected populations (Levin and Lenski 1985). But there are other reasons why susceptibles may be maintained in a population. One is deleterious mutations at loci involved in resistance. Another is that continuing coevolution may mean that counter-adaptations are constantly arising in parasite populations, and lack of resistance is perhaps a consequence of time lags. Nevertheless, it difficult to imagine that the energy and material produced during a immune response in vertebrates is not without cost; presumably it is this which necessitates the need for clonal expansion and acquired immunity, rather than innate pre-emptive immunity, if indeed hosts have the potential to respond to any antigen.

Other evidence for resistance-associated costs include: the existence of autoimmune conditions and pathology due to host effector mechanisms rather than the pathogen-damage (e.g. schistosomaisis, hepatitis B, elephantaisis, acute intestinal responses to nematode infections (Behnke *et al.* 1992) and

of parasites which exploit defenses used by hosts against other pathogens (e.g. *Leishmania* spp., HIV); the generally negative effects of malnutrition on immunocompetence; and the effects of extra reproduction on susceptibility to disease (e.g. Festa-Bianchet 1989, Norris *et al.* 1994). More specifically, snails refractory to trematode infection have lower fecundity than unexposed controls (Minchella and LoVerde 1981), which might represent fitness costs associated with facultative host responses (Keymer and Read 1991). In addition, relationships between MHC haplotype and growth and fecundity parameters have been reported (Bonner 1986, Dietert *et al.* 1990), which suggests that this locus controls more than antigen presentation to lymphocytes, and artificial selection for increased resistance in domestic and laboratory animals often results in reduced fecundity, body size or life expectancy (e.g. Brindley and Dobson 1981, Siegel *et al.* 1983, Kloosterman *et al.* 1992). These results suggest a fundamental trade-off between allocating nutritional resources to lymphoid tissue (and host defence) or to reproductive component. Whether trade-offs revealed by such selection experiments persist in the long term is difficult to ascertain. We are only aware of one selection experiment on a natural host-parasite system (albeit maintained in the laboratory); here, resistance was again associated with decreased fitness in the absence of the parasite (Boots and Begon 1993; Box 4).

Direct, compelling evidence of fitness costs associated with resistance in natural populations is lacking. What is needed ideally is measurements of genotype by environment interactions for fitness-related traits in the wild, with exposure to parasites as the environmental factor. Just such an interaction is qualitatively described in a recent report of bumblebees (*Bombus terrestris*) parasitised by conopid flies (Müller and Schmidt-Hempel 1993). Parasitised bees stay in the field overnight rather than return to the hive. This has the effect of cooling the parasitoids which retards their developmental rate. Parasitised hosts therefore live longer, but at the cost of reduced help to the mother colony.

Measurements of the relative costs of different modes of resistance in the same host species would also be valuable; in vertebrate models, antigen- and germ-free environments, together with pharmacological agents and gene-knock out therapy provide the potential for disarming specific modes of resistance. These technological innovations offer the possibility of separating the cost of resistance from the cost of parasitism, but the extent to which they can produce data relevant to natural populations is unclear.

## 3.4 Virulence

What little theory and empiricism is available on the evolution of parasites themselves is, for the most part, concerned with the evolution of virulence. Extant theory (reviewed by Levin and Svanborg Edén 1990, Frank 1992)

**Box 4.** Costs of resistance to granulosis virus by Indian meal moths.

Six populations of the Indian meal moth *Plodia interpunctella* were maintained in the laboratory (Boots and Begon 1993). Three populations served as virus-free controls. The others were infected with self-perpetuating granulosis virus. The virus can be lethal, and is transmitted following host death. After two years, moths were cultured for two generations in the absence of the virus to rule out maternal affects and infection of assayed populations. The life histories of the selected and control populations were then compared. Resistance, as measured by $LD_{50}$'s, were almost twice as high in the populations maintained with the virus. This increased resistance was associated with longer larval development times and reduced egg viability which, in the absence of the pathogen, reduced fitness (measured as $r$) by 15% in the lines maintained with the virus. Maintaining the selected moths for two further generations in the absence of the virus reduced this difference to 8%.

Because mortality rates are dose-dependent, so too were the fitness benefits of resistance in the presence of the pathogen. Resistance had a selective advantage when virus inocula were small enough to induce mortality rates of less than 86% in the selected lines and 90.5% in the control lines. When doses were larger and mortality higher, the benefits of resistance were insufficient to outweigh the costs. Estimated mortality rates in the field are sufficiently low to allow the resistance detected in these selection experiments to spread, despite its associated cost.
Costs of resistance in Indian meal moths have also been suggested by a correlation between resistance to granulosis virus' and developmental times in six wild and two laboratory populations (Vail and Tebbets 1990).

focuses on the trade-off parasites face between destroying their food source (through host damage) and rapid growth and transmission, and now has some qualitative support (e.g. Ewald 1983, Bull *et al.* 1991, Herre 1993). But, with the exception of the myxoma virus in Australian rabbits, there have been no quantitative tests of theory. In that one case, theory has had limited quantitative success.

Anderson and May (1982), May and Anderson (1983) – see also Levin and Pimentel (1981) – used a simple differential equation model, a so-called 'SIR' model, to describe the dynamics of the interaction between rabbit and virus. The model can be used to derive an expression for the fitness of the pathogen, specifically the net reproductive rate or $R_0$ of the pathogen, in terms of the model parameters. This expression can in turn be used to predict the competitively superior strain of the pathogen. Anderson and May's key insight

is that the trade-off between death rate and recovery rate can be captured in the model by using existing data to empirically fit the recovery rate as a function of the death rate. This allows them to express the fitness of the pathogen in terms of the death rate of infected hosts; in other words, in terms of virulence. The resulting prediction is that pathogen fitness (transmission rate) is maximised for an intermediate level of virulence ($R_0$ is reduced by host immunity if pathogens are too benevolent, and by host death if they are too virulent). This matches the situation in Australia, but only qualitatively. In fact, the average level of virulence of myxoma strains in the field in Australia is substantially higher than Anderson and May's prediction.

Dwyer *et al.* (1990) attempted to improve Anderson and May's prediction by adding various kinds of realistic biological complexity. In particular, that changes in virulence lead directly to changes in the horizontal transmission rate of the virus, and that rabbit reproduction varies between seasons. In spite of this considerable increase in complexity (an increase in the number of parameters from 5 to 22), Dwyer *et al.*'s model performed only marginally better. Of course, many additional details might affect the coevolution of rabbit and virus, and it is difficult to know which would explain the discrepancy between theory and data. The issue proved controversial at the meeting and during the writing of this report. Some pointed out that sound quantitative estimates of relevant trade-off functions are difficult to obtain. Others pointed to the absence of explicit genetics in extant models and argued that incorporating quantitative genetics is the way forward. Many intuitively felt that models ignoring host resistance were likely to be at best incomplete. Still others believed, along with Anderson and May (1983 pp. 420–421), that taking into account details about the relationship between virulence and transmissibility (e.g. Massad 1987) is probably enough to reconcile theory and data, at least to accuracies consistent with common sense. The debate emphasised the issue of how close should we expect the fit of epidemiological models to be, and how might we distinguish empirically among different models producing equally good (or poor!) fits to the same data.

An alternative route to answering questions about the evolution of virulence is to work on a simpler and more experimentally tractable system. Insect baculoviruses, for example, are fatal and directly transmitted, they successfully evade host immune responses, and they are amenable to field experiments (Dwyer and Elkinton 1993). This reduced complexity relative to myxomatosis allows for easy estimation of $R_0$ in terms of virulence, transmissibility, and so forth. Encouragingly, quantitative predictions of the outcome of competition between different strains of a baculovirus of gypsy moths have been borne out by initial field competition experiments (Dwyer *et al.* unpublished).

Epidemiological approaches to the evolution of pathogen virulence thus

show the ability to accurately predict *a priori* the mean level of virulence of pathogens in the field. So far, however, no attempts have been made to explain the vast amount of variability in virulence that is seen amongst most pathogen populations, such as found in populations of *T. gondii* mentioned above, and in gerbil leishmaniasis (Dye and Davies 1990). Although it is possible that this variability is due strictly to ecological details, the more likely scenario is that the genetics of either host or pathogen are involved. Attempts to understand variability in pathogen virulence may thus lead to greater integration of ecology and genetics in the population biology of disease. Further provocative ideas about what current theory on the evolution of virulence does not even begin to explain are given in Levin and Svanbord Edén (1990). They suggest that virulence might be better viewed as an inadvertent consequence of within-host selection.

Before leaving the topic of virulence, we note that different authors use virulence in different ways. In some cases, disease severity in natural populations is at issue (e.g. Ewald 1983); in this sense, virulence is a property of the host-parasite interaction, and as much to do with host resistance as any parasite feature. Others take virulence to be a genetic trait of the pathogen itself (e.g. Levin and Svanbord Edén 1990). This latter sense is that used in the myxoma case, where changing virulence was assayed in standardised hosts (laboratory rabbits). In the plant literature, virulence is more often taken as the replication rate of the parasite within a host (e.g. Burdon 1987, Frank 1993). Whether these semantic differences obscure any conceptual difficulties is unclear. What is obvious, however, is that authors should explicitly define what they mean by virulence.

# 4 The future

We are only too well aware of what we did not cover during the meeting. For instance, nothing was said of the determinants and consequences of the genetic structure of parasite populations, of the congruence (or otherwise) between host and parasite phylogenies, or of the evolution of parasite life history strategies. Amongst the issues we did discuss, the ratio of ignorance to understanding was frightening enough. We do not believe that that was just a consequence of our expertise. Below, we attempt to list those unresolved issues which caught our interest during the meeting. However, we emphasise that this list is somewhat arbitrary and certainly incomplete; current knowledge is so limited, it is difficult to define even the central issues.

- How does incorporating genetics into population dynamical models affect the outcome? For example, what role might genetic variation play in stabilising host-parasite interactions?

- What epidemiological patterns are a consequence of genetic variation?
- Can we avoid over parameterisation of models incorporating genetical and population dynamical considerations? When is the genetics sufficiently simple to allow adding simple multi-clone dynamics into extant population dynamical models; when is the genetical and population dynamics sufficiently chaotic that the models can be treated as stochastic? Are explicit quantitative genetics necessary? Would they make things simpler?
- How should we incorporate immunological processes into models of host-parasite coevolution. Is there a conflict between somatic immune evolution within a host and conventional germline genetics? Perhaps in long lived hosts, the former is sufficiently described by extant models of the latter? Are there interesting interactions in shorter-lived hosts? To what extent do epigenetic processes like maternal transfer of acquired immunity impact on host-parasite coevolution?
- How do the mechanisms of host resistance affect the evolutionary and ecological dynamics of host and parasite? There are strong parallels with the study of aposematism, where the mechanism of predator learning has a major impact on the type of warning coloration that evolves (Guilford 1992).
- Under what circumstances are particular resistance mechanisms favoured by selection? For instance, when should plastic responses evolve? Is selection for improved immunocompetence actually for better nutritional acquisition? How does selection act on maternal tolerance or on concomitant immunity?
- How is population variance in immunocompetence partioned? What is the relative importance of differences in the ability to respond to parasite infection typically noted as species-specific, individual-specific and so on. If 'higher' vertebrates have the ability to respond to an infinite antigen diversity, why are there such differences?
- To what extent do we understand variation in virulence? Is the current emphasis on optimising parasite transmission sufficient?
- What are the consequences of considering evolutionary and population dynamic disequilibrium? Endemic persistence at population dynamic equilibrium, typically emphasised in evolutionary analyses, may be of less interest in a host-parasite context, where non-equilibrium states are clearly of great relevance (invasion of new pathogens, biological control, epidemics). Furthermore, the fitness of many traits in host-parasite

systems are typically both frequency and density-dependent. Yet most extant models of the evolution of virulence, for example, attempt to optimise parasite fitness assuming population dynamical stability. If such assumptions are inappropriate, how can we do away with them? One possibility is suggested by Nee and May (1993) in the broadly related context of intraspecific brood parasitism.

- Are epidemics the major source of selection on hosts, or are chronic infections more important? Does the nature of selection differ?

- Are there any generalities about the consequences of introducing new pathogens into a host population? Do we only hear about the disasters? Do the disasters only occur when there is a reservoir or continuous source of the pathogen?

- Are rare host and parasite genotypes at a selective advantage? This is particularly important in terms of the evolution of resistance to antiparasitic chemicals. The interplay between host-parasite population dynamics and genetics can be very complex. For example, Anderson *et al.* (1991) use simple models for the spread of anthelminthic resistance in nematode populations to demonstrate potentially intricate interactions between the dynamics of drug-resistant and susceptible parasite populations and the mating probability of rare genotypes.

- Is there heritable variation in the ability of both host and parasite to respectively resist and infect? Both of these issues lie at the core of notions about host-parasite coevolutionary cycles, yet there is precious little evidence for either from natural populations (see Lively and Apanius, this volume). Related to this, are parasite genotypes more successful at infecting the relatives of their hosts? There is some evidence of increasing mortality of measles for successive infections in the same human families in Senegal, although this has been attributed to more intense contract rates between relatives rather adaptation of the virus to genetically related people (Garenne and Aaby 1990).

- Are there any generalities about local coadaptation of hosts and parasites? More experiments involving sentinel organisms and reciprocal infections are needed. In such experiments, how can well adapted hosts be distinguished from poorly adapted parasites (and vice versa)?

- Sexually transmitted diseases are apparently ubiquitous in animals (Smith and Dobson 1992). Pollen and pollinator-transmitted diseases are also common in plants and have many features in common with venereal diseases in animals (Cooper *et al.* 1988, Antonovics 1992,

Thrall *et al.* 1993). How do STDs affect the evolution of host mating systems? For example, if sex is an anti-parasite adaptation how are STDs exploiting mating systems? What are the evolutionary consequences of STDs where transmission depends on the frequency of infectives rather than on host density, and thus requires different epidemiological framework?

## Coda

We left the Newton meeting with the feeling that there was much to be done. The success of the NeoDarwinian Synthesis in evolutionary biology was in large part because it made sense of the enormous range of disparate facts collected by natural historians over several centuries. A similar (but infinitely more expensive) set of facts is beginning to be accumulated about host-parasite interactions by cellular and molecular parasitologists. Developing an evolutionary interpretation of these phenomena is an exciting challenge.

There was also a strong feeling that attention to genetics may lead to the emergence of richer and more valuable epidemiology. Quantitative analyses well grounded in theory are timely, but will not be easy, because of the additional complexity added by genetic parameterisation. But conceptual and technical advances place us in a position to escape from the inertia that has, in this context, swept genetics under the epidemiological rug.

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# Beyond Host-Pathogen Dynamics

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## 1 Introduction

Historically, both empirical and theoretical population ecology have largely been preoccupied with one- and two-species systems. There are two very good reasons for this. The first is the sheer difficulty of extending studies to even three species both from the point of view of the analysis of models, and perhaps even more from the point of view of collecting dynamical data from multi-species systems. The second is that despite the obvious fact that no population exists in isolation, or interacts with only one other species, there are many contexts in which interaction strengths are such that two-species systems, at least, are an acceptable approximation to the truth. Nonetheless, and more specifically, there is strong motivation for extending the study of host-pathogen dynamics to that of multi- (that is, more than two species) interactions, in that there are contexts in which it is necessary to do so that may be fundamental (the role of pathogens, and indeed population dynamics, in community structure) or applied (elaborated on below).

Here we look beyond host-pathogen dynamics. We focus on 'ecological' systems, where host density is itself a dynamical variable, because the questions that have motivated us relate to host dynamics rather than the changing balance between diseased and healthy individuals in a host population of unchanging size. We refer, though, to a limited amount of epidemiological work where this demonstrably throws light on the systems on which we concentrate.

The systems themselves fall into two classes. The first has a single species of pathogen and a multiplicity of host species (in practice, host-host-pathogen systems), though within this we touch briefly on systems in which one of the 'hosts' is not itself infected but competes with another host which is. The second class has a single species of host and a multiplicity of predators (in the broad sense) at least one of which is a pathogen or parasite. We concentrate on host-pathogen-pathogen systems, spend rather less time on host-parasite-parasite and host-pathogen-parasitoid systems and touch briefly on host-pathogen-predator systems. The structures of the various relationships mentioned in this paragraph are illustrated diagrammatically in Figure 1.

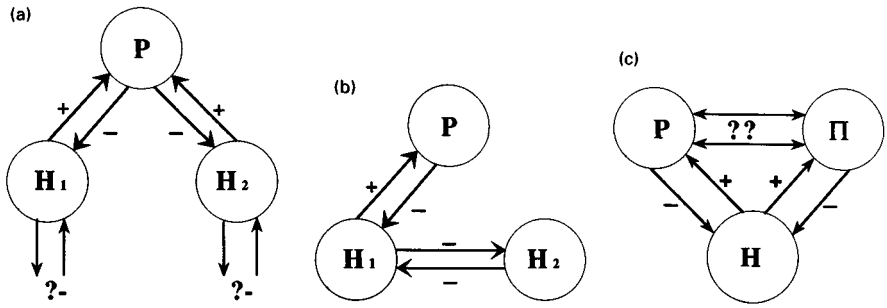


Figure 1: Diagrammatic illustrations of the interactions considered in this article. (a) Host-host-pathogen interactions, with or without host self-regulation. (b) Two competing 'hosts', only one of which is actually affected by a pathogen. (c) A host affected by a pathogen or parasite ($P$) and another natural enemy ($\Pi$) which may be either another pathogen or parasite, a parasitoid or a predator.

# 2 Host-host-pathogen and related interactions

## 2.1 Empirical studies of host-host-pathogen interactions

Empirical studies of host-host-pathogen interactions present a striking contrast with those of host-pathogen-pathogen systems, described below. In the latter, despite serious and widespread limitations in the available data, there has at least frequently been an interest in the manner in which two species of pathogen interact in their effect on their common host. Host-host-pathogen data, on the other hand, come largely in the form of two (or more) related host-pathogen data sets. Specifically, a great deal is known about the host ranges of pathogens of all types of taxa, and in the case of insect pathogens, for example, the relative pathogenicities of a pathogen to two or more species of host are often known in terms of $LD_{50}$s or related measures (see, for example, Entwistle and Evans (1985) for data on baculoviruses). Much less is known about the potential three-way interactions. This probably reflects a more widespread concentration in ecology on conventional competition for resources, rather than apparent competition (Holt 1977) between species sharing a predator or pathogen.

Nonetheless, a number of relevant studies do exist. Most notable perhaps is Park's (1948) laboratory investigation of two species of flour beetle, *Tribolium confusum* and *T. castaneum*, and their shared sporozoan parasite, *Adelina triboli*, which in single-species culture had a far greater impact on the

latter than on the former host. In the absence of the parasite, *T. castaneum* usually eliminated its competitor beetle from culture; but in its presence, the competitive outcome was usually reversed. Similar results were obtained by Sibma *et al.* (1964) using oats, barley and a root-feeding nematode, *Heterodera avenae*. Furthermore, Anderson and May (1986) discuss a number of vertebrate-host field studies in which a resident host is apparently driven to extinction by an invading species, mediated by their shared pathogens (e.g. the loss of much of the endemic Hawaiian bird fauna (Warner 1968) and the extinction of caribou in Nova Scotia and New Brunswick after the introduction of white-tailed deer harbouring a nematode highly pathogenic to caribou (Anderson 1972, Holmes 1979)). Unfortunately information about these interactions is mainly anecdotal in nature.

This 'conservation' interest in host-host-pathogen systems is by no means limited to past extinctions. There are a number of important cases where a host species harbouring a pathogen or parasite is widely believed to pose a present threat to a domesticated or semi-domesticated host species or even to ourselves. Badger populations are thought by many to be a reservoir from which infections of bovine tuberculosis are spread to cattle (e.g. Benham and Broom 1989). Foxes may be a reservoir from which rabies infections spread to cats and dogs or even humans (e.g. MacDonald 1980). On the other hand, domestic cattle seem likely frequently to be the reservoir from which rinderpest infections spread to wild ungulates (for example Shanthikumar *et al.* 1985).

A second applied problem that can be viewed, in essence, in host-host-pathogen terms, is the use of pathogens in the control of pests. The second host in such a case would be a non-target species, which, even as a general principle, it would be undesirable to harm, and which may actually be of positive conservation interest, as, for example, when baculoviruses are released to control a lepidopterous pest, but can also affect non-pest members of the local butterfly fauna (see, for instance, Payne (1988)). The data that are officially sought, and hence obtained, when such releases are being planned to control insect pests are host-range data, i.e. data on the range of hosts that the pathogen is capable of infecting, even if only at an extremely high dose. What are not apparently available are data on a wide range of parameters from each of the host-pathogen interactions (not only $LD_{50}$s, but also, say, pathogen productivities, never mind transmission parameters), to say nothing of data (comparable to Park's, above) on the population dynamics of the three species interaction.

## 2.2 Host-host-pathogen models

### 2.2.1 Direct transmission and no self-regulation

The first host-host-pathogen model to be studied in which the host populations are dynamical variables was that due to Holt and Pickering (1985). In this model infection is transmitted directly and the host populations are not self-regulated. The equations can be cast in the form

$$\frac{dH_1}{dt} = r_1 H_1 - \alpha_1 Y_1, \tag{2.1}$$

$$\frac{dY_1}{dt} = \beta_{11} X_1 Y_1 + \beta_{12} X_1 Y_2 - \Gamma_1 Y_1, \tag{2.2}$$

$$\frac{dH_2}{dt} = r_2 H_2 - \alpha_2 Y_2, \tag{2.3}$$

$$\frac{dY_2}{dt} = \beta_{22} X_2 Y_2 + \beta_{21} X_2 Y_1 - \Gamma_2 Y_2. \tag{2.4}$$

Here, $H_i$ is the density of the total population of host species $i$, $Y_i$ is the density of infected (and also) infectious individuals in this population, and $X_i = H_i - Y_i$ is the density of susceptible, uninfected individuals. Furthermore, $r_i$ denotes the intrinsic per capita rate of increase of species $i$, $\alpha_i$ is the rate, per infected individual, of pathogen-induced mortality and $\Gamma_i$ is the net rate, per infected individual, of loss of infected individuals (due to recovery, natural mortality and pathogen-induced mortality). Finally, $\beta_{ij}$ is the transmission coefficient of disease from host species $j$ to host species $i$, defined in such a way that $\beta_{ij} X_i Y_j$ is the rate of infection of susceptible hosts of species $i$ as a consequence of their interaction with infected hosts of species $j$. Two points are worth noting here. First, the present notation differs from that used by Holt and Pickering but is equivalent to it except that they included the possibility of a pathogen-induced reduction of host reproduction. Second, some of the mathematical results presented later rely on the biologically-justified assumption that parameters such as $r_i$ or $\alpha_i$ (or others introduced above or below) are positive.

The problem is, of course, to classify the dynamical behaviour of the system by finding suitable conditions corresponding to various qualitatively different behaviours.

Holt and Pickering concentrate on the case ($\alpha_i > r_i$) where each host species $i$ would be regulated by the pathogen at the point equilibrium $(H_i^*, Y_i^*)$ if alone with it. There are four possible equilibria which can be expressed, in an obvious notation, as $(0,0,0,0)$, $(H_1^*, Y_1^*, 0, 0)$, $(0, 0, H_2^*, Y_2^*)$ and $(H_1^\dagger, Y_1^\dagger, H_2^\dagger, Y_2^\dagger)$. In the second and third of these one species eliminates the other in the presence of the shared pathogen; in the fourth the two host species and the pathogen coexist. The densities at the coexistence equilibrium

are given by

$$\begin{aligned} H_1^\dagger &= \alpha_1 Y_1^\dagger / r_1, & H_2^\dagger &= \alpha_2 Y_2^\dagger / r_2, \\ Y_1^\dagger &= \beta_{22}(\beta_{11} Y_1^* - \beta_{12} Y_2^*)/B, & Y_2^\dagger &= \beta_{11}(\beta_{22} Y_2^* - \beta_{21} Y_1^*)/B, \end{aligned} \tag{2.5}$$

where

$$B = \beta_{11}\beta_{22} - \beta_{12}\beta_{21}. \tag{2.6}$$

The requirement that these are biologically relevant, in the sense that the densities are positive, leads to the following results.

1. When $\beta_{11} Y_1^* < \beta_{12} Y_2^*$ and $\beta_{22} Y_2^* < \beta_{21} Y_1^*$ (which implies $B < 0$), the coexistence equilibrium is relevant.

2. When either $\beta_{11} Y_1^* > \beta_{12} Y_2^*$ and $\beta_{22} Y_2^* < \beta_{21} Y_1^*$ or these two inequalities are reversed, the coexistence equilibrium is not relevant.

3. When $\beta_{11} Y_1^* > \beta_{12} Y_2^*$ and $\beta_{22} Y_2^* > \beta_{21} Y_1^*$ (which implies $B > 0$), the coexistence equilibrium is again relevant.

Using the standard linearisation techniques involving the Jacobian, Holt and Pickering show that, in case (1), both the equilibria $(H_1^*, Y_1^*, 0, 0)$ and $(0, 0, H_2^*, Y_2^*)$ are stable, in case (2) the first is stable and the second unstable (or vice versa) while in case (3) both are unstable. They are unable to complete the stability analysis for the coexistence equilibrium algebraically but, based on numerical studies, they make the hypothesis that coexistence is relevant and stable if and only if no other equilibrium is relevant and stable. Their numerical studies offer no evidence for the existence of stable cycles. The origin is always unstable in all the models discussed here.

Putting together the results of the last two paragraphs leads to the required dynamical classification. This can then be given a biological interpretation by considering the meaning of the pivotal condition

$$\beta_{ij} Y_j^* > \beta_{ii} Y_i^*. \tag{2.7}$$

This corresponds to the situation in which, on average, a susceptible individual of species $i$ experiences a more intense 'force of infection' when invading an equilibrium of species $j$ alone with the pathogen than it experiences in an equilibrium of its own species alone with the pathogen. A convenient shorthand for this is to say that 'species $i$ is more affected by inter- than by intra-specific infection'.

Using this idea and those above on the biological relevance and stability of the equilibria, leads to results entered in Table 1. This gives a classification of possible outcomes for two hosts sharing a pathogen, when the two hosts

| Host species 1 | Host species 2 | Holt and Pickering (1985) | Begon *et al.* (1992) | Bowers and Begon (1991) | Begon and Bowers (1994) |
|---|---|---|---|---|---|
| sufficiently pathogenic; inter>intra | sufficiently pathogenic; inter>intra | contingent elimination | contingent elimination | — | contingent elimination |
| sufficiently pathogenic; inter>intra | sufficiently pathogenic; inter<intra | species 1 eliminated | species 1 eliminated | species 1 eliminated | species 1 eliminated |
| sufficiently pathogenic; inter<intra | sufficiently pathogenic; inter>intra | species 2 eliminated | species 2 eliminated | species 2 eliminated | species 2 eliminated |
| sufficiently pathogenic; inter<intra | sufficiently pathogenic; inter<intra | infected coexistence | infected coexistence | — | infected coexistence |
| insufficiently pathogenic | sufficiently pathogenic; inter>intra | — | species 2 eliminated | — | species 2 eliminated |
| insufficiently pathogenic | sufficiently pathogenic; inter<intra | — | infected coexistence | — | infected coexistence |
| insufficiently pathogenic | insufficiently pathogenic | — | infected coexistence | — | infected coexistence |

Table 1: The outcomes in the various host-host-pathogen models when both hosts would be regulated if alone with the pathogen

would each be regulated by the pathogen if alone with it. The table contains results for other models but we shall concentrate on the current one here. This indicates that the outcome depends on whether both, one or neither of the host species are more affected by inter- than by intra-specific infection (inter > intra). If both are, there is elimination of one or other host (and regulation of the survivor) contingent on the initial densities; if one is, there is elimination of the host more affected by inter- than intra-specific infection (and regulation of the survivor); if neither are, there is coexistence of both hosts and the pathogen. This can largely be understood when it is realized that condition (2.7) means that species $i$ is insufficiently tolerant of the inter-specific infection to be able to invade an equilibrium of the alternative species $j$ and the pathogen.

We cannot continue without commenting on the criterion 'sufficiently path-

ogenic' which appears in Table 1 but is inactive for the present model. On general grounds – and with the hindsight provided by studies described below of more complex models – it is clear that the failure of a new species to invade an established equilibrium will not only depend on there being a sufficiently high transmission of infection to it. The mortality consequent on this transmission – resulting from the pathogenicity of the disease – will also need to be sufficiently high. In the present model, the pathogenicity needed to regulate a single host is always 'sufficient' for its possible elimination when the pathogen is shared.

The case of non-regulatory disease is considered briefly by Holt and Pickering. They state that if the disease cannot regulate either host species, then it is obvious that it cannot lead to the exclusion of either host. If the disease regulates species 1 but not species 2, then eventually species 1 will be excluded from the community, while species 2 grows exponentially. The results are entered in Tables 2 and 3 but the discussion of these tables is deferred until later when the classification criteria that appear there emerge naturally.

In their summary, Holt and Pickering emphasize several points. The close parallel between the outcomes for two regulated hosts and the classical Lotka-Volterra competitive model is stressed. The two hosts are subject to 'apparent competition' (Holt 1977, 1984) for 'pathogen-free space' (Jeffries and Lawton 1984, 1985), as opposed to conventional competition for a common resource. The model also identifies, via criteria discussed above, those factors that must be assessed to predict the consequences of shared infectious disease for species coexistence. Additionally, it leads to two conclusions which appear to apply for a broader range of models. First, given certain assumptions, including that disease is the only regulatory factor, the prevalence of infection (or fraction of hosts infected) is independent of the presence or absence of an alternative host species. Second, for the range of models in question, stable coexistence is not possible for a disease transmitted only between host species (i.e. between alternate hosts as with definitive hosts and intermediate hosts or vectors).

### 2.2.2 Free-living infective stages and no self-regulation

The next model to be studied in which two hosts share a pathogen (Bowers and Begon 1991) involves indirect transmission via free-living infective stages but once again host populations which are not self-regulated. The equations are:

$$\frac{dH_1}{dt} = r_1 H_1 - \alpha_1 Y_1, \tag{2.8}$$

$$\frac{dY_1}{dt} = \nu_1 X_1 W - \Gamma_1 Y_1, \tag{2.9}$$

$$\frac{dH_2}{dt} = r_2 H_2 - \alpha_2 Y_2, \tag{2.10}$$

$$\frac{dY_2}{dt} = \nu_2 X_2 W - \Gamma_2 Y_2, \tag{2.11}$$

$$\frac{dW}{dt} = \lambda_1 Y_1 + \lambda_2 Y_2 - (\mu + \nu_1 H_1 + \nu_2 H_2) W. \tag{2.12}$$

The last of these equations models the dynamics of the free-living infective stages of density $W$. These are produced at per capita rates $\lambda_1$ and $\lambda_2$ and have intrinsic death rate $\mu$. Their consumption by and subsequent infection of susceptible hosts involves the parameters $\nu_i$.

This model has only three equilibria: $(0,0,0,0,0)$, $(H_1^*, Y_1^*, 0, 0, W_1^*)$ and $(0,0,H_2^*, Y_2^*, W_2^*)$ so coexistence is not possible. In the case of two hosts which would each be regulated by the pathogen if alone with it, relevance and stability calculations give rise to results which conform with the pattern found above. However, a different mathematical condition corresponds to the notion that 'host $i$ is more affected by inter- than by intra-specific infection'. In fact (2.7) is replaced by

$$W_j^* > W_i^*. \tag{2.13}$$

As entered in Table 1, we see that not only is this consistent with the impossibility of coexistence but it also indicates that contingency cannot occur. The only possible outcome is the elimination of one host and the regulation of the other – the survivor being the species which tolerates the greater density of free-living stages. There is a satisfying parallel here with the results of models of conventional competition where the winning consumer is the one which tolerates the lower abundance of the resource (Tilman 1977, Armstrong and McGehee 1980). One point to note here is that the surviving species – say 1 – does not always enjoy a stable point equilibrium at $(H_1^*, Y_1^*, 0, 0, W_1^*)$. For some parameter values satisfying $W_1^* > W_2^*$, this is replaced by a stable cycle 'containing' the point. The classification principle embodied in the Table must therefore be read as accepting the replacement of point equilibria by associated cycles. Once again the condition of sufficient pathogenicity is automatically satisfied.

The possible outcomes when one or more of the host populations would not be regulated by the pathogen if alone with it are considered in some detail. The results are immensely more complicated that those of Holt and Pickering and this complexity can only be a consequence of the free-living infective stages. Contrary to the above, even if the disease cannot regulate either host species, it can still lead to the exclusion of one host (while the other grows exponentially and the disease persists). However, there are many possible varieties of exponential dynamics and these are sometimes expressed in a way that is contingent on initial densities. It is also no longer the case that, if the disease regulates species 1 but not species 2, then eventually species 1 will be excluded from the community, while species 2 grows exponentially. This only happens for certain regions of parameter space. In other regions other

outcomes are possible: species 1 may be regulated and species 2 eliminated or else both host populations may enjoy one of a variety of exponential dynamics. Outline results are included in Tables 2 and 3 but once again the classification criteria appearing in these must be left for later discussion.

Bowers and Begon consider the parallels in the regulated-regulated case between their work and that of Holt and Pickering. Coexistence and contingency are missing here because there is a common pool of infected particles which leads to a symmetry between inter- and intra-specific processes. If there were two pools (produced by the different host species), the full range of outcomes should be possible (see below). The most striking general feature, perhaps, is that the extension to include free-living stages generates a wealth of alternative behaviour not found in the direct transmission case. Bowers and Begon also consider the application to microbial pest control. One of the two hosts is thought of as a pest which, it is hoped, the pathogen will control and the other is thought of as a non-target species which it is undesirable to harm. This requires characterization of 'pest' and 'non-target' in terms of biological parameters which cuts down the possible regions of parameter space. The models suggest that, broadly, non-targets are unlikely to be seriously threatened in such cases and also that non-targets, far from undermining pest control, are quite likely to contribute to its efficacy.

### 2.2.3 Direct transmission and self-regulation

The next shared pathogen model to be studied was that of Begon *et al.* (1992). In this model infection is transmitted directly and, for the first time, both hosts are subject to self regulation. The model allows one to study how the interplay between self- and pathogen regulation determines the behaviour of the system. The equations describing the model are:

$$\frac{dH_1}{dt} = r_1 H_1(1 - H_1/K_1) - \alpha_1 Y_1, \tag{2.14}$$

$$\frac{dY_1}{dt} = \beta_{11} X_1 Y_1 + \beta_{12} X_1 Y_2 - \Gamma_1 Y_1, \tag{2.15}$$

$$\frac{dH_2}{dt} = r_2 H_2(1 - H_2/K_2) - \alpha_2 Y_2, \tag{2.16}$$

$$\frac{dY_2}{dt} = \beta_{22} X_2 Y_2 + \beta_{21} X_2 Y_1 - \Gamma_2 Y_2. \tag{2.17}$$

The quantities $K_i$ are, as usual, the carrying capacities of the hosts.

This model has possible equilibria of the form: $(0,0,0,0)$, $(K_1,0,0,0)$, $(0,0,K_2,0)$, $(K_1,0,K_2,0)$, $(H_1^*,Y_1^*,0,0)$, $(0,0,H_2^*,Y_2^*)$ and $(H_1^\dagger,Y_1^\dagger,H_2^\dagger,Y_2^\dagger,)$. The first three of these are unstable whatever values the parameters take. In the case of two hosts which would each be regulated by the pathogen if alone with it, relevance and stability calculations again begin

by yielding results which conform to the established pattern. The mathematical condition which replaces (2.5)/(2.7) is now

$$\beta_{ij} Y_j^* > \beta_{ii} \hat{Y}_i, \tag{2.18}$$

where $\hat{Y}_i$ denotes the density of infected individuals encountered when species $i$ is alone with the pathogen *in the absence of self regulation*. We interpret (2.18), as usual, to mean that 'host $i$ is more affected by inter- than by intra-specific infection' but now need to have in mind the expanded form 'host $i$ is more affected by inter-specific infection in the presence of self regulation than it would be by intra-specific infection even in its absence'. The results for the present model are entered in Table 1 which shows that now there is an extra classification criterion active. Each host species can either be 'sufficiently pathogenic' or not. The mathematical condition corresponding to such sufficiency is

$$\alpha_i > r_i \tag{2.19}$$

which is not automatically satisfied now by pathogen-regulated hosts. The new possibilities in Table 1 reflect the fact that the species characterized by insufficient pathogenicity cannot be eliminated even if it is worse affected by inter- than by intraspecific transmission.

The case of two (pathogen-) unregulated hosts is also considered. It is concluded that if

$$\frac{(H_{1,T} - K_1)}{K_1} \frac{(H_{2,T} - K_2)}{K_2} > \frac{\beta_{12}\beta_{21}}{\beta_{11}\beta_{22}} \tag{2.20}$$

then uninfected coexistence results with the hosts at their separate carrying capacities. Otherwise there is a jointly regulated state of infected coexistence. In (2.20), $H_{i,T}$ is the threshold density for species $i$ alone with the pathogen and this is the key to the biological interpretation presented in Table 2. For both host species here the threshold density exceeds the carrying capacity since they are not regulated by the pathogen. The right-hand side of (2.20) is a measure of the relative strength of the interspecific infection pathways (inter-transmission) while the left-hand side is a measure of the joint threshold surplus. If the former is insufficient to overcome the latter, uninfected coexistence results; if it is sufficient – and notice that this does not necessarily require interspecific transmission to exceed intraspecific – infected coexistence is found.

Begon *et al.* (1992) also consider the case of one regulated host and one unregulated host. The classification can again be cast in a form which, it transpires, is applicable more generally.

For one pathogen-regulated host and one pathogen-unregulated host the present model gives results which only depend on (2.18) and (2.19). In principle, biologically, one can imagine that the 'joint threshold' surplus may exceed

| Host species 1 | Host species 2 | Holt and Pickering (1985) | Begon *et al.* (1992) | Bowers and Begon (1991)[1] | Bowers and Begon (1994) |
|---|---|---|---|---|---|
| interspecific transmission < joint threshold surplus | | intrinsic exponential growth — pathogen extinct | uninfected coexistence | variety of exponential growths — pathogen extinct or persistent | uninfected coexistence |
| interspecific transmission > joint threshold surplus | | | infected coexistence | | infected coexistence |

[1] In this case, interspecific transmission equals joint threshold surplus.

Table 2: The outcomes in the various host-host-pathogen models when both hosts would be unregulated if alone with the pathogen

the 'inter-transmission' so that uninfected coexistence may come into play. However, the left-hand side of (2.20) is negative here and so the possibility is not active. The results in Table 3 are understandable in terms of invasion criteria.

One mathematical point underlying the above should be noted. With self regulation, it is effectively impossible to produce algebraic formulas for the densities at infected coexistence equilibrium. Furthermore, even if this had been done, it would be quite unreasonable to expect that the associated stability analysis could be carried out algebraically. Therefore it is necessary to make the conjecture, supported by extensive numerical studies, that no infected coexistence equilibrium is ever stable and biologically relevant when any other equilibrium is – but when no other equilibrium is stable and biologically relevant then one and only one infected coexistence equilibrium is so. Even for the model without self regulation Holt and Pickering had to make a parallel conjecture. An equivalent conjecture – supported by numerical studies and sometimes relaxed a little – is necessary for each of the models discussed below.

One of the central messages here concerns the difference that incorporating self regulation makes in respect of the coexistence of two hosts and their shared pathogen. Without self regulation, as discussed above (Holt and Pickering 1985), this can only occur for two pathogen-regulated hosts and then only by the mechanism corresponding to 'inter < intra' for both hosts in Table 1. As remarked previously, this may be thought of as the partitioning of enemy-free space in a process of apparent competition. With self-regulation there are several other possibilities. Coexistence, for example in the final case in Table 1, may be 'resource mediated' in the sense that it is related to high $r$ (intrinsic resource) levels and high $K$ (environmental resource) levels.

| Host species 1 | Host species 2 | Holt and Pickering (1985) | Begon *et al.* (1992) | Bowers and Begon (1991)[0] | Begon and Bowers (1994) |
|---|---|---|---|---|---|
| interspecific transmission > joint threshold surplus | sufficiently pathogenic; inter>intra | — | species 2 eliminated | species 2 eliminated | species 2 eliminated |
| interspecific transmission < joint threshold surplus | not (sufficiently pathogenic; inter>intra) | species 1 eliminated<br>species 2 grows exponentially | — | 1 eliminated 2 exponential<br>or<br>other exponential growths, pathogen extinct or persistent | uninfected coexistence<br>or<br>contingency between uninfected coexistence and infected coexistence |
| interspecific transmission < joint threshold surplus | sufficiently pathogenic; inter>intra | — | — | species 2 eliminated | contingency between species 2 elimination and uninfected coexistence |
| interspecific transmission > joint threshold surplus | not (sufficiently pathogenic; inter>intra) | species 1 eliminated<br>species 2 grows exponentially | infected coexistence | 1 eliminated 2 exponential<br>or<br>other exponential growths, pathogen extinct or persistent | infected coexistence |

[1] In this case, interspecific transmission equals joint threshold surplus.

Table 3: The outcomes in the various host-host-pathogen models when host 1 would be regulated if alone with the pathogen and host 2 unregulated

(The latter is needed for pathogen-regulation.) It may combine elements of both of these mechanisms as for two regulated hosts with one experiencing 'insufficient pathogenicity' and the other 'sufficient pathogenicity' but 'inter < intra'. It may occur for one regulated and one unregulated host (the final entry for this model in Table 3) in similar ways. Finally, coexistence, may even occur for two unregulated hosts (Table 2) where it is mediated by interspecific transmission.

### 2.2.4 Free-living stages and self-regulation

The considerable change of picture resulting from including host self regulation for directly transmitted diseases suggests that this must be done for indirectly transmitted infections. We outline here work of Begon and Bowers (1994) which addresses this problem. The basic equations are:

$$\frac{dH_1}{dt} = r_1 H_1(1 - H_1/K_1) - \alpha_1 Y_1, \tag{2.1}$$

$$\frac{dY_1}{dt} = \nu_{11} X_1 W_1 + \nu_{12} X_1 W_2 - \Gamma_1 Y_1, \tag{2.2}$$

$$\frac{dW_1}{dt} = \lambda_1 Y_1 - (\mu_1 + \nu_{11} H_1 + \nu_{21} H_2) W_1, \tag{2.3}$$

$$\frac{dH_2}{dt} = r_2 H_2(1 - H_2/K_2) - \alpha_2 Y_2, \tag{2.4}$$

$$\frac{dY_2}{dt} = \nu_{22} X_2 W_2 + \nu_{21} X_2 W_1 - \Gamma_2 Y_2, \tag{2.5}$$

$$\frac{dW_2}{dt} = \lambda_2 Y_2 - (\mu_2 + \nu_{22} H_2 + \nu_{12} H_1) W_2. \tag{2.6}$$

This model includes two pools of free-living infective stages and so should be an improvement over Bowers and Begon (1991) for this reason too. Results for this model are similar to those for the model immediately above. Consequently, we shall mainly note changes.

The model has possible equilibria of the form: $(0,0,0,0,0,0)$, $(K_1,0,0,0,0,0)$, $(0,0,0,K_2,0,0)$, $(K_1,0,0,K_2,0,0)$, $(H_1^*, Y_1^*, W_1^*, 0, 0, 0)$, $(0,0,0,H_2^*, Y_2^*, W_2^*)$ and $(H_1^\dagger, Y_1^\dagger, W_1^\dagger, H_2^\dagger, Y_2^\dagger, W_2^\dagger)$. The regulated-regulated classification (Table 1) now works with (2.18) replaced by

$$\nu_{ij} W_j^* > \nu_{ii} \hat{W}_i, \tag{2.7}$$

where $\hat{W}_i$ again applies *in the absence of self regulation*. The condition for 'is sufficiently pathogenic' remains

$$\alpha_i > r_i. \tag{2.8}$$

The mathematical condition replacing (2.20) is

$$\frac{(H_{1,\text{eff}} - K_1)}{K_1} \frac{(H_{2,\text{eff}} - K_2)}{K_2} > \frac{\beta_{12}\beta_{21}}{\beta_{11}\beta_{22}}, \tag{2.9}$$

where

$$H_{i,\text{eff}} = H_{i,T}^{\text{DIR}} + \frac{\Gamma_i}{\lambda_i}(K_i + \frac{\beta_{ji}}{\beta_{ii}}K_j) \tag{2.10}$$

with $H_{i,T}^{\text{DIR}}$ denoting the threshold density that would apply if there were direct transmission and

$$\beta_{ij} = \nu_{ij}\lambda_j/\mu_j. \tag{2.11}$$

The classification for the case unregulated-unregulated (Table 2) applies as previously with (2.20) replaced by (2.29).

The classification of the case regulated-unregulated needs modification to incorporate free-living stages. We now find (Table 3) that (2.29) can be satisfied in this case. The presence of one pathogen-regulated host does not rule out the shared pathogen system driving the pathogen to extinction. Such an outcome is possible either definitely or as one of a pair contingent on initial densities. When the unregulated species is characterized as not having both 'sufficient pathogenicity' and 'inter > intra', there is contingency with a state of infected coexistence. When the unregulated species has both the above properties, there may be contingency with the state in which it is eliminated. Notice that the first of these possibilities requires a relaxation of the conjecture on infected coexistence of the type mentioned above.

Clearly, given self regulation, the inclusion of free-living stages alters the picture. The state of uninfected coexistence is more likely and, in particular, can now occur in the regulated-unregulated case which complicates the possibilities there considerably. The reason for this is presumably associated with the losses which can occur before infection is transmitted. The inclusion of self regulation changes the application to pest-non-target problems in biological control. Neither uninfected coexistence nor the elimination of the non-pest are likely, so attention is focused on the relevant features of infected coexistence (Begon and Bowers 1995). Figure 2 illustrates this dynamically.

### 2.2.5 The inclusion of host immunity

All the above work is limited by the absence of host immunity. Preliminary results are available for hosts which can mount an immune response in the case of direct transmission with or without host self-regulation (Norman *et al.* 1994). The major notational difference is that $\Gamma$ has a component $\gamma$ which now denotes the rate at which hosts recover not to become susceptible again but to become immune. With this new use of $\gamma$ understood, it is easy to present the new results by reference to the old ones. For simplicity, we shall restrict attention to the case with self regulation. Condition (2.18) remains the same except that $\hat{Y}_i$ is now the density (alone with the pathogen) for a host which can mount an immune response. The effect of this on the likelihood of coexistence is still under investigation. Condition (2.19) becomes

$$\alpha_i > r_i + r_i\gamma_i/b_i, \tag{2.12}$$

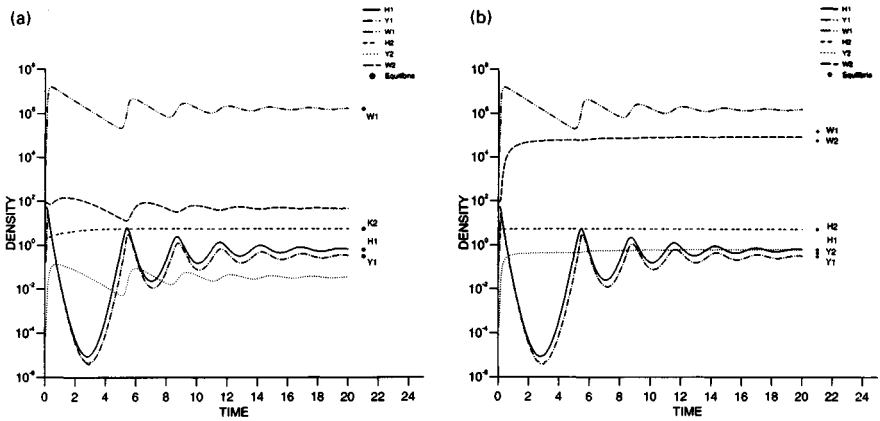


Figure 2: The dynamics of a pest - non-target - pathogen interaction (with free-living stages and self-regulation) in relation to equilibrium values for each host when alone with the pathogen. In (a) the non-target species 2 is uninfected when alone with the pathogen; in (b) it is infected. In both cases host densities are little affected by the sharing of the pathogen.

where $b_i$ is the intrinsic per capita death rate of species $i$. The effect of this is to tend to make infected coexistence – when there is at least one regulated host – more likely when an immune response is displayed. Finally, there are no changes at all in condition (2.20). The outcomes in the unregulated-unregulated case are unchanged.

### 2.2.6 General remarks

Several general points emerge from our discussion and from the Tables in particular. Including extra factors such as host self-regulation and pathogen free-living stages leads to an increased diversity of outcomes. In the regulated-regulated case the basic model suggests that the only mechanism for coexistence is apparent competition. The inclusion of host self-regulation reveals the extra mechanism of resource mediation and also demonstrates that mixtures of the two mechanisms may yield coexistence. Additionally, it explains how the above can lead to coexistence for one regulated and one unregulated host. It also shows that, even for two hosts which would not support the pathogen if alone with it, there is a mechanism – mediation by interspecific transmission – which allows infected coexistence when the pathogen is shared. The inclusion of free-living stages of the pathogen in the story leaves the picture for two regulated or two unregulated hosts essentially unchanged but suggests that due to losses in the process of transmission of infection a pathogen shared between a regulated and unregulated host may be driven to extinction.

Since the above picture only emerged gradually, by looking at models of increasing complexity, it is important to consider whether it is now essentially finished. This has two aspects. First, are the conclusions robust in the sense that they will not be perturbed if the detailed forms of the models are changed (say by altering the way self-regulation is included) without broadening the biological context? Second, will new possibilities emerge as additional biological factors (such as latent periods and density-dependent pathogenicity) are included? These are important but largely open questions.

## 2.3 A host-competitor-pathogen model

A model due to Anderson and May (1986) involves two direct competitors, one subject to a pathogen. The model therefore bears a superficial resemblance to host-host-pathogen models, but examines the effect of a pathogen on conventional competition rather than the effect of apparent competition on two hosts. In the present notation the model takes the form

$$\frac{dH_1}{dt} = a_1X_1 - b_1H_1 - b_{11}H_1^2 - b_{12}H_1H_2 - \alpha_1Y_1, \tag{2.13}$$

$$\frac{dH_2}{dt} = r_2H_2 - b_{22}H_2^2 - b_{21}H_2H_1, \tag{2.14}$$

$$\frac{dY_1}{dt} = \beta_1X_1Y_1 - \Gamma_1Y_1 - b_{11}Y_1H_1 - b_{12}Y_1H_2. \tag{2.15}$$

Here, $b_{ij}$ denotes the competition coefficients (both intra- and interspecific) and the parasite is assumed to reduce the reproductive rate of infected hosts to zero. In the absence of disease, competition may result in stable coexistence, either species winning, or an outcome contingent on initial densities. Without giving details, Anderson and May describe how invasion by a pathogen can substantially alter this. In some cases, infection of a superior competitor can facilitate the coexistence of an otherwise excluded inferior competitor. (Infection of an inferior competitor does not change such an outcome.) When without disease there is contingency, infection can lead to the uninfected species always winning or to stable coexistence from some initial conditions and the uninfected competitor winning from others. However, if there is coexistence before invasion, there is invariably coexistence after.

# 3 Host-pathogen-pathogen and related interactions

## 3.1 Empirical studies of host-pathogen-pathogen interactions

An overall impression of what is known of the biology of host-pathogen-pathogen interactions may be gained from an overview of multiple infections

in insects, since insect pathogens, by virtue especially of their potential role in the biological control of pests, are an extensively studied group. Harper (1986), in the most recent extensive review of the subject, makes it plain that multiple infections are common in insects, but that the literature on them is both limited and confused. Similar comments, regarding both frequency and limitations, are almost certainly appropriate in other groups of hosts.

There have been numerous studies on the mortality effects of two pathogens together on individuals or cohorts of insect hosts in the laboratory, most of which have also examined the effects of each pathogen alone. Other laboratory studies have looked for possible interference between pathogens more directly by examining the distributions of two pathogens within a host, either at the individual cell or the whole-body level. There have also been many reports of naturally occurring mixed infections of insects, though virtually none of these have provided quantitative data on single and mixed prevalences. There have been rather fewer studies on the efficacy of multiple introductions in the field for controlling insect pests, and not all of these have examined the efficacy of each pathogen alone. And not surprisingly, there appear to have been no studies of the population dynamics of multiple infections.

A degree of confusion has arisen because different studies have analyzed and classified the outcomes in different ways when two pathogens have affected a single host species. Harper (1986) proposed that from an applied point of view these outcomes could be classified as (i) additive (the level of host mortality is indistinguishable from what would be expected if the pathogens acted independently), (ii) synergistic (the level of host mortality is higher than expected), or (iii) antagonistic (the level of mortality is lower than expected). From an ecological point of view, however, it is preferable to expand this classification, so that the effects of the two species of pathogen are considered separately (Knell unpublished). Then the possible outcomes are : 0 0, 0 +, 0 −, + −, + + and − −. In this classification, at its simplest, the symbols 0, + and − refer to levels of mortality indistinguishable, higher and lower, respectively, than those expected if the pathogen acted alone. Thus, for example, in a '+ −' interaction, when two pathogens are consumed together by a cohort of hosts, the number of hosts dying with a pathogen 1 infection is higher than if the hosts had received the same dose of pathogen 1 alone, whereas the number of hosts dying with a pathogen 2 infection is lower. On the other hand, from an ecological or population dynamical point of view, host mortality rates may not be the only, nor even the most important, aspect of the outcome of a mixed infection. The number of infective particles produced by each pathogen species, for example, may also be of great importance. Hence, even a single designation such as + − may be inadequate as a description of a pathogen-pathogen interaction.

There have not been enough appropriate studies for the relative frequencies of these different types of outcome to be gauged with any degree of confidence. In particular, many of the studies that can be classified according to Harper's scheme cannot be fitted into the present, more extensive scheme, because only the overall mortality rates, not the causes of individual mortalities, were monitored. Nonetheless, an examination of the studies that have been carried out (Harper 1986, Knell unpublished) makes it clear that a range of types of interaction does occur. Only 0 − is apparently unrepresented, but this comes close to being represented in cases of competition (− −) which are notably asymmetric (e.g. Bird 1959). The interactions 0 0, 0 + and + + seem to be rare. The notation + ? would be necessary in a number of cases, where either the overall rate of mortality is increased (at least one of the pathogens must be benefitting), but mortalities have not been attributed to individual pathogens, or one pathogen is reported only to occur in the presence of a second pathogen.

However, the distribution of examples to particular classes is likely to be misleadingly simple. In practice, the outcomes in many examples depend both on the timings of the initial infections and the sizes of the initial inocula. For example, Boucias and Nordin (1978) found that *Hyphantria cunea* granulosis virus (GV) had a natural advantage in its homologous host (i.e. *H. cunea*), but that a nonhomologous *Diacrisia* GV could prevent infection with the homologous GV if given at a sufficiently high dosage. Bird (1959) found that inoculation of *Choristoneura fumiferana* with GV one or two days before inoculation with a nuclear polyhedrosis virus (NPV) resulted in replication of both, but when fed simultaneously in equal dosages, only NPV infection was found. Hence, any attribution to a particular class of interaction must necessarily represent a typical rather than a general or inevitable outcome.

Clearly, the diversity of interactions between pathogens within individual insect hosts is immense, and it is no doubt matched by the diversity in hosts from other taxa (see, for example, Dobson's (1985) review of parasites (essentially helminths) in vertebrates – discussed below). One of the most exciting challenges confronting those that study host-pathogen-pathogen interactions must surely be to understand how this diversity at the level of the individual host is translated into patterns at the level of the dynamics of whole populations. This refrain is given a reprise below when models are discussed.

## 3.2 Host-pathogen-pathogen models

Models of the dynamics of a host species affected by two species of pathogen have developed in tandem with models of the dynamics of two (or more) competing strains of a single pathogen within a host. These, starting with the work of Levin and Pimentel (1981), have generally been driven by a concern with the evolutionary dynamics of infectious diseases, especially myxomatosis

in rabbits. The models are dealt with together here, though mainly from the perspective of two separate pathogen species. All such models can readily be traced to the host-pathogen formulations of Anderson and May (1979, 1981), and all can be related to the following general model:

$$\frac{dX}{dt} = rX + e_1Y_1 + e_2Y_2 + e_{12}Y_{12} - \beta_1XY_1 - \beta_2XY_2 - \beta_{12}XY_{12}, \quad (3.1)$$

$$\frac{dY_1}{dt} = \beta_1XY_1 + \beta_{12,1}XY_{12} + \gamma_{12,1}Y_{12} - \Gamma_1Y_1 - p_2Y_1Y_2 - p_{12,2}Y_1Y_{12}, \quad (3.2)$$

$$\frac{dY_2}{dt} = \beta_2XY_2 + \beta_{12,2}XY_{12} + \gamma_{12,2}Y_{12} - \Gamma_2Y_2 - p_1Y_2Y_1 - p_{12,1}Y_2Y_{12}, \quad (3.3)$$

$$\frac{dY_{12}}{dt} = (p_1 + p_2)Y_1Y_2 + p_{12,2}Y_1Y_{12} + p_{12,1}Y_2Y_{12} - \Gamma_{12}Y_{12}. \quad (3.4)$$

The meanings of the parameters in these equations for the models of Levin and Pimentel (1981), Levin (1983a,b), May and Anderson (1983), Anderson and May (1986), Hochberg and Holt (1990) and Adler and Brunet (1991) are compiled in Table 4, having translated the notations of the various models to a common form. Table 4 thus shows the relationships of the models to one another.

In equations (3.4), $X$, $Y_1$, $Y_2$ and $Y_{12}$ are the densities of uninfected hosts, hosts infected with pathogen 1 only, hosts infected with pathogen 2 only, and doubly-infected hosts respectively. The parameter $r$ is the net intrinsic rate of increase of uninfected hosts; the parameters $e$ describe the contribution of infected hosts to the pool of uninfected hosts (by reproduction and/or recovery); the parameters $\beta$ are the coefficients of transmission of disease from infected to uninfected hosts; the parameters $\gamma$ describe the recovery of infected hosts to either an uninfected or a 'less' infected state (e.g. $\gamma_{12,1}$ : recovery from doubly-infected to infected with pathogen 1 only). The parameters $\Gamma$ describe the overall intrinsic loss rate of infected individuals. This may occur through natural mortality, pathogen-induced mortality or recovery. Finally, the parameters $p$ are the coefficients of transmission of disease from infected to already-infected hosts (hence producing doubly-infected hosts).

There are a number of points that emerge from Table 4.

1. None of the models examined to date have included either free-living infective stages or host self-regulation. The practical reasons for this require no elaboration, but the potential importance of these omissions has nonetheless been established above in the context of host-host-pathogen models.

| Parameter in the general model | Parameters in the specific models of: Levin and Pimental (1981), May and Anderson (1983) | Levin (1983a,b) | Anderson and May (1986) | Hochberg and Holt (1990) | Adler and Brunet (1991) |
|---|---|---|---|---|---|
| $r$ | $a-b$ | $a_x-b$ | $a-b$ | $a_x-b$ | 0 |
| $e_1(e_2)$ | $a$ | $a_{Y_1}+\gamma_1$ | $a$ | $a_{Y_1}+\gamma_1$ | $\gamma_1$ |
| $e_{12}$ | – | $a_{Y_{12}}$ | – | – | 0 |
| $\beta_1(\beta_2)$ | $\beta$ | $\beta_1$ | $\beta_1$ | $\beta_1$ | $\beta_1$ |
| $\beta_{12}$ | – | 0 | – | – | $\beta_1+\beta_2$ |
| $\beta_{12,1}(\beta_{12,2})$ | – | 0 | 0 | 0 | $\beta_1$ |
| $\gamma_{12,1}(\gamma_{12,2})$ | – | $\gamma_{12,1}$ | – | – | $\gamma_2$ |
| $\Gamma_1(\Gamma_2)$ | $b+\alpha_1$ | $b+\alpha_1+\gamma_1$ | $b+\alpha_1$ | $b+\alpha_1$ $+\gamma_1-\nu_1$ | $\gamma_1$ |
| $p_2$ $(p_1)$ | $\pm p$ | $p_2$ | $\pm p$ | $\pm p$ | $p_2$ |
| $p_{12,2}(p_{12,1})$ | – | 0 | – | – | $p_2$ |
| $\Gamma_{12}$ | – | $b+\alpha_{12}$ $+\gamma_{12,1}+\gamma_{12,2}$ | – | – | $\gamma_1+\gamma_2$ |

Table 4: Relationships between the various host-pathogen-pathogen models discussed in the text (where further explanation of the notation may be found).

2. Most notably, perhaps, most studies have eliminated the doubly-infected hosts from consideration (Levin and Pimentel 1981, May and Anderson 1983, Anderson and May 1986, Hochberg and Holt 1990), accounting for most of the dashes in Table 4. The implication is that doubly-infected individuals, if they exist at all, quickly revert to single infection. This being so, the potentially separate processes of (a) further infection of either of the singly-infected classes, and (b) recovery of doubly-infected hosts to either of the singly-infected states may all be condensed into a single parameter, $p$, representing the net rate of conversion of $Y_2$ individuals, say, into $Y_1$ individuals. Clearly, the net rate of conversion in the reverse direction is then $-p$ (Table 4). As Hochberg and Holt (1990), in particular, note, the two pathogens may thus be seen as not only competing for their common resource, the hosts, but also as a predator consuming a prey.

3. This elimination of the $Y_{12}$ class is much more appropriate with two strains of a single pathogen than with two separate species of pathogen. Two strains of the same pathogen will occupy effectively the same niche within the host, and the superior within-body competitor can indeed be expected to rapidly eliminate its inferior. By contrast, the range

of within-body outcomes documented above for two separate species of pathogen cannot be encompassed by the single parameter, $p$. There seems little doubt that one of the major challenges facing modellers in this area is to extend present models in order to investigate the possible links between patterns in the outcomes of interactions between pathogens within individual hosts and patterns at the level of three-species population dynamics.

Furthermore, since in vertebrate hosts the within-body patterns will reflect, in part, the host's immune response, host-pathogen-pathogen models hold out the enticing prospect of forging links between recent work on within-body dynamics and the dynamics of three species' populations.

4. Of the models that include the $Y_{12}$ class, that of Adler and Brunet (1991), which is actually extended to include $n$ species or strains of pathogen, has been included, despite the fact that it runs counter to the general intention to discuss ecological rather than epidemiological models. This has been done firstly because it is, in other respects, the most complete to date, and secondly because it establishes the potential value of analyses using approximations based on the densities $(Y_1 + Y_{12})$ and $(Y_2 + Y_{12})$, i.e. all individuals infected with a pathogen, whether or not infections are mixed.

5. Adler and Brunet were concerned to make technical rather than biological points, and Levin (1983a,b), in the only other analysis including $Y_{12}$ , was unable to complete his analysis, and unable, too, to provide clear biological criteria distinguishing different patterns of dynamical behaviour. Hence the messages to emerge from host-pathogen-pathogen models must derive from the several closely-related studies that exclude $Y_{12}$ (Table 4), of which the fullest and most recent, and that on which the following summary is based, is that of Hochberg and Holt (1990).

### 3.2.1 The Hochberg and Holt model

In order to investigate the conditions for coexistence of the hosts with both pathogens in models without $Y_{12}$, assume, as all previous analyses have effectively done, that each pathogen is able to regulate ('coexist with') the host alone ($\Gamma_i > e_i$). Assume additionally that pathogen 2 is the species with the higher basic reproductive rate ($R$), and which therefore depresses the abundance of uninfected hosts to a lower level, when interacting with the host alone. This means that

$$\beta_2/\Gamma_2 > \beta_1/\Gamma_1 \tag{3.5}$$

which is tantamount to saying that pathogen 2 is superior at exploiting healthy hosts. Coexistence then requires:

$$1 - \frac{e_2}{\Gamma_2} < \frac{rp}{\beta_2\Gamma_1 - \beta_1\Gamma_2} < 1 - \frac{e_1}{\Gamma_1}. \tag{3.6}$$

Each of these inequalities ensures that the associated pathogen can invade. A unique three species equilibrium point is ensured and a partial stability analysis is possible.

Since the two outer terms in equation (3.6) are both positive, and less than 1, a series of more particular conditions may be generated, namely:

$$p > 0, \tag{3.7}$$

$$\beta_2\Gamma_1 - \beta_1\Gamma_2 > rp, \tag{3.8}$$

$$\frac{e_2}{\Gamma_2} > \frac{e_1}{\Gamma_1}, \tag{3.9}$$

$$(1 - \frac{e_2}{\Gamma_2})\frac{\beta_2\Gamma_1 - \beta_1\Gamma_2}{p} < r < (1 - \frac{e_1}{\Gamma_1})\frac{\beta_2\Gamma_1 - \beta_1\Gamma_2}{p}. \tag{3.10}$$

Hence, it can be seen that coexistence of all three species requires:

1. that one species of pathogen (here, 1) is superior at exploiting already-infected hosts (equation (3.7)), but the other is superior at exploiting healthy hosts (equation (3.5)), to a degree which sufficiently offsets the interference advantage enjoyed by the first pathogen (equation (3.8));

2. that this second species is also less virulent (equation (3.9)), in the sense that hosts infected by that pathogen give rise to a larger number of healthy hosts over the course of their infection; and

3. that the intrinsic rate of increase of the host (equation (3.10)) must be neither too high (in which case the superior exploiter of healthy hosts would be excluded, presumably because it cannot properly use its advantage since healthy hosts are unlikely to be a limiting resource), nor too low (in which case the superior exploiter of infected hosts would be excluded, presumably because of the low availability of healthy hosts, for which it is the inferior competitor).

In summary, therefore, coexistence occurs, at intermediate host productivities, between a virulent, efficient exploiter of infected hosts, and a less virulent, efficient exploiter of healthy hosts, more capable than the virulent pathogen of depressing host abundance.

Interestingly, Hochberg and Holt (1990) contrast their results with those from host-parasitoid-parasitoid models (e.g. May and Hassell 1981). In the latter, where the parasitoids need to kill their hosts, the intrahost/extrahost

trade-off as a basis for coexistence is even more straightforward. Low to moderate pathogenicities in the pathogens blur the precision of this trade-off.

On the other hand, aside from coexistence, if only one of the inequalities (3.6) is satisfied, then one pathogen predictably eliminates the other; while if both inequalities are reversed, the outcome is contingent on initial densities: no three-species coexistence is possible, but either pathogen can exclude the other, so long as it has an appropriate density advantage. A full exposition of the biological conditions for these outcomes may be derived from an exploration of equation (3.6), and they are discussed by Hochberg and Holt (1990). The main messages are that one pathogen will always eliminate another if it is superior at exploiting both healthy and infected hosts, while a pathogen superior at exploiting healthy hosts is more likely to exclude competitively a pathogen superior at exploiting infected hosts if the virulence of the former is high, whereas the reverse exclusion is more likely to occur if the virulence of the superior exploiter of infected hosts is low. Hence, the contingent outcome occurs, at intermediate host productivities, when the pathogen that is superior at exploiting healthy hosts (higher $R$) is also more virulent.

Finally, by re-stating equation (3.6) in terms of equilibrium densities of the single- and multiple-pathogen systems, Hochberg and Holt (1990) point out that when the parasites coexist at a point equilibrium, (a) the total prevalence of infection is intermediate to the equilibrium single-species prevalences, (b) the density of susceptible hosts is intermediate to their densities in the single-pathogen systems, and (c) the system is competitive in the sense that each pathogen depresses the abundance of the other pathogen. However, Hochberg and Holt's numerical studies of the local stability criterion, derived in the usual way from the Jacobian, suggest that the three-species point equilibrium may be unstable, giving rise to what appear to be limit cycles. These seem to occur when pathogen 1 (superior at exploiting infected hosts) is only just able to regulate the host, but when its superiority with infected hosts is similar in magnitude to the superiority of pathogen 2 with healthy hosts.

## 3.3 Host-parasite-parasite studies: Dobson (1985)

Dobson (1985) reviewed empirical studies of host-parasite-parasite (predominantly vertebrate-helminth) systems and also developed host-parasite-parasite models based on the host-parasite (essentially helminth) formulations of May and Anderson (1978), Anderson and May (1979). Empirical studies were divided between those potentially exhibiting exploitation competition, and those in which interference competition had either been demonstrated or strongly implied. With exploitation, the proportion of hosts bearing a particular parasite either alone or in a mixed infection was given, as well as the degree of aggregation of each parasite within the host population. The examples illustrate one of the main conclusions of Dobson's models: that in-

creased aggregation promotes coexistence because it reduces the level of joint exploitation by decreasing the degree of co-occurrence of different parasite species. Similar conclusions have been drawn from investigations of competitive systems more generally (e.g. Atkinson and Shorrocks 1981, Ives and May 1985). Dobson also points out, however, that no data are available on parasite pathogenicity in any of the systems studied, which is regrettable in the present context, since his models also highlight the importance of differential virulence in species coexistence.

The data on interference comprise a listing of the effects on two species of parasite when they co-occur within the same host individual. These range from no effect, through displacement from a preferred site of attachment, and reduction in survival or establishment, to total exclusion from hosts infected with the other species. Of nineteen studies, every one was asymmetric and fourteen were classified as + 0. This high prevalence of asymmetry again repeats the findings from other competitive systems (e.g. insects – Lawton and Hassell (1981)).

Dobson's basic model deals only with exploitation, and suggests that three-species coexistence will only occur if the parasite that is less pathogenic is sufficiently aggregated to avoid the depressant effects of its competitor parasite, though he makes the point, as mentioned above, that increased levels of aggregation in either species promote coexistence. He then extends this model, to include interference beween the parasites, and unlike the host-pathogen-pathogen models described above, therefore, is able to make a start in encompassing the range of interactions exhibited within individual hosts. Specifically, an interaction term $c_{ij}$ is defined (not Dobson's notation) to describe the pattern of co-occurrence of parasite species $i$ and $j$ . Thus, $c_{ij} < 0$ in the equation for parasite species $i$ indicates that hosts containing species $j$ are less likely than otherwise to contain species $i$ which therefore suffers (true interference); $c_{ij} > 0$ in the equation for species $i$ indicates that hosts containing species $j$ are more likely than otherwise to contain species $i$ which therefore benefits (in a sense, 'negative' interference); and $c_{ij}$ may also be set to 0 in either or both equations in order to generate + 0, − 0 or 0 0 interactions.

The effect of this modification, in the simplified 'epidemiological' system which he examines, in which host density is assumed to remain constant, is to alter the straight zero isoclines of the exploitation model to curved isoclines (on the mean burden of parasite 1, mean burden of parasite 2 phase-plane). The straight isoclines give rise, in standard Lotka-Volterra fashion, to coexistence, definite elimination of one parasite, or elimination contingent on initial densities. With interference, the isocline of a parasite that benefits from the presence of the second parasite is curved outwards into the phase-plane, while the isocline of a parasite that suffers from the presence of the second

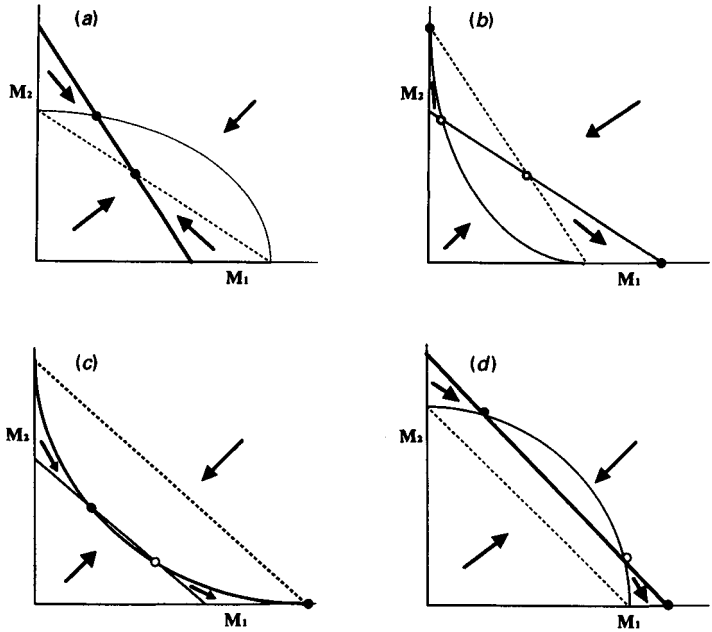


Figure 3: Graphical representation of results from Dobson's (1985) host-parasite-parasite model including interference between the parasites. Thick lines: species 1 zero isoclines; thin lines: species 2 zero isoclines; shaded circles: stable equilibria; open circles: unstable equilibria. $M_i$ is the mean parasite burden of species $i$. A parasite that gains from the presence of a second parasite species has a zero isocline that curves (equivalent straight isocline dashed) out into the $M_1$-$M_2$ phase-plane; one that loses has an isocline that curves back (true interference). With (a) coexistence and (b) contingent elimination, interference changes the quantitative but not the qualitative outcome, but (c) and (d) can alter predictable elimination to contingency between elimination and coexistence.

parasite is curved inwards towards the origin of the phase-plane. However, the intersects on the two axes remain unaltered. Hence, with coexistence and contingent elimination, interference does not alter the outcome of the interaction, though parasite densities at equilibrium and the details of the contingency may alter considerably (Figure 3). On the other hand, where one species would predictably have eliminated the second under exploitation alone, interference may alter this to an outcome contingent on initial densities, where either the original winner still wins, or there is stable coexistence of both parasites with their host (Figure 3), generated by the balance between one parasite's 'intrinsic' superiority and the net benefit gained by the other through interference – a theme clearly established above.

Overall, therefore, Dobson's work illustrates the additional effect of the statistical distribution of parasites on the outcome of host-parasite-parasite interactions, and shows clearly that both the qualitative and the quantitative nature of these outcomes are dependent on the interplay between statistical distributions, pathogenicities and interference (negative or positive) between parasites within individual hosts.

## 3.4 Host-pathogen-parasitoid studies: Hochberg *et al.* (1990)

Hochberg *et al.* (1990) examined a model of host-pathogen-parasitoid dynamics. The model equations are:

$$N_{t+1} = FN_t(1-I)f(P_t), \tag{3.11}$$

$$W_{t+1} = gQ_{t+1}/h, \tag{3.12}$$

$$Q_{t+1} = h(Q_t - (\Omega/\beta)\ln(1-I)), \tag{3.13}$$

$$P_{t+1} = cN_t[(1-\phi I)(1-f(P_t))], \tag{3.14}$$

$$(1-I)_t = \exp(-[N_t(I[f(P_t)+\phi\{1-f(P_t)\}]) + \frac{W_t}{\lambda/\alpha - q}] \,/\, N_t). \tag{3.15}$$

In this formulation the dynamics is discrete and $N$ and $P$ are the host and parasitoid population densities. In the absence of disease, $F$ is the host's finite rate of increase, $c$ is the average number of female parasitoid progeny per host attacked (assumed to be one) and $f(P_t)$ is the fraction of hosts that escape parasitism. The authors take this to be

$$f(P_t) = (1 + aP_t/k)^{-k}$$

where $a$ is a measure of the per capita searching efficiency of the parasitoid and $k$ of the clumping of attacks. Each generation $t$ of hosts is assumed to suffer a separate epidemic in which a varying fraction $(1-I)$ of the hosts escape infection. We denote by $W$ the density of free-living infective stages of the pathogen and note that $q$ of these are needed to cause an infection. During the epidemic, stages in $W$ are transferred at a per capita rate $\Omega$ to a separate pool of density $Q$. It is assumed that, at the end of each epidemic, there are no infected hosts and no active free-living stages $W$. The epidemic at generation $t$ is described by differential equations but, in the absence of interference between infection and parasitism, these can be integrated over the entire course of the epidemic. The results – which include the implicit equation determining $I$ – can then be generalized to include the interference parameter $\phi$. This takes values between 0 and 1 and reflects the relative dominance of the parasitoid and the pathogen in hosts that harbour both. These generalizations are then used in the above discrete formulation which

also embodies the idea that the next epidemic begins with a fraction $g$ of the pool $Q$ left at the end of the previous epidemic becoming active as $W$ while a fraction $h$ remain in $Q$.

It is shown through an analysis of invasion that parasitoid and pathogen may coexist with constant, cyclic or chaotic populations. A second possibility is that one enemy may unilaterally exclude the other. Finally, the outcome may be the exclusion of the pathogen by the parasitoid or vice versa in a way which is contingent on the initial densities. These outcomes clearly echo those described above, as do, in essence, the conditions that determine which of them apply, since these concern four main factors: (i) the relative extrinsic potentials of the competing enemies (searching efficiency, transmission, survival), and (ii) their relative intrinsic potentials (such as $\phi$), repeating the theme that coexistence requires some balance between the competitive superiority of one enemy with healthy hosts and the competitive superiority of the other within infected hosts; (iii) the aggregation of parasitoid attacks, which blurs the intrinsic/extrinsic trade-off as it did in Dobson's host-parasite-parasite model; and (iv) the host's finite rate of increase – important here as it was in the host-pathogen-pathogen model. Interestingly, moreover, in contrast to the results of the host-pathogen-pathogen model, host density depression may be greater in a mixed infection than with either enemy alone – a result of obvious pertinence to the use of mixtures of natural enemies in the biological control of pests. This occurs as parasitoid search tends away from randomness and the competitive dominance within the host favours the pathogen, and the authors suggest that a comparable outcome could arise if the distribution of pathogen transmissions were aggregated. Presumably, the results of host-pathogen-pathogen models could be similarly modified.

Data from host-pathogen-parasitoid systems are relatively good where they deal with competitive interactions between parasitoids and pathogens for individual hosts, and the importance in this of priority effects and so on (see, for example, Hochberg (1991a,b) and the review in Harper (1986)). Regrettably, though, as Hochberg *et al.* remark, scant attention has been paid to field studies that compare the effects on a host of a pathogen and a parasitoid together with those of either enemy alone; and even less attention has been paid to linking effects at the individual host and the population levels – the empirical theme that has recurred perhaps most stridently throughout this review. One interesting and notable exception, however, concerns the European corn borer, *Ostrina nubilalis*, its microsporidan pathogen *Nosema* sp., and its parasitoids *Lydella thompsoni* and *Macrocentrus grandii*. It has been suggested (Lewis 1982, Siegel *et al.* 1986) that the observed breakdown in the regulatory abilities of *L. thompsoni* (e.g. Sandlan *et al.* 1983) and *M. grandii* (Andreadis 1980, Siegel *et al.* 1986) during the 1960s may have coincided with the introduction of *Nosema* sp. However, recent work based

on the interaction of *L. thompsoni* and *Nosema* sp. within the host casts some doubt on the validity of this hypothesis (Cossentine and Lewis 1988).

### 3.5 A host-pathogen-predator model

To study the effect of a pathogen of the prey on an existing predator-prey interaction Anderson and May (1986) introduced the following extension of the conventional Lotka-Volterra model:

$$\frac{dH}{dt} = rX - (b+\alpha)Y - c((1-f)X+Y)P, \tag{3.16}$$

$$\frac{dY}{dt} = \beta XY - (b+\alpha)Y - cYP, \tag{3.17}$$

$$\frac{dP}{dt} = \delta HP - dP. \tag{3.18}$$

The notation is largely obvious. Note that $H = X + Y$; also $\delta$ is a rate coefficient for predator population growth, $d$ is the predator's per capita death rate, $c$ is a rate coefficient for consumption of prey by predators and $f$ is a value between 0 and 1 which models a lower rate of consumption of susceptible as opposed to infected prey. Infected prey are taken not to reproduce.

Several outcomes are possible and the picture is much the same for elaborations of the basic model. If the prey is held below the threshold value $H_T$ by the predators, the pathogen cannot establish itself. Conversely, the predators will be driven to extinction if the pathogen regulates the host population at a level below that needed to maintain the predators. Between these limits, coexistence occurs and sometimes the pathogen can induce stable limit cycles where in the absence of the pathogen the interaction would be stable and non-oscillatory. Overall, the parasite invasion tends to destabilize the predator-prey interaction. (The interaction between red grouse, their caecal nematode parasites and their mammalian predators has been examined both empirically and through models by Hudson *et al.* (1992).)

## 4 The future

There is clearly great scope, within each of these systems, for further extension and elaboration of the theoretical work, but the single theme that emerges most clearly at present is the pressing need for quantitative data on the population dynamics themselves and for data that can parameterise even the present models.

Of the questions that arise from such studies, three may be highlighted.

1. For the application of host-host-pathogen models to the situations of either a target pest, a pathogen planned for release to control that

pest, and a non-target species which it is undesirable to harm, or a domesticated species, a pathogen which might threaten that species, and a species in nature that is also affected by, and can act as a reservoir for, that pathogen, do the data sets currently available come close to being adequate? Or do the data sets currently available indicate a need for alternative models? Variants of these questions can clearly be directed at other multi-species interactions in other applied contexts.

2. Given that the extension from two to three species leads to markedly different biological problems but requires only the elaboration of existing mathematical techniques, how should we view the (possible) further extension to four or more species? More specifically, will distinctively new biology and/or mathematical techniques need consideration, and, in particular, should some statistical dynamical approach be employed if more than a few species are to be studied?

3. Is there a need for host-pathogen-pathogen models which capture fully the possibilities of inter-pathogen interactions beyond their shared requirement for a common host? – thus perhaps drawing together the fields of 'conventional' host-pathogen population modelling and the redirection of the general approach to the study of within-body dynamics.

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# Glossary

## *C. Watt, A.P. Dobson and B.T. Grenfell*

Words in slanting font indicate cross references

**Acquired Immunity** — see *Immunity*

**Adjuvant** — A substance that non-specifically enhances the immune response to an antigen.

**Aetiology** — The study of the causative factors of disease (USA: etiology).

**Age-structured Model** — A mathematical model in the which the host population is partitioned into different age classes. This type of model can thus be used to consider the consequences of such factors as age-dependent *infection* and *mortality rates* and immunity.

**Aggregation** — Organisms show an aggregated spatial distribution when they co-occur significantly more than would be expected from a (completely random) *Poisson distribution*. This clumping is reflected in a variance/mean ratio significantly greater than unity. *Macroparasites* are almost invariably aggregated in their host population, the majority of hosts harbouring a few or no parasites and a few hosts harbouring large parasite burdens. Aggregated distributions are often well described empirically by the *negative binomial distribution*; the degree of aggregation is inversely proportional to the negative binomial parameter, $k$. Aggregation generally arises from some source of *Heterogeneity* in the host or parasite population.

**Anamnestic Response** — Secondary immune response (i.e. response to an antigen to which the individual has previously been exposed), involving immune memory.

**Anaphylactic Response** — A hypersensitive *immune reaction* to a second or subsequent exposure to an antigen. This response can range from reddening and itching of the skin to respiratory failure and death.

**Anergy** — Immunological unresponsiveness.

**Anorexia** — Loss of appetite.

**Antibody** — A protein produced in the blood of vertebrates in response to an *antigen*. The antibody produced is able to bind specifically to that antigen, and plays a role in its inactivation or removal by the *immune* system.

**Antigen** — A substance, generally foreign, capable of inducing *antibody* formation.

**Anthelminthic** — A drug used specifically against *helminths* or worm *infections.*

**Arbovirus** — A member of a diverse group of viruses which use Arthropods as *vectors* and are *transmitted* in their saliva to the *definitive host.*

**Arrestment or hypobiosis** — Period of dormancy during the parasitic larval stages of many nematode species.

**Autosome** — Any chromosome which occurs on one of an homologous pair in a diploid nucleus, i.e., any chromosome which is not a sex chromosome.

**Bacteraemia** — The presence of live bacteria in the blood (USA: bacteremia).

**Baculovirus** — A group of viruses that are highly *pathogenic* to insects (see Briggs *et al.*, this volume).

**Breakpoint or Transmission Breakpoint** — A critical average worm burden below which mating frequency is too low to maintain persistance in a population of a *dioecious* parasite species.

**Carrier State** — The state in which an infected individual shows no *symptoms* but is capable of *transmitting* an *infection*; occurs in many bacterial infections such as tuberculosis.

**Carrying Capacity** — The equilibrium number of individuals of a species that an area or defined habitat can support; the density at which the population should equilibrate in the absence of interspecific *competition, predation, disease*, and stochastic fluctuations.

**Chemotherapy** — The treatment of *infection* by means of chemicals (drugs) which have a specific toxic effect on the parasite.

**Chemoprophylaxis** — The use of chemicals (drugs) to prevent *infection* or *disease.*

**Co-evolution** — Changes in the genotypes of two or more species that are a direct consequence of the species' interaction with one another.

**Commensalism** — The loosest and least obligatory form of inter-specific association; the species show a minimal metabolic dependence on each other and can usually survive independently of their association, although at some disadvantage to those individuals of the same species which remain in association; used in ecology to describe close associations in which one species benefits while the other is unaffected.

**Community** — Studies of parasite communities have divided their different components into a hierachy that differentiates between the parasites that are present within in an individual host and those present in a population of hosts. The *infrapopulation* is defined to include all members of a parasite species within a single host, while a parasite *infracommunity* includes all of the infrapopulations of different species within an individual host. The *metapopulation* represents all of the infrapopulations of an individual parasite species within a host population. The component parasite community represents all of the *infracommunities* within a host population. The most all-embracing organization is the *suprapopulation* which includes all of a given parasite species, regardless of life cycle stage; the *compound community* consists of all the parasite communities within an ecosystem; see Esch *et al.* (1990).

**Compartmental Model** — A mathematical model where the hosts are divided into different *infection* or *disease* categories or compartments (e.g. *susceptible*, infected, recovered). This type of model is generally applied to *microparasites*, but is also used for *macroparasites*, either when parasite *intensity* cannot easily be measured directly (e.g. filariasis), or when there is *direct multiplication* in the host (e.g. in intermediate hosts of trematodes). A **prevalence model** is concerned with the proportion of the population in each compartment.

**Competition** — The detrimental interaction between two or more organisms of the same (intraspecific), or different (interspecific), species which use a common, limited resource.

**Contact Rate** — The average frequency per unit time with which infected individuals contact, or otherwise put themselves in a position to transmit an *infection* to, *susceptible* individuals.

**Contagious Disease** — see *Infectious Disease.*

**Contagious Distribution** — see *Aggregation.*

**Critical Community Size** — The minimum host population size (and density) required to allow a *parasite* to persist. See *Transmission Threshold.*

**Cross-sectional Survey** — Survey which examines the *infection* and/or *disease* status of a host population (generally sub-divided by age, sex and other categories) at one point in time.

**Definitive Host** — In *macroparasites*, the host in which the parasite reproduces sexually.

**Density-dependent** — Population mechanisms or effects whose intensity of action increases with increasing population density; when they reduce

fecundity or increase mortality (e.g. parasite-induced host mortality), such effects tend to regulate the net population density. Theoreticians call such effects nonlinear. **Inverse density dependence**. Potentially destabilising positive feedback on population growth or decline. Can be caused by time delays in density dependent processes, for example, parasite-induced reductions in host reproductive rate. Also occur in parasite populations when density falls below *breakpoint*.

**Deterministic Model** — A mathematical model which assumes that all parameters and variables are not subject to random variation and that the state variables are continuous quantities.

**Diagnosis** — Identification of the *pathogen* causing clinical *disease*.

**Dioecious** — Having the two sexes in separate individuals.

**Direct Life Cycle** — A life cycle in which the parasite is *transmitted* directly from one host to the next without an intermediate host or *vector* of another species.

**Direct Multiplication** — The multiplication of a *parasite* within an individual host, where the products of the multiplication are at the same life cycle stage. The norm for *microparasites*. This does not generally occur in parasites with *indirect life cycles*, where in most cases multiplication occurs only when the adult reproduces sexually, and the larvae must pass through intermediate hosts before maturing. In some *helminths*, the digeneans and some cestodes, there is asexual reproduction in the intermediate host.

**Disease** — The debilitating effects of *infection* by a *parasite*; sometimes incorrectly used to refer to the disease-causing parasite. It is possible for a host to be infected by a parasite but to show no *symptoms* of disease.

**Dormancy** — see *Arrestment*.

**Efficacy** — An index of the potency of a drug or treatment, usually estimated as the average proportion of parasites in any host killed by a single dose or short-term course of the treatment.

**Eigenvalue** — Fundamental parameter associated with square matrices. Has a number off applications in theoretical ecology, epidemiology and population genetics. For example, the largest (dominant) eigenvalue of a matrix describing the growth of a seasonally reproducing age structured population represents the asymptotic logarithmic growth rate of the population.

**Endemic** — A *parasite* whose *prevalence* does not exhibit wide fluctuations through time in a defined location.

**Epidemic** — A sudden, rapid spread or increase in the *prevalence* or *intensity* of a *parasite* or *disease*. An epidemic is often the result of a change in circumstances which favour pathogen transmission such as a rapid increase host populations density, the introduction of a new parasite (or genetic strain of a parasite) to a previously unexposed host population.

**Epizootic** — The sudden spread of a *parasite* or *disease* through a non-human population; equivalent to an *epidemic* in human populations.

**Fecundity** — The capacity of a population to produce offspring; also used to describe quantitative measures of *per capita* reproductive rate.

**Fitness** — A term used to denote the relative contribution (in the form of offspring) an individual makes to the next generation. When a characteristic is genetically determined, its effect on that individual's fitness may be termed the 'relative selective value' of that gene.

**Frequency-dependent** — A population mechanism or genetic trait whose intensity of action or quality varies with its prevalence within the total population.

**Helminths** — Members of the five classes of parasitic worms: Monogenea, Digenea, Cestodes, Nematodes, and Acanthocephalans.

**Herd Immunity** — A term used to describe the immunological status of a population of *hosts* (as opposed to an individual organism) with respect to a given *parasite*. The level of herd *immunity* is determined by the net rates at which individuals acquire (by recovery from *infection*) and lose their immunity (by death, or decay of specific *antibody* protection).

**Host** — see *Parasite*

**Heterogeneity** — Simple host-parasite population models commonly assume that the interacting populations are, in most senses, homogeneous. In fact, significant heterogeneities (genetic, spatial, age- or sex-related, etc), in infection rate or other processes, are often crucial influences on host-parasite dynamics and the success of parasite control programmes.

**Hypobiosis** — see *Arrestment*.

**Immunity** (sometimes confusingly termed *resistance*, or more correctly, **specific resistance**) — The ability to combat *infection* or *disease* due to the presence of *antibodies* or activated cells. Essentially it can be divided into three types: (a) **acquired immunity** is conferred on an individual after recovery from a disease; (b) **natural** or **innate immunity** is inherited from parents, or in some cases antibodies may be passed across the placenta and therefore are present in the blood at birth; (c) **artificial immunity**

may be induced by the injection of either a *vaccine*, denatured *antigens* of a *parasite* (which induces production of antibodies and thus gives active artificial immunity), or antiserum which contains antibodies and thus may be used when the host is already infected. As well as strengthening the host's resistance, this also confers passive artificial immunity against any subsequent infection.

**Immunopathology** — Host pathology arising from an excessive or misdirected immune response.

**Immunosuppression** — Suppression of the immune response by drugs, parasites or the host's own immune regulatory mechanisms. Immunosuppression may be specific or non-specific.

**Incubation period** — The time that elapses between *infection* with a parasite and the onset of *disease*.

**Indirect life cycle** — A life cycle which requires one or more *intermediate hosts* or *vectors* before the *definitive host* is reinfected.

**Infection** — The presence of a *parasite* within a *host*, where it may or may not cause *disease*.

**Infectious (or Contagious) Disease** — *Disease* caused by *infection* with a *parasite* which can be *transmitted* from one individual to another, either directly (e.g. measles) or indirectly, by a *vector* (e.g. malaria).

**Infectious period** — Period during which the infected individual is able to *transmit* an *infection* to a *susceptible* host or *vector*. The infectious period may or may not coincide with the *disease*.

**Inoculum** — The number of *parasites* (or volume of a suspension of parasites) used to initiate a colony of *microparasite infection* within any host individual.

**Intensity** — either (i) the mean number of *parasites* within infected members of the host population, or (ii) the mean parasite burden of the entire population. It is important to distinguish between these two usages, as unless *prevalence* is 100%, the latter will be smaller than the former.

**Interleukins** — A group of peptides that signal between cells involved in the immune system.

**Intermediate Host** — see *Vector*.

**Latent Infection** — An *infection* which is causing no *disease*.

**Latent Period** — The period when an individual is infected but not yet capable of transmitting the *infection*.

**Life Expectancy** — The average length of life, or longevity, of the individuals of a population under the stated conditions (e.g., life expectancy from birth). See *Mortality Rate.*

**Linkage** — The tendency for two or more non-allelomorphic genes (i.e., genes in the same chromosome which do not exhibit independent assortment) to remain associated through several generations.

**Linkage Disequilibrium** — The extent to which gene frequencies differ from the values they would have if the gene loci segregated independently.

**Longitudinal Survey** — Survey which follows the *infection* and/or *disease* status of a group of individuals over time, often used to track the status of cohorts of hosts.

**Macroparasites** — *Parasites* which in general do not multiply within their *definitive hosts* but instead produce transmission stages (eggs and larvae) which pass into the external environment or to *vectors* (e.g., the parasitic *helminths* and arthropods). The immune response elicited by these metazoans generally depends on the number of parasites present in a given host and tends to be of a relatively transient nature.

**Major Histocompatibility Complex (MHC)** — A cluster of tightly linked genes which code for protein molecules that are attached to the surface of cells and are used by the immune system to recognize own or foreign material.

**Metazoans** — All multicellular animals.

**Microparasites** — *Parasites* which undergo direct multiplication within their *definitive hosts* (e.g., viruses, rickettsia, bacteria, fungi, and protozoa). Microparasites are characterized by small size, short generation times, and a tendency to induce *immunity* to reinfection in those hosts that survive the *primary infection.* Duration of infection is usually short in relation to the *expected life span* of the host (there are, however, important exceptions, e.g., the slow viruses).

**Molluscicides** — Chemical substances which kill snails or other molluscs.

**Morbidity** — State of feebleness, weakness, unhealthiness, or debility.

**Mortality Rate** — The death rate in a population. The net mortality rate is defined as the sum of all the instantaneous forces of mortality operating at any time (formally, the reciprocal of the population life expectancy). The force or impact of any mortality factor varies directly with the numbers of individuals in a cohort dying due to that cause of mortality. Mortality rates can be defined as operating additively if the elimination of one source

of mortality produces a net decrease in the total population mortality rate but no detectable increase in the observed instantaneous rates of mortality of the other operating factors. Mortality is said to be compensatory if removal of one source of mortality produces an increase in deaths from other sources such that the observed net mortality rate is maintained at its previous level. In the case of depensatory mortality, reduction in one source of mortality results in reduction in deaths due to other causes (e.g., parasite-induced susceptibility to predation).

**Multiple Infection** — An *infection* in which an individual *host* is infected by more than one species of *parasite*. In these circumstances the host individual contains an infracommunity of parasites.

**Mutualism** — An association between two species from which both species benefit. If one species cannot survive in the absence of the other the association is called obligate mutualism.

**Negative Binomial Distribution** — see *Aggregation*.

**Notifiable Diseases** — Diseases, usually infectious, cases of which must, by law, be reported to a health officer or local government authority.

**Overdispersion** — see *Aggregation*.

**Pandemic** — A widely distributed *epidemic*.

**Panzootic** — A widely distributed epizootic, often affecting more than one host species.

**Panmictic** — Characterized by, or resulting from, random matings.

**Parasite** — An organism exhibiting a varying but obligatory dependence on another organism, its *host*, which is detrimental to the survival and/or *fecundity* of that host. See also *microparasite* and *macroparasite*.

**Parasitoid** — An abundant group of insects (about 10% of known insect species) which use the egg, larval, or pupal stage of another insect as a host for a significant period of their own development, then kill that host by emerging to continue the next stage of their life cycle.

**Paratenic or Transport Host** — Additional host, in the life cycle of some macroparasites, in which no development occurs.

**Parthenogenesis** — Reproduction without fertilization; asexual reproduction.

**Patency** — see *Pre-patent Period*.

**Pathenogenicity** — The degree to which a *parasite* tends to cause *disease* in its *host*, and the severity of the disease caused. Often measured in terms

of the host *mortality* attributable to parasitism. Its expression is affected by conditions prevailing in the host, particularly nutritional status.

**Polymorphism** — The existence of different forms of individuals within the same population of a species, or more specifically, gene loci at which there are variant alleles at intermediate frequencies. If the frequencies of the alleles are stable, i.e., return to their previous values following a perturbation, the polymorphism is said to be balanced. If the polymorphism only occurs sporadically, it is said to be transient.

**Poisson Distribution** — Discrete frequency distribution, which would describe counts arising from a completely random distribution of *parasites* between *hosts*. For the Poisson distribution, the variance and mean of counts are equal. *Macroparasites* generally show *aggregation* in their distribution (signalled by a variance/mean ratio significantly greater than unity).

**Predator** — An animal that kills its victim, the prey item, and then feeds on it in order to subsist until the next kill.

**Pre-patent Period** — The time from *infection* (generally first infection) until a female *helminth* starts to produce eggs. Equivalent to the latent period in microparasitic infections. This is followed by the *patency* of the infection.

**Prevalence** — The proportion of the host population with *infection* or *disease*, often expressed as a percentage. A measure of how widespread an infection or disease is.

**Prevalence Models** — see *Compartmental Models*

**Primary Infection** — The first *infection* of a given *parasite* in an individual *host*.

**Prophylactic** — Any substance, object, treatment, or action which reduces the spread of *infection* or *disease* through a population of *hosts*.

**Protozoan** — Any unicellular animal.

**Protease** — Enzyme which cleaves proteins.

**Recrudescence** — Reappearance of *disease* in a *host* whose *infection* has been *latent*.

**Relative Selective Value** — see *Fitness*

**Reproductive Rate, Ratio** or **Number** (of infection) — There are three types mentioned in the text: (1) **Basic Reproductive** or **Reproduction**

**Ratio, $R_0$** — A dimensionless parameter which encapsulates the biological details of different transmission mechanisms. For *microparasites*, $R_0$ is defined as the average number of secondary cases of *infection* resulting from one primary case introduced into a population of *susceptible* individuals. For *macroparasites*, $R_0$ is the average number of female offspring (or just offspring in the case of hermaphroditic species) produced by a mature female *parasite*, which achieve reproductive maturity, in the absence of density-dependent constraints on parasite establishment, survival, or reproduction. (2) **Effective Reproductive Ratio, $R$** — The number of secondary cases (*microparasites*) or female offspring (*macroparasites*) produced in a host population not consisting entirely of *susceptible* individuals (microparasites) or within which density-dependent constraints limit parasite population growth. Under conditions of stable, *endemic infection*, $R = 1$.

**Resistance** — (1) (in *parasites* or *vectors*) The reduction in *susceptibility* to *chemotherapy* (drugs) or to chemical *vector* control (e.g. insecticides) due to genetic selection. (2) (in the host) The ability to resist *infection* by a *parasite*. **Specific resistance** is the resistance a host possesses by virtue of its immune system. **Nonspecific resistance** includes all other mechanisms for resisting the invasion of parasites, including physical barriers such as the skin and phagocytic cells, and nonspecific secretions such as lysozyme an the secretions of the mucus membranes.

**Selection Coefficient, $s$** — A measure of the strength of selection operating against a genotype; the difference between the relative selective value or *fitness* and 1; formally defined as the proportionate reduction in the gametic contribution of a particular genotype compared with a standard genotype.

**Seroconversion** — Development of circulatory *antibody* to a *parasite*.

**Serology** — The study of *antigen-antibody* reactions. Serological tests use specific antigen-antibody reactions. They can be employed to characterize either antigen or antibody, and are frequently used in determining the current *infection* status, or previous exposure to infection, of hosts. They lead to estimates of sero-*prevalence*, often expressed as serological profiles as a function of host age.

**Serotype** — The possession of certain *antibodies* by an individual host — also refers to type of *parasite*, distinguished by laboratory immunologic test.

**Sporogony** — Spore formation; reproduction by fission in protozoans and other *microparasites*.

**Stochastic Model** — A mathematical model which takes into consideration the effects of random variation in one or more of its parameters or variables. The predictions of the model therefore are not single points but probability distributions. It is important to distinguish demographic stochasticity, which arises from the discreteness of individuals (and individual events, such as reproduction, infection and death) and environmental stochasticity. The latter is a statistical description of more-or-less unpredictable variations in population parameters or variables which we cannot explain more systematically.

**Susceptible** — (1) (adjective) Accessible to or liable to infection by a particular *parasite*. (2) (noun) Susceptible individual — either naive (previous uninfected) or having lost *immunity*.

**Symptom** — A condition of the body felt by an individual when suffering from a *disease*. Here it has been more loosely used to cover any piece of evidence used in diagnosis or identification of infected individuals.

**Transmission** — The process by which a *parasite* passes from a source of *infection* to a new *host*. There are two major types: **horizontal** and **vertical** transmission. The majority of transmission processes operate horizontally, e.g., by direct contact between infected and *susceptible* individuals or between disease *vectors* and susceptibles. There are six main methods of horizontal transmission: (1) ingestion of contaminated food or drink, (2) inhalation of contaminated air droplets, (3) direct contact, (4) injection into a tissue via an animal's saliva or bite, (5) invasion via open wounds, and (6) penetration of the host by actively searching parasite transmission stages (e.g. *schistocome meracidia* or *cercariae*. Vertical transmission occurs when a parent conveys an infection to its unborn offspring, as occurs in HIV in humans or in many *arboviruses*.

**Transmission Threshold** — Level of transmission below which an *infection* is unable to maintain itself within the host population (or populations, in the case of *indirectly transmitted infections*). See *Critical Community Size*.

**Vaccine** — A sterile liquid medium containing avirulent strains of a specific *parasite* and often an *adjuvant*, introduced into the body of a *susceptible* individual to stimulate the production of *antibodies* and thus induce active artificial *immunity* against that parasite. May contain live attenuated parasite strains or killed parasites (or parts thereof).

**Vector** — Strictly speaking, any animal (or object) which *transmits parasites*. In *diseases* with *indirect life cycles* the intermediate hosts are often referred to as vectors (this is the commonest usage), while in diseases transmitted by contamination a variety of nonspecific organisms can act as vectors.

**Vectorial Capacity** — In *vector*-borne *infections*, the vectorial capacity is analogous to the contact rate in infections with *direct transmission.* It is a function of (a) the vector's density in relation to its vertebrate host, (b) the frequency with which it takes blood meals on the host species, (c) the duration of the *latent period* in the vector, and (d) the vector's survival function or life expectancy.

**Viraemia** — The presence of virus in the blood stream.

**Virion** — A mature virus particle.

**Virulence** — The case *mortality* rate of a *parasite.*

**Zoonosis** — A *parasite* naturally *transmitted* between humans and other vertebrate species.

## Reference

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