Andrés Díaz Lantada *Editor*

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ISBN 978-1-4614-6788-5 ISBN 978-1-4614-6789-2 (eBook)
DOI 10.1007/978-1-4614-6789-2
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2013936717

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

To my beloved Melike,

Shall I compare thee to a summer's day?
Thou art more lovely and more temperate.
Rough winds do shake the darling buds of May.
And summer's lease hath all too short a date.
Sometime too hot the eye of heaven shines,
And often is his gold complexion dimmed,
And every fair from fair sometime declines,
By chance or nature's changing course untrimmed:
But thy eternal summer shall not fade
Nor lose possession of that fair thou ow'st,
Nor shale death brag thou wand'rest in his shade,
When in eternal lines to time thou grow'st.
So long as men can breathe or eyes can see,
So long lives this and this gives life to thee.

William Shakespeare

To our daughter Seda,

When you set out for Ithaka
ask that your way be long,
full of adventure, full of instruction…
… Have Ithaka always in your mind.
Your arrival there is what you are destined for.
But don't in the least hurry the journey.
Better it last for years,
so that when you reach the island you are old,
rich with all you have gained on the way,
not expecting Ithaka to give you wealth.
Ithaka gave you a splendid journey.
Without her you would not have set out.
She hasn't anything else to give you.

And if you find her poor, Ithaka hasn't deceived you.
So wise you have become, of such experience,
that already you'll have understood what these Ithakas mean.

Constantine P. Cavafi

Foreword

Last decades have seen remarkable advances in computer-aided design, engineering and manufacturing technologies, multivariable simulation tools, medical imaging, biomimetic design, rapid prototyping, micro- and nano-manufacturing methods, and information management resources, all of which provide new horizons for the Biomedical Engineering fields and the Medical Device Industry.

Advanced Design and Manufacturing Technologies for Biomedical Devices covers such topics in depth, with an applied perspective and providing several case studies that help to analyze and understand the key factors of the different stages linked to the development of a novel biomedical device, from the conceptual and design steps to the prototyping, validation, and industrialization phases.

Main research challenges and future potentials are also discussed, taking into account relevant social demands and a growing market already exceeding billions of dollars. In time, advanced biomedical devices will decisively change methods and results in the medical world, dramatically improving diagnoses and therapies for all kinds of pathologies. But if these biodevices are to fulfill present expectations, today's engineers need a thorough grounding in related simulation, design, and manufacturing technologies, and collaboration between experts of different areas has to be promoted, as is also analyzed within this handbook.

The text is aimed at anyone working or simply interested in the Biomedical Engineering fields and the Medical Devices Industry, including physicians; scientists; and biomedical, chemical, electrical, and materials engineers. It is also a comprehensive introduction for students taking part in Biomedical Engineering Graduate Programs or Master's Degrees as well as for researchers planning to carry out their PhD in parallel to the development of novel biodevices, for improving diagnostic or therapeutic approaches to handle complex pathologies. Designed for maximum readability, without compromising scientific rigor, this handbook provides a current overview

of this rapidly evolving discipline, also discussing main research challenges and future potentials.

I truly hope it might be of help for students and researchers and even motivate them to follow some of the research directions outlined.

Madrid, Spain Andrés Díaz Lantada

Acknowledgements

No book is ever the product of one person's efforts, and certainly this one was no different. It would never have become truth without the help and suggestions of many supportive relatives, friends, and colleagues, only a proportion of which I have space to acknowledge here.

I owe a great deal to my colleagues and students at Universidad Politécnica de Madrid who, through their own research, comments, and questions, have encouraged, supported, and enlightened me.

Particularly Prof. Dr. Pilar Lafont Morgado, through her patient guidance with her always bright comments, has deeply influenced my perspective of engineering, research, and teaching. She has helped to improve the results of several chapters, with her experience of a career devoted to researching and teaching at the University. She has provided the forward-looking approach of a pioneer in several research lines, with multidisciplinary experience in combining CAD-CAE tools and rapid manufacturing for product development, linking the world of microsystems with bioengineering, studying contact phenomena in different media, or applying standards and structured methodologies to machine design.

I am very grateful to Mr. Pedro Ortego García, whose expertise has been of great help for the manufacture and trials of many of the prototypes included, as case studies, in the different chapters of the handbook.

I am also very thankful to Prof. Dr. Jürgen Stampfl for his support and wise advice during my spring research stay in Viena, where several designs and prototypes were developed. Also to Prof. Dr. Carlos Ojeda from Piura, Perú, whose contributions to computer-aided manufacturing and personalized design have made me remember our doctorate times with joy.

Of course to my parents, Andrés and Piedad, for a whole life of dedication and love, hoping they are proud of their son.

Above all to my wife Melike Erol (the essence of joy-made person) and to my daughter Seda (whose laughter is a continuous source of inspiration).

Muchas gracias a todos,

Madrid, Spain — Andrés Díaz Lantada

About the Editor

Prof. Dr. Andrés Díaz Lantada studied Industrial Engineering and specialized in Mechanical Engineering at Universidad Politécnica de Madrid (UPM), Spain (www.upm.es). He obtained his PhD in Mechanical Engineering in 2009 with a thesis on "Methodology for the structured development of medical devices based on active polymers," which received UPM Extraordinary Prize and 2nd Prize from the Official College of Industrial Engineers of Madrid. He has worked for 10 years as researcher at the Mechanical Engineering Department of this University and collaborated actively with its Product Development Laboratory, both in research and teaching tasks.

Nowadays he works as Associate Professor Doctor at UPM and teaches subjects, both at graduate, postgraduate, and doctoral levels, as well as specialization courses. His main teaching activities are related with the subjects "Computer-aided Mechanical Engineering," "Design and Manufacturing with Polymers," "Development of Medical Devices," and "Biomechanics & Bioengineering."

At the same time he is actively researching in different areas related with product development, specially focused on medical devices, including rapid prototyping technologies, CAD-CAE-CAM tools, and active materials for improving diagnostic and therapeutic applications of biodevices. Recently he has launched the "Fractal Bio" proposal, linked to the study and development of novel solutions for tissue engineering based on rapid manufacturing of fractal surfaces, within the technology-based innovative enterprises program "Actua UPM." Currently he is the contact researcher from UPM at the "European Virtual Institute on Knowledge-based Multifunctional Materials."

He is cofounder member of the UPM Research Group on "Machines Engineering" (since 2007) and of the UPM Innovative Teaching Group for "Integrated Mechanical Engineering Teaching" (since 2006), both groups under the headship of Chair Professor Pilar Lafont. Among some teaching proposals he has edited a special number on "Learning through Play in Engineering Education" and is currently editing a special number on "Impact of collaboration between Academia and Industry on Engineering Education," both for the International Journal of Engineering Education.

Andrés Díaz Lantada has published more than 100 peer-reviewed scientific publications (20 in journals from the JCR and 20 more included in ISI-WOK), several books, including the "Handbook on Active Materials for Medical Devices: Advances and Applications" from PAN Stanford Publishing, and book chapters and is coinventor of 10 patents related with the use of active materials for improving sensing/actuating capabilities of medical products and with improved solutions for Tissue Engineering. Recently he has organized and chaired the Special Session on "Active Materials for Medical Devices" and the Special Session on "Rapid Prototyping for Improving the Development of Biodevices" at the Biostec – Biodevices 2009 and 2010 "Intl. Confs. on Biomedical Electronics and Devices."

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Chapter 1
Introduction to Modern Product Development

Andrés Díaz Lantada and Pilar Lafont Morgado

Abstract The application of systematic design methodologies, together with relevant advances in computer-aided design, engineering and manufacturing technologies, novel materials and micro/nano-manufacturing resources, has reshaped product development in the last 20 years, greatly improving aspects such as time-to-market and overall project costs, as well as final product or device quality and overall performance.

These methodological and technological improvements have also a remarkable impact in the development of novel medical devices and all kinds of products in the biomedical field. The main objective of this handbook is to cover them in depth, as an aid to teaching-learning tasks and with the intention of helping researchers facing their first projects linked to biomedical engineering and to the development of biodevices.

This first chapter is focused on providing a general description of the product development process, covering its typical stages (detection of a relevant need, planning and specifications, conceptual design, basic engineering, detailed engineering, production and product market life) and the systematic methodologies commonly applied, providing a schematic historical perspective, together with an overall view of additional methods for ensuring end quality.

This introduction to modern product development is complemented by the additional information provided in the following chapter, regarding specific relevant aspects to be taken into account when the development process is linked to a medical device. The overview of novel technologies and advances in materials science included in the third chapter provides for the introductory section of this handbook, before explaining in detail the different advanced design and manufacturing technologies of interest in the subsequent chapters.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_1,

1.1 An Introduction to Product Development

According to the main language academies, a "product" (from the Latin *productus*), in its principal meaning, is "anything that has been produced", or an expanded definition might be, "anything useful manufactured or made that contributes economic value".

If we look more deeply at the meaning of "engineering", we can take the definition provided by "ABET (Accreditation Board for Engineering and Technology)", according to which: "Engineering is the profession in which a knowledge of the mathematical and natural sciences gained by study, experience and practice is applied with judgement to develop ways to utilise, economically, the materials and forces of nature for the benefit of mankind". In line with this designation and bearing in mind the reality of industry, we can enumerate the main jobs done by engineers in the course of their work:

- Design and calculation of products, processes, facilities and plants in every area of industry
- Research, development and innovation in products, processes and industrial methods
- Preparing, leading and managing projects in every area of industry
- Managing, planning and supervising multidisciplinary teams
- Strategic planning of quality systems, production systems and environmental management
- Financial management of projects and industrial concerns
- General management or technical work or research and development projects in the plants and factories of industrial concerns

According to the degree of dedication required by the work set out, three types of engineer can be defined for the present-day world Aparicio Izquierdo et al. (2005):

- Production engineers – They produce goods and services. They keep the means of production in working order and manage them efficiently.
- Design engineers – They design new products and new processes. They take an active part in research, development and innovation.
- Management engineers – They decide and control the techno-economic and political processes on an entrepreneurial level in local, national and global contexts.

In whichever case, many of the problems facing engineers in their jobs are closely linked with the design and development work of new products, a large percentage of which are intended to help solve other more complex problems or

evaluate the performance of certain functionalities of a system (as is the case with test equipment and test benches and machines).

In other cases, particularly in research centres and universities, the development process is more oriented towards showing the feasibility or usefulness of a new function, geometry, material, technology or process concerning a product.

In these situations, the process usually ends up proving such feasibility or usefulness as a result of a prototype being obtained that is not only capable of rousing the interest of the scientific community but also that of the main companies in the sector concerned that might be willing to start up production and market the concept. Thus, design and development engineers, often called designers, contribute with their work to finding solutions and developing specific products. They also have important responsibilities as their ideas, knowledge and skills are decisive in deciding the technical, economic and safety aspects of a product.

It is important to emphasise that due to the complexity of modern technology, only on very rare occasions can an entire product development process be carried out by an individual organisation. This task usually requires considerable human and technical resources which involve difficulties of organisation and communication.

To increase a new product's chances of success, the development process must be methodically and exhaustively planned and systematically executed. Not only must technical and financial feasibility be considered but also concepts like the end-safety associated with using the product and the environmental impact that its use might have in addition to the human factors that can influence the different stages of the design process. Using wide-ranging information sources and following the recommendations laid down in regulations is also highly recommended for a successful outcome.

A development methodology should, therefore, integrate different issues so that the overall process is logical and comprehensible, as the following section will explain. To achieve this, it is essential for the process to be divided into stages and tasks, each with its own individual method and way of going about the job.

The following section sets out the main stages to be found in most general theories of design engineering and product development (Roozenburg and Eeckels 1995; Pahl and Beitz 1996; Muñoz-Guijosa et al. 2005; Ulrich and Eppinger 2007), also applicable to more complex projects (De Cos 1999a, b).

Although this work is focused on the design of medical devices, it is important to point out that the main stages of development of these types of products basically coincide with the stages proposed by the systematic methodology about to be explained.

Nevertheless, several additional considerations need to be borne in mind that will be explained later, together with the considerable modifications required that are linked to working with novel design and manufacturing technologies, as well as new biomaterials, that may help optimise applying this general methodology to the specific case of medical devices or, more generally, "biodevices".

1.2 Systematic Methodologies for Product Development

1.2.1 The Need for Systematic Methodologies in Engineering

Depending on the variety of the problems and tasks involved in developing products, design actions have multiple facets. Firstly, they are dependent on basic scientific and technological know-how but also on the individual experience of different design engineers and their specific knowledge in the area related to the product under development.

It should be remembered that designers have the prime responsibility for a product's technical and economic aspects and also for the efficient development process of its commercial aspects by adapting it to limited schedules and costs. It is therefore important to have designed a process or methodology that will lead to appropriate guaranteed solutions. This methodology must be flexible but at the same time capable of being planned, optimised and verified. However, this approach can only lead to success if all those taking part in the design have the necessary knowledge and work systematically. It is important to make a distinction between the science of design and design methodology. The science of design uses scientific method to analyse the structure of technical systems and how they relate to the environment, with the purpose of developing rules for these technical systems by taking the system components and examining how they are related.

However, design methodology is a specific way of acting to design technical systems that get their knowledge from the teachings of design science and cognitive psychology as well as from practical experience in different sectors. It includes action plans for connecting the different work and design stages in accordance with content and the organisation envisaged; strategies, rules and principles for reaching general and specific goals; and methods for of solving the problems individual design or partial tasks. In line with this approach, a design methodology should:

- Encourage a direct approach to problems
- Foster creativity and understanding
- Facilitate the search for optimal solutions
- Be based on the methodical application of knowledge
- Be compatible with the methods and discoveries of other disciplines
- Maintain the interest of the participants
- Be easily learned and taught
- Reduce times, costs and errors

The approach set out should lead those involved in design to find possible solutions more quickly and directly than if they were working purely from intuition or experience. These two qualities are obviously important for any design process. In any case the use of a systematic methodology is not at loggerheads with intuition or experience, but simply attempts to expand and channel the potential of talented designers, while demonstrating that successful solutions do not only depend on creativity or intuition or experience but on a whole range of factors.

If the problem and design-linked tasks are structured, we also manage to recognise that existing solutions can be applied to solve concrete problems and speed up the stages of the overall process. It also lets us use powerful computer-aided design tools suited to optimising specific tasks.

These tools will be discussed further on. On the other hand, it is essential to use systematic procedures to properly organise information flows resulting from the design project and to prepare all the paperwork required to start up product production and any after-sales procedures.

Below is an explanation of how the product design process evolves until it reaches the most utilised present-day systematic methodologies, which will then be explained in detail.

1.2.2 A Brief Historic Perspective

It is difficult to find the origins of what we call "systematic design". To offer but one example, anyone studying the diagrams and sketches of Leonardo da Vinci can hardly fail to observe the depth of his analysis and how he systematically used variations to suggest possible solutions and be able to compare them (Taddei and Zanon 2006; Kaiser and König 2006; Bautista et al. 2007).

Up to the Industrial Revolution, product design and development work was essentially linked to art and craft and only with the gradual mechanisation of processes halfway through the nineteenth century, emerged a need to optimise the use of materials and to perform detailed studies on strength, stiffness, wear, friction, assembly and maintenance (Reuleaux 1875a, b).

However, it was not until the twentieth century that a systematic evaluation of these parameters was put forward as a way of gradually reaching an optimal solution. Just before the Second World War, a need was beginning to be noticed to rationalise product design processes, but progress in this direction was hampered by the following factors:

- An absence of effective methods for representing abstract ideas
- The widespread belief that design was an art and not a technical activity that could be carried out methodically and not just through creativity

A large-scale use of systematic design methodologies would have to wait for these limitations to be overcome, for the introduction of a more widespread use of automation and for the appearance of more modern data processing procedures.

Modern ideas on systematic development were given an enormous boost by relevant figures (Kesselring 1951, 1954; Tschochner 1954; Matousek 1957; Niemann 1950/1965/1975), whose revolutionary ideas continue to suggest ways of solving and dealing with specific tasks related to machine and product design processes (Kaiser and König 2006; Erkens 1928).

During the 1940s and the 1950s, Kesserling put forward a method based on successive approaches where each approach optimised different variables in line with

technical and economic criteria. He also proposed several principles like "minimal production costs", "minimal weight and volume", "minimal loss" and "optimal functionality and operability".

On the other hand, in the 1950s Tschochner emphasised the importance of four basic design factors: the principles of functionality, material, shape and size, similar to what Matousek would later do, but emphasising the need to consider the principles of functionality, material, manufacture and geometry.

Niemann's approach designed in the 1960s and 1970s consisted in starting out design by defining a general outline for the product with the main sizes to be worked on in greater depth. To this end, the overall design continued to be divided into different parts that could be developed in parallel. The optimal solution was finally reached by a systematic variation of all the possible solutions.

These progressive approaches towards ever more systematic methodologies for product design were mainly performed by university lecturers who had learned the fundamentals of design and development during their practical class contacts with increasingly complex products. They realised that not only was it possible to apply more mathematical concepts, physical principles, information theory-based methods and systematic design but that with the gradual increase in the division of work it was becoming indispensable.

Their designs were evidently strongly influenced by the industries they worked for, but many of their principles suitably modified can be adapted to numerous cases of design in other sectors. The currently accepted principles for effectively carrying out new product development are based on the ideas of the foregoing authors, as well as on the series of design steps that subsequently set apart important researchers (Hansen 1956; Kuhlenkamp 1971).

In general terms, these researchers talk of "pre-studies", "defining the basic principle", "basic design" and "detailed design" as the main stages. They are also listed in "design guidelines" written by organisations like the "VDI (Verein Deutscher Ingenieure)" or the "ISO (International Organization for Standardization)" in reference to global testing and quality management.

1.3 Typical Stages Involved in Product Development

The outcomes of previous research, satisfactorily proven through numerous developed products, led to a slightly modified work structure (Roozenburg and Eeckels 1995; Pahl and Beitz 1996; Muñoz-Guijosa et al. 2005; Ulrich and Eppinger 2007) which includes planning, conceptual design, basic engineering and detailed engineering, although a clear dividing line cannot always be set between these stages.

Defining Objectives and Planning. This broadly consists of the strategic decision taken by a company, university or research centre, as to which products or ideas must be developed to satisfy the new social needs, taking account of the scientific-technological and socio-economic circumstances of the time. To set about a product idea that will be successful, the state of the market has to be fully understood and

especially customers and their needs. Thus, market and customer requirements become the major stimuli for developing new products.

However, these stimuli frequently have other origins, the most important of which are politics, the appearance of new technologies, processes, materials, discoveries or research results and environmental issues. Neither should the role played by internal stimuli be underestimated (arising in the company, university or technology centre itself) when it comes to making a decision about a new product. Among these internal stimuli are new ideas or outcomes related to research activity and the implementation of new means of production as well as production being made more rational and diversified.

Depending on the stimuli mentioned, the main tasks to be included in the "defining objectives and planning" stage are:

- Situation analysis – By carrying out an in-depth study of the company and its products, together with market analysis and other possible information sources, a thorough analysis can be reached of the starting out point.
- Drawing up search strategies – By bearing in mind the companies' aims, strengths and weaknesses, as well as market gaps and needs, certain areas or promising fields can be discovered where ideas can be sought to be applied.
- Finding product ideas – From the search in the chosen field for new applications, functions, principles of functionality, geometries, materials, energy management methods and other alternatives, a set of product ideas can be found.
- Choosing product ideas – Depending on the company's aims and market needs, the set of ideas found are evaluated in order to choose the most attractive product idea.
- Defining the product to be developed – By evaluating the different alternatives against a list of requirements, a product proposal or definition is reached together with some initial objectives concerning costs, prices and schedules.

Conceptual Design. This is the stage where a decisive global principle is reached or a basis for reaching a satisfactory solution based on identifying crucial problems and choosing the right functional principles that in combination will attain the set objective.

If this stage is to be properly tackled, a series of prerequisites must be fulfilled linked to a correct conclusion of the previous stage. The objective must therefore be clearly stated and, in principle, be technically and financially viable. In addition, the designer must be informed of the needs of this conceptual design stage and the existence of possible solutions that allow proceeding directly to the design or basic engineering stage.

The scope and depth required for the conceptual design stage must also be pre-established. Related to the above, the main tasks included in this stage are listed below:

- Abstraction for identifying basic problems – The decisive designs and principles based on traditional methods cease to provide optimum responses in the face of scientific-technological advances concerning technologies, materials or

procedures, which adequately combined usually provide the key to more effective new solutions. On the other hand, every industry, company or research centre has countless experiences, which, although valuable, can lead to prejudice and hinder the creative process. For this reason, particularly at the outset of a new product design, designers must make an effort of abstraction and distance themselves from the influences of conventional ideas and focus on analysing the list of requirements and setting out the fundamental problem or problems in an objective manner.

- Setting functional frameworks – Having set out the basic problem to be solved, a global function must be obtained based on energy flows, mass and signals so that a relationship between the inputs to and outputs from the plant, machine, part or object to be designed can be established. This global function can then be divided into less complex sub-functions and a lower level of abstraction, all of which can be individually dealt with to facilitate the search for solutions. Combining and relating these sub-functions leads to the so-called functional framework. It is advisable to draw up several functional frameworks depending on whether it is wished to optimise costs, functionalities, quality, development time or other factors.
- Designing functional frameworks – After establishing the different functional frameworks, the principles of functionality for each of the sub-functions need to be sought. When they have been found, they should be properly interconnected to produce all the different possible functional frameworks that fulfil the global function. In line with the different preferences (cost, timeframe, quality and others), a table of choices can be made to choose the most suitable functional frameworks.
- Obtaining the decisive principle – By taking the functional frameworks, the different decisive principles to be evaluated can be obtained based on the different techno-economic criteria and preliminary calculations that can lead to the choice of the most adequate decisive principle (proposal for a preliminary solution or product concept) that can be worked on.

Basic Engineering. When the decisive principle has been decided, it is time to specify the underlying ideas behind this preliminary proposal for a solution or product concept. During the basic engineering stage (also often called basic design), the design engineers have the task of defining the basic shapes and geometries that characterise the product and must also choose the preliminary materials and appropriate manufacturing processes. It is at this stage when technical, technological and economic considerations become of vital importance. In other words, the mission of this stage is to provide a definitive general outline of the product to be developed, on which an effective analysis can be performed concerning function, duration, manufacture, assembly, functionality, costs and safety.

Unlike the conceptual design stage, the basic engineering stage is subject to numerous checks, which means the work of analysis and synthesis constantly alternate and complement each other. An enormous effort also needs to be made

regarding the compilation of information to make it easier to evaluate solutions, identify errors and continuously optimise.

The complexity of this stage is also greater because many actions have to be performed simultaneously. Subtasks need to be repeated when high levels of information are reached and because any change in an area or subarea has repercussions on all the rest. For these reasons, it is impossible to set a series of steps to be strictly adhered to that will ensure the basic engineering will come to a successful conclusion. However, the following approach may be followed in general terms:

- Choose the relevant product requirements.
- Make scale drawings with the existing spatial constraints and evaluate the required free spaces.
- Draw up a basic outline to decide which components will be required to fulfil the main functions.
- A preliminary design of the parts and components that fulfil these main functions.
- Draw up a basic outline to decide which components will fulfil the remaining secondary functions.
- Draw up the preliminary designs of parts and components that fulfil these secondary functions.
- Evaluate the designs using both technical and economic criteria.
- Decide the overall preliminary design.
- Optimise the chosen design, eradicating any weak points that may have arisen during evaluation.
- Make proposals for improvement and checking if cost and quality objectives are met.
- Prepare a basic preliminary parts and documentation list for production and assembly. This documentation comprises the starting point for the detailed engineering stage.

During the basic engineering stage, it is very useful to use check lists to ensure that when designing the different parts intended for the main product functions, all the various aspects have been taken into account. Of these aspects the most important are:

- Function
- Principle of functionality
- Design
- Safety
- Regulations
- Ergonomics
- Manufacturing
- Quality control
- Assembly
- Transport
- Operation

- Fault detection
- Recycling
- Maintenance
- Cost
- Timescale

Alongside this stage, as part of the work to compare designs and check geometries and functionalities, it is very useful to produce prototypes that will aid decision-making and help reduce the number of design iterations and minimise both the timescales and costs associated with product development. Currently, a distinction is made between virtual prototypes, the result of computer-aided design, simulation, calculation and manufacturing programs ("CAD-CAE-CAM" programs) and physical prototypes that coincide with the traditional concept of "original product sample for testing and checking".

The appearance of support "software" for engineering design work and its gradual incorporation into industry since the end of the 1980s, together with growing operational and calculating capacity, have caused major changes to the way design processes are carried out. Information exchange has become easier enabling countless effects in combination to be taken into account using multivariable simulations and enabling forecasts to be made concerning the influence of parameters such as the material or the manufacturing process on the end quality.

All these "software" tools can be included in a set of computer tools for managing the life cycle of a product or "PLM programs (product lifecycle management)" (Stark 2004; Saaksvuori and Immonen 2008). These capabilities enable a company to effectively manage and develop their products and related services throughout their economic life. All companies also need to manage the communications and information with their customers ("CRM tools or programs (customer relationship management)"), with their suppliers (programs called "SCM (supply chain management)") and company resources (programs referred to as "ERP (enterprise resource planning)").

These three groups of software programs together with the PLM programs complete the four cornerstones of the information technology infrastructure that enable the main needs of a company to be addressed.

More directly linked to product development in line with the approach taken here, PLM tools that include the following types of software programs come to the fore for performing tasks like:

- PPM (product and portfolio management) – These are programs aimed at helping determine the optimal combination or sequence for the projects proposed for the company to successfully achieve its objectives in accordance with its economic and technological strategy and actual market requirements. These tools help analyse resources, costs, investment, production schedules and how one project affects another.
- CAD (computer-aided design) – These programs support design engineers, architects and other design professionals in their work, which is to make their designs a reality. They usually have 2D and 3D drawing systems for creating files

or have all the information on a product's geometry and its different parts, as well as its plans. Changes can be made, symmetries are included, scale designs and numerous operations that can help make changes to the design.

- CAE (computer-aided engineering) – These computer programs allow simulating designs that have usually been made with CAD programs, and apply kinematic, dynamic, thermal or fluid mechanics considerations to the geometries designed and, above all, the chosen materials. They allow analysing how changes will affect the product or its parts and help optimise the number of prototypes or tests required.
- CAM (computer-aided manufacturing) – These programs lend support to prototype manufacturing work and end products by converting the information on part geometry from a CAD program into a code that can be understood by numerical control, manufacturing or rapid prototyping machines. On occasions it has a similar mission to CAE programs, letting part quality be simulated according to the manufacturing process used as well as allowing a study on geometries and materials.
- PDM (product data management) – These are programs focused on facilitating the records and paperwork of the processes to create, modify and revise any of the parts of a product. The information stored ranges from specifications, CAD file diagrams, plans, manufacturing documents, assembly documents, tenders, test specifications and quality control, as well as financial reports.

In recent years, the boundaries between these types of software are shrinking with the ever more frequent appearance of packs that combine different modules to provide a global response to all the aforementioned needs.

As explained, these technologies can provide assistance at every product design stage as well as production start-up, market placement and after-sales services. The benefits of using them become obvious at the basic engineering stage where their use is even more justified in the detailed engineering stage where the amount of information handled increases rapidly, as will be explained further on.

Regarding prototypes, the industrial importance taken on over the last decade by the so-called manufacturing and rapid prototyping technologies should be emphasised. These technologies enable physical parts to be directly obtained in a short time (hours or a few days) from the designs made with the help of a computer using "CAD-CAE-CAM" programs.

They are of great help in optimising design iterations, help the early detection of errors and speed up production start-up. They are usually either based on "layer manufacturing technologies" (like laser stereolithography or selective laser sintering) or on material elimination manufacturing processes (high-speed numerical control machining). The different technologies available mean that prototypes can be obtained in a wide range of metal, ceramic and polymeric materials with remarkable precision (Freitag and Wohlers 2003; Lafont Margado et al. 2000; Díaz Lantada et al. 2007).

Depending on the objective and the similarity to the end product, the physical prototypes are usually divided into the three following levels:

- Level "A" prototypes (commonly called "A-samples"). These are demonstration prototypes for analysing shapes, geometries and other more subjective aspects (like aesthetics, visual impact or ergonomics) related to the product under development.
- Level "B" prototypes (commonly called "B-samples"). These are functional prototypes intended for checking the behaviour of different product parts and their functionalities. Although they are generally made of nonfinal materials, these tests are usually performed with limits on certain applications.
- Level "C" prototypes (commonly called "C-samples"). These are prototypes with similar materials and behaviour to the end product although the manufacturing methods used to obtain them do not coincide with the methods used in production. These level "C" prototypes are usually manufactured for final checks, to prepare production start-up and for obtaining official approval as part of the detailed engineering stage which will be dealt with further on.

However, the end of the basic engineering stage and the beginning of the detailed engineering stage cannot be precisely delimited as there is always some overlap that is to the benefit of the overall process.

Detailed Engineering. Once the final basic design has been obtained, work must be begun on the requirements of the shape, properties, size and tolerances of the different parts. The final choice of manufacturing and assembly must also be done as well as final cost evaluation. The outcome of this stage is the definitive technical specifications of the product: a list of functionalities, production plans and the specifications including the instructions for assembly, disassembly and operation. Based on this information or technical documentation, production start-up can be undertaken as well as the placing of the product on the market. According to the above, detailed engineering work can be divided into the following:

- Finalising the end design – The different parts are fully defined by means of plans or 3D geometry CAD files, and materials, tolerances, adjustments and other details are specified.
- Parts integration – By means of full comprehensive plans or CAD assembly files which define the product as a whole.
- Finalising paperwork – For an unambiguous definition of the product and be able to launch production.
- Final checks – As to compliance with general regulations and company standards. Precision of size and tolerances, the availability of standard or catalogue parts and other checks.

The basic and detailed engineering stages can often be brought together in one single-design stage with a global focus where the level of detail is gradually added.

The ever more generalised use of CAD-CAE-CAM technologies and the already mentioned PLM tools has promoted this gradual fusion between stages, which also simplifies any information exchange between the agents involved in product design.

Other authors with a similar outlook to that set out (Roozenburg and Eeckels 1995) also include production and marketing planning actions in the methodology they

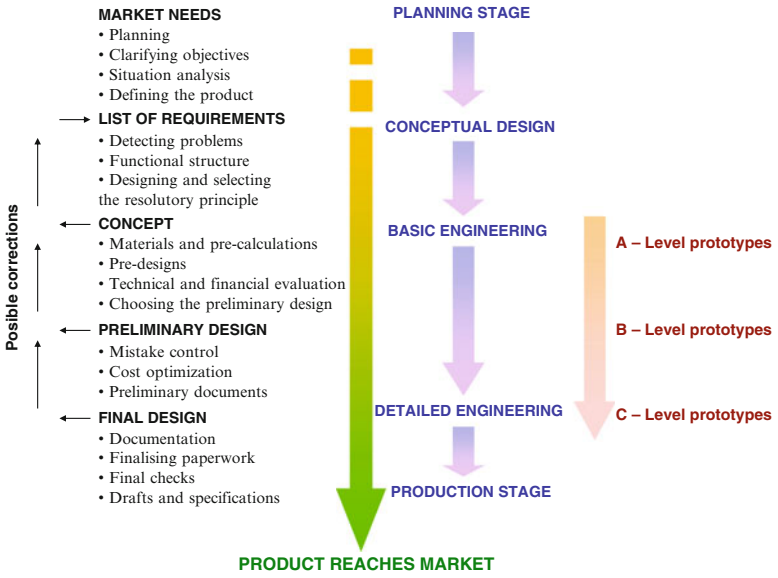

Fig. 1.1 Systematic methodology diagram for product design

put forward, since the overall design of a product requires considerable human resources and materials to be assigned as well as production, distribution and sales strategies and other after-sales services.

Figure 1.1 shows a full design process diagram with explanations (objectives and planning, conceptual design and basic and detailed engineering) (Díaz Lantada 2009, 2012).

1.4 Additional Methods for Ensuring Quality

The history of industrial design usually recognises three quality leaps regarding design approach and the fundamental reasons behind that design; these changes of approach are directly related to the three following concepts (whose application also changes product development methodologies):

- Productivity – The main objective at the start of the Industrial Revolution since the very existence and survival of emerging industry depended on this concept.
- Safety – A concept that has gradually taken on importance throughout the twentieth century as society became more aware, with increasing economic growth together with the technological progress that enabled safer systems to be introduced. At first, it was considered to be a factor that hampered production, but later it was shown that productivity and safety contributed synergy, and so, manufacturing safe products safely became paramount.

- Quality – A notion that especially over the last three decades has become a basic goal of production processes and developed products. Referring to product design it can be understood to mean "the set of properties of the design process that enables products to be set in production that fulfil the needs envisaged at the outset".

Whatever the circumstances, reaching acceptable levels of quality involves more and more the company as a whole, and product design means taking account of quality issues throughout the entire design process already explained. A good starting point is the ISO 9000 series set of standards which set out the basis for applying quality procedures in different organisations and the associated tasks, such as product design, production and manufacturing processes and commercial activities. The standards advocate that the best way to attain top quality is to take measures that will avoid failure by systemising processes and quantifying the parameters that have most bearing on quality.

The implications involved in this set of standards and how they relate to the European Union's so-called New Approach Directives will be dealt with in the discussion of standards included towards the end of the following chapter, with a special emphasis on the design of medical devices. Another key factor for attaining high levels of quality in product design tasks is to correctly interpret the customers' requirements and be exact in defining the initial specifications.

In principle, the key factors for attaining high levels of quality are:

- Systemising the design process by using structured methodologies
- Identifying potential faults and taking countermeasures
- Identifying any potential disturbances to the input parameters that might affect the output parameters and take countermeasures
- The participation of all departments (design, production, testing, quality, sales, purchases, commercial and any others) in the aforementioned tasks
- Learning based on the defects of previous products

Tools to Ensure Design Quality. To ensure quality throughout the design stage and methodically take account of the key factors, the use of various tools is becoming widespread, of which the most important are:

- "QFD (quality function deployment)" and related methodologies – Such tools help to take into account market and user demands when tackling the development of a new product. By using several matrixes for quantifying the need of relevant changes linked to the enterprise services and production system, materials and processed used, global quality optimisation is promoted and final results improved. "QFD" is designed to help planners focus on characteristics of a new or existing product or service from the viewpoints of market segments, company strategies or new technology-development needs. It is applied in a wide variety of services, consumer products and emerging technology products.
- The use of "Failure Trees" – This is a tool for systemising and enhancing the process and for detecting potential faults and disturbance factors. It is incorporated at the conceptual design stage once the product's functional framework is

available with the general function and all the sub-functions involved in the product's proper working, all of which must be checked. The different functions and sub-functions are checked one by one, thinking of how they could fail and searching out any possible faults and then looking for the possible causes and disturbances that could lead to those faults. When any possible causes of faults have been assessed, countermeasures are designed for each one. If necessary, the concept is redesigned, the design is improved or the procedures for manufacture, assembly, logistics, quality, maintenance and others are modified. As the work required to complete a fault tree for an entire product is considerable, this method is usually limited to decisive issues and critical processes. It is advisable for designers to make this way of working part of their everyday activities and so apply these concepts almost by intuition.

- "FMEA method (failure mode and effects analysis)" – This method, originally designed for the "Apollo" program, is more powerful than the fault tree since it quantifies the absolute importance of every fault mode by using the so-called RN, risk number, which is quantified according to the probability of fault occurrence and the probability of its being detected. Therefore, risks can be classified in order of importance and priorities set for searching for and executing countermeasures. It is widely used nowadays in all industrial sectors. However, the use of this method requires expert staff in all departments. The "FMEA" is usually reviewed several times during product design and possible countermeasures, responsible persons and control dates are set. This method helps ensure the quality but above all the safety of the product right from the design stage, which has previously proven to be of great help in fields such as machine design (Muñoz Sanz et al. 2007).
- Quality meetings – Specially designed to avoid difficult-to-solve faults in the advanced stages of development. The starting point is usually a check list based on questions concerning the experience of previous designs. Members of all departments usually take part in these meetings where countermeasures are suggested and persons are proposed for being responsible for applying the measures in the set timeframe. Once again, it is essential to emphasise the importance of fluid communication between all those involved in the product design process if a successful outcome is to be reached.

Additional tools for ensuring quality include several standards, which provide systematic descriptions of methodologies for direct application. Among such standards it is important to cite the ISO 9000 family for quality management, the ISO 14000 and 19000 families for quality audits and environment, the OHSAS 18000 standards on security and health and the ISO 28000 family on supply chain quality.

In the Biomedical field, quality and security insurance are intimately linked to assessing the effectiveness and risks related to a novel device, including aspects such as biocompatibility testing, as introduced in Chap. 2, detailed in Chap. 15 and incorporated to the global biodevice development systematic methodology described in Chap. 17.

1.5 Main Conclusions

This first chapter has focused on providing a general description of the product development process, covering its typical stages (detection of a relevant need, planning and specifications, conceptual design, basic engineering, detailed engineering, production and product market life) and the systematic methodologies commonly applied, providing a schematic historical perspective, together with an overall view of additional methods for ensuring end quality.

Such systematisation, together with relevant advances in design and manufacturing technologies, as well as in materials science and engineering, which are central part of this handbook, has reshaped product development and deeply influenced the medical device sector, improving quality, performance and capabilities of biodevices, together with a more adequate control or aspects linked to the viability of every project, including time-to-market and overall development costs.

This introduction to modern product development is complemented by the additional information provided in the following chapter, regarding specific relevant aspects to be taken into account when the development process is linked to a medical device. The overview of novel technologies and advances in materials science included in the third chapter provides for the introductory section of this handbook, before explaining in detail the different advanced design and manufacturing technologies of interest in the subsequent chapters.

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Chapter 2
General Considerations for the Development of Biomedical Devices

Andrés Díaz Lantada and Pilar Lafont Morgado

Abstract The development process of medical devices and of any products oriented to interacting with biological systems (biodevices) involves several special features deriving from the typical multidisciplinary characteristics of such devices and of their surrounding environment.

Therefore, the systematic development methodologies previously described have to integrate several additional special considerations and indeed very specific recommendations, for adequately helping to face up with the development of novel biodevices.

Aspects such as the existence of a relevant medical need; the effects of biological conditions; the selection of adequate biomaterials, sometimes with unusual mechanical and chemical properties; the consequences of corrosion; or the sterilisation methods available have to be considered, almost from the beginning, when developing a new biodevice. Development teams also integrate normally engineers, physicians, biologists and personnel from different disciplines, and sometimes, communication problems, together with project delays and even cost mismatches, arise. All this has to be taken into account in these projects.

The regulatory framework is also especially noteworthy in the medical device field, due to their potential harm when interacting with tissues and organs, and different directives have to be followed carefully. The most relevant EU directives of application for medical devices, together with advices included in important ISO standards, as well as some discussion and comparison with approaches from other countries (United States' FDA, Asian market…), are commented at the end of the chapter.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_2,

2.1 Basic Concepts Linked to Medical Devices or Products and Biodevices

A definition of medical device according to Council Directive 93/42/EEC of 14 June 1993 is "Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- Diagnosis, prevention, monitoring, treatment or alleviation of disease.
- Diagnosis, monitoring, treatment, alleviation or compensation for any injury or handicap.
- Investigation, replacement or modification of the anatomy or of a physiological process.
- Control of conception, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means".

According to the US Food and Drug Administration, "A medical device is an instrument, apparatus, device, machine, appliance, implant, in vitro agent or other similar or related article, including a component part, or accessory which is:

- Recognized in the official "National Formulary" or the "United States Pharmacopoeia", or any supplement to them.
- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, in man or other animals.
- Intended to affect the structure or any function of the body of man or other animals and which does not achieve any of its primary purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes".

The first devices to come to light that fit these definitions date back to the Ancient Age. Evidence has been found in Ancient Egypt of various surgical instruments for performing trepanations and other surgical operations, as well as instruments intended for use in mummification and splints made of bamboo, cane, wood or the bark of trees. These would most surely have also been used to treat broken bones in living patients. An engraving made around the year 2800 B.C. at the entrance to the tomb of Hirkouf bears witness to the oldest use of a crutch.

Many of the principles referring to different conditions and their treatment are attributed to the Ancient Greeks (Laín Entralgo 1973). They may be considered the first to use a scientific methodology and were also the first to describe their history and progress in detail. Homer himself in his epic on the Trojan Wars reveals knowledge of the lesions of that period and the treatments used.

Between 430 and 330 B.C., a vitally important Greek text was compiled known as the "Corpus Hipocraticum". It was named after Hippocrates, who was called the

father of medicine. Hippocrates was born on the Island of Cos around the year 460 B.C. and died at a ripe old age in 370 B.C. He is known for having endowed medicine with a scientific, systematic methodology and for having defined for the first time the position and role of the doctor in society. Hippocrates possessed a thorough knowledge of fractures. He knew the principles of traction and counter-traction and developed special splints for tibia fractures similar to an external brace. He also designed the Hippocratic bench or "scamnum" to provide a support when realigning fractured bones.

Although many centuries have passed, the Hippocratic Oath continues to occupy a prominent position in medical practice.

Subsequently, Herofilus came to the fore in Alexandria in the third century BC for his study of the human body by dissecting corpses, which up to now had been considered sacred with anatomical studies only being performed on animals. There is clear proof that during the third to first centuries BC in Alexandria, postmortems were performed for the first time for investigative and diagnostic purposes and for which very advanced instruments were required.

During the second century BC of the Roman Empire, the most important figure of the period was Galen who stood out for his observation of medical phenomena and his attempts to find an answer. He carried out post mortems on dead gladiators in the coliseum at Pergamon. When this empire fell, all scientific progress came to a halt leaving only copyist monks in monastery libraries to act as the transmitters of ancient culture.

Then came the rise and development of Arab culture with its contributions to medicine and surgery. Avicenna (980–1037) stood out for his use of cauterisation by means of a hot iron, an instrument used to destroy organic tissue by the use of heat and also to stop bleeding. With the onset of the Renaissance, medicine and surgery was again given an impulse with the appearance of illustrated treatises on anatomy like the one by Vesalius (1514–1564). These advances continued throughout the following centuries with the ensuing improvements in surgical techniques as well as methods of anaesthesia.

However, the main advances in medical devices that came about throughout the 19th and 20th centuries were unfortunately as a result of the Great Wars. One example that speaks for itself is that in London alone in the Second World War, it has been calculated that over 260,000 l of blood were donated.

It is the direct responsibility of those of us who devote our lives to the progress of science and technology to make this situation change so that in the future such progress will never again be linked to a country's military might or be driven by the need to find a response to the effects of war but instead will be devoted to improving the life quality of human beings as its main objective.

At present, the world market for medical devices is estimated to stand at over 200 billion Euros and shows an annual growth of around 8 % (growth only surpassed by the pharmaceutical sector).

The European Union, as a whole, is the second producer with a market share of 30 %, with Spain as the fifth producer in the European Union with an EU market share of around 6 % (Pammolli et al. 2005). Different factors and technological

advances in recent decades have boosted the enormous growth of this highly economically important industrial sector, whose social impact is equally important. Set out below are the main factors that must drive study in this field and the never-ending search for solutions, as well as the main advances that have led to the rapid industrial expansion of this sector in recent years.

Socioeconomic Factors

- The considerable increase in life expectancy in the developed countries has led to a notable increase in the demand for implants, prostheses and orthopaedic devices as the number of patients with degenerative diseases has also increased. According to United Nations demographers, in around 5 years, there will probably be more people over 60 than children under 15.
- Nowadays, one out of every ten people is 60 or over, but in 2050, it is predicted that these figures will reach one in five, and the number of persons over the age of 80 will multiply five times. Greater longevity must go hand-in-hand with preserving the life quality of this group.
- The rising birth rate in underdeveloped countries together with the difficulty of access to basic needs favours the appearance of epidemics but whose treatment can be improved by the use of new devices for the controlled delivery of drugs, the use of disposable surgical instruments, birth control devices and other recent or predicted future developments of this industrial sector.

Recent Technological Advances

- Improvements to purchasing systems, processing, analysis and telecommunication of physiological signs, which have enabled patients to be more precisely monitored, both in the short term (e.g. during surgical operations and post-ops) and in the long term (studying the evolution of pathologies), by also enabling biological systems to be modelled and contribute physiopathological significance to the parameters found from processing (Deutsch et al. 2007, 2008; Cerutti 2008).
- The development of systems that interact between computers and the nervous systems of living beings based on two-way implants for receiving electric signals from the body and supplying current directly to the nervous system, which will open up new horizons for the treatment of neurological disease (Gasson et al. 2005; Warwick 2008).
- New micro-manufacturing and nano-manufacturing techniques, some based on the manufacturing techniques of integrated circuits but applicable to many more materials and shapes, have led to enormous reductions in the end-size of implantable devices with the additional possibility of fitting them with micro-instrumentation to endow them with “intelligence” (Gad-el-Hak 2003; Schwartz 2006).
- Optimising the product design process thanks to a combination of CAD-CAE-CAM and rapid prototyping which speed up the production start-up of devices by reducing intermediate stages and minimising costs (Kuklick 2006).

- The development of new bioabsorbable materials that are body compatible which degrade a certain time after being implanted while only producing non-toxic matter that can be eliminated or metabolised by the body. Outstanding progress has been made in the synthesis of bioabsorbable and biodegradable polymers that can be applied to a large number of devices designed for the controlled delivery of drugs (Lendlein and Langer 2002), as well as for support tasks for tissue engineering (Freed et al. 1994; Kawanishi et al. 2004).
- The discovery of new active materials that enable functionalities to be inbuilt and so open up new horizons for the development of active implantable medical devices thanks to their potential use as sensors and actuators (Davis 2003; Lendlein and Kelch 2005; Wong and Bronzino 2007; Peterson and Bronzino 2008).

These advances mutually favour one another and used in combination can provide multiple novel responses to conditions for which, up to a decade ago, there was no adequate treatment. All this has boosted the development of prototypes for a large number of medical devices, many of which benefit from the use of active materials.

The following section provides an introduction to the systematic process of product development and goes on to examine the further considerations that must be borne in mind should the device under development respond to a medical need. It will then go on to examine the influence of these considerations on the different stages of the proposed systematic process.

2.2 Special Issues for the Development of Biodevices

2.2.1 Special Difficulties

The design process of medical devices has a series of added difficulties that involve considerable changes and additional issues regarding the systematic methodology for designing the products previously mentioned.

These additional challenges, difficulties or issues can be classified into the three different groups set out below:

- Technical issues – These are related to the geometries, materials and the principles of functionality that can be utilised in a specific device as they are bounded by the implications involved by their contact with human body tissue. They are also bounded by the influence of the corporeal environment on the in-service performance of the materials used and their progressive deterioration due to this environment.
- Legal issues – The direct action on the body of the developed devices and their associated risks increase the responsibility of those involved in the design and give rise to certain changes to the prescribed methodology. The design process of medical devices is therefore subject to strict rules, and care must be taken to

adhere to the specific standards if end product safety is to be maximised. The official approval process for these devices also adds to the overall complexity of their development.

- Human issues – These are linked to the particular complexity of the design process for these products which require multidisciplinary teams with experts from the different branches of science, particularly, medicine, engineering, biology, chemistry and physics, among others, but which can lead to specific communication or coordination problems. On the other hand, it is important to point out that developing a new device should emerge as a result of a real human need, a factor that will be examined more closely further on.

The main additional issues to be taken into account when setting out to develop a new medical device are explained in the following subsections. Reference will also be made to the systematic methodology design stages explained previously, together with reflections on how the different issues influence these stages.

2.2.2 The Importance of a Relevant Medical Need

New developments and innovations in medicine and especially in the field of medical device design usually stem from a problem-related need, and then, a technological solution is found to solve the problem and satisfy the need (Kuklick 2006).

It is true that on some occasions a new technology or material can bring novel diagnostic or therapeutic solutions to concrete problems, but these technologically motivated products (instead of medically) only have an economic or social impact on rare occasions.

Thus, most companies and technology centres given over to the design of medical devices, as well as more effective devices, are based on the application of efficient technologies for resolving very specific clinical or surgical needs. The approach of studying new technologies and examining any possible applications by searching out medical needs is more linked to scientific research projects than with product development, which means that the results are not materialised in the form of commercial products.

However, both approaches have their own advantages and are perfectly valid depending on what the objective is. So, when designing a product, it is usually more effective to start out from a need and look for a technology to solve the problem. Although, if it is wished to promote scientific progress the option of developing a new technology and attempting to apply it to solve the needs of many varied sectors probably makes more sense.

Therefore, this handbook looks to both approaches. It shows the development of medical devices based on the use of novel technologies and materials, whose study and subsequent development is motivated by real medical needs requiring a technological solution.

On the other hand, throughout these development processes scientific and technological contributions are made concerning the use of design and manufacturing technologies for different conceptual trials linked to innovative developments, novelties that may find a use in future medical applications or even other sectors.

Regarding the development of new medical devices, it is important to emphasise that the need to provide a solution to a medical problem must be kept in mind at the very first "defining objectives and planning" stage. If no such need exists, it is hardly sensible to begin to develop a new product to provide a solution to a problem that does not exist or that is being satisfactorily solved by other means.

One particular skill of entrepreneurs or researchers in the field of medical devices is therefore the ability to search out and understand important clinical or surgical needs. It is a complex issue where it is not enough to carry out questionnaire-based market studies or an analysis of existing products to find gaps in the market. Often, there is no other product for comparison, particularly if the product to be developed is completely new.

All of this, in conjunction with the basic aims to ensure, lengthen and improve patients' quality of life, while at the same time generating economic and social value, complicates decision-making and the search for needs on which to work. Therefore, defining objectives for the development of medical devices is a particularly complex issue.

2.2.3 Biomaterials

As with the concept of medical device, there are various satisfactory definitions for the notion of "biomaterial". The term generally designates any material used in the manufacture of devices that interact with biological systems and that are applied in the different branches of medicine (Wong and Bronzino 2007; Peterson and Bronzino 2008). This definition includes materials with very different properties and classifiable into different families, such as metals, ceramics, polymers and composite materials. According to their origin they can also be classified as natural or synthetic. Another possible classification is based on the influence the biomaterial has on the body or the extent of the reaction it produces on surrounding tissues, the following division being generally accepted:

- Bio-inert materials – Characterised by their low reactivity in the body, which means they can coexist with the surrounding tissue without any apparent change to the functions and properties of this tissue. Typical materials of this kind used in implantable devices are tantalum, titanium, aluminium, magnesium and some zirconium oxides.
- Biodegradable or bioabsorbable materials – They have the capability to be body compatible and to degrade a certain time after implant, giving rise to non-toxic products that can be eliminated or metabolised by the body. Some materials of

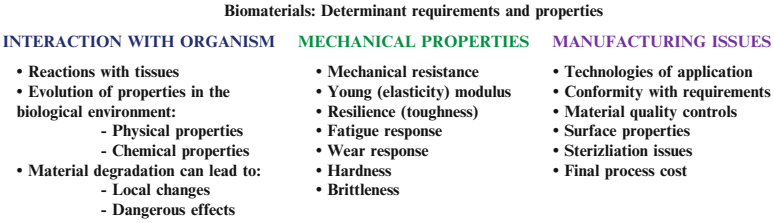

Fig. 2.1 Properties and determining factors for choosing biomaterials

this family are porous hydroxyapatite, the salts of calcium phosphate and some polyurethanes.

- Bioactive materials – They have the ability to form direct chemical ties with the surrounding tissue allowing this tissue to grow freely on their surface. Some examples of these materials are high density hydroxyapatite and tricalcic phosphate.

All materials used in medical device development, particularly those that will be in contact with body tissues, must meet a set of manufacturing and chemical requirements and properties and body-compatibility requirements, which are mainly mechanical. These are listed in Fig. 2.1 and Table 2.1 shows typical examples of synthetic materials applied to obtain medical devices.

2.2.4 Body Conditions

When it comes to choosing suitable materials for a product under development, during the basic engineering stage it is usually essential to consider the environment in which the product is going to act. The particular case of medical devices is no exception and body conditions play a deciding role when choosing materials.

Conditions such as a temperature of around 37 °C are not extreme for the materials used in medical devices. However, if active material-based devices are used whose activation is based on a change in temperature, the limits admitted by the body must be taken into account, as will be commented later.

Although temperatures are not usually a big problem, the biomechanical demands and chemical circumstances of the body are usually decisive when choosing the appropriate material for a medical device.

Regarding the mechanical demands, it is essential to bear in mind not only the nominal value of the demand but also the complete load cycle and the number of load cycles to be supported by the device. A typical hip prosthesis may be subjected to $3 \cdot 10^6$ load cycles per year, which in the case of a person of 25, with a 70-year life expectancy, would mean around 108 load cycles in the most unfavourable scenario. Although loads and load cycles depend directly on weight and each specific patient's

Table 2.1 Examples of materials in medical applications

Material	Main applications
Metals and alloys	
Stainless steels	Clamping fractures, stents and surgical instruments
Co-Ti, Ti-Al-V, Ti-Al-Nb, Ti-13Nb-13Zr, Ti-Mo-Zr-Fe	Bone and joint prostheses, clamping fractures, dental implants
Co-Cr-Mo, Cr-Ni-Cr-Mo	Bone prostheses, clamping fractures, dental implants, heart valves
Ni-Ti	Self-expanding stents, bone plates, clamping fractures, orthodoncy wires
NiTi, NiNbTi	Coating for biocompatible implants
Gold alloys	Dental repairs
Silver products	Antibacterial agents
Platinum and Pt-Ir	Electrodes
Amalgam of Hg-Ag-Sn	Dental repairs
Ceramics	
Aluminium	Joint prostheses, dental repairs
Zirconium	Joint prostheses
Calcium phosphates	Bone repairs, metal and alloy surface coatings
Glass	Bone prostheses
Porcelain	Dental repairs
Carbon coatings	Heart valves, percutaneous devices, dental implants
Polymers	
Polyethylene UHMWPE	Joint prostheses
Polypropylene	Sutures
PET	Sutures and vascular prostheses
Polyamides	Sutures
PTFE	Vascular prostheses and in vitro tissue growth
Polyesters	Vascular prostheses and drug delivery devices
Polyurethanes	Devices in contact with blood
PVC	Conducts for pumping operations, drug delivery and others
PMMA	Contact lenses
Silicones	Implants and soft tissue replacement
Hydrogels	Ophthalmology and drug delivery
PVA, PCL, PLGA…	Scaffolds for tissue engineering
Composites	
Bis-GMA – quartz	Dental repairs
PMMA – glass filling	Dental repairs and bone cements

level of activity, it is patently obvious that the effects of mechanical fatigue in the response of the materials used need to be taken into account.

On the other hand, any variation in the chemical state of the environment is decisive when choosing a particular material for a device. In this respect, any changes in the pH of the body fluids must be carefully examined.

Blood pH usually remains between 7.38 and 7.41. However, after an operation the pH may increase locally up to 7.8 and then decrease to around 5.5, returning to its normal value after a few weeks.

Infections or haematomas can also give rise to local variations in the pH and situate it between values of 4 and 9.

These variations are important when choosing material (and its processing) for a metal prosthesis where a proper resistance to corrosion must be ensured.

Likewise, the pH of saliva, usually between 5 and 7, is a determining factor when choosing materials for implants or dental repairs.

According to the issues considered up to now, we will summarise the most important requirements to be met by a medical device and the materials of which it is made:

- It must not be toxic or carcinogenic, cause a minimum adverse reaction and be chemically stable and corrosion resistant, as will be explained in detail further on in connection with biocompatibility.
- It must be capable of withstanding considerable forces and variables inside the human body, that is to say, in a highly corrosive environment.
- It must be capable of being shaped into complex forms in order to adapt to the geometrical requisites of the body.

From an economic point of view, it is also desirable for biomaterials as well as their manufacturing and transformation processes to be relatively low cost with a high market availability to avoid dead time during the development process.

Explained below are some of these requirements in relation to the functions that medical devices usually need to perform. Also analysed is the influence of the body on that performance.

2.2.5 Biocompatibility

Like other important scientific concepts that evolve over time, the definition of biocompatibility has gradually changed with the advances made in materials intended for medical devices. Until a few years ago, a biocompatible material was one that did not harm the body. They were basically inert materials "possessing the property of not causing any harm or toxic affects to biological systems".

However, new developments, including those that are active material-based, have made this definition change to "the capability of a material to properly fulfil its mission in a specific application for a particular patient". The concept thus presents four basic aspects:

- Biocompatibility makes no reference to an isolated event or phenomenon. It applies to a set of processes that include diverse mechanisms for an interaction between the material and the surrounding biological tissue.

- Biocompatibility refers to a material's capability to perform a function in the body and not simply to remain inert in the body. Moreover, the material's capability to carry out its function not only depends on the physical–chemical properties inherent to the material but also on its interaction with tissue.
- It is important to take account of the positive response on the part of the particular patient or host of the device. A lack of response is no longer sought, but that the response, however slight, should be in accordance with the device's function.
- The most up-to-date definition also makes reference to the specific application. For example, the same material with different geometries or in different organs, in one case can be a final biocompatible application, whereas in the other situation it may fail.

Biocompatibility cannot therefore be considered an intrinsic material property, but must be approached from a more global perspective that involves the whole set, material–application–body.

A good starting point for looking at biocompatibility throughout the different medical device development stages can be found by consulting ISO Standard 10993 on the "biological evaluation of medical devices". It describes a guided process for choosing the tests required to evaluate a device's biocompatibility depending on its degree of contact with body tissue and risks associated with its use. It also includes various procedures for performing specific tests.

In principle, right from the basic engineering stage, it is reasonable to choose materials that have given positive results in other applications, but throughout the detailed engineering stage the material chosen for the new application needs to be checked in every case to ensure that it meets biocompatibility requirements by carrying out the tests (both in vitro and in vivo tests) described in the Standard.

2.2.6 Mechanical Behaviour

Metal materials are used in implants and prostheses for their remarkable mechanical properties and particularly for their high static and dynamic strength. The main properties to consider when choosing a metal material to withstand mechanical forces are flow tension, tensile strength, elasticity modulus and fatigue resistance. These can be known from the information provided by the suppliers or be obtained through the appropriate tests.

Ceramic materials offer an excellent resistance to compression, for which reason they are used in numerous applications in Odontology. However, their performance in the face of flexion and fatigue is insufficient because the forces appearing cause the cracks to appear and propagate, which leads to a fragile rupture of these materials.

Among the properties to be considered when choosing polymeric materials that are to be subject to forces as part of implants or prostheses is that they should have a remarkable tensile strength, flow tension and fatigue resistance.

Moreover, with polymers the influence of working temperature on these properties must be taken into account when consulting supplier information or carrying out tests to determine such information.

Set out below are certain general issues related to the mechanical aspects that influence the response of different materials in their useful life as component parts of medical devices.

Test-related issues – In ideal conditions the tests for determining mechanical properties should be performed in an environment identical to the human body where the device is going to work. In practice, due to technical and financial difficulties and timelines, they are normally carried out at ambient temperature and in contact with the air. However, when assessing any possible degradations, tests can be performed in fluids that simulate body properties (isotonic solutions with blood and others).

Fatigue-related issues – Implants and prostheses receive cyclical loads during body movement that promote the appearance of cracks in zones where the tensions are usually concentrated due to irregularities in the microstructure of the material because of surface finish defects or inappropriate design. Influencing factors on this phenomenon such as shape, material, manufacturing process, surface finish and others make it difficult to measure the fatigue resistance of a specific part in the design stage, which is why test results have to be resorted to.

However, testing implants under real load and contour conditions that simulate actual implant performance inside the body is also a very complex and expensive task. Therefore, standardised tests are normally performed with a sample of the candidate materials or the information provided by the suppliers. To assess behaviour in the face of fatigue, the tests described in the documents prepared by the ISO TC164/SC5 committee or those explained in US standards like ASTM F1160, F1440, F1539, F1659, F1717 and F1798 can be used.

Wear-related issues – Resistance to wear is also a decisive criterion when choosing a biomaterial as excess wear cam leads to the premature failure of an implant or prosthesis. It is also important to point out that the residue from the wear must be body compatible in order to prevent the appearance of infection or long-term rejection. Information on this can be found in ISO Standard 10993 (Parts 13–15) which suggests criteria for assessing body compatibility and wear residue.

Other test methods for assessing the performance of different implant materials and different geometries can be found in the documents prepared by the ISO TC150/SC4 committee or in US standards like ASTM F732, F1714 and F1715.

For example, wear in contact between polymers like UHMWPE and metal alloys or ceramic materials has been studied for over 40 years. In general, research into material wear for prostheses goes along one of the following three lines:

- The use of test machines to do basic research into wear mechanisms by using samples of different materials

- Assessing complete prosthetic mechanisms during the in vitro test period when they are subjected to static or dynamic loads using simulators
- Analysing the in vivo evolution of prostheses implanted in patients using medical imaging technology

Elasticity-related issues – As already explained, the need for high static and dynamic strength has led to the extended use of metals and alloys for designing prostheses and implants, particularly cobalt alloys and titanium alloys. However, there are still a number of unsolved problems associated with the use of these alloys, some due to their stiffness being higher than the bones in which they are housed.

Numerous studies show that the bone areas surrounding an implant that receive less load suffer loss of bone mass and therefore mechanical strength (osteoporosis), a phenomenon attributed to the difference in stiffness between implants and the bones in which they are housed, which leads to unequal distributions of forces in the implant-bone contact zone.

Proposals for more flexible solutions to encourage the prosthesis to accompany the bone in its movements and obtain force distributions more like those in a healthy body have led to materials with lower elasticity moduli to be sought and developed.

Composite materials with a polymeric matrix are currently being tested as candidates to replace cobalt or titanium alloys, although problems of degradation and tribological difficulties are hindering it in vivo application.

The mechanical issues set out affect different stages of the previously mentioned systematic design methodology. In principle, in the basic engineering design stage the mechanical demands to which the device will be subjected should be precisely defined.

The family of materials most suited to bearing these loads should also be selected. In the detailed engineering stage, the main candidate materials are compared and the final material is chosen.

2.2.7 Corrosion and Deterioration

We have already introduced the problems linked to the body as a corrosive environment and how this has an influence on the final compatibility of devices, as well as being a determining factor for choosing materials during the basic engineering stage.

Some additional issues are examined below that depend on the material family that is to be integrated into the specific device.

Corrosion in metals – The metals used as biomaterials must be noble and resistant to their surroundings (body fluids). Various types of corrosion mechanisms have been observed in the metal materials forming part of implantable devices – general corrosion local corrosion or “pitting”, corrosion due to a concentration of tensions, corrosion due to fatigue and intergranular corrosion.

In whichever case, for a material to be considered resistant to bodily effects, the annual corrosion rate must be lower than $25 \cdot 10^{-6}$ mm/year. A series of standard tests have been developed for assessing behaviour of implant materials in the face of corrosion, such as those set out in ISO Standard 8044 prepared by the ISO TC156 expert committee or those set out in US standards such as ASTM F746, F897, F1801, F1814 and F1875. For assessing the behaviour of coatings in the face of corrosion, the tests described in the ISO TC107/SC7 documents can be followed.

Corrosion in ceramics – Corrosion tests for ceramic materials are not habitual as the ceramic oxides normally used in structural implants are very few. However, some ceramics do show certain in vivo corrosion which affects their mechanical behaviour.

For this reason, in the detailed engineering stage a very exact definition of the manufacturing processes and the transformations required for these materials is very important, as well as specifying the required purity and density (in general, the greater the density the less the porosity and the greater the resistance to corrosion).

Corrosion in polymers – Although the physiological functions and chemical reactions taking place in the body do not occur at high temperatures or with radioactive effects, combining an electrolyte with active biological species, like catalytic enzymes and free radicals, constitutes a particularly reactive environment which leads to a certain degradation of numerous polymers.

Of the individual mechanisms linked to polymer degradation in the body (Davis 2003), there are:

- Depolymerisation
- Cross-linking
- Oxidation
- Adhesive filtering
- Hydrolysis
- Crack generation and propagation
- Physical ageing

These mechanisms and their possible effects on the final product must be borne in mind at the basic engineering stage when choosing the most suitable materials for body circumstances as well as for making decisions as to the use of additives that can restrict these problems. The geometries and ways of joining parts can also have an influence on the appearance of these phenomena.

It is therefore important to take notice of the recommendations in the manufacturers' design manuals and technical catalogues for the final material to be chosen in the detailed engineering stage.

Test procedures for evaluating the effects of residue resulting from the corrosion and degradation of polymeric, ceramic and metal materials (and their influence on the biocompatibility of the final materials) can be found in ISO Standard 10993, parts 13, 14 and 15, respectively.

2.2.8 Sterilisation

Sterilisation is also essential for all implanted materials and devices. In medical practice, financial considerations often lead to surgical instruments and costly equipment being used over and over, which means they need to be sterilised after each use with a new patient.

Every sterilisation method must pursue the same objective: to eliminate or destroy living organisms and viruses present in the biomaterial or the medical device to be implanted. This process is usually quantified by the so-called SAL or sterility assurance limit.

The details of the sterilisation method are determined from tests until the SAL obtained (the probability that an implant will not be sterile after the process) is less than 10^{-6}.

The principal sterilisation methods (Davis 2003, Simmons 2004; Kuklick 2006) are explained below:

Steam sterilisation – Steam or autoclave sterilisation is a simple method based on exposing the device to saturated steam at 120 °C for 15–30 min (once the entire implant surface has reached 120 °C) at a standard pressure of 121 kPa. This is the most widely used method for sterilising metal surgical instruments. The method's main advantages are its effectiveness, rapidity, simplicity and lack of toxic residue. However, the high temperature, humidity and pressure during this type of sterilisation cause the hydrolysis, softening and degradation of many medical grade polymers and problems with any adhesives that may have been used.

Ethylene oxide sterilisation – This is used as a low temperature process that is compatible with many materials. The device is placed in a vacuum chamber into which ethylene oxide is injected at a concentration of 600–1,200 mg/l. The steriliser is usually kept at a temperature of between 30 °C and 50 °C and 40–90 % relative humidity during the process which lasts from 2 to 48 h. It is usually used for sterilising a wide range of devices such as surgical sutures, intraocular lenses and devices for repairing ligaments and tendons or heart valves.

The main disadvantage is that ethylene oxide is toxic and possibly carcinogenic, and so, its use in implantable devices is controversial. Eye contact or inhalation of the vapours resulting from the process should always be avoided.

Sterilisation by radiation – Ionising gamma ray radiation from cobalt-60 isotopes is used in dosages ranging from 25 to 40 kGy. The dosage is controlled by a dose meter to ensure the integrity of the device so that it will not be radioactive after the process and can be used immediately.

This is an appropriate process when materials cannot withstand the high autoclave temperatures. It is widely used for sterilising sutures, clips, metal implants, knee and hip prostheses and other implants. It has also been commonly accepted as the most suitable way of sterilising polymeric materials such as polyethylene, polyesters, polystyrenes, polysulphones and polycarbonates. Some exceptions are polytetrafluoroethylene ("PTFE" commonly known as Teflon) because of its extreme sensitivity to radiation.

It is a simple, fast method that can be precisely controlled, but it is not without certain difficulties. In some cases the method can produce a certain oxidation of the polymers sterilised by this method, as has been recorded in some "UHMWPE" implants. This usually leads to an increase in density and crystallinity, as well as a loss of the mechanical properties linked to the greater stiffness acquired.

However, this problem can be considerably reduced by carrying out the process in an inert gas atmosphere (argon, nitrogen) or in a vacuum chamber to reduce the presence of oxidising species and enhance the properties and useful life of "UHMWPE" devices.

New sterilisation techniques – Sterilisation in low temperature plasma is one method that has given positive results over the last decade, since it is not linked to the use of dangerous products and does not generate toxic waste. Hydrogen peroxide is usually used as the gas to form the plasma and the process is carried out at temperatures below 50 °C with cycle times of between 75 min and 3 h.

Ionised gases such as argon, nitrogen, oxygen and carbon dioxide have also been used to destroy surface microorganisms with low processing times of between 15 and 30 min.

The process has been used to sterilise polymers like polylactic acid ("PLA"), polyglycolic acid ("PGA") and its copolymers ("PLGA").

Carbon dioxide in a supercritical state has also been used to inactivate bacteria in applications including biodegradable polymers such as "PLA" and "PLGA" for drug delivery systems as well as prostheses made of polyester fabric.

So, sterilisation is usually an after-sales activity that is applied to a developed product. However, it also has an influence on the design process since as a prior step to in vivo tests in the detailed engineering stage, the device under development must also be subjected to sterilisation with the purpose of minimising any risks associated with these in vivo tests.

2.2.9 Multidisciplinary Teams

Product design projects connected with developing a new medical device are probably the ones requiring a team trained by experts from a number of fields, especially if the device incorporates means of detection or can be activated for the diagnosis or active treatment of some condition. A standard design team for these devices is usually made up of doctors, pharmacologists, engineers, computer experts, physicists, chemists and biologists in addition to economics and law graduates to deal with the financial and legal aspects. The design process obviously benefits from such a wealth of approaches and at the same time is a highly attractive working environment. However, the availability of experts in specific fields can also give rise to problems of communication (misunderstandings, lack of precision, lack of information, false suppositions) that can cause the timescales and costs of specific work to go off course and even lead to personal conflicts that affect the project as a whole.

We need to be aware that working in a global context is ever more usual and that the participation of designers, suppliers and customers from different countries who have a decisive influence on the design process means an increase in communication problems. It is worthwhile making yet another effort to improve understanding as the wide-ranging points of view of multinational teams can be a tremendous help in finding more consistent solutions. Some strategies for using a common language throughout the design process will be discussed further on (use of documents to define the initial situation, a general use of the International Units System, the participation of experts or communication "facility advisors"), together with certain teaching-related considerations and proposals, a key tool for providing a short-term response to the potential growth of this sector.

2.2.10 Regulations

The intrinsically complex process of product development linked to the additional problems already mentioned connected with medical devices means that consulting the recommendations regarding regulatory standards for the different design stages often marks the difference between a successful design process and an unviable one.

The concept of regulatory standards is closely linked to end medical device quality and safety, for which reason it deserves to be dealt with separately in the next sub-chapter.

2.3 Discussion on Applicable Standards

2.3.1 Standards in Conventional Product Development

As stated earlier on, quality and safety are interlinked and together with productivity constitute the basic issues to be taken into consideration in product design and mark all the difference between successful strategies and ones that are not.

Indeed, the trade promotion sought by the European Union through the internal market required additional safety issues for the products commercialised in that market, so that such promotion would not have any negative consequences on the products marketed, particularly industrial products.

This led to a common community policy being adopted based on the "new approach directives", whose application has enabled an homogenised framework of technical references to be established that are valid for all community countries and which hold sway over specific domestic requirements which cannot prevail over the framework. This means an abolition of technical barriers which is coherent with the disappearance of customs barriers.

Therefore, the new approach directives for different product types or sectors set out the basic safety and quality requirements to be met by these products, as well as the checks and tests that must be passed (before duly recognised bodies), before receiving the "CE mark" and being able to be marketed in the European Union.

In order to give "this new approach" solid foundations, the European Union and, in particular, the Commission have used quality techniques applied to the context of product conformity in respect of the applicable European requirements, basing them specifically on the triad of standardisation–certification–accreditation, in order to endow the tests and checks with guidelines and patterns that can be commonly accepted.

Given that standards and quality have come to occupy an important position in the community marketing policy for industrial products, it is not surprising that this official European initiative should end up becoming part of the most widely accepted international standards in the field of quality, to be exact ISO Series 9000 standards.

It is important to distinguish between directive and standard since the new approach directives are mandatory for placing products on the market in the European Union (obtaining the CE mark), while the standards of organisations like the ISO are proposals or recommendations for working more methodically and effectively.

However, the use of ISO Series 9000 quality standards is recognised by many of the new approach directives as a means of showing conformity with the requirements of these directives and specifically to allow the use of the CE mark.

On the other hand, conformity with the 45000 Series European standards provides organisations with "conformity assessment", the presumption of conformity with the technical criteria set out in the directives.

Thus, the use of 9,000 Series or 45,000 Series standards is not one of the mandatory requirements of the new approach legislation but is one possible way of demonstrating conformity.

The directives that apply to the design of medical devices in the European Union are explained further on in greater detail.

2.3.2 Regulations and the Development of Medical Devices

Directives. Regarding the development of medical devices in the European Union, there are three directives (with their associated amendments) which must be taken into account in order to be able to market the products under development:

- Directive 93/42/EEC regarding medical devices
- Directive 90/385/EEC regarding active implantable medical devices
- Directive 98/79/EC regarding medical devices for in vitro diagnosis

2.3.2.1 Directive 93/42/EEC Regarding Medical Devices

This directive applies to medical devices and accessories where a "medical device" comes under the definition cited at the beginning of the chapter, which can be summarised as "any instrument, apparatus, tool, material or other article, either used on its own or in combination with others, including the operating system required for it to be properly applied in the way intended by the manufacturer for use in human beings".

A "medical accessory" is an article, which, although it is not a device, has been manufactured to be used together with a device in such a way that its use is compatible with the use of the device as intended by the manufacturer.

Medical devices are classified under two headings in line with the classification standards laid down in Annex IX of the directive. The application of these classification standards is governed by the device's intended purpose, the risks associated with its use, the extent of contact with body tissue or the time it will remain in the human body. Therefore, medical devices in order of danger/increasing responsibility may be "Class I", "Class II a", "Class II b" or "Class III".

Before manufacturing and placing the device on the market, the manufacturer or its authorised agent in the European Union must subject it to different types of controls depending on how it is classified if the device is to bear the CE mark.

These controls are listed below:

For "Class I" Devices

For sterilised devices and devices with a measuring function, the "CE declaration of conformity" must be obtained before placing them on the market and then at the manufacturer or agent's choice:

- The "CE verification" by a notified body
- Approval of the "production quality system" by a notified body
- Approval of the "product quality system" by a notified body

Other devices must pass the "internal production control", that is, all the technical documentation necessary for the product's declaration of conformity in line with the requirements of the directives must be prepared and submitted to evaluation.

For "Class II a" Devices

At the manufacturer or agent's choice, these products must obtain:

- The "EC declaration of conformity" and depending on the choice
  - The "EC verification" by a notified body
  - Approval of the "production quality system" by a notified body
  - Approval of the "product quality system" by a notified body

These alternative procedures are mandatory for sterilised devices.

- As an alternative the manufacturer must receive approval of the "total quality assurance system" by a notified body, with the exception of having to apply the product design examination.

For "Class II b" Devices

At the manufacturer or agent's choice, these products must obtain:

- The "EC type examination" and depending on the choice:
  - The "EC verification" by a notified body
  - Approval of the "production quality system" by a notified body
  - Approval of the "product quality system" by a notified body
- As an alternative the manufacturer must receive approval of the "total quality assurance system" by a notified body, with the exception of having to apply the product design examination.

For "Class III" Devices

At the manufacturer or agent's choice, these products must obtain:

- The "EC type examination" and depending on the choice:
  - The "EC verification" by a notified body
  - Approval of the "production quality system" by a notified body
  - Approval of the "product quality system" by a notified body
- As an alternative the manufacturer must receive approval by the "total quality assurance system" by a notified body, including having to apply the product design examination.

For devices intended for clinical research and custom-made devices, the manufacturer must prepare a declaration in accordance with the criteria in Annex VIII of the directive. These research-oriented devices should not to bear the CE conformity mark.

The directive does not identify any quality system standard, but the requirements provided to create the quality system are subject to ISO 9000 Series regarding the total quality system, the production quality system and the end product quality system. In order to evaluate the technical competence of the notified bodies, the member countries of the EU must implement the criteria laid down in Annex XI of the directive.

2.3.2.2 Directive 90/385/EEC Regarding Active Implantable Medical Devices

This directive applies to active implantable medical devices, that is to say, "any medical device (as defined previously) that depends on an electrical power supply to operate it (or any energy source not directly generated by the human body or by the force of gravity) and which must be totally or partially inserted into the human body by surgical or medical means, or into a natural orifice by medical intervention and remain permanently installed after the procedure".

Before placing the product on the market, the manufacturer must subject it to the procedures to evaluate conformity that are laid down in the directive. Except for custom-made medical devices and those intended for clinical research, the manufacturer may opt to:

- Follow the procedure laid down in the "CE declaration of conformity" (approval and verification of the total quality system by a notified body) supplemented by the product design examination
- Subject a model to the "EC type examination" by a notified body in conjunction with one of the following processes:
  - The "EC verification" for devices by a notified body
  - The "EC declaration of conformity"

For devices intended for clinical research and custom-made devices, the manufacturer must prepare a specific declaration. These devices do not have to bear the CE mark.

This directive does not identify any quality system standard either, but the requirements provided to create the quality system are subject to ISO 9000 Series standards regarding the total quality system, the production quality system and the end product quality system.

2.3.2.3 Directive 98/79/EC Regarding Medical Devices for In Vitro Diagnosis

This directive covers in vitro devices, whose mission is to examine the specimens and samples derived from the human body, reagents, instruments and specimen receptacles linked to these tests. Placing these devices on the market is once again subject to conformity with the directive. In greater detail, for the directive an in vitro diagnostic medical device is "any medical device including reagents, calibres, control material, instruments, apparatus, equipment or systems which used on their own or in combination are intended for in vitro use to examine specimens, including blood and tissue, derived from the human body in order to obtain information on: pathologies, congenital defects, safety and compatibility with potential receivers or therapeutic measurement monitoring".

This definition must be examined in conjunction with what has already been stated for a medical device; for instance, several scaffolds for tissue engineering can be considered implantable devices, devices for in vitro diagnosis or even active implantable devices, depending on their final purpose.

Although these devices do not act directly on the human body, the responsibility connected with their use is still very high as they can be used to supplement the design process of other implantable or active medical devices. In addition, their use in detecting conditions, congenital defects and for monitoring, directly affects the patient, which means the reliability and rapidity of these devices are determining factors.

For this reason, in vitro diagnostic devices are divided into four classes in order of risk and must be subject to different controls according to the operating instructions in the directive before being placed on the market. The alternatives that can be chosen by manufacturers are similar to what has already been stated regarding the previously mentioned directives and can be examined in more detail by referring to the directive.

Specific regulations – As we have already seen for conventional products, when developing medical devices and sanitary products, in general terms, following the recommendations on quality and procedures laid down in ISO 9000 Series standards, in conjunction with some specific features of ISO 13485 and 13488 standards, although not obligatory, is one way of demonstrating conformity with the requirements of the three specific directives and specifically allow the use of the CE mark.

However, there are certain standards and documents regarding very specific aspects of medical device development which are worth looking at and trying to implement, apart from the ISO 9000 Series, when developing a product from this sector intended for placement on the market, such as:

- ISO Standard 10993 on the "biological evaluation of medical devices".
- ISO Standard 13485 on "sanitary products, quality management systems and regulatory requirements" (replaces Standard EN 46001). It lays down the requirements for a quality management system where an organisation needs to demonstrate its ability to design, develop and supply related sanitary products and services that consistently fulfil the customer's needs and the regulations applicable to sanitary products and related services. The main objective of ISO 13485 is to facilitate harmonised regulatory requirements for quality management systems and sanitary products. Consequently, it includes some specific requirements for sanitary products and excludes some requirements of ISO Standard 9001.
- ISO Standard 13488 on "sanitary products, quality management systems and specific requirements for the implementation of ISO Standard 9002" (replaces Standard EN 46002). In conjunction with ISO Standard 9002, it specifies the quality requirements for a company producing, installing and distributing medical devices.
- ISO Standard 14971 on the "application of risk management to sanitary products". This indicates the process to be followed by designers in order to identify

the risks associated with medical devices including those intended for in vitro diagnosis, so that these risks can estimated and evaluated and attempted to be controlled by corrective actions and then verify the impact and effectiveness of such corrective actions. It can be applied to every step of the life cycle of the medical device in question.

- ISO Standard 15223 on the "symbols to be used with labels, labelling and information to be supplied with medical devices". This identifies the requirements for the design and use of any symbols that may be intended to provide safe, effective information about medical devices.

Together with these general standards referring to the area of medical devices, throughout the design process of these products, it can be extremely useful to refer to the specific regulations connected with the methods for characterising and testing the different materials so that objective comparisons can be made of any possible alternatives or be of help in choosing suppliers (depending on the regulations used to verify materials or products).

At the same time regulations are in a constant state of flux as they attempt to adapt to safety and market quality requirements and to cover the latest advances in science and technology that demand changes to product designs. It is therefore important to regularly check updated references (www.iso.org).

The situation in other countries – In general, in order to assess the biocompatibility of a medical device, the strategies complying with what is laid down in ISO Standard 10993 are acceptable usually both in Europe and in Asia (Kuklick 2006).

However, in the United States the test procedures of the US Pharmacopeia, used to subsequently request product certification from the FDA (Food and Drug Administration), have certain differences compared to ISO standards. Generally speaking, ISO procedures are stricter, which means that companies intending to market their products both in Europe and the United States must follow ISO requirements. Nevertheless, in both cases, after applying ISO methods and before placing products on the US market the requirements of the FDA must be carefully checked and if necessary additional testing be done. It may even be necessary to enlist the help of FDA reviewers to clarify matters.

Research and regulations – As we have seen from our examination of the new approach directives concerning medical devices, for products intended for clinical research and custom-made products, the manufacturer must prepare a declaration in line with the criteria of the appropriate directive.

However, it is not necessary to undergo such strict examinations as for products intended for the market. In fact, medical devices for research or custom-made ones do not have to bear the CE mark.

A certain relaxation as to the application of standards would seem reasonable in the case of research devices as they are often intended to demonstrate the feasibility of a certain functional principal, often as part of the design process of a product to be placed on the market in the long term. This additional freedom is aimed at encouraging a creative spirit rather than rejecting solutions and alternatives because

of regulatory difficulties. It encourages technical feasibility (and economic) studies concerning the use of novel materials or technologies.

Finally, it is important to mention the "Helsinki Declaration" enacted by the World Medical Association in 1964 with six subsequent amendments, the latest being in 2008 and currently in force. The declaration is a proposal of ethical principles for medical research in human beings, including the research of human material and identifiable information. It also deals with the ethical issues involved in vivo tests conducted on animals as a prior step to their being conducted on humans.

Although application of the Declaration is not mandatory for placing a new device on the market, it establishes a set of ethical principles that can guide and assist researchers to make decisions in medicine-related matters, as well as assisting those of us who are dedicated to "biomedical engineering" work. The purpose of these decisions is to ensure the well-being of any persons taking part in research, over and above any other considerations, and as a result more effective and safer products are obtained.

The principles of the Helsinki Declaration are also beginning to take on economic (as well as ethical) importance, compliance with which is a sine qua non of being awarded biomedical research projects in many countries. This can be seen in calls for the current National I + D + i Plan for the 2008–2011 period and constitutes a strategic point of Spanish policy in matters of research, development and industrial innovation, in a similar way to what happens in other European countries.

2.4 Main Conclusions

Various socio-economic factors are driving the growth of the medical device development industry, all aimed at providing alternative diagnostic and therapeutic and sometimes more effective solutions than those currently available. This growth will be based on recent scientific and technological progress. However, if this growth is to be given a solid foundation and the proportion of devices finally being placed on the market increased, it is important that systematic product design methodologies are used that have been duly adapted in line with the specific additional considerations required for the medical devices to be properly developed.

After studying the stages usually used in a systematic product design methodology and analysing how the main special considerations mentioned influence this methodology, we can evaluate which steps and considerations require deeper analysis as a result of their greater relative importance.

Table 2.2 quantifies the influence of different special considerations on medical devices in the systematic design process stages. It also includes the device's useful life due to the implications involved in post-production activities.

This table can also be used as a control tool throughout the design process to ensure that the special considerations of greatest influence at each stage have been taken into account before a stage is deemed to have been completed.

It should be pointed out that in medical device development projects, there are many additional factors that have a decisive impact on the useful life of these devices

Table 2.2 Influence of different factors on the development process of medical devices. Degree of influence: *average **high ***very high

	Medical device development					
Special considerations	Specifications and planning	Conceptual design	Basic engineering	Detailed engineering	Production start-up	Device's useful life
Medical need	***	**	**	*		***
Biomaterials	*	**	***	**	*	***
Body conditions	**	*	**	**		***
Biocompatibility	**	*	***	**	**	***
Corrosion	*	*	**	**	*	***
Mechanical performance	*	*	**	**	*	***
Sterilisation			*	*	*	***
Communication	***	**	**	***	**	*
Regulations	*	*	*	***	***	***
Quality	*	***	***	***	***	***

and which involve special difficulties. However, the use of systematic structured design methodologies, keeping to regulations, and a constant concern for quality and good communication within the design team can help lead to effective, safe end products.

Any projects arising out of clear medical needs (clinical, surgical, diagnostic or therapeutic) where initial requirements are accurately defined will have a far greater chance of success. The basic engineering stage is a particularly critical part of the design due to its being responsible for contributing specific solutions to the devices main functions. On the other hand, adhering to certain ethical standards and principles connected with the direct repercussions to be had on a person's health by using these devices can also be highly useful throughout the design process, particularly for making decisions or choosing alternatives that cannot simply be based on technical criteria alone.

The last thing to be examined should be any modifications or additions to the stages of the proposed methodology that will make it easier to implement new technologies or materials (especially "active or intelligent materials" and "new biomaterials") to the design of medical devices that will lead to notable clinical, surgical, diagnostic or therapeutic advances. This is essential for promoting the growth of this sector and addressing the ever-increasing needs of society.

The core of this handbook (Chaps. 3–15) is devoted to explaining novel design and manufacturing technologies and strategies with impact on the biomedical field, while Chaps. 16–18 summarised the knowledge acquired along this handbook for

implementing more adequate systematic methodologies oriented to biodevices. Several concepts covered in present chapter will be detailed further on in such last chapters.

Standards Summary

Main Organisations

- International Organization for Standardization "ISO" (www.iso.org)
- The World Medical Association (www.wma.net)

"New Approach" Directives Related to the Medical Industry

- Directive 93/42/EEC related to "medical devices"
- Directive 90/385/EEC related to "active implantable medical devices"
- Directive 98/79/EC related to "medical devices for "in vitro" diagnosis"

Standards Related to the Development of Medical Devices

- ISO 10993 standard on "biological evaluation of medical devices"
- ISO 13485 standard on "sanitary products, quality management and regulatory affairs"
- ISO 13488 standard on "quality systems, medical devices, sanitary products and especial requirements for applying ISO 9002 standard"
- ISO 14971 standard on "application of risk management to medical devices and sanitary products"
- ISO 15223 standard on "symbols used for labelling and information provided together with medical devices"

Standards and Associations Related to Medical Imaging

- DICOM standard (Digital Imaging and Communications in Medicine): strategic document (http://medical.nema.org)
- Medical Imaging and Technology Alliance (www.medicalimaging.org)
- NEMA (The Association of Electrical and Medical Imaging Equipment Manufacturers) (www.nema.org)

Additional Documents of Interest

- Council of Europe "Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine: Convention on Human Rights and Biomedicine" (1994)
- UNESCO "Universal Declaration on the Human Genome and Human Rights" (1997) and "Guidelines for Implementation" (1999)
- World Medical Association "Declaration of Helsinki. Ethical principles for medical research involving human subjects" (current revised edition 2008)

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Chapter 3
Brief Overview of Novel Technologies with Impact in the Biomedical Device Industry

Andrés Díaz Lantada and Pilar Lafont Morgado

Abstract The central objective of this handbook is to provide detailed information about different design and manufacturing technologies, most of them developed or greatly improved in the last two decades, with remarkable impact in the design and production of novel medical devices and biodevices.

Following chapters provide such detailed information, but it is also important to supply now, after having analysed the systematic methodologies for product development and the special issues connected to medical devices, an overall approach to the mentioned design and manufacturing technologies, many of them linked to recent developments in materials science.

In consequence, this chapter presents a brief summary of the most outstanding advances that have a decisive influence on the medical device (and more generally biodevice) development industry. Advances are grouped in six main categories, including "medical imaging technologies", "computer-aided design, engineering and related tools", "rapid manufacturing technologies", "micro-fabrication technologies", "advances on materials science and nanotechnology" and "novel geometries and biomimetic designs".

Each of these categories will be detailed in depth, sometimes occupying a couple of chapters, along the whole handbook, being present one a kind of more specific second introduction. Finally, after revising all the design and manufacturing technologies, here introduced, this handbook will provide a proposal for structured methodology and some examples of teaching-learning experiences involving the development of novel biodevices with the help of several technologies.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_3,

3.1 Novel Needs, Novel Technologies and Novel Capabilities

Last decades have seen remarkable advances in computer-aided design, engineering and manufacturing technologies, multi-variable simulation tools, medical imaging, biomimetic design, rapid prototyping, micro- and nano-manufacturing methods and information management resources, all of which provide new horizons for the Biomedical Engineering fields and the medical device industry.

This handbook covers such topics in depth, with an applied perspective and providing several case studies that help to analyse and understand the key factors of the different stages linked to the development of a novel biomedical device, from the conceptual and design steps, to the prototyping, validation and industrialisation phases.

Chapters 1 and 2 have provided an introduction to product development and some important special considerations when the process is linked to the development of a novel biodevice. This chapter provides a panorama of technologies that are promoting remarkable alternative approaches for obtaining biodevices with improved diagnostic and therapeutic capabilities.

Such technologies include medical imaging tools, computer-aided design and engineering resources capable of helping with the use of novel geometries for biomimetic approaches, computer-aided manufacturing and rapid prototyping/manufacturing technologies, several advances in materials science and novel micro-/nano-manufacturing technologies, as schematically described in Fig. 3.1.

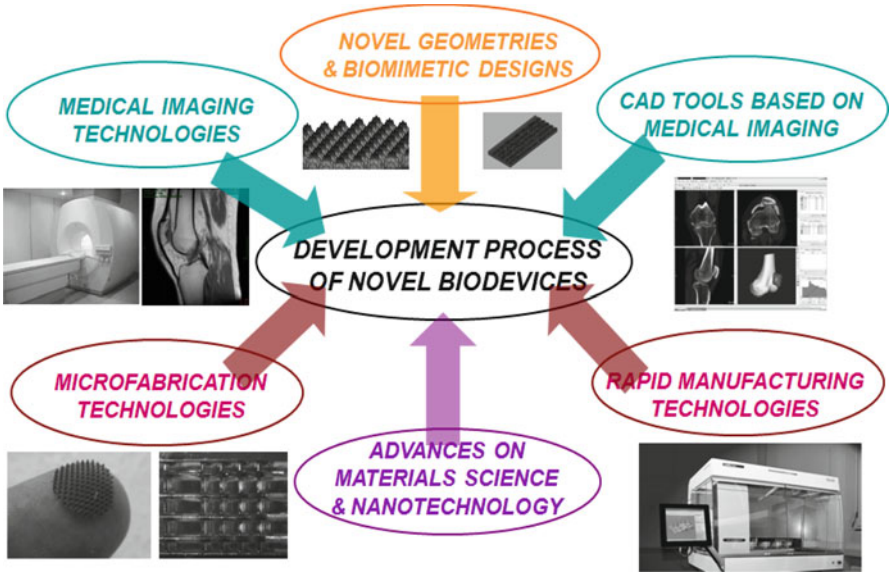

Fig. 3.1 Main fields of technology already promoting relevant advances in Biomedical Engineering and the medical device industry

These advances are covered in depth in following chapters, although it is interesting to introduce them here and to provide some definitions for a better readability of this handbook.

Therefore, this chapter closes the introductory three-chapter section of this handbook. Chapters 5–8 constitute the handbook section devoted to the design of advanced biodevices, including aspects linked to computer-aided design, to medical imaging as design input for personalised biodevices, to the use of very special geometries for biomimetic designs and for controlling several geometrical and mechanical features of biodevices and to the use of simulations for improving the whole design process.

Subsequently, Chaps. 9–14 constitute this handbook section devoted to the manufacture of novel biodevices, including topics linked to the use of computer-aided manufacturing resources, to the expansion of solid freeform additive manufacturing technologies for the rapid manufacture of complex or very special geometries, to the use of rapid moulds for promoting the utilisation of biomaterials and to the evolution of micro- and nano-manufacturing technologies in the biomedical field, as well as a brief introduction to the biofabrication sector.

Once designed and manufactured, or even during the design process, the performance of novel biodevices must be assessed by means of in silico, in vitro and ex vivo/in vivo trials before tackling final clinical trials and production, what is detailed in Chap. 15.

Finally Chaps. 16–18 summarise the, providing some additional details on the promotion of creativity in research projects, detailing a more complete methodology for systematic development oriented to biomedical devices and highlighting the importance of teaching–learning tasks for a continuously growing industry, including some cases of study linked to project-based learning in Biomedical Engineering.

Some final annexes include relevant references and websites linked to the biomedical field and to the medical device industry, detail important publications of the field and provide some additional resources for most proactive researchers, such as Matlab-based design programmes.

Anyway, we believe that summarising in this chapter some basic terms and definitions, linked to these relevant fields of technology, even if somehow recurrent (as more exhaustive introductions are provided in each specific chapter), constitutes a valuable introduction to forthcoming chapters and can be useful for the readers.

3.2 Advances on “ICT” (Information and Communication Technologies)

Advances in micro-manufacturing processes and materials science led to the progressive enhancement of the performance of electronic devices, to the advent of personal computer in the late 1970s, to the evolution of telecommunications, to the Internet’s reaching a critical mass in the early 1990s and to the massive use of

computers, Internet and related telecommunication technologies, just two decades after 1990.

Nowadays, our lives are greatly influenced (and indeed helped) by the use of these ICT; teaching resources and methodologies, from schools to universities, have deeply changed; working environments and workers' performance are tightly bounded to the use of computers, very especially in fields linked to engineering; human relations and infrastructures are also promoted or ruled by means of computers; and we can therefore speak of an "information age".

Such information age, also commonly known as the "computer or digital age", is an idea that the current age will be characterised by the ability of individuals to transfer information freely and to have almost instant access to information that would have been difficult or impossible to find previously. Hence, the impact of ICT on current evolution of science and industry, and on the pace at which very relevant discoveries are being made, is indeed enormous and is even analysed as a novel industrial revolution.

Most advanced design and manufacturing technologies covered in this handbook are based on the use of computers or controlled by them, as will be clearly understood when reading the different chapters. In fact, thanks to the use of computers/information and communication technologies, newly developed biodevices benefit from enhanced designs; from much more adequate manufacturing processes, capable of working with very special geometries and remarkable biomaterials; and from the benefits of in silico validation, thanks to simulation resources for a more systematic design analysis, prior to the manufacture of prototypes for in vitro and in vivo trials, all of which optimises costs and schedules of development projects and helps to obtain more effective and secure solutions for Biomedical Engineering. A more adequate management of patient information is also promoted, what is also linked to more personalised solutions.

In such a rapidly evolving field, this handbook just tries to provide a state-of-the-art review of design and manufacturing technologies with current or potential impact on Biomedical Engineering and on the medical device industry, as well as to provide interesting and real cases of study, linked to the application of these advances technologies, for supporting the explanations, together with analyses on main research trends. A continuous update of the topics covered here can be achieved by attending congresses on the field, such as the annual "BIOSTEC International Joint Conference on Biomedical Engineering Systems and Technologies", which usually includes the biodevices, biosignals, bioinformatics and healthINF conferences.

3.3 Advances on Medical Imaging Technologies

The advances seen in recent decades in different medical image capture systems (mainly, computed tomography (CT), Doppler echo scans, nuclear magnetic resonance (NMR) or magnetic resonance imaging (MRI) and positron emission

tomography (PET), as well as more novel combinations PET/CT) have led to a remarkable increase in the diagnostic capabilities of these pieces of equipment as well in the reliability of the diagnoses made based on this information and the therapeutic decisions taken as a result (see referenced standards and associations in Chaps. 2, 5, and Annexes).

Main differences between the different medical imaging (MI) technologies can be explained by means of the type of radiation they use, as further detailed in Chap. 5.

It is relevant to highlight that, during last two decades, biodevice personalisation has been greatly promoted by combining medical imaging technologies and the related outer-/inner-corporal information, with computer-aided development tools. In short, the information obtained using some of these medical imaging can be almost directly converted in three-dimensional objects (replicating the geometries and structures of human body and biological systems) and can subsequently be used as input in CAD programmes, for designing personalised medical devices adapted to the morphologies of such biostructures.

There are several software tools, for handling the information obtained from medical imaging technologies and enabling computer-aided design, engineering and prototyping tasks. They are usually referred to as "MIMICS-like" programmes (due to the relevance of MIMICS (Materialise NV)). Among such programmes, due to their industrial impact and quality of results, it is important to mention at least:

- MIMICS (Materialise NV), for general purpose applications
- Simplant (Materialise NV), especially oriented to odontology
- Surgiguide (Materialise NV), especially oriented to odontology
- 3D Doctor, for bone modelling from CT scan and soft tissue from MRI
- Analyze (Mayo Clinic), for handling images from MR, CT and PET
- MRIcro software, for converting medical images to Analyze format
- Biobuild, for converting volumetric imaging data to RP file formats
- Volume Graphics, for general purpose applications

Several design procedures and applications are discussed in detail in Chap. 5, and final manufacture of such personalised devices is covered in more depth in Chaps. 9 and 10. Chapter 14 details also the importance of medical imaging and related design resources for obtaining microstructural details of biomaterials and biostructures, as a help for forthcoming advances in the field of biofabrication.

3.4 Advances on Computer-Aided Design and Engineering

Computer-aided design (CAD) consists of using computer systems to assist the creation, modification, analysis and optimisation of a design. Initial developments were carried out in the 1960s, linked to the aeronautic and automotive industries, although it was not until the 1980s that these tools started to be used in small and mid-size companies, thus reducing the need of draftsmen. Initially designs

attainable with CAD tools were mainly 2D, but nowadays the use of 3D modelling packages is widespread, due to its versatility.

Nowadays, it has become an essential set of tools with relevant benefits for any kind of industrial product development process, such as overall project cost and time optimisation, what becomes especially relevant in the field of novel medical devices. Application fields include architecture, automotion, aeronautics, naval and mechanical engineering, automation and electrical engineering, chemical engineering and materials science and, especially linked to the purpose of this handbook, biomedical engineering. The promotion of information exchange among clients, developers and suppliers, during a whole new product development process, is also noteworthy.

CAD is intimately connected to several additional technologies, most of them working on the basis of an initial computer-aided designed part or product, such as computer-aided engineering (CAE), covered in Chap. 8; computer-aided manufacturing (CAM), detailed in Chap. 9; product data management (PDM), among others, all of them integrating the more general term of product lifecycle management (PLM) technologies.

Computer-aided engineering (CAE) refers to the general use of software to aid in engineering tasks, in its broadest sense even including computer-aided design and computer-aided manufacturing; although in product design, CAD is perceived as the starting point for designing a part, CAE involves the simulations carried out upon a CAD part in order to verify geometries and materials and CAM is linked to the simulations realised upon a CAD part to prepare manufacturing processes and to the automated control of machine tools during production.

Novel computer-aided innovation (CAI) tools are even aiming to support enterprises throughout the complete innovation process, by incorporating methods and tools, which structure is partially inspired by modern innovation theories as TRIZ, ASIT, axiomatic design, mind mapping, brain storming/brain writing and lateral thinking, among others, some of them explained in detail in Chap. 15.

Currently, most used computer-aided development resources integrate or try to integrate most of the aforementioned modules and are normally referred to as "CAD-CAE-CAM" technologies. Figure 3.2 shows an evolution of scientific documents linked to CA-x technologies, carried out using the search facilities of the ISI Web of Knowledge (Thomson Reuters) webportal, in which the impact of computer-aided design and engineering in industry can be clearly perceived.

Some relevant CAD-CAE-CAM resources with actual relevance in several industrial fields, including Biomedical Engineering, several of them used as support of the design and simulation processes detailed in the following chapters, include (although are not limited to):

- Combining CAD-CAE-CAM capabilities:
  - Solid Edge (Siemens PLM Solutions)
  - NX-8.0 (Siemens PLM Solutions)
  - Catia v.5 (Dassault Systèmes)
  - Solid Works (Dassault Systèmes)

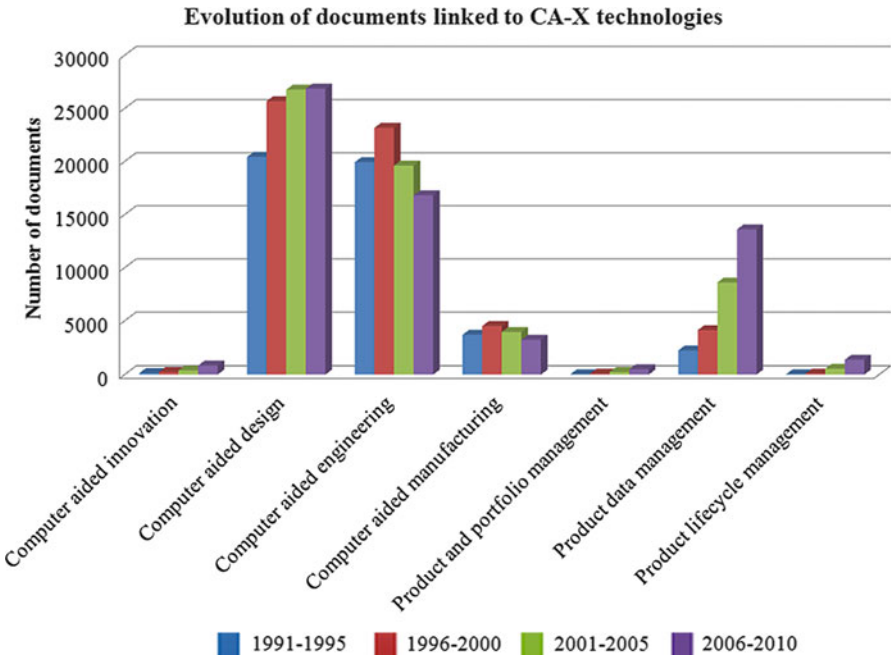

Fig. 3.2 Evolution of scientific documents linked to CA-x technologies

- Autodesk Inventor (Autodesk)
- Rhinoceros

- Oriented to CAE tasks:
  - Abaqus (currently Dassault Systèmes)
  - ANSYS (ANSYS Inc.)
  - Nastran (MSC Software)
  - Patran (MSC Software)
  - Comsol Multiphysics (COMSOL)

3.5 Radical Advances on Manufacturing Technologies and Materials Science

Rapid prototyping and manufacturing technologies allow researchers to obtain physical parts in a short period (hours or days), directly from the designs created with the help of computers using computer-aided design, engineering and manufacturing "CAD-CAE-CAM" programmes, a procedure that constitutes a radical advance in the manufacturing field and that has completely reshaped product development processes, as detailed in Chap. 10.

Such technologies significantly help to optimise the design iterations, allowing for the early detection of errors and speeding up the whole development process. They are generally based on automatic additive or layer-by-layer manufacturing processes (and they are also referred as layer manufacturing technologies or "LMT").

In some cases, very fast manufacturing processes involving material removal, such as high-speed numerical control machining (governed by "CAM" resources, see Chap. 9), are also included within the concept of rapid prototyping, or "RP", although the term is normally linked to additive processes.

As the operation principle is based on deposition processes or layered manufacturing, the creation of very complex geometries, including inner details, can be carried out directly from the associated CAD files, and currently, the geometrical limitations are more linked to the designers' ability, than to the manufacturing process.

Almost all departments involved in the overall process of launching a new product benefit from the systematic use of these RP technologies. A previous prototype is a physical communication tool that reduces the risk of possible misinterpretation, as may occur if only CAD designs or plans are used, and allows subjective features (aesthetics, ergonomics) to be analysed.

The various technologies available can operate and manufacture prototypes using a wide range of metals, ceramics or polymers, both with synthetic and biological origin and with outstanding precision. The possibility of using biomaterials and even "living materials" for additive manufacturing has given birth to the new field of biofabrication, whose potential is describe in Chap. 14.

There are other more recent technologies with an optimised precision of a few micrometers or even hundreds of nanometers, also capable of using materials for specific applications in biomedical engineering, such as obtaining implantable devices or manufacturing scaffolds for tissue engineering processes, as will be discussed in Chaps. 10–12.

Certain "rapid tooling" technologies within rapid manufacturing are also noteworthy, as they can produce tools and parts for injection moulds quickly and economically, either by reproducing the geometry of physical models, through shape copying processes (copying the geometries from rapid prototypes), or by directly manufacturing such tools and parts in an additive way.

These "rapid tooling technologies" and "rapid form/shape copying processes" are described in more detail in Chap. 11, although Fig. 3.3 includes also a brief schematic introductory description of the different connections between rapid prototyping and rapid tooling, thus covering main processes in the field of rapid manufacturing.

It is important to note that these remarkable advances on rapid manufacturing have been only possible thanks to other very relevant progresses in several scientific and technological disciplines that complement each other, including:

- Materials science and technology – As several rapid manufacturing technologies are based on relatively new polymers and biopolymers, as well as on powder and microstructured raw materials.

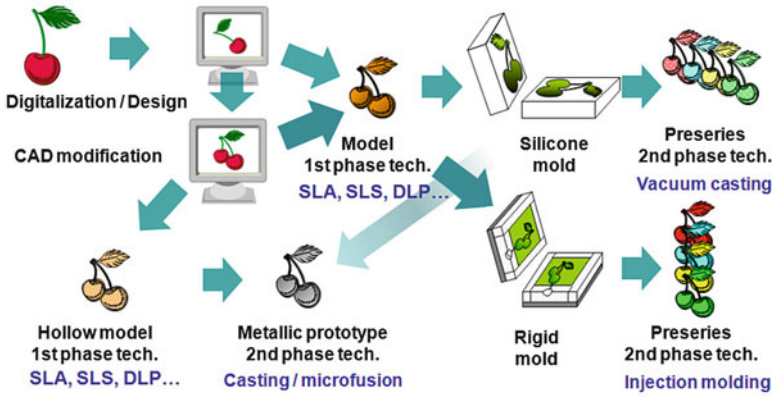

Fig. 3.3 Schematic global panorama of rapid manufacturing. Including input from medical images and CAD-CAE-CAM continuous support (Adapted from H. Lorenzo and P. Lafont, Product Development Laboratory, Universidad Politécnica de Madrid)

- Laser technology and related processes – Because laser is used for promoting photo-polymerisation reactions and sintering and melting processes, all of these relevant for layer-by-layer additive manufacture.
- Information and communication technologies – As these technologies work controlled by computers, even using wireless approaches (as the novel Cube machine from 3D Systems).
- Automation and electronics – Because of the use of automated micro-positioning systems, stepper motors and similar resources for implementing rapid prototyping resources.

3.6 Main Conclusions

The technological convergence of several emerging fields, including materials science, information and communication technologies, medical imaging, design and simulation resources and micro- and nano-manufacturing tools, is promoting the development of devices with highly advanced features with remarkable diagnostic and therapeutic applications in biology and medicine.

In fact, last two–three decades have seen remarkable advances in computer-aided design, engineering and manufacturing technologies, multi-variable/multi-scale simulation tools, medical imaging, biomimetic design, rapid prototyping, micro- and nano-manufacturing methods and information management resources, all of which provide new horizons for the Biomedical Engineering fields and the medical device industry.

As already commented, this handbook covers such topics in depth, trying to provide an applied perspective and detailing in depth several case studies that help

to analyse and understand the key factors of the different relevant stages, linked to the development of a novel biomedical device, from the conceptual and design steps, to the prototyping, validation (including several steps with progressive level of risk) and industrialisation phases.

This chapter has focused on providing a panorama of these technologies that are promoting remarkable alternative approaches for obtaining biodevices with improved diagnostic and therapeutic capabilities. Several essential basic terms and definitions have been introduced here, even though forthcoming chapters provide additional more exhaustive introduction sections, as a way of helping readers to obtain and overall perspective of the aspects covered along this handbook, thus hoping to enhance readability.

Important connections between topics and related chapters have been also detailed, as a way of highlighting again the importance of technological convergence of these emerging fields, as well as for letting readers perceive in advance how the different chapters complement each other.

The structure of the whole handbook on Advanced Design and Manufacturing Technologies for Biodevices has been described, and the relationship between the different main blocks ("Introduction to Product Development and to the Biomedical Field and Related Novel Technologies", "Design Technologies for Biodevices", "Manufacturing Technologies for Biodevices", "In silico, In Vitro and ex vivo/In Vivo Validation of Biodevices" and "Additional Methodological Aspects and Teaching-Learning Experiences") has been detailed.

References[1]

On Computer-Aided Design and Engineering Resources[2]

http://usa.autodesk.com, March 2013
http://usa.autodesk.com/3ds-max, March 2013
http://usa.autodesk.com/autodesk-inventor, March 2013
http://usa.autodesk.com/product-design-suite, March 2013
http://www.3ds.com/es/products/catia, March 2013
http://www.plm.automation.siemens.com/en_us/products/nx/nx8, March 2013
http://www.plm.automation.siemens.com/en_us/products/velocity/solidedge, March 2013
http://www.rhino3d.com, March 2013
http://www.solidworks.com, March 2013

More linked to calculation tasks:

http://www.3ds.com/products/simulia/portfolio/abaqus/overview, March 2013
http://www.ansys.com, March 2013

[1] Some relevant websites linked to different technologies with impact on the biomedical field summarised in this chapter are included below.

[2] More linked to design tasks:

http://www.comsol.com, March 2013
http://www.mscsoftware.com/products/cae-tools/msc-nastran.aspx, March 2013
http://www.mscsoftware.com/products/cae-tools/patran.aspx, March 2013
http://www.mathworks.com, March 2013

On Medical Imaging and Design Based on Medical Images

http://biomedical.materialise.com/mimics, March 2013
http://biomedical.materialise.com/mis, March 2013
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Chapter 4
Computer-Aided Design (CAD) Technologies for Biodevices

Andrés Díaz Lantada and Pilar Lafont Morgado

Abstract Computer-aided design (CAD) consists of using computer systems to assist the creation, modification, analysis, and optimization of a design. Initial developments were carried out in the 1960s, linked to the aeronautic and automotive industries, although it was not until the 1980s that these tools started to be used in small and midsize companies, thus reducing the need of draftsmen. Initially designs attainable with CAD tools were mainly 2D, but nowadays the use of 3D modeling packages is widespread, due to its versatility.

Nowadays it has become an essential set of tools with relevant benefits for any kind of industrial product development process, such as overall project cost and time optimization, what becomes especially relevant in the field of novel medical devices. Application fields include architecture, automotion, aeronautics, naval and mechanical engineering, automation and electrical engineering, chemical engineering and materials science, and especially linked to the purpose of this handbook, biomedical engineering. The promotion of information exchange among clients, developers, and suppliers, during a whole new product development process, is also noteworthy.

CAD is intimately connected to several additional technologies, most of them working on the basis of an initial computer-aided designed part or product, such as computer-aided engineering (CAE), computer-aided manufacturing (CAM), product data management (PDM), among others, all of them integrating the more general term of product lifecycle management (PLM) technologies.

This chapter supplies an introduction to computer-aided design and its most typical resources, details relevant connections with other computer-assisted tools, and

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_4,

provides different case studies linked to the development of real biodevices by using different simple CAD operations. Some current limitations and future trends, which will be discussed in following chapters, are also introduced.

4.1 Introduction to Computer-Aided Design (CAD)

The new technologies have had a profound effect on the professions devoted to three-dimensional design work. Processes like modeling, performing basic stress and deformation analyses, and even the production of rapid prototypes can be currently done by a single designer without any need for a range of specialists (Unver 2006; Díaz Lantada et al. 2007; Lorenzo Yustos et al. 2009). Therefore, an experienced designer can be more effectively in touch with what any design decision involves, which means the overall product development process is optimized in terms of schedules and costs and can even be customized (Grote and Antonsson 2009), as already explained in the introductory chapters of the handbook.

However, this discipline, commonly known as "industrial design," focused towards the development of new products to satisfy customer needs is relatively modern, and its application in the biomedical field even more. It has its origins in the philosophy and practice of movements like "Arts and Crafts" and the Bauhaus ("form follows function") and spreads rapidly to the United States, using products that had more exclusive forms while still being practical, as a way of promoting sales (Gropius 1935). The term "industrial" design is used because it is linked to the development of products that are manufactured through industrial processes and because it is aimed at promoting a product's effectiveness.

Due to its origins, industrial design began to be taught exclusively in art schools and design workshops (in the most aesthetic sense of the word), ignoring the major technical aspects of product development, such as carrying out stress and deformation studies, selecting materials according to mechanical criteria (not only aesthetic criteria), optimizing geometries for greater strength, thermal effects, and others (Pahl and Beitz 1996). These more technical analyses have traditionally been omitted or performed by engineers using very powerful but also very specific calculation programs, with which designers limited themselves to design (in line with geometric and aesthetic criteria) and engineers limited themselves to calculation (in line with theoretical criteria).

It was not until the last decade that this traditional gap between design and calculation programs gradually began to close. A few years ago, it was difficult to apply the potential of calculation programs (like ANSYS or ABAQUS) to study parts with complex geometries designed with the help of other purely oriented CAD resources. Also the design programs that now enable complicated parts to be produced were lacking in computer-aided engineering (CAE) modules for calculation tasks. The steps forward in producing universal formats (.igs, .stl…) to facilitate communication and the exchange of information between designers and engineers, together with the improvements to different "CAD–CAE–CAM" packages or

"computer-aided design, engineering, and manufacturing" software are now helping overcome these difficulties. Among all the great benefits currently available, we need to mention the gradual inclusion of high-quality calculation packages in design programs, which link the design and calculation stages without the inconvenience of having to convert formats (with related information losses).

In addition, the continuing improvements in the power/cost ratio of computers that can operate these programs (usually only used by large companies because of their high cost) have meant that many schools, universities, small and medium enterprises, and free-lance teams of designers can now afford the academic or professional licenses and offer their services for design projects.

When choosing a CAD–CAE, there are several basic factors to be taken into account, which other authors have already dealt with in detail (Rubio García et al. 2005, 2007). The following important issues need to be mentioned:

- Design capabilities of the software package and the quality of results
- Calculation capabilities of the software package and the quality of results
- The possibility to exchange information with other applications
- Use in our industrial environment (depending on the sector of interest)
- Use in research and academic work
- License and maintenance costs
- Final application: specific or commercial software
- Learning difficulty

Detailed below is a brief comparison and historical perspective of main CAD–CAE resources (although for more specific details about CAE please see Chap. 8), adapted from our previous research (Díaz Lantada et al. 2010) by including some more relevant packages, whose industrial expansion is noticeable. Figure 4.1 includes some examples of industrial parts typically obtainable with the help of CAD resources, as an introduction to its specific applications for the development of biodevices mentioned in the following sections.

NX: Siemens PLM (Product Lifecycle Management) Solutions. This is a CAD–CAE–CAM–PLM package (for the computer-aided design, analysis, manufacture, and management of products) developed by Siemens PLM Software, widely used in the product development industry and the automobile, aeronautics, and railway industry. It is currently a direct competitor of CATIA and ProEngineer; however, its use in Spanish industry is still less than that of other programs, like CATIA (from Dassault Systemes), probably because French companies have a larger influence on Spanish industry (especially in the aeronautic sector) than German or American companies.

The truth of the matter is that it evolved from an initial package called Unigraphics, whose original software was prepared by United Computing. In 1977 Mc Donnell Douglas took over United Computing to found the Mc Donnell Douglas Automation Unigraphics Group, until that was taken over by Structural Dynamics Research Corporation (SDRC), which meant that Unigraphics became merged with SDRC's I-DEAS software, with a gradual evolution towards the current NX. Since its

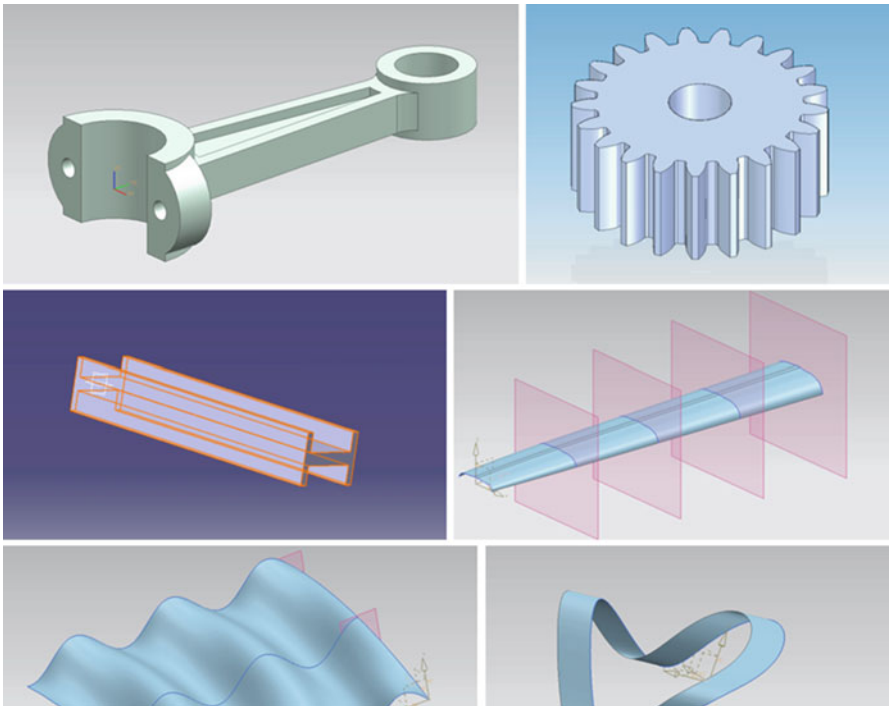

Fig. 4.1 Examples of the design of solids and surfaces: rod, gear, wing, beam, cover deck, and heart-like figure

acquisition by Siemens AG, Siemens PLM Software has enhanced its PLM and work capabilities with a wide range of operating systems (Linux, Unix, versions of Windows, and Mac OS X).

Solid Edge. This is a parametrical 3D parts program based on computer-aided design system software (CAD). It enables parts to be modeled in different materials, laminated sheeting, assembling sets, welding, and plan drawing functions for engineers. It is one of the packages that have caused people to move massively from 2D CAD to 3D CAD, due to its rapid learning curve, with the ensuing advantages on every level of work. Through software supplements from other companies, it is compatible with some PLM (Product Lifecycle Management) Technologies which help manage the whole life of a product, from its conception to its market withdrawal.

It was presented in 1996 and initially developed by Intergraph as one of the first CAD-based environments for Windows NT. In 2007 it was acquired by Siemens AG (purchased from UGS Corp., which, in turn, had purchased it in 1998) and is now beginning to form part of all its production and engineering plants, for which reason it is undergoing considerable changes. This will undoubtedly open up the way to sectors that were until now condemned to use certain software due to a lack of compatibility of their files with other CAD packages. This means information from

other CAD tools can be edited (NX-6, Catia, Autodesk Inventor, SolidWorks, ProEngineer, IronCAD, among others) and is expanding to other sectors of industry like the railway, automobile, or aeronautics sectors. One of its most marked recent improvements of this version is the transfer of files to other platforms and the implementation of the "Engineering Reference," a tool for designing conventional engineering parts, such as gears, shafts, bolts, and springs.

CATIA. Computer-Aided Three-Dimensional Interactive Application is a commercial CAD–CAM–CAE program produced by the French company Dassault Systèmes. The program is designed to provide aid from the conceptual design stage (CAD) to the production stage (CAM) and the product analysis stage (CAE). It is presently running its V5 version, which in recent years has replaced the AIX-based CATIA V4, and is also available for Solaris, IRIX, and HP-UX, due to its capability to work with Microsoft Windows.

It was initially developed for use in the aeronautic industry, with a large emphasis on the handling of complex surfaces. CATIA is also widely used at present in the automobile industry for designing and developing bodywork components, more in Europe than in North America. To be specific, companies like the VW Group (Volkswagen, Audi, SEAT and Škoda), BMW, Renault, Peugeot, Daimler AG, Chrysler, and Porsche make full use of the program, although some of them are recently resorting to NX-Siemens PLM Solutions. The construction industry has also included the use of software for designing buildings with a high complexity of form; the Guggenheim Foundation Museum in Bilbao, Spain, is a well-known architectural milestone that exemplifies the use of this technology, although more typical from architects is the use of AutoCAD, now evolved into Autodesk (see below).

SolidWorks. It is a 3D mechanical CAD also under continued development by Dassault Systèmes, currently used by more than a million engineers worldwide, due to its rapid learning curve and to the use of parametric feature-based approach, like most remarkable CAD packages follow. It includes also some validation (through simulations) tools and product data management resources. Another main advantage is that it can read (and save) files from (or into) all main common CAD formats.

SolidWorks Corporation was founded in December 1993 by Jon Hirschtick, who recruited a team of engineers to build a company that developed 3D CAD software that was easy to use, affordable, and available on the Windows desktop and released its first product, SolidWorks 95, in 1995. In 1997 Dassault Systèmes, acquired the company and currently owns 100 % of its shares.

Autodesk Inventor. Autodesk Inventor is a 3D modeling CAD developed by Autodesk Inc., whose evolution is briefly described below. Due to its rapid learning curve and to the incorporation of movement simulation and finite element method based calculations, it is direct competitor of the already mentioned Solid Edge and SolidWorks. It also includes import–export capabilities for interchanging information with the CAD resources detailed before.

Autodesk Inc. is best known for its AutoCAD (initially 2D and nowadays 3D) software. It is an American multinational corporation founded in 1982 by John

Walker, coauthor of AutoCAD, and its actual impact on Architecture is beyond all possible explanation, as it has completely reshaped the way architects work, in just three decades. Currently is the most successful company devoted to design software, and its evolution in the last years is too complex to explain here.

Its conversion from an initial focus on 2D architecture to a more versatile approach providing solutions for every kind of 3D design needs in all types of industries is highly remarkable, as well as its progressive inclusion (or acquisition) of new resources, including Autodesk Inventor for conventional product design, Autodesk Moldflow for simulating injection molding production tasks. Its Autodesk Education Community provides several solutions online for their limited used in universities and teaching centers, what constitutes a relevant marketing strategy, and is also of great help for the Academic world in current times.

This brief introduction has described some of the most used CAD resources and the industrial impact of all of them is noteworthy. Other CAD systems have been specifically designed for working under operative systems different to the more extended Windows (such as Unix, Linux, BSD/OSX). Many of them are also interesting, especially for designers using Mac OS X architectures and for very specific applications, but we have limited our analysis to the most used and versatile ones. Next section is devoted to detailing the typical modules of CAD resources.

4.2 Conventional CAD Software Modules and Tools

The degree of complexity and capabilities of CAD packages is continuously evolving, for promoting the development of more complex products and their more secure development, trying to optimize schedules and costs. First computer-aided resources were 2D based and included just some sketch tools comparable to those from Microsoft Paint, although with some additional capabilities. However, the remarkable progresses realized, especially in the 1980s and 1990s, has totally changed the performance of CAD programs and promoted a wide set of 3D design features, as well as specific modules for all kinds of industries.

Among typical modules included in CAD software, it is important to cite the following ones:

- Sketcher – for drawing 2D objects and plans
- Part modeling – for designing conventional 3D parts
- Sheet metal/plastic design – for designing 3D parts with homogeneous thickness
- Assembly – for arranging assemblies of 3D parts, obtaining complex products and geometrical verification
- Movement simulation – for simulating and verifying the possible movements of complex assemblies and detecting eventual collisions
- Plant layout – for helping engineers and architects with the distribution of furniture and machines in buildings, offices, and factories

- Routing – for helping engineers and architects with the distribution of electrical, pneumatic, or hydraulic connections in buildings, offices, and factories

Several of the aforementioned CAD packages (including NX, Catia, Autodesk Inventor, SolidWorks, and Solid Edge) are also beginning to include additional simulation modules, based on calculations by application of the finite element method, for solving mechanical, fluidic, thermal… phenomena, and for helping with part or product in silico validation. However, as this Chap. 4 focuses especially on CAD, we will describe in more detail such modules, more linked to CAE, in Chap. 8.

Design operations from the sketcher are similar to those from any 2D drawing application. Focusing in more detail on the 3D design operations from the "part modeling" modules, which constitute the core of CAD programs, there are some typical tools to be highlighted:

- Sketch-based operations – These include operations like "extrude," "hole," "revolve," "emboss," "groove," or "sweep" that allow obtaining 3D parts or incorporating features upon 3D objects, by using the information of a 2D sketch projected in a determined direction, along a path or around an axis.
- Curve-based operations – Main commands include "mesh surface," "surface blend," or "shell" and are usually aimed at designing surfaces, starting from 3D curves, for subsequently obtaining solid parts based on such surfaces (by thickening or by closing a volume with surfaces for further solid conversion).
- Design of common geometries – Normally a CAD software includes a set of tools for directly defining geometries such as spheres, ellipsoids, cones, cubes, cylinders, prisms, and tubes.
- Boolean operations – These allow the combination of normally very simple 3D geometries using Boolean logic for producing more complex geometries. Boolean commands include "add," "subtract," "combine," and "intersect."
- Pattern features – These operations help to increase the complexity of a product by replicating or reproducing already designed geometries. Among possible operations, it is important to cite "pattern feature," "copy/replicate," "mirror," "move (with or without associative copy)," "rotate (with or without associative copy)," and "instance geometry."
- Final operations – These are usually oriented to providing an additional end quality for the part under design and normally aimed at obtaining soft parts by eliminating sharp edges or for preparing manufacture (in the case of draft angles for some geometries of injection molds). Typical commands are usually referred as "blend," "chamfer," "styled corner," "draft," or "draft angle."

There are also several additional resources for promoting design quality and helping designers, such as the possibility of including reference planes and of working with different reference systems, the capacity of measuring distances, areas and volumes or the application of several colors, shadows, lights, and a very complete set of rendering effects for enhancing visual aspect and normally linked to marketing tasks.

In any case, due to the remarkable number of modules, features, operations, and possibilities, when first trying to assess the use of CAD software for a novel project or for promoting product development, it is advisable to follow a specific course (Díaz Lantada et al. 2009, 2010), even though the use of tutorials available at "youtube" and other information exchange websites can be also helpful for beginners and even for experts.

As different CAD packages have several tools and features in common, once a researcher has mastered one of the available programs, it is indeed much easier to understand the principles of alternative ones and take advantage of the benefits from using different resources.

4.3 Linking CAD with Other Technologies and Sharing Files

Geometries obtained with the help of CAD tools can be further studied and simulated and serve as basis for subsequent development stages, including manufacture, thanks to the possibility of linking such files with those used by many other computer-based tools. Of course such link is direct with CAE–CAM technologies, as already explained and detailed in Chaps. 8 and 9.

But such CAD files serve also as basis for developing ad hoc programs for solving specific problems using high-level programming languages. Not only CNC-automated manufacturing machines and additive manufacturing technologies (see Chap. 10) can be programmed directly from the information included on CAD files, but also automated inspection operations upon final parts for quality control, or even linkage with haptic devices for surgical training of guidance, can be achieved.

Due to its impact on teaching and practice of all types of engineers, it is very interesting to cite here Matlab (The Mathworks Inc.), a technical computing software with integrated programming language (M language), whose perhaps most remarkable feature is the collaborative environment provided among its users community.

Several of the downloadable programs available at the Matlab's file exchange website (www.mathworks.com/matlabcentral/fileexchange) are connected to importing geometries from CAD files or exporting surfaces and solids to different CAD formats. Such geometries, after conversion to Matlab, are handled as matrixes containing the coordinates of the part's outer surface or inner volume, and it is possible to develop additional programs for specific purposes.

The impact of CAD in all industrial fields is so important that Matlab has developed specific modules for importing parts, products, and assemblies and subsequently carrying out movement simulations, promoted by multi-body dynamics, or finite element analyses for simulating complex phenomena. Possibilities are evolving continuously, thanks to the progressive convergence of several emerging technologies.

The possibility of sharing CAD files with other users, product designers and developers, customers or potential clients is also worth of attention. As already

highlighted, promoting information exchange among all the participants linked to a development project (including developers and all external influences) is a key aspect in systematic design methodologies and CAD resources have had a great influence in promoting these aspects. In fact CAD has progressively integrated product data management modules and has been finally integrated within PLM or product lifecycle management solutions. In the medical device industry, being an especially tightly controlled sector, with several directives of application and very relevant standards to be followed, an adequate information management takes a prominent place and CAD helps to manage related projects. For promoting information exchange in more conventional applications, there are even some open-access-free downloadable CAD tools, such as Google SketchUp, which also provides an online library of 3D parts for sharing files with designers worldwide. Even though its capabilities are more limited than those from more professional CAD software (Autodesk Inventor, Catia, NX-8.0, Solid Edge, SolidWorks, ProEngineer…), it is important to mention the Google SketchUp "soften" tool, useful for obtaining "organic" designs from very simple forms.

These tools also help with commercial product selection tasks, when designing a novel machine or device, as the manufacturers of components (motors, gearboxes, bearings, shafts…) usually include downloadable CAD files of their products available at their websites. Typical examples include the indeed complete product library of SKF, for designing transmissions, or the 3D IKEA furniture appliance, for use in AutoCAD, Google SketchUp, and other 3D rendering software, when selecting new furniture for home or office.

Import/export capabilities of main CAD resources are also relevant for aiding simulations, linked to in silico validation of biodevices (CAE tools, see Chap. 8), and for helping with the manufacture of prototypes and production launch (CAM tools, see Chaps. 9 and 10). Such capabilities are continuously progressing and everyday novel formats try to provide "universal" solutions for 3D geometry and related information exchange (among typical formats we can cite: .stp, .stl, or .igs). Sometimes format conversion leads to information loss and geometries cannot be properly read, so there is much place for improvement, also as regards file size when using such conversions.

In the biomedical field, the possibility of linking designs with information obtained from medical imaging technologies is also worth of attention, as analyzed in several occasions within the handbook (see Chap. 5, together with the introductory Chaps. 1 and 2).

4.4 Case Studies: Designs Based on Solid Operations

This section provides a couple of examples of the possibilities of computer-aided design programs for rapidly designing real biodevices, similar to many commercial solutions, by combining very simple solid-based operations with the advantages of using Boolean and pattern-based commands.

First example is linked to the field of Tissue Engineering and serves as an introduction to "scaffolds," which will be covered several times along the handbook. Tissue engineering combines biological and engineering knowledge to provide artificially developed substitutes for tissues and organs linked to repair and replacement therapies.

A key element involved in tissue engineering processes is the matrix or scaffold which serves as substrate or framework for cell growth, aggregation, and tissue development (Langer and Vacanti 1993). These scaffolds must be porous so as to allow cell migration during the colonization process as well as the transport of nutrients and waste to and from cells, but they have to be also resistant enough to withstand possible mechanical demands and long-term stresses, especially if final implantation is desired.

Additionally, as cells are able to feel their microenvironment and substrate texture upon which they lie by changing their morphology, cytoskeleton configuration, and intra- and extracellular signaling, increasing efforts are being focused on design and manufacturing technologies to generate and modify the structure and surface of biomaterials (Thomas et al. 2010; Buxboim and Discher 2010).

Aspects such as porosity, pore size, and surface micro-texture promote cell adherence, migration, and proliferation within the scaffold, for subsequent differentiation into relevant cell types. Thus, the scaffold plays a fundamental role in most tissue engineering strategies as its properties can deeply influence the global success of new tissue formation and the controlled design fabrication of the scaffold structures is becoming increasingly important for novel approaches within regenerative medicine (Bartolo et al. 2009; Tan et al. 2010).

Computer-aided design-based scaffolds are therefore a matter of research, as these technologies allow the design of controlled micro-architectures, whose main features can be in silico validated through FEM-based simulations and further rapidly manufactured with the help of additive manufacturing resources, as Chaps. 8, 10, and 11 will describe in detail.

Figure 4.2 shows a scaffold design example starting from a cylinder, which is replicated several times for obtaining a layer of cylinders, layer that is subsequently rotated, translated, and copied for constructing a woodpile-like structure. Final combination of the geometries by means of a Boolean operation leads to a solid part. In fact the design obtained here is very similar to commercial solutions from manufacturers such as 3D Biotek, well known for its solutions for tissue engineering obtained using rapid prototyping approaches.

It is important to remark that such a design can be obtained in less than 5 min, and, if the parametric design tools available in most CAD software are used, a whole series of designs, with different pore size, pore distribution, and mechanical endurance, can be achieved in a couple of hours. Such efficiency provides an additional illustration of the importance and versatility of these computer-aided technologies for promoting all kind of projects linked to the development of novel biodevices.

The design has been obtained with the help of NX-8.0 (Siemens PLM Solutions), which is also used as support tool for obtaining most of the designs included in the whole handbook.

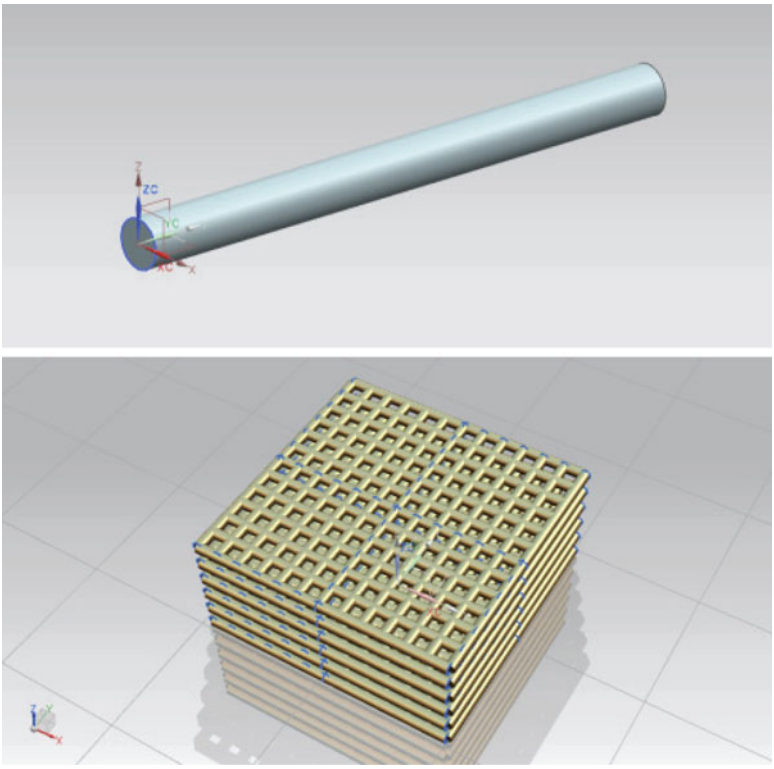

Fig. 4.2 Three-dimensional scaffolds for tissue engineering studies obtained using an additive design procedure

Figure 4.3 shows an alternative option for designing porous structures, in this case again oriented to obtaining a scaffold for promoting studies in the field of Tissue Engineering. In this case, design starts from a simple sphere replicated in perpendicular directions for covering the XY plane, thus obtaining a layer of spheres, which is subsequently copied and replicated several times along the "z" direction, for obtaining a cube full of spheres. Final part is achieved by subtracting the set of spheres from a cube using a Boolean operation. The rendering features also provided promote a more visual appeal for helping marketing tasks.

The actual benefits of using these kinds of lattice and porous structures, with so regular features, is still controversial, as the irregular features of real organisms cannot be so easily replicated. Chapter 6 provides some possible alternatives linked to the use of fractal and non-Euclidean geometries, trying to give additional tools for producing biomimetic multi-scale designs, which may lead to improved mechanical, tribological, and biological characteristics for final implants.

Anyway further details on the design process of porous and lattice structures, as well as some special related resources, are detailed in Chap. 7, as based on them several possibilities arise for the design of all kinds of biodevices, not only for tissue

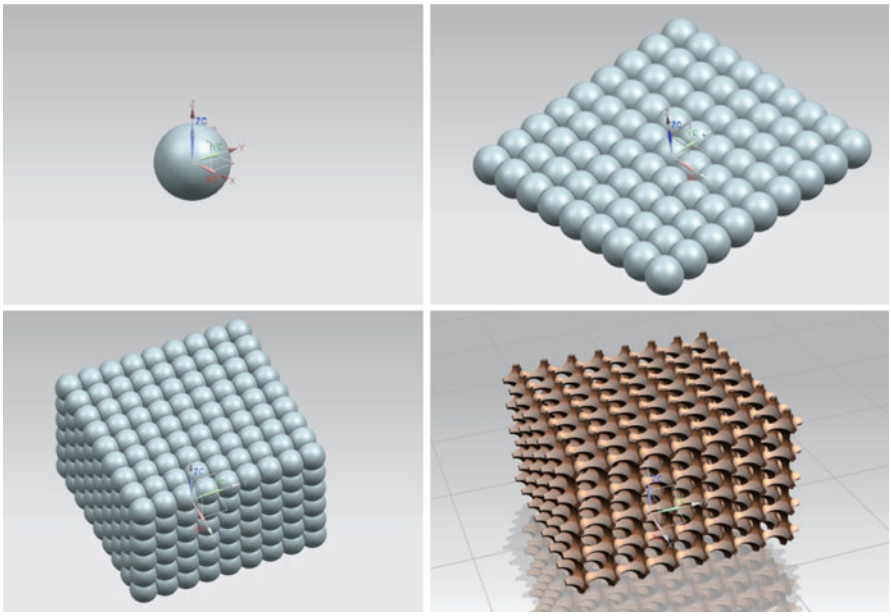

Fig. 4.3 Three-dimensional scaffold for tissue engineering studies obtained by combining additive and subtractive design procedures

engineering but also aimed at obtaining implantable prostheses or prostheses for promoting minimally invasive surgical procedures.

4.5 Case Studies: Designs Based on Surface Operations

Another field of Medicine directly linked to Bioengineering and greatly benefiting from the use of simple implants, easily designable with the help of CAD tools, is cardiovascular surgery. As a very brief introduction, cardiovascular surgery is the surgery of heart and great vessels, carried out by cardiac surgeons and usually linked to treating the complications of ischemic heart disease, correcting congenital heart diseases, treating heart valvular diseases (with different origins such as endocarditis, rheumatic heart disease, and atherosclerosis), and including also heart transplantation.

There are several specialties within cardiovascular surgery, including open heart surgery, beating-heart surgery, minimally invasive surgery, or pediatric (and even prenatal) cardiovascular surgery, which are beyond the scope of this handbook. Anyway, many of cardiovascular-related procedures benefit from the use of stents, either balloon-mounted or auto-expandable.

A stent can be briefly described as an artificial tube inserted into a natural conduit in the body to prevent or heal a disease-induced and localized flow constriction.

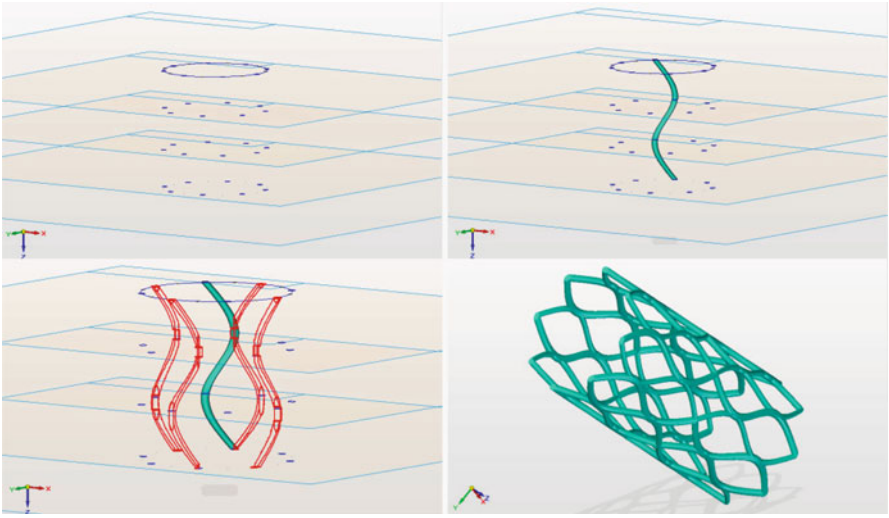

Fig. 4.4 Vascular stent designed with the help of surface tools, mirror features, and Boolean operations

The term may also refer to a tube used to temporarily hold such a natural conduit open, in order to allow access for surgery. Besides helping in cardiovascular surgery for treating coronary arteries and several blood vessels, as well as for simplifying surgical procedures, stents are also used for changing the morphology of organs such as urethra, aorta artery, esophagus, ureters, prostate, or bronchia, among many others.

Figure 4.4 shows the design process of a stent, whose geometry is in essence similar to that of commercial devices, although a wide set of different types can be found.

First of all four parallel planes at a fixed distance are constructed. On the first plan a central circumference is drawn, and eight more small circumferences, with their centers regularly distributed along the central circumference, are also included. Such circumferences are projected to the parallel planes. Using the "surface through curves," or a similar command, the first partial thread of the stent is designed with an "S" shape. By closing the upper and lower part of the thread with several circles, the surface can be transformed into a solid body. Final design is achieved by a combination of symmetries and Boolean operations.

In this case the design has been carried out with the help of Solid Edge, which provides also a very friendly interface for easily selecting the available design commands. Again the design can be obtained rapidly, surely in less than half an hour, and the use of parametric design tools helps to obtain series of stents trying to provide more personalized solutions.

Such parametric design tools may also be helpful for expanding the product portfolio of an enterprise devoted, for instance, to the development of cardiovascular stents and wishing to explore novel applications of their technologies and designs, linked to other organs and pathologies.

Next design example is linked to the development of an annuloplasty ring for treating mitral valve insufficiency. The mitral valve is made up of two components whose mission is to channel the blood from the auricle to the left ventricle. Firstly, there is the so-called mitral valve complex comprising the mitral ring, the valves of the mitral valve, and the commissures joining both valves. Apart from the mitral valve complex itself, this valve has the so-called "tensor" complex, which in turn comprises the tendinous chords, which continue with the papillary muscles attached to the left ventricle. A failure of any of these elements leads to functional changes in the mitral apparatus, such as mitral insufficiency and many hemodynamic repercussions.

Mitral insufficiency is defined as the systolic regurgitation of blood from the ventricle to the left auricle, due to incompetence in mitral valve closing. This can arise for three main reasons including a primary disease of the mitral valve, an anatomic or functional alteration in the papillary chords and muscles, or a disorder in the correct function of the auricle and the left ventricle (Gillinov 2003).

Valve reconstruction is currently the preferred treatment for mitral insufficiency provided this is possible. With the aid of preoperative transesophagic echocardiography, lesions can be located and a surgeon can evaluate if valve repair is possible and design an exact plan for any operation required.

The object of this surgery is not simply limited to eliminating mitral insufficiency but in many cases to reconstructing the geometry of the entire mitral valve apparatus to ensure a durable repair.

Surgically restoring the geometry to normal consists in augmenting or reducing the abnormal vellums, replacing broken or short tendinous chords using "Goretex" type sutures or using an annuloplasty ring for improving stiffness.

Carpentier's description of a rigid prosthetic ring to allow a selective reduction of the entire mitral ring opened the way to modern mitral repair (Carpentier 1983). Annuloplasty consists in inserting the said ring-shaped device via the jugular vein into the coronary sinus and after applying traction, retraction, or heat, it reduces its perimeter, thereby reducing the mitral ring and improving the contact between the valve vellums, which in turn leads to a reduction in the patient's degree of mitral insufficiency.

The computer-aided design of such annuloplasty rings can be carried out, and even personalized with the help of cardiac computed tomography and additional software resources (see Chap. 5), in just a couple of hours. The example further explained shows a simple design, similar to commercial ones, such as the "GeoForm" model (from Edwards Lifesciences Corporation) or the "Duran" model (from Medtronic Inc.).

The process begins with the construction of a three-dimensional line for being the axis of the annuloplasty ring. Such line, following several points introduced by their 3D Cartesian coordinates, is designed with the help of a "spline" command, available at any CAD software.

Splines, in their mathematical definition, are sufficiently smooth polynomial functions that are piecewise-defined (or point by point defined) and possess a high degree of smoothness at the places where the polynomial pieces connect (usually known as "knots" and here corresponding to the points introduced by their 3D Cartesian coordinates).

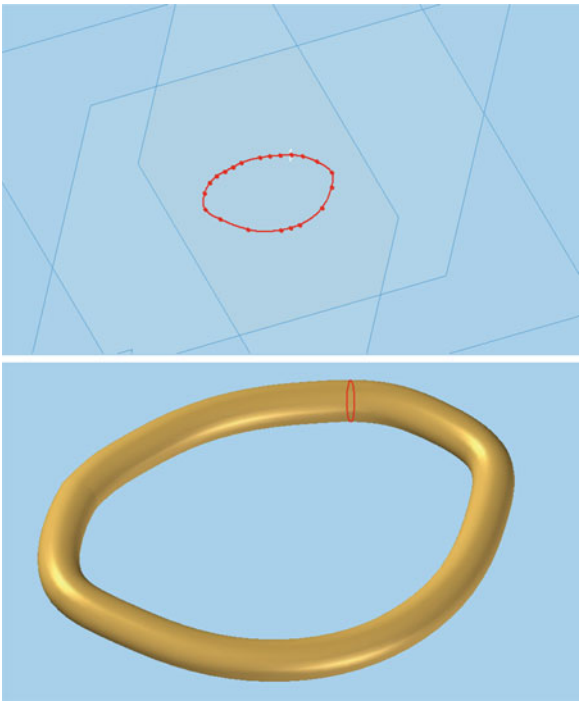

Fig. 4.5 Annuloplasty ring for mitral valve insufficiency design with the help of computer-aided design resources

Once the spline, adapted to the form of mitral valve, is obtained, a point of the spline is selected and a reference plane, normal to the spline and containing such point, is constructed. A 3 mm circumference contained in the reference plane and with center on the intersection point between plane and spline is then drafted. By using the "sweep" command, the circle is made to follow the whole spline, hence leading to final solid annuloplasty ring.

This biodevice has been again designed with the help of Solid Edge, whose "spline" command allows the easy introduction of points by their (x, y, z) 3D coordinates, just as contained in an Excel table (Fig. 4.5). Such connection with MS Excel is especially noteworthy and simplifies designs based on splines and 3D curves.

Other CAD resources, even when capable of importing coordinates from tables, do not always provide such a direct process.

4.6 Main Conclusions

Computer-aided design (CAD) consists of using computer systems to assist the creation, modification, analysis, and optimization of a design. Due to their relevant versatility, these CAD resources have become an essential set of tools with many significant benefits for any kind of industrial product development process, such as overall project cost and schedule optimization, aspects that become especially relevant in the field of novel medical devices.

This chapter has supplied an introduction to computer-aided design and its most typical resources, detailed relevant connections with other computer-assisted tools and provided different case studies linked to the development of real biodevices by using different, but very simple, CAD operations. Some current limitations and research trends, which will be discussed in following chapters, have been also introduced.

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Chapter 5
Medical Imaging-Aided Design of Personalized Devices

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Abstract Medical imaging comprises the different technologies and processes used to generate images of the human body (or any kind of biological systems) for clinical purposes, including diagnosis and surgical training, and medical studies, normally linked to anatomy and physiology.

There are several medical imaging technologies grouped in families, including radiology, nuclear medicine, endoscopy, thermography, high-precision digital photography, many kinds of microscopy, and ultrasound-based imaging. Recent advances on information and communication technologies have allowed product designers to tend bridges between the information obtained from the use of medical imaging tools and computer-aided design programs.

In short, the information obtained using some of these medical imaging can be almost directly converted in three-dimensional objects (replicating the geometries and structures of human body and biological systems) and can subsequently be used as input in CAD programs, for designing personalized medical devices adapted to the morphologies of such biostructures.

This chapter revises the most relevant of these medical imaging technologies for the development process of personalized medical devices and provides case studies linked to personalization based on high-precision photography, cardiac computed tomography, and nuclear magnetic resonance. Main support software for converting medical images into 3D CAD files is also discussed.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_5,

Final manufacture of the personalized biodevices can be accomplished with help of several computer-aided manufacturing and solid free-form fabrication or additive manufacturing technologies, as described further on in several examples along the handbook.

5.1 The Advantages of Device Personalization

In conventional product development personalization is aimed at suiting consumers' unique tastes and hence improving marketability and final increase of enterprises' outcomes. Several strategies are typically followed, such as designs focused on parametric and modular products, on producing an important number of different accessories, on providing attachable external features (protecting cases, stickers…), and on final ergonomic adjustment to client upon acquisition, among other possibilities.

Impact of personalization and its influence on product design can be clearly appreciated in conventional industries, such as the automotive or the mobile phone sectors. Color, shape, size, and functionalities are day-by-day more personalized for making consumers feel special. In most cases such personalization is also linked to the concept of programmed obsolescence, as customers' tastes change (or are promoted to change) very rapidly and repairing conventional products is no longer "fashionable" or economically viable.

Novel design and manufacturing resources currently allow the cooperation of customers along the whole design process in several industrial sectors, such as furniture, transport, inner architecture and decoration, consumer electronics, toys, or jewelry. The use of CAD–CAE–CAM, together with rapid prototyping facilities, allows for such approaches, and unique part series are more and more frequent. The final cost is not so dramatic as it may appear, as these novel technologies are also evolving and several of them are available for less than 1,000 €. In fact with around 5,000 € for design, digitalization, and manufacturing resources, a very complete development workshop can be arranged.

In Biomedical Engineering, personalization is usually pursued for providing a remarkable solution for an especially unconventional and complex pathology, for promoting diagnostic or therapeutic capabilities of a device by a better adaptation to patient's morphology and for supplying enhanced technical helps designed by a more detailed application of ergonomic principles. In such a field personalization is in most cases a relevant need, not just a luxury, and its social impact justifies carrying out continued research for its promotion.

During last two decades, biodevice personalization has been greatly promoted by combining medical imaging technologies and the related outer/inner-corporal information, with computer-aided development tools. In short, the information obtained using some of these medical imaging can be almost directly converted in three-dimensional objects (replicating the geometries and structures of human body and biological systems) and can subsequently be used as input in CAD programs, for designing personalized medical devices adapted to the morphologies of

such biostructures. Several procedures and applications are discussed in detail in the following sections. Solid free-form fabrication or additive manufacturing technologies (Chap. 10) help with final manufacture of personalized biodevices in a wide set of biomaterials for subsequent potential implantation.

5.2 Imaging Tools for Promoting Design Personalization

The advances seen in recent decades in different medical image capture systems (mainly, computed tomography (CT), Doppler echo scans, nuclear magnetic resonance (NMR) or magnetic resonance imaging (MRI), and positron emission tomography (PET), as well as more novel combinations PET/CT) have led to a remarkable increase in the diagnostic capabilities of these pieces of equipment as well in the reliability of the diagnoses made based on this information and the therapeutic decisions taken as a result (see referenced standards and associations).

Main differences between the different medical imaging (MI) technologies can be explained by means of the type of radiation they use, of the final precision and of their several application fields.

For example, nuclear magnetic resonance imaging uses nonionizing radiation, while computed tomography or positron emission tomography uses ionizing radiation. Normally NMR is more linked to obtaining images from soft tissues, while CT usually focuses on hard tissues (even though such conventional separation has blended in the last decade, in fact our case studies provided in next sections use NMR for designing a prosthesis adapted to bone and CT for designing a prosthesis adapted to muscle).

PET is more used as a diagnosis support tool in oncology and neurology, usually together with an additional result from more precise anatomical imaging. In fact PET scans are increasingly read alongside CT or magnetic resonance imaging (MRI) scans, with the combination (called "co-registration") giving both anatomic and metabolic information (what the structure or organ is and what it is doing biochemically). More modern PET scanners are now commercially available with integrated high-end multi-detector-row CT scanners (so-called PET/CT).

CT and MRI scanners are able to generate multiple two-dimensional cross sections (called tomographs or "slices") of tissue and further three-dimensional reconstructions. Early PET scanners had only a single ring of detectors; hence, the acquisition of data and subsequent reconstruction was restricted to a single transverse plane. More modern scanners now include multiple rings, essentially forming a cylinder of detectors.

The medical community is also currently benefitting from the opportunity to exchange information from different medical image capture systems among centers and researchers. This is thanks to the "DICOM" (Digital Imaging and Communication in Medicine) standard and its generalized usage as a working format for different three-dimensional image reconstruction software, particularly with the introduction of version DICOM 3.0 in 1993.

Programs like "MIMICS" (Materialise NV) have also appeared (see the list provided below) which not only enable three-dimensional reconstruction to be performed from medical images but also basic operations on these images and their conversion to other formats accessible to "CAD–CAM" design and manufacturing programs.

As already explained in previous chapters, these CAD–CAM programs (Solid Edge, Catia, NX-8.0, Autodesk-Inventor, I-DEAS, Rhino, Solid Works, and others) comprise a wide range of computer tools that assist engineers, architects, and design professionals in their work. Simulations for in silico assessment of designs can also be performed with the help of CAE resources.

The power of these software packages quoted, and their being able to be used to handle information from medical imaging as a basis for the designs, means that currently the design of personalized prostheses can be performed in a question of hours while also making easier comparisons between alternative designs (Hieu 2002; Harrysson 2007).

Nonetheless, the use of personalized prostheses or implants has historically been something occasional and practically always the result of research projects between Academia and hospitals. This is basically due to the limits of cost and timeline problems that have prevented these personalized prostheses or implants, from competing with standard mass-produced designs.

However, the considerable industrial expansion experienced in recent years by a range of technologies called "rapid prototyping (RP) technologies," normally based on high-speed computer numerical control machining or on additive manufacturing approaches (see Chap. 10), that enable schedules and costs to be reduced by manufacturing parts directly from geometric information stored in CAD–CAM program files, is presenting new opportunities for a personalized response to the development of implants and prostheses, the social impact of which could turn out to be highly positive (Schwarz 2005; Kucklick 2006).

Progressive linkage between CAD tools, MIMICS-like software, and CAM-assisted manufacturing is highly beneficial for the development of personalization in all kinds of products and industries and very special in the biomedical field. Main of such programs together with applications in the product development sector have been previously reviewed (Díaz Lantada and Lafont Morgado 2011) and are actualized further on, providing some examples of how the use of CT imaging is indeed versatile:

There are several software tools, for handling the information obtained from medical imaging technologies and enabling computer-aided design, engineering, and prototyping tasks. They are usually referred to as "MIMICS-like" programs (due to the relevance of MIMICS (Materialise NV)). Among such programs, due to their industrial impact and quality of results, it is important to mention at least:

- MIMICS (Materialise NV), for general purpose applications
- Simplant (Materialise NV), especially oriented to odontology
- Surgiguide (Materialise NV), especially oriented to odontology
- 3D Doctor, for bone modeling from CT scan and soft tissue from MRI

- Analyze (Mayo Clinic), for handling images from MR, CT, and PET
- MRIcro Software, for converting medical images to analyze format
- Biobuild, for converting volumetric imaging data to RP file formats
- Volume Graphics, for general purpose applications

Listed below are the main applications of computerized tomography (as a representative technology within the medical imaging sector), together with software for processing medical images and "CAD-CAE-CAM" tools, for optimizing product design and development activities:

- Personalized designs (Bibb and Brown 2000; Chang et al. 2003; Díaz Lantada et al. 2010a, b)
- Reverse engineering, modular developments, and design optimization (Flisch 1999; Vasilash 2009)
- Object reconstruction (Effenberger et al. 2008; Vasilash 2009)
- Prototyping and trials (Flisch 1999; Effenberger et al. 2008)
- Inspection of inner details and defects during manufacturing processes (Losano et al. 1999; Effenberger et al. 2008)
- Inspection of inner details and crack propagation during service life (Losano et al. 1999, Effenberger et al. 2008)
- Nondestructive evaluations (Losano et al. 1999, Effenberger et al. 2008)

These technological combinations provide novel ways of tackling more efficiently the design process but also for validating manufacturing processes and verifying service life. It is very important to mention that the whole process is economical and nondestructive.

Next sections provide examples of biomimetic imaging-based designs, for comparing the use of high-precision photography, nuclear magnetic resonance imaging, and computed tomography, as input for constructing CAD files of personalized devices, as well as for comparatively discussing current limitations and main challenges.

5.3 Case Study: Biomimetic CAD Design of Skin

The use of mathematical models to generate biomimetic surfaces (see Chap. 6), especially thanks to the gradual employment of recursive and fractal models, often yields good approximations to the microtopography of living organisms, though it poses certain limitations when generating 3D CAD files for subsequent use in conducting simulations and obtaining physical prototypes using computer-aided engineering and manufacturing (CAE-CAM) tools. Said surfaces generated from mathematical models do, however, on occasion present excessive homogeneity or self-similarity, meaning that the imprecision of living organisms that are responsible for certain interesting properties cannot be adequately represented.

In this section we present a fast, low-cost, and efficient alternative method to yield biomimetic CAD files of the microtopography of human skin, files that can subsequently be used as an aid for simulating various interactions (mechanical, thermal, fluid, etc.) between the environment and the skin, as well as for the micromanufacturing of small specimens, whose texture resembles that of skin.

The process relies on the use of a high-resolution photographic camera to obtain images of the area being analyzed and on converting the resulting images into altitude matrixes, which are then used to obtain the CAD files that imitate the details of the original three-dimensional geometries. Using a similar process several microtopographies and microtextures of living organisms can be mimicked and further used for designing biodevices and implants with improved features.

The skin is the body's most extensive organ, forming the main barrier between internal organs and the external environment. It accounts for around 16 % of the body's weight. It has a surface area of some 2 m^2, and it varies in thickness between 0.5 mm at the eyelids and 4 mm at the heel. As the body's first line of defense, it is constantly exposed to potentially harmful environmental agents, including solid, liquid, and gaseous materials; sunlight; and microorganisms. Although the skin can be bruised, lacerated, burned, or infected, its unique properties allow it to engage in a constant cycle of healing, exfoliation, and cellular regeneration.

To fulfill its protective role, the skin is home to a permanent flora of microorganisms. There are relatively innocuous strains that protect the skin's surface from other, more virulent microorganisms. A thin layer of lipids covers the skin and contains oily bactericidal acids that protect against penetration by harmful microorganisms. The skin, thus, also doubles as an immunological barrier. It also has other important functions such as temperature regulation, somatosensation, and the synthesis of vitamin D.

There is a great amount of variation between the different body parts in terms of the skin's structure. This makes a description of the "normal skin" covering each body surface difficult. There are clear differences in the properties of skin, for example, the thickness of the layers, the distribution of sweat glands, and the amount and size of hair follicles. Nevertheless, skin does have certain structural properties that are common to all parts of the body.

It always consists of three layers: the epidermis (outer layer), the dermis (internal layer), and the subcutaneous adipose layer (hypodermis). The basement membrane separates the first two layers, while the subcutaneous tissue, a layer of loose connective tissue and adipose tissue, connects the dermis to the body's underlying tissues (Simandl 2009).

The skin's functions depend greatly on the properties of its outermost layer, the epidermis, meaning that properly simulating its surface microtopography is necessary in order to conduct studies on the interactions between the environment and the human body. However, most recent studies on the computer-aided graphical generation of human skin have involved simulations of large areas of the human body, eschewing micrometrical details in almost every case, as this would have entailed time- and computer-intensive calculations.

Some researchers have focused on modeling wrinkles and the effects of aging (Boissieux et al. 2000; Yang and Zhang 2005; Zhuo et al. 2006) in an effort to enhance the appearance of animated characters in entertainment programs and in the video-game industry, as well as to simulate the effects of various cosmetic products.

Leading studies have resorted to generating wrinkles along vector fields so as to incorporate additional textures to surface meshes (Bando et al. 2002). In order to take into effect biomechanical aspects, recent research has resorted to using the boundary element method to simulate skin defects and to analyze their effect on other anatomical structures (Tang 2002), though detailed effects of the surface topography were omitted.

On occasion, physical prototypes have also been constructed to simulate the mechanical features of the epidermis, the dermis and subcutaneous fat. These models used polymeric materials of different rigidity and hardness to complement surgical training simulators, especially as these relate to devices for minimally invasive laparoscopic surgery (Munro et al. 1994).

In terms of the biomimetic design of anatomical elements, numerous researchers have resorted to the use of medical imaging tools (mainly computerized tomography and nuclear magnetic resonance), in combination with software to process said images (such as MIMICS, Materialise NV) and CAD programs. The availability of CAD files with the geometry of body structures, both muscular and bone tissues, has thus served to aid in the development of personalized implants (Kucklick 2006; Díaz Lantada et al. 2010b), especially when combined with rapid prototyping techniques (Winder and Bibb 2005; Kim 2008).

The accuracy of the aforementioned medical imaging systems, however, still does not allow for a faithful reproduction of the details associated with the surface microtopography of tissues, though new advances in micro-CT (see Chap. 14) technology are constantly yielding significant improvements (Shi et al. 2008; Guo et al. 2010).

The use of CAD-CAE-CAM (computer-aided design/engineering/manufacturing) tools is also applicable to tissue engineering, having given rise to a new field of study called computer-aided tissue engineering, a field that was initially associated with anatomical imaging, with modeling and simulation, and with surgery planning (Sun and Lal 2002).

This, in conjunction with new advances in biomanufacturing (see also Chap. 14) and associated biomaterials-based additive manufacturing tools (bioplotters), points to the manufacture of small body structures in the not-too-distant future (Mironov et al. 2009).

In any event, so as to profit from the advantages stemming from the increased accuracy of aided manufacturing systems aimed at producing artificial biostructures, we must continue to delve deeper into the biomimetic design of tissues and to improve aspects related to the generation of surface microtopographies, the effects of which are crucial to the proper operation of the tissues that we wish to mimic.

The biomimetic processes typically employed involve the use of mathematical models, such as fractals (Mandelbrot 1982), and can output surface textures to CAD files, which can be converted to formats that can be exported to CAE-CAM software.

These files in adequate formats can then be used, in conjunction with finite element analysis techniques, to conduct simulations as a prelude to the manufacture of physical prototypes (Díaz Lantada et al. 2010b, Biocoat), though imitating the desired topography is not always simple.

In this section an alternative low-cost approach is used, relying on the use of a high-resolution photographic camera to obtain images of the area being studied, and on the conversion of the resulting images into altitude matrixes, which can then yield the CAD files that imitate the details of the original three-dimensional geometries, in a process described below.

The skin surface photographed for present case study measures 9 mm × 6 mm, yielding 640 × 480 pixel images, meaning that the size of the details captured is on the order of 20 μm, which is sufficiently precise for the majority of micromanufacturing techniques currently available (see Chap. 11), as well as for analyzing any kind of cutaneous pathology. The areas photographed correspond to two sections of fingerprint from the index finger and the back of the hand, in the area of the knuckles, of two 30-year-old researchers. This is done so as to determine the viability of the system when acquiring images of different parts of the body.

The images are processed using Adobe Photoshop to convert them to gray scale, followed by filtering to soften highlights. The images, saved in the .raw format, are then input to a program (courtesy of M.Sc. Eng. Alvaro Salmador) that converts the gray scale to an altitude scale. The program also converts the files into the .stl format for subsequent use in computer-aided design programs.

Different options are available for the CAD software used to convert from surface meshes, in .stl format, to conventional solid CAD pieces. Particularly important is the use of software specifically designed to handle .stl files (Materialise Magics, VisCAM, Solid View, MeshLab, among others) or the use of so-called mesh-to-solid programs, which transform .stl meshes into formats typically recognized by other CAD software. In our case, we used the CAD-CAE-CAM NX-8.0 software (Siemens PLM Solutions) to represent the .stl surfaces and the solid CAD pieces, with the final rendering.

Subsequent conversions to .iges format allows for an additional exchange of information with more specific calculation programs, such as Ansys or Abaqus, as well as with programs specifically designed for additive rapid prototyping with 3D Lightyear by 3D Systems.

As mentioned earlier, the design process starts by converting the image of a photograph, expressed as a matrix with information on the colors (or the gray scale) for each coordinate pair (x, y) on the plane, into a matrix in which the colors or gray scale are replaced by data on the altitude of each point on the photograph.

To achieve this, the darkest pixels in the image are assigned a zero altitude, representing the bottom of the folds in the skin. The image's brightest pixels are assigned an altitude based on reference information and models (Boissieux et al. 2000; Jacobi et al. 2004; Yang and Zhang 2005) that provide different typical values for the height of wrinkles, depending on region of the body and age of the subject.

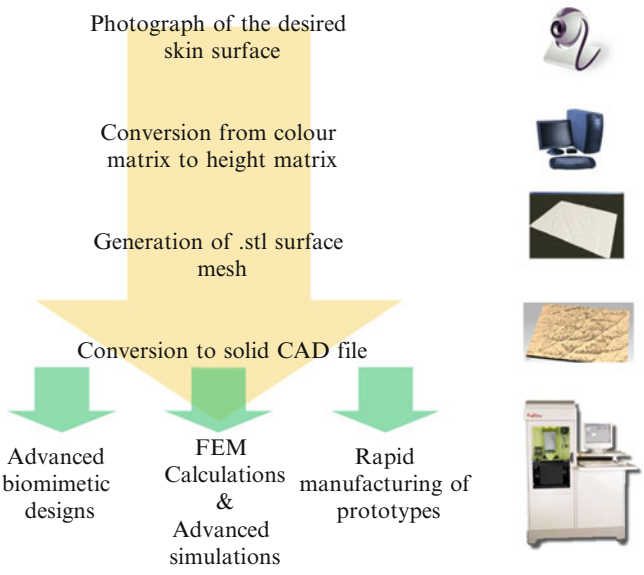

Fig. 5.1 Diagram of the design process and of associated potential post-processes

In our case we use a maximum difference of 160 μm for the fingerprints and of 240 μm for the folds in the back of the hand. Values between these maximum and minimum values are linearly interpolated, although the Maio algorithm used by some systems to display 3D images of fingerprints can also be used (Maio and Maltoni 1997). An additional scaling along the x- and y-axes contained in the plane of the original image may also be necessary to adapt the size of the meshed surface to the actual dimensions of the area photographed, which in this case was 9×6 mm^2.

Once the altitude matrix is obtained, it is converted into a .stl format surface mesh, which allows for subsequent processing by specific CAD software. Since surfaces with negligible thickness, like the intermediate meshes in .stl format, cannot be manufactured with the aid of RP technologies, nor do they allow for simulations based on the application of finite element analysis, they must first be converted into solid pieces with a nonzero thickness. The first step in this process can be achieved with the typical CAD tools used to automatically generate molds (core and cavity) from surfaces.

In the second step, the core can be cut at the desired distance to obtain the desired surface but with a certain thickness. Or a prismatic block can be used on which to imprint the wrinkled surface before finishing the process by combining the block and the cavity. The general outline for the design process, including possible simulation and computer-aided manufacturing activities, is detailed in Fig. 5.1.

Final rendering is shown in Fig. 5.2, after a brief additional explantation. Subsequent conversions to .iges format allows for an additional exchange of information with more specific calculation programs, such as Ansys or Abaqus, as well as with programs specifically designed for additive rapid prototyping with 3D

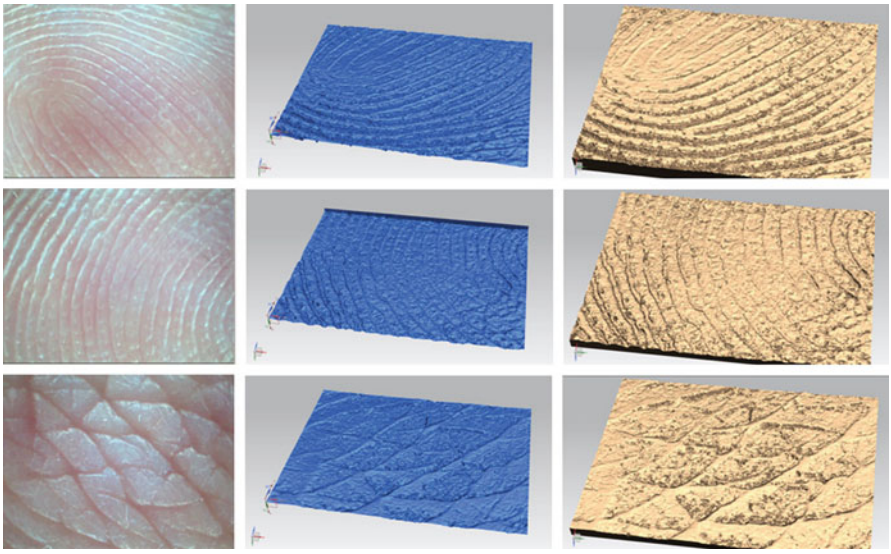

Fig. 5.2 Summary of results. Left column: original photographs (9×6 mm^2 each). *Center column*: associated surface meshes in .stl format. *Right column*: CAD files. *Top and center rows*: fingerprints. *Bottom row*: back of the hand, area of the knuckles (Image acquisition system and .stl format conversion courtesy of M.Sc. Eng. Alvaro Salmador)

Lightyear by 3D Systems and recent open access solutions linked to projects such as RepRap.

Figure 5.2 shows the main stages of the process for obtaining files of CAD solids from photographs of the skin through an intermediate mesh-conversion step in .stl format. The first rows show the process as applied to fingerprints, and the bottom row shows an example involving the surface topography of the back of the hand. This latter example can be directly applied to other parts of the human body or biological systems for promoting biomimetic biodevices.

The final thickness of the CAD files depends on the intended purpose of said files. If it is desired to conduct FEM-based simulations, it must be adapted to the thickness of the epidermis for fluid analyses, in which surface effects are dominant. The thickness of the dermis may have to be included too if the goal is to analyze mechanical stresses/strains and their effect on subcutaneous anatomical components. If the goal is to build prototypes, the minimum layer thickness attainable with the various technologies must be considered and the thickness adapted always depending on final application. Some of these possible applications include producing anatomical models for surgical training, manufacturing microtextures for studying contact phenomena, or, in the future, the biomanufacturing in the laboratory of small patches of skin for use in operations.

Figure 5.3 shows how the use of a filter to eliminate highlights can, on occasion, have a notable influence on the quality of the resulting surface mesh, since such

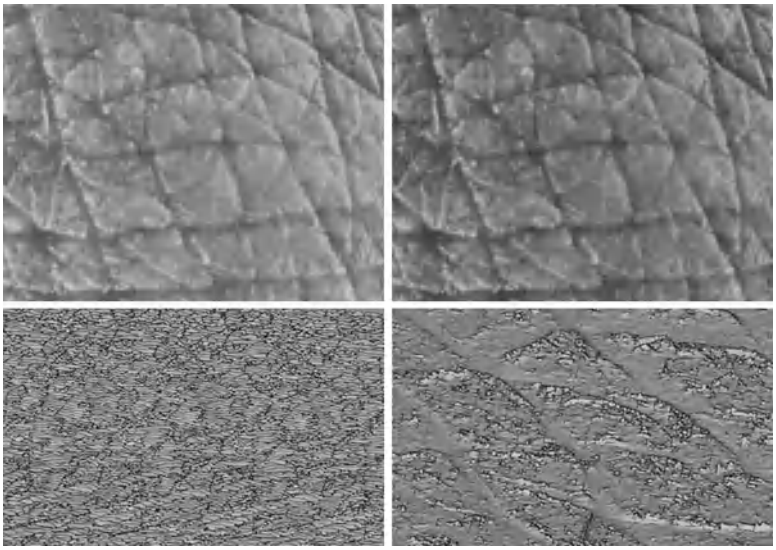

Fig. 5.3 Filtering effects: enhanced precision due to misleading effects stemming from highlights

filtering aids in reducing dramatic artificial height differences stemming from sudden changes in sharpness in the original photographs.

The 3D images shown help to demonstrate the simplicity and effectiveness of the process described. They also help to validate its applicability for producing biomimetic designs of skin from different parts of the human body. The process has been tested with skin from the fingerprints and from the back of the hand, but the extension to other areas of interest to the cosmetics industry, like the face, arms, and legs, is immediate.

The process has been validated on hairless parts, as in most of the studies referenced and based on optical acquisition systems (Jacobi et al. 2004), though it would be interesting to analyze its effects in depth with a view to the generation of .stl meshes and CAD files. It is important to note that for regions of skin measuring some 60 mm^2, reproductions with details on a scale of 20 μm were obtained, something that is nearly impossible to achieve using laser digitalization or medical imaging techniques, even if micro-CT is used.

Moreover, the process described is based on technologies that are much more accessible and innocuous to patients and as such has clear educational implications. One of the current limitations, however, is the appearance of edge effects for areas of skin larger than those described. This can be resolved by developing a movable pickup to acquire images, which could then be jointly connected and transformed into the associated surface meshes and CAD files.

Our process can also be utilized to analyze parameters such as the average rugosity and the depth of the wrinkles and to conduct additional studies on the influence of age or cutaneous pathologies on texture (Smalls et al. 2005) and the subsequent

aspect of human skin, as well as in activities involving human recognition. It also has potential applications in veterinary medicine and zoology.

In terms of the rapid manufacture of complex surface microtextures, previous research has helped to validate the use of conventional rapid prototyping technologies to obtain biomimetic surface details on the order of 0.4–4 mm (Díaz Lantada et al. 2010a). Other manufacturing processes based on copying biological structures by using physical or chemical vapor-deposition methods to produce micro-scaffolds have attained details on a scale of tens of microns (Lakhtakia et al. 2009; Pulsifer et al. 2010).

In any case, there are multiple computer-aided manufacturing techniques that can utilize the information in CAD files to produce objects with biomimetic microtextures using multiple materials. A brief comparison of those technologies is included in Chaps. 10 and 11.

A similar method, based on processing high-resolution photographs, can be applied to a multitude of other biological organisms to mimic surface textures with which to achieve special visual or contact phenomena effects and apply them to surfaces on consumer products, as already employed by fabrics based on the morphology of shark skin (Speedo Fastskin), surfaces of components based on dolphin skin (Pavlov 2006), paints and lacquers that aid in achieving self-cleaning surfaces and based on the surface of lotus flower leaves (Barthlott and Neinhuis 1997), and other applications.

The method can also be carried out starting directly from SEM images of the surfaces of different animals and plants, depending on the desired degree of precision and without needing complex and expensive technologies (sometimes also needing specific installations and protected laboratories) such as nuclear magnetic resonance (NMR) and computed tomography (CT), whose application fields and levels of detail attainable are also discussed in next sections, providing also a couple of case studies.

This proposal also has applications in the field of tissue engineering, since it can aid in producing CAD files with geometries that imitate the surface characteristics of different fabrics for subsequent simulation of their behavior with the aid of FEM-CFD software, as has already been done with certain biomimetic surfaces (Pavlov 2006). It should prove interesting to use this type of file to assess the response | of tissues with different designs in terms of their surface texture and the response of different fluids so as to analyze their hydrophobic and impermeability characteristics.

Regarding the reproduction of biological structures, the proposed design method, with the help of high-precision additive manufacturing technologies, may well be an important complement to current bioreplication techniques, such as sol–gel, atomic layer deposition, PVD/CVD, or imprint lithography and casting, for several industrial applications (Pulsifer and Lakhtakia 2011). For large series of parts, soft-lithographic approaches and micro-replication techniques, such as micro hot-embossing and microinjection molding, may also be good choices (see Chaps. 11 and 12).

5.4 Case Study: Personalized Prosthesis Adapted to Hard Tissue

The case study detailed in this section as an example details the process for producing a customized hip prosthesis design from the helpful information of medical images. The aim was to produce a non-cemented prosthesis where the metal part is pressure mounted inside the femur and must therefore be made to fit the available space. More detailed information may be found in the references (Osuna 2008; Ojeda Díaz 2009; Ojeda Díaz et al. 2009).

Just as a brief revision, hip replacement is a surgical procedure in which the hip of the patient is replaced by a prosthetic hip. Such joint replacement orthopaedic surgery is generally conducted to relieve arthritis and related pain or to fix severe physical joint damage as part of hip fracture treatment. A total hip replacement (total hip arthroplasty) consists of replacing both the acetabulum and the femoral head, while hemi- (or half) arthroplasty generally only replaces the femoral head.

The prosthesis used in hip replacement consists of different parts, the acetabular cup, the femoral component, in which this case study focuses and the articular interface. The femoral component is designed to fit in the femur, normally by removing a part of the bone and shaping the remaining part to accept the prosthetic component.

There are two main types of femoral components, cemented, based on adhesive fixation between prosthesis and bone, and uncemented, based on friction for promoting stability. Final prosthesis-type selection depends on several factors, including age of the patient, mechanical strength of the bone, as assessed with the help of medical imaging, life expectancy, among others.

Even though the potential benefits of personalized femoral components for hip replacement is still controversial, it is clear that, if taking the geometry of patient's femur as design input for the femoral component, required bone adaptation (through boring, milling and cutting) during surgical intervention should be lower and lighter.

The usual procedure for carrying out a customized examination with a view to using a prosthetic device usually begins either by taking a computerized tomography (CT) or a nuclear magnetic resonance (MRI/NMRI) of the patient needing the prosthesis.

Then, with the aid of .dicom or .dcm (Digital Communications in Medicine) format, the information from the CT or MRI can be transferred to a program such as "Mimics," so that it can be displayed in 3D. These programs usually include modules that allow selecting part of the patient's bone geometry and storing it in .stl or .igs formats that can be read by other CAD programs, for ad hoc design operations, after processing the images (Fig. 5.4) "slice by slice."

Having selected the relevant part of the patient's femur (in this example, the internal cavity, to which the metal part of a customized prosthesis must be adapted), this three-dimensional geometry can be transferred to a valid format for a design program and this femoral zone can be used as the basis for a customized prosthesis design, as can be seen in Fig. 5.5.

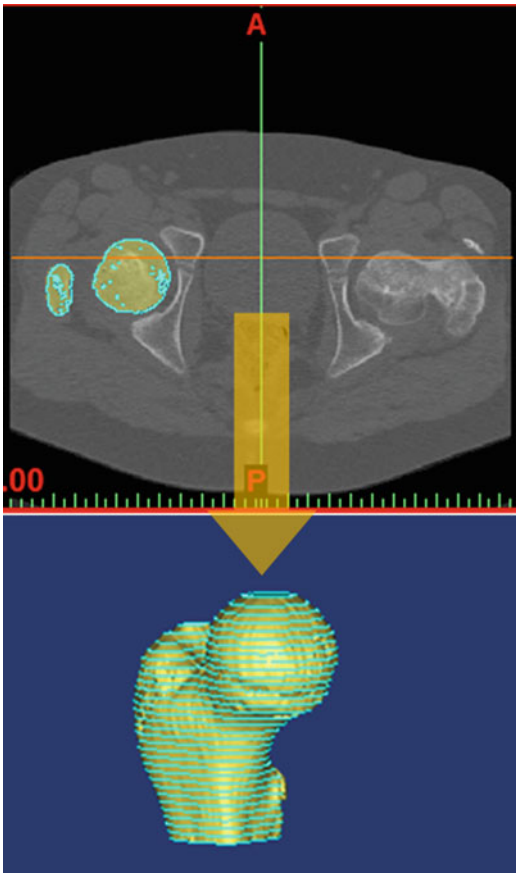

Fig. 5.4 3D reconstruction of femur based on the information from NMR images. Mimics software for computer-aided designs based on medical images

In this case it has been done by using a "surface through curves" command for obtaining external surface of the femoral component. Final solid part is obtained by closing such external surface with simple geometrical elements and accepting the automatic Solid Edge's proposal of "converting to solid." The CAD designs can further be converted into formats recognized by CAE programs, for verifying through FEM-based simulations that final biodevice will withstand service loads.

Similar developments are simple to carry out, especially when trying to adapt a design to a hard tissue, which is normally very well highlighted in CT/NMR medical images. Important applications include the design of all kind of bone prosthesis, as well as scaffolds for tissue engineering, whose biomimetic design is now promoted thanks to advanced in quality and precision of acquisition systems, as discussed in Chap. 14. Designs adapted to soft tissues are less common, as soft tissue density is normally more similar to that of surrounding fluids, cartilages and biostructures, In any case next section provides an interesting example linked to cardiovascular surgery.

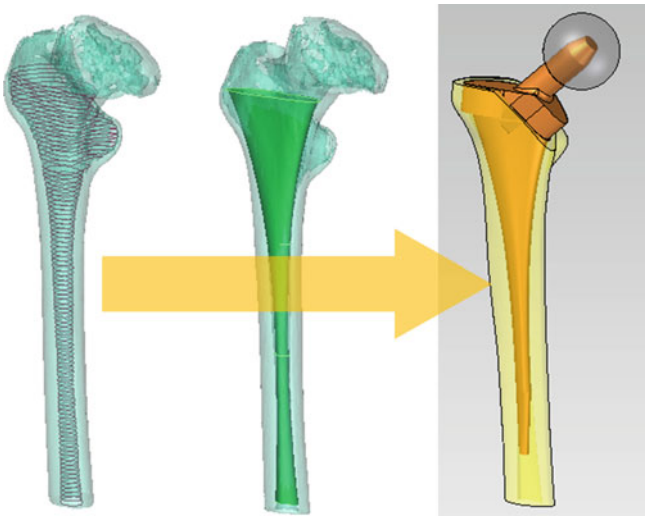

Fig. 5.5 Example of personalized prosthesis designed from the information of CT images. Mimics combined with solid edge as software support tools

5.5 Case Study: Personalized Prosthesis Adapted to Soft Tissue

Previous chapter provided some brief notes on cardiovascular surgery and on the use of annuloplasty rings for mechanically supporting the cardiac tissue of the left atrioventricular union and reducing the problem of mitral valve insufficiency.

The large number of alternative designs for annuloplasty rings (at least 20 models are extensively used) chosen according to the patient, their pathology, and the cardiologist or heart surgeon's experience shows that the design of these rings is a problem that is not yet solved. In fact, on most occasions various models and sizes of these implants are set out on the operating table, so that the most suitable one can be chosen, by direct inspection during the operation itself, thereby increasing the number of decisions to be made and the schedule of the operation.

Although the use of personalized annuloplasty rings, manufactured for each patient according to the size and morphology of their valve complex, could be very beneficial for the treatment of mitral insufficiency, this possibility has been limited for reasons of deadlines and costs, as well as for design and manufacturing difficulties. This section attempts to explain a possible alternative, which thanks to the state of current technology may lead to the treatment of mitral insufficiency using personalized annuloplasty rings.

In order to begin the personalized design procedure, we need inner information of patient's heart morphology; what has been managed with the help of a Philips helicoidal CT with 64 detectors (Fig. 5.6 shows some examples of the kind of graphical information obtainable).

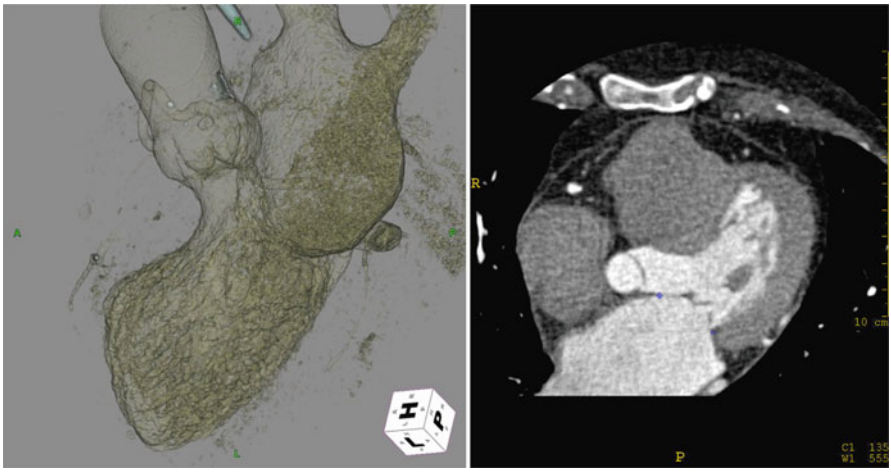

Fig. 5.6 Image of the left atrioventricular union, where mitral valve is place (*left*) and slice showing the leaflet insertion points marked in *blue* (*right*) (Courtesy of Raquel del Valle – Lennox Hill Heart and Vascular Institute NY)

Main problem for this personalized procedure is that the density of the mitral ring (fibrous tissue) is very similar to that of the auricular and ventricular myocardium and that of the valve leaflets, which means it is not identified as a separate structure by any of the imaging techniques currently available for clinical evaluation. In fact, the main advances linked to the development of personalized prostheses have been traditionally linked to bone structures, since bone tissue density is very different from surrounding biostructures and tissues and can thus be more easily identified for subsequent computer-aided design tasks.

In this study we have to resort to the use of an alternative way for assessing the morphology of mitral valve by measuring "slice by slice." Using the Philips TC software, the valve leaflets insertion points can be located "slice by slice" (as marked in Fig. 5.6 in blue) and in consequence obtain a three-dimensional form of the patient's mitral annulus.

However, such software does not include output format for CAD programs so the Cartesian coordinates of the mentioned insertion points have to be written down, as provided by the Philips software, for subsequent introduction in the CAD program. Such introduction can be directly done by constructing points with the associated CAD command or by importing the coordinates directly from an Excel file.

Once the 3D location of the insertion points is clear, a spline can be constructed as basis for the solid ring, either "point by point" or "through table." After the mentioned spline (Fig. 5.7 upper image), adapted to the form of patient's mitral valve, is obtained, a point of the spline is selected and a reference plane, normal to the spline and containing such point, is constructed.

A 2.5-mm circumference contained in the reference plane and with center on the intersection point between plane and spline is then drafted. By using the "sweep"

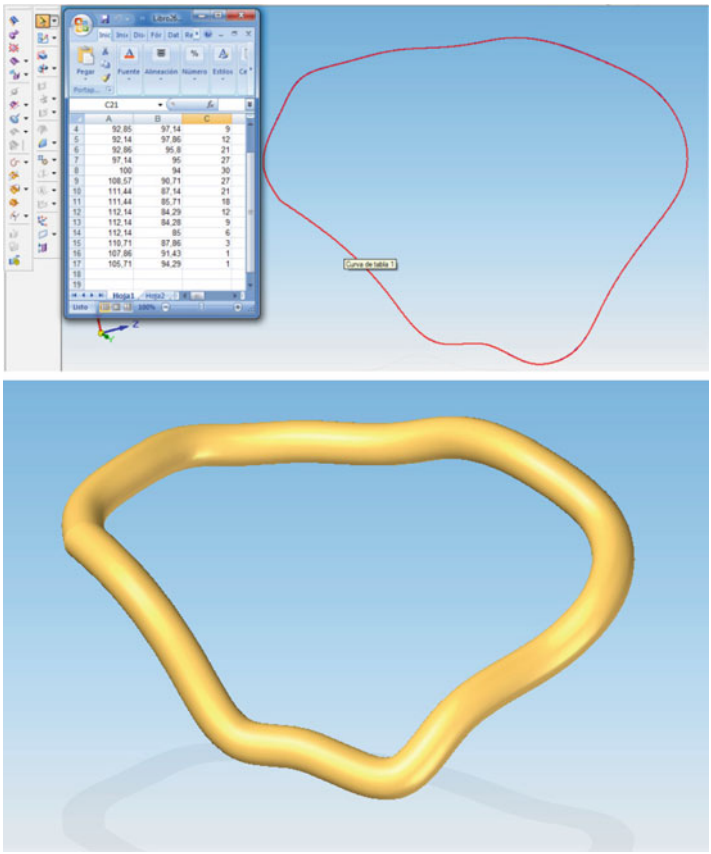

Fig. 5.7 Annuloplasty ring for mitral valve insufficiency: personalized design with the help of MI and computer-aided design resources

command, the circle is made to follow the whole spline, hence leading to final solid annuloplasty ring of Fig. 5.7. Additional details of the whole design process, here just summarized for providing an outline of case study, can be found by consulting the reference section (Díaz Lantada et al. 2010b).

This biodevice has been again designed with the help of Solid Edge, whose "spline" command allows the easy introduction of points by their (x, y, z) 3D coordinates, just as contained in an Excel table. Such connection with MS Excel is especially noteworthy, as already remarked in Chap. 4, and simplifies designs based on splines and 3D curves. Other CAD resources, even when capable of importing coordinates from tables, do not always provide such a direct process.

Future in vitro and in vivo trials will provide additional validation to the proposed methodology; however, we believe that combination of medical imaging technologies with designs programs constitutes a powerful tool for virtual validation and design optimization, before carrying out more time and cost expensive trials, as those analyzed in Chap. 15.

5.6 Main Conclusions and Future Research

Several technological advances during the last two decades have promoted novel approaches to product design and development. The generalized use of computer-aided design and simulation tools, together with the advances in materials science and manufacturing technologies, has enabled the development of more complex geometries and products.

The additional possibility of using the information obtained from medical imaging (MI) technologies as input for computer-aided design and for computer-aided engineering programs has opened up new horizons for carrying out personalized and ergonomic designs, as well as for promoting all kinds of tasks linked to product design and reverse engineering (reconstruction of damaged products, reproduction of delicate parts and studies related to inner non-visible geometries, among others), whose applications in Biomedical Engineering are highly relevant.

This chapter has tried to cover some of the most important applications for such combination of medical imaging and design technologies, including some case studies related to successful developments of biodevices and prostheses, so as to analyze the most common procedures and in order to provide advice for conventional difficulties.

It is important to note that the impact of combining information from medical imaging technologies with the advantages of novel design and manufacturing tools is so remarkable, and its applications so widespread, that we can speak of "MI-aided product development" or even "MI-aided engineering."

Main present challenges for improving the end quality and industrial impact of such developments are linked to further increasing MI precision (although some remarkable recent advances on micro-CT are commented on Chap. 14) and usability, probably by means of augmented reality, simplifying the connection between medical imaging equipments and CAD resources and producing easier to acquire equipments, whose current cost is typically above 100,000–200,000 €.

Regarding such costs of digitization equipment, laser scanners, and CCD (charge coupled device) film digitizers are much more economic (around 1,000–60,000 €) than CT scanners or NMR equipment (from 150,000 even up to 500,000 €). However, laser and optical systems do not allow the reproduction of inner details, so important not only for personalized design processes but also for noninvasive in-service verifications.

New trends in the medical imaging industry are trying also to mount different technologies, for combining their respective advantages, in one machine (CT + PET, CT + SPEC-single photon emission tomography…) and regarding biodevice development process enhancement, perhaps it would be very positive to combine in one machine the fastness of laser scans with the capabilities of reproducing inner details of computed tomography. Such advances, together with an increase in precision and more competitive prices will help to spread the industrial applications of these technologies and their final impact on biomedical science and health.

Standards and Associations Related to Medical Imaging

- DICOM standard – Digital Imaging and Communications in Medicine: Strategic Document (http://medical.nema.org).
- Medical Imaging and Technology Alliance (www.medicalimaging.org).
- NEMA – The Association of Electrical and Medical Imaging Equipment Manufacturers (www.nema.org).

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Chapter 6
Fractal Geometry for Biomimetic Design of Biodevices

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Abstract Computer-aided design helps to enhance product development process in an indeed remarkable way, especially as it can also be combined with computer-aided engineering and manufacturing resources. However, due to its initial applications in the automotive and aeronautic industries, the geometries typically attainable with these CAD resources can be described as soft and simple, as such simplicity is very well suited for production.

When designing novel biodevices adapted to biological systems or trying to mimic the complex characteristics of organs and biostructures, for promoting more adequate interactions, CAD resources are sometimes limited, as features, such as porosity, roughness and surface–volume ratio, among others, cannot be easily controlled with conventional design operations.

Fractal geometries, usually defined recursively or based on random processes, are more adequate for modelling and mimicking the complexity of biosystems and are starting to be used in biodevice design, as recent advances on manufacturing technology and also on materials science allow their automated production.

In this chapter, we focus on some relevant fractal models for better controlling the aforementioned features and describe an adequate design procedure for using such geometries in CAD resources. Some case studies linked to prostheses design and tissue engineering are also included, as an introduction to more complex devices included in forthcoming chapters about additive manufacturing technologies and micro-fabrication.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_6,

6.1 Fractals and Nature

Euclidean geometry is limited for describing and modelling the complexity of our Universe. Some of Euclid's axioms were in fact revised during nineteenth and twentieth centuries, by the introduction of alternative geometries, more adequate for describing complex objects and phenomena, such as elliptic and hyperbolic geometries for describing planets and perceptual distortions (Bolyai and Lobachevsky) or even studying the nature of light (Einstein's Theory of General Relativity). More recently, the complexity and auto-similarity of several natural systems and natural occurring phenomena has given birth to the field of fractal geometry.

The use of fractal models for mimicking such natural surfaces can prove to be useful for design tasks. Fractals are rough or fragmented geometric shapes that can be split into parts, each of which is (at least approximately) a reduced-size copy of the whole. The term *fractal* was coined by Benoît Mandelbrot in 1975 and derives from the Latin *fractus* meaning "broken" or "fractured"; benchmark handbook on fractal geometry and nature explains the birth of this novel geometry in depth (Mandelbrot 1983). The term is used to describe complex geometries that are too intricate to be formulated in conventional Euclidean terms, with properties like self-similarity and defined usually with simple recursive procedures. The mathematical equations defining fractals are "nowhere differentiable" and cannot be measured in conventional terms.

A fractal usually has a "fractal dimension" exceeding its topological dimension and that may fall between the integers. For instance, fractal surfaces, due to their roughness and intricate appearance (when looked at close range), are more than bidimensional, even though their overall appearance (when looked from the distance) is planar. Additionally fractal and random paths, even though their unifilar appearance, can end up covering the whole reference plane, when the path length increases, thus being sometimes even bidimensional. Several definitions of fractal dimensions can be found in the references (Mandelbrot 1983; Falconer 2003), and the details are out of the scope of this handbook; although, in some models used latter on, we will refer to the fractal dimension of some surfaces (with fractal dimensions between 2 and 3), normally directly connected with a parameter of the defining equation.

Since the early works linked to fractal geometry, it became clear that they could be used for describing the geometries, patterns and roughness of natural objects. Although fractals are commonly considered to be infinitely complex (due to their usual recursive definitions), "approximate fractals" are easily found in nature, which usually display self-similar structure over an extended, but finite, scale.

By limiting the steps applied in a recursive definition of a conventional fractal, approximate fractals can be obtained, which mimic very complex natural geometries. Natural objects that are approximated by fractals include clouds, mountains, lightning bolts, coastlines, snowflakes, various vegetables and several corporal and animal geometries (Mandelbrot 1983; Falconer 2003).

6.2 Overview of Applications for Biodevices

Several studies have focused on the importance of surface topography and microtexture for promoting positive effects in all kinds of biomedical devices (De la Guerra Ochoa et al. 2012), from implantable prosthesis to extracellular matrixes and scaffolds for cell growth and tissue engineering. These textures have a significant influence in osseointegration of prosthesis, cell proliferation and tissue growth given that those cells and tissues seem to be more "comfortable" and spread more quickly when faced with biodevices with similar surface properties.

In addition the use of biomimetic surfaces can help to introduce numerous desirable phenomena in machine, mechanical and structural elements, thus improving contact between parts, reducing wear or even obtaining self-cleaning objects (Barthlott and Neinhuis 1997; Groenendijk 2007). However, the process of introducing desired roughness on the surfaces of man-made objects is still mainly linked to carrying out machining operations, laser processing or chemical attacks. In all these cases, post-processing operations can be difficult to control, and it would be very positive to directly impose special topographies from the design stage.

During the last decade, increasing attention has been paid to using fractals for promoting modelling, design and simulation tasks in several areas of biomedical engineering; some of them also linked to the development process of novel biodevices. The most remarkable ones include:

- Modelling the behaviour of microorganisms. Several studies have been reported on the use of fractal models for describing the growth and expansion rate of bacteria and for evaluating the dynamics of coexisting species of microorganisms (Tsyganov et al. 2007).
- Modelling complex organisms and their systems. Regarding complex organisms (including human anatomy), fractals have been applied to modelling systems of pulmonary and blood vessels and vascular networks as well as for carrying out subsequent fluid mechanics simulations (Lin et al. 2004).
- Modelling the surfaces of organs and tissues. Recent interest has appeared in the use of fractals for mimicking the surfaces of organs and tissues and thus improving the designs and in vivo performance of several prosthetic devices (Longoni and Sartori 2010).
- Designing biomimetic biodevices, such as scaffolds for tissue engineering or prostheses with improved tribological properties (Díaz Lantada 2010a, b, and c; 2012a, b).

In fact, very recent interest has appeared in the use of fractals for mimicking the surfaces of organs and tissues and thus improving the designs and in vivo performance of several prosthetic devices, although some limitations linked to the design procedure still have to be overcome.

The processes explained in this chapter allow defining and controlling the texture and roughness of surfaces from the design stage, with help of computer-aided design tools. Its application to obtaining biomimetic surfaces based on different

fractal models, with further application in the development of scaffolds for tissue engineering and biomimetic surfaces with enhanced tribological behaviour (super-hydrophobic and super-hydrophilic, among others), is also detailed

The mentioned computer-aided designs, together with additional calculation and manufacturing technologies, (the already-explained CAD–CAE–CAM), have become essential tools for developing products and have important impact on the development of these kind of fractal-based biodevices, as described here and further discussed in Chaps. 10, 11, 12 and 14.

Next section details some adequate fractal/non-Euclidean models for their application in further design tasks linked to biodevices. The whole process including application to concrete biodevices and final manufacture is additionally detailed towards the end of this chapter.

6.3 Useful Fractal Models for Designing Biodevices

We propose and explain in this section the use of mathematical fractal models for designing the complex and highly irregular surfaces of biomimetic objects. In this way, parameters such as roughness, waviness and skewness can be controlled from the design stage and adapted in a more efficient way to the requirements of final application.

Final multi-scale surface z(x,y) can be considered as the sum of two different surfaces (z_m (x,y) for the micro-texture and z_n (x,y) for the nano-texture), each providing a relevant component at a different scale level. Fractal models can be applied to controlling both the micro- and nano-texture or just for providing a micro- or nano-texture upon an already available geometry (planar of wavy surfaces in some of the following examples).

Therefore, this proposed process offers the possibility of tailoring the surface micro-/nano-texture (in combination with adequate manufacturing technologies) for inducing important contact phenomena, such as super-hydrophobicity/super-hydrophilicity, enhanced osseointegration and improved lubrication.

The following designs of surfaces and substrates, as a basis for further design of prostheses and biodevices, are based either on static or on dynamic models. The static models used here included fractional Brownian fractal surface models and on Mandelbrot–Weierstrass equations, while the dynamic models are developed upon Kardar–Parisi–Zhang and Langevin equations.

Information regarding the different terms of such equations and main design parameters is included further on, even though more precise details can be found in relevant references of the field of fractal geometry (Weierstrass 1886; Mandelbrot and Van Ness 1968; Mandelbrot 1983; Berry and Lewis 1980; Kardar et al. 1986; Falconer 2003; Coffey et al. 2004).

6.3.1 Designs Based on the Combination of Mandelbrot–Weierstrass Equations

Several formulations of the basic Mandelbrot–Weierstrass equation can be used for obtaining fractal geometries. In our case, we detail in the following pages the influence of parameter change for the two formulations included below, one using product of summatories and the other using sum of summatories.

Even though fractals usually have a recursive definition, infinitely complex, natural fractals can be modelled by limiting such definitions to a finite extent. In the cases here exposed, such limitation consists of programming the process for obtaining the matrix of heights $Z(x,y)$, stopping the summatories when a finite number $n=k$ is reached. Otherwise an infinite loop would appear and computation would lead nowhere.

Hence, each value $z(x,y)$ is obtained by using the following expressions, but limiting the number of terms of the summatories to $n=100$, even though lower values, even with $n\approx 10$, can be also adequate for obtaining fractal surfaces if our computation resources are more limited. Once the matrix with surface point coordinates is obtained, the Matlab "surf" command helps to represent it. Some additional details on computation can be found by having a look at the Matlab (The Mathworks Inc.) code of the different programmes included in the Annexes of the handbook.

$$z(x,y) = A^{D-1}\sum_{n=1}^{\infty}\frac{\cos(2\pi\gamma^n x)}{\gamma^{(2-D)n}}\sum_{n=1}^{\infty}\frac{sen(2\pi\gamma^n y)}{\gamma^{(2.D)n}}$$

$$z(x,y) = A^{D-1}\sum_{n=1}^{\infty}\frac{\cos(2\pi\gamma^n x)}{\gamma^{(2-D)n}} + B^{D-1}\sum_{n=1}^{\infty}\frac{sen(2\pi\gamma^n y)}{\gamma^{(2.D)n}}$$

$$A = \text{constant}$$
$$B = \text{constant}$$
$$1 \le D \ge 2$$
$$\gamma \ge 1$$
$$n \in N$$

In such expressions, A and B are constants, normally for scale adaptation, and D and γ are also constants for tuning aspects such as roughness or fractal dimension. The following Figs. 6.1–6.6 show the effect of parameter change on surface texture and morphology. Depending also on the square grid used, more or less "spiky" surfaces can be obtained. In any case, design should be always made on the basis of final application, that is, if the final device is going to interact with cells, details should be needed in the range of tens of microns, while if final device is intended to promote additional antibacterial or special tribological properties, details in the range of hundreds of nanometres may be needed.

$$z\ (x,y) = A^{D-1} \sum_{n-1}^{\square} \frac{\cos(2\pi\gamma^n x)}{\gamma^{(2-D)n}} \sum_{n-1}^{\square} \frac{sen(2\pi\gamma^n y)}{\gamma^{(2.D)n}}$$

$$A = 1 \qquad n = 100$$

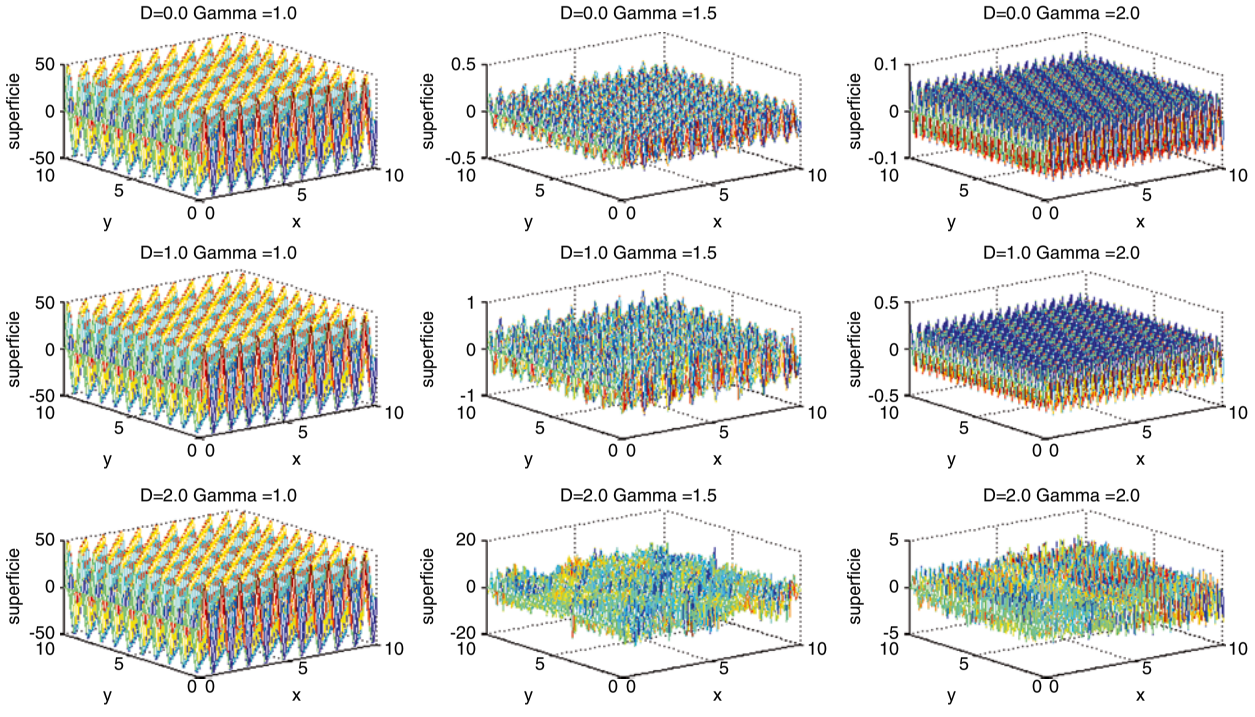

Fig. 6.1 Fractal surfaces based on the Mandelbrot–Weierstrass equation for further design of biodevices. Effect of parameter change: $A = 1$, $n = 100$, $D = 0$; 1; 2, $\gamma = 1$; 1.5; 2

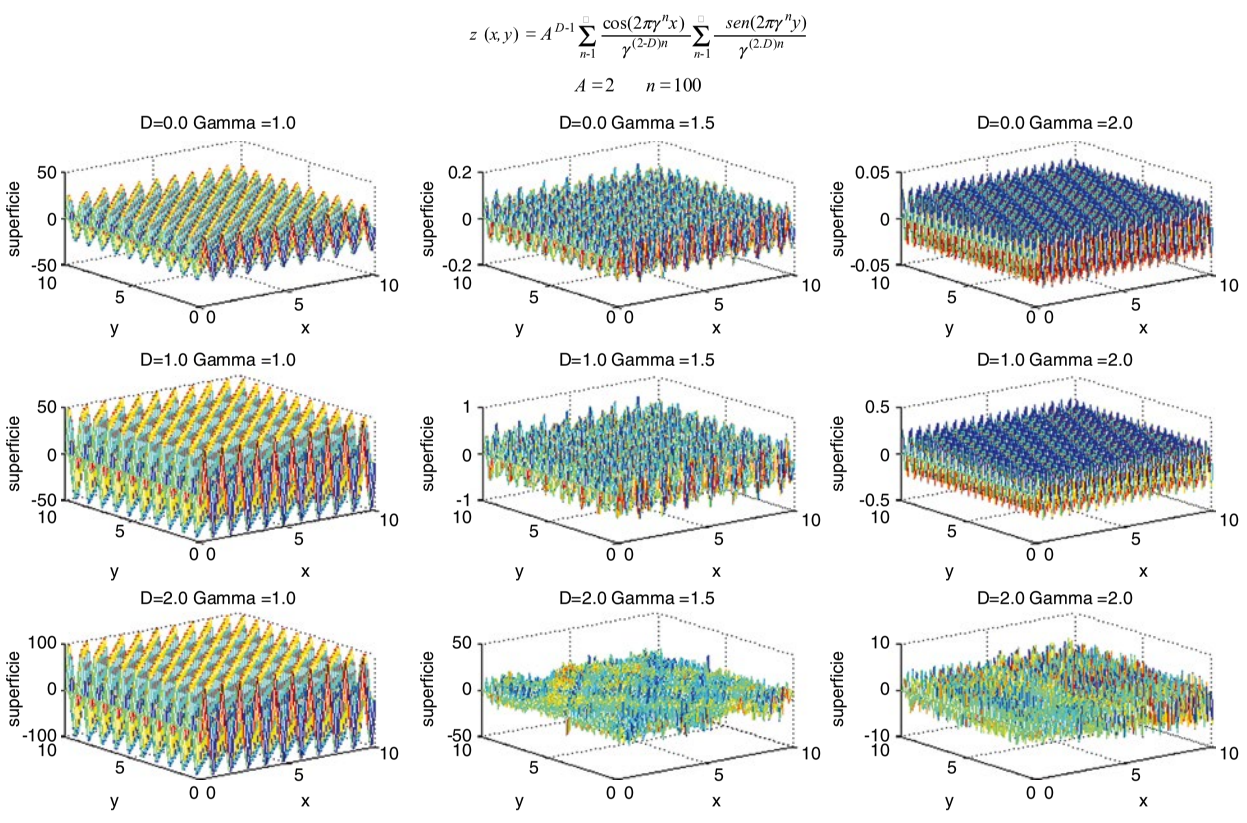

Fig. 6.2 Fractal surfaces based on the Mandelbrot–Weierstrass equation for further design of biodevices. Effect of parameter change: $A = 2$, $n = 100$, $D = 0$; 1; 2, $\gamma = 1$; 1,5; 2

$$z\ (x,y) = A^{D-1} \sum_{n-1}^{\square} \frac{\cos(2\pi\gamma^n x)}{\gamma^{(2-D)n}} \sum_{n-1}^{\square} \frac{sen(2\pi\gamma^n y)}{\gamma^{(2.D)n}}$$

$$A = 5 \qquad n = 100$$

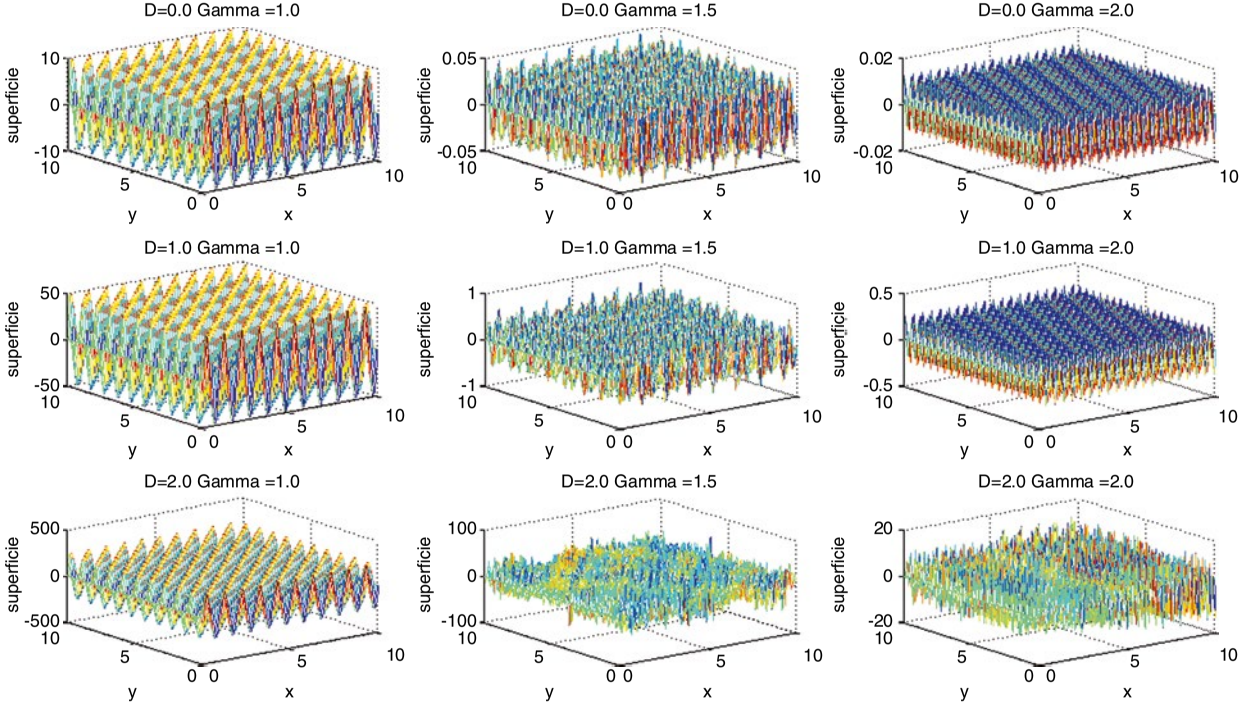

Fig. 6.3 Fractal surfaces based on the Mandelbrot–Weierstrass equation for further design of biodevices. Effect of parameter change: $A = 5$, $n = 100$, $D = 0$; 1; 2, $\gamma = 1$; 1,5; 2

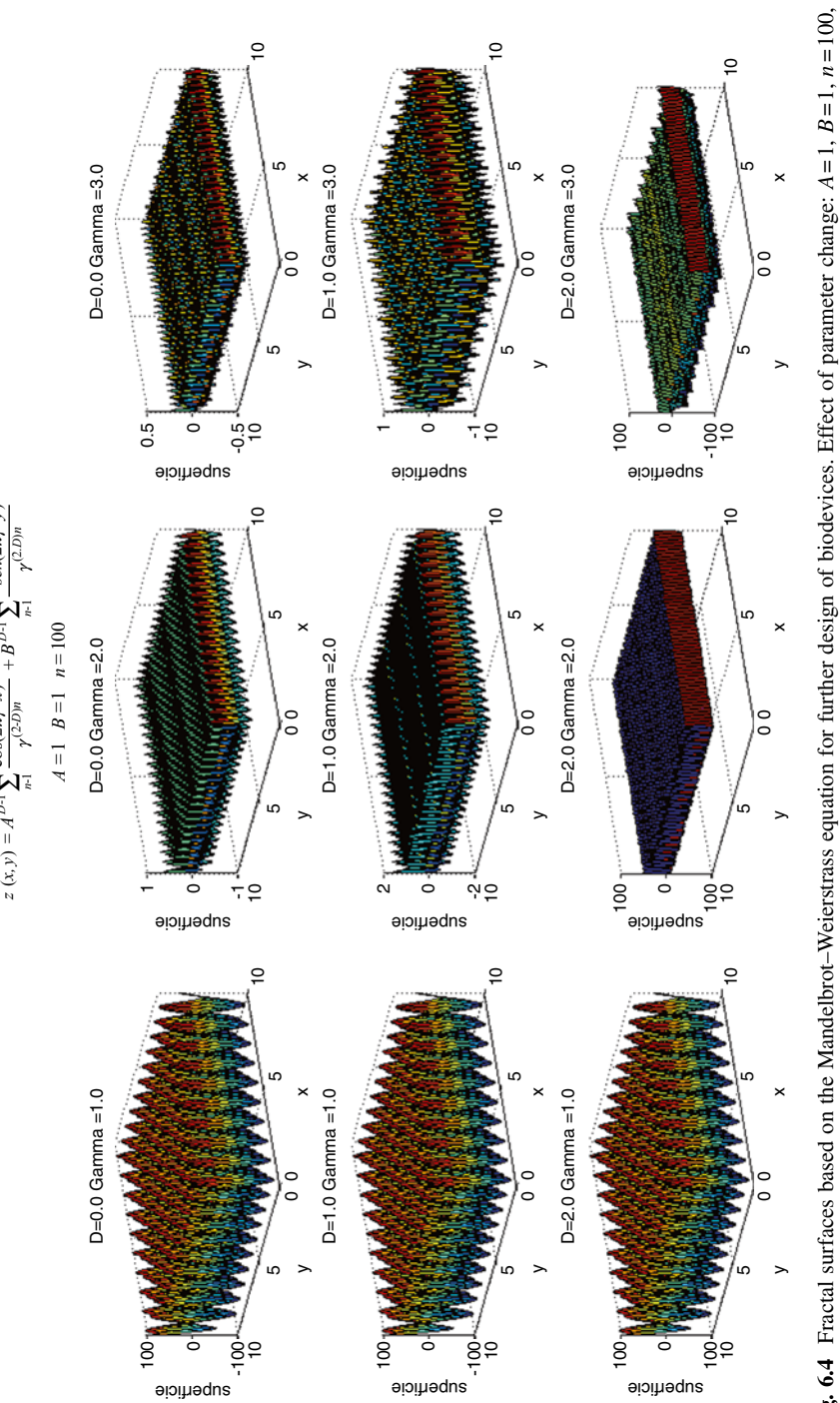

Fig. 6.4 Fractal surfaces based on the Mandelbrot–Weierstrass equation for further design of biodevices. Effect of parameter change: $A=1$, $B=1$, $n=100$, $D=0$; 1; 2, $\gamma=1$; 1,5; 2

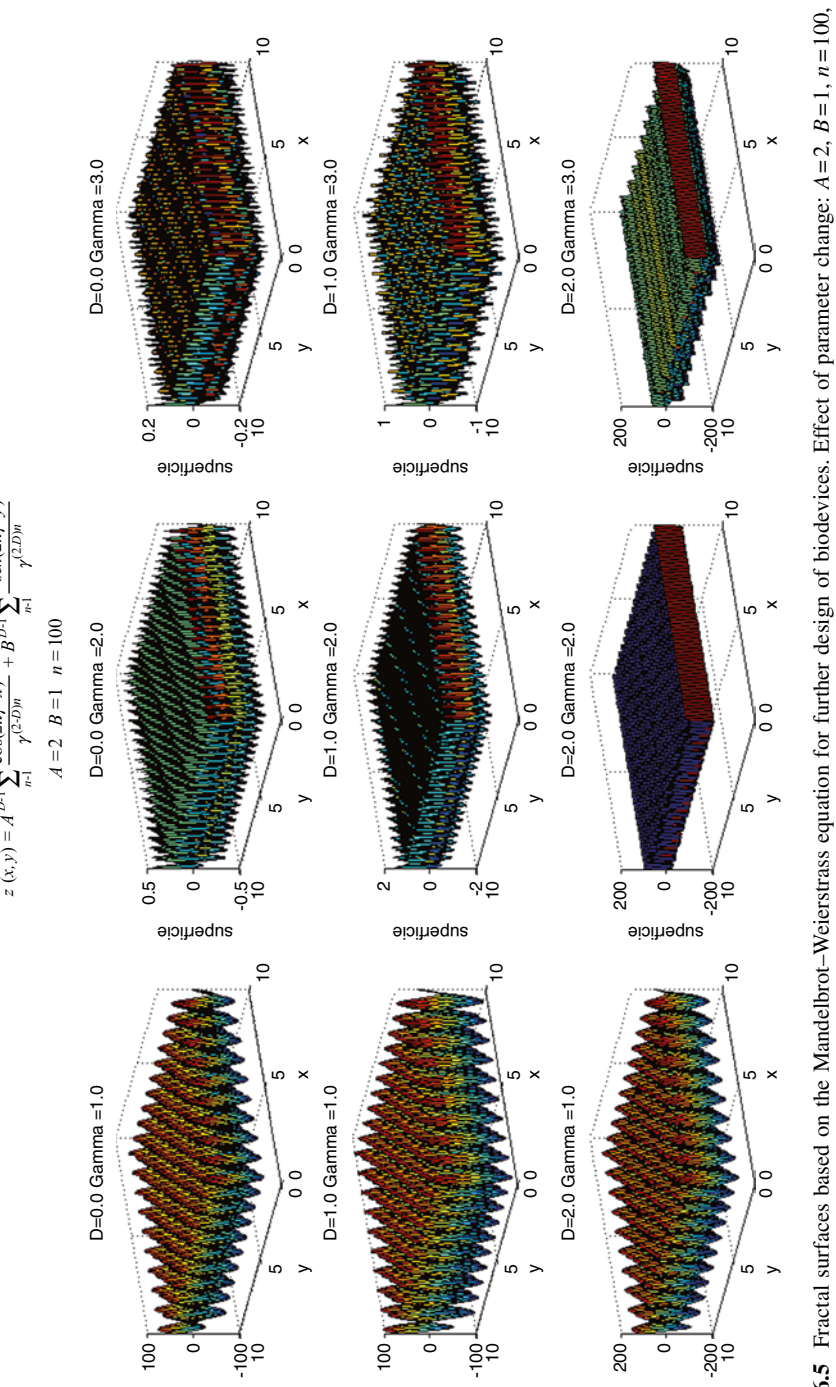

Fig. 6.5 Fractal surfaces based on the Mandelbrot–Weierstrass equation for further design of biodevices. Effect of parameter change: $A=2$, $B=1$, $n=100$, $D=0$; 1; 2, $\gamma=1$; 1,5; 2

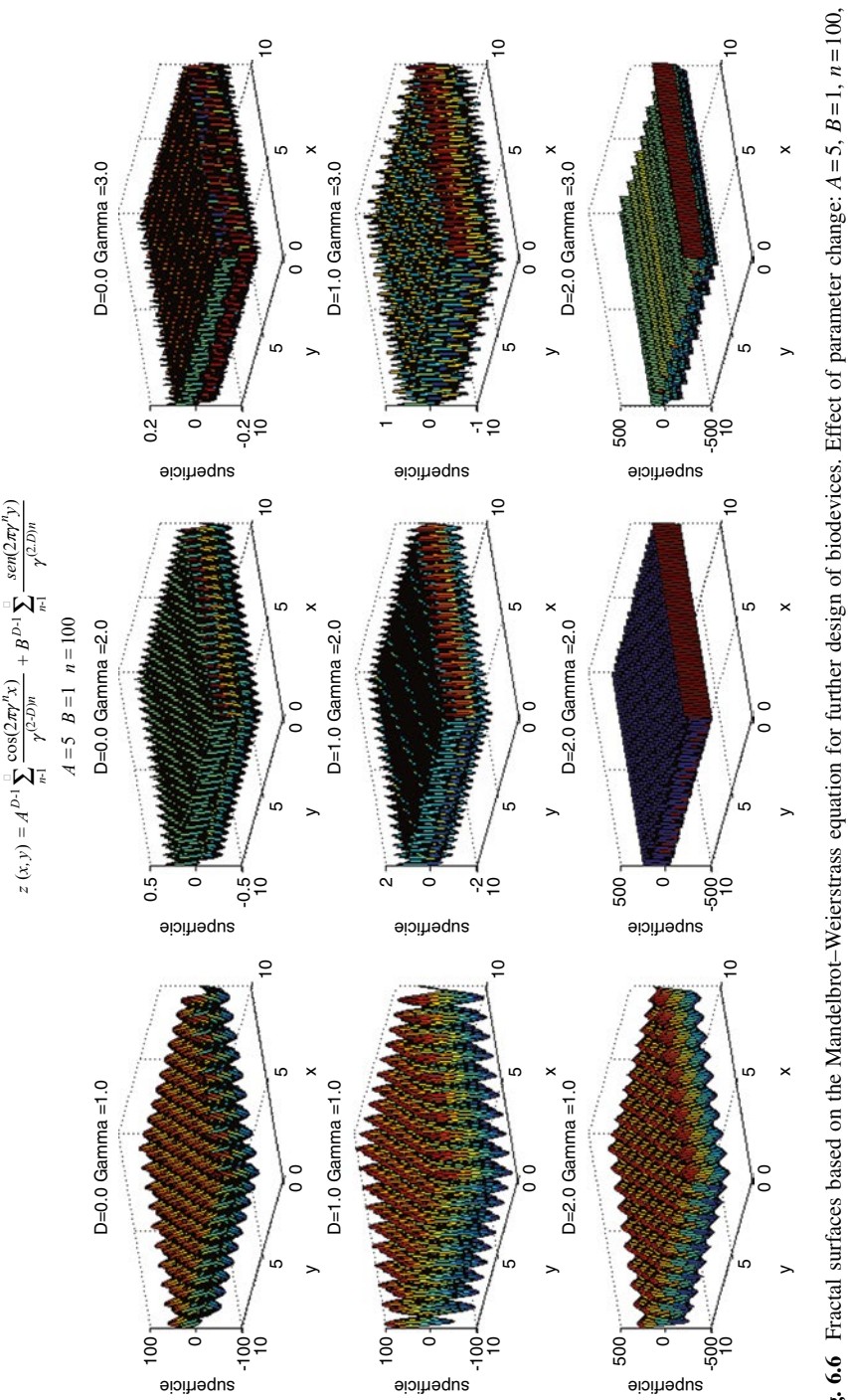

Fig. 6.6 Fractal surfaces based on the Mandelbrot–Weierstrass equation for further design of biodevices. Effect of parameter change: $A = 5$, $B = 1$, $n = 100$, $D = 0; 1; 2$, $\gamma = 1; 1{,}5; 2$

6.3.2 Designs Based on Fractional Brownian Models

Fractional Brownian fractal surfaces have proved to be very adequate for modelling the micro-textures of natural surfaces (Mandelbrot 1983; Falconer 2003) and their application to biodevices, such as scaffolds for promoting cell growth, and the beginning of tissue formation has been already validated by our team (Díaz Lantada 2012a).

Further studies linked to its application to the design of alternative biodevices for several applications, such as promoting osseointegration of implants and especial contact phenomena, should be addressed and the following explained design procedure may be consequently of help.

The following equation gives the height "z" of the mentioned fractional Brownian fractal surfaces, when assessing the function over a grid of points given by their (x,y) coordinates. The model uses several random functions (A_k, B_k, C_k), several control constants (λ, α, m) and an initial height function "z_0" can also be introduced:

$$z(x,y) = z_0 + \sum_{k=1}^{\infty} C_k \bullet \lambda^{-\alpha k} \bullet \sin(\lambda^k [x \bullet \cos(B_k) + y \bullet \sin(B_k) + A_k])$$

Figure 6.7 shows the result of evaluating a fractional Brownian fractal function over a grid of 60×60 points (corresponding to a scaffold of 30 mm×30 mm) and the influence of introducing changes in the control parameter "α".

In this example, we use a planar surface (z_0=0) as basis for the fractal, although multi-scale-based design approaches may wish to combine, for instance, an initial surface with micrometric features, upon which fractal nanometric details are applied or even combinations of fractal surfaces with different levels of detail.

Upper image of Fig. 6.7 corresponds to α=0.8 (fractal dimension around 2.2 with maximum roughness depth reaching 1.2 mm), and lower image of Fig. 6.7 corresponds to α=0.2 (fractal dimension around 2.8 with maximum roughness depth reaching 2.5 mm). Even though we are referring in this example to a mm×mm×mm scale, it is important to note that the matrixes obtained give just numerical values and, depending on final application, we can focus on mm, microns, or nanometres. In any case, we have to take into account the level of desired detail of the biostructure being mimicked and the level of detail subsequently attainable with final manufacturing technologies.

The calculations have been carried out with help of Matlab software (Mathworks, version R2009) and the data obtained are stored in three-column matrixes [X, Y, Z]. The command "surf" helps to represent the surfaces linked to the mentioned matrixes. Some additional details on computation can be found by having a look at the Matlab (The Mathworks Inc.) code of the different programmes included in the Annexes of the handbook, hoping it may be of help for carrying out future designs of biodevices and medical appliances.

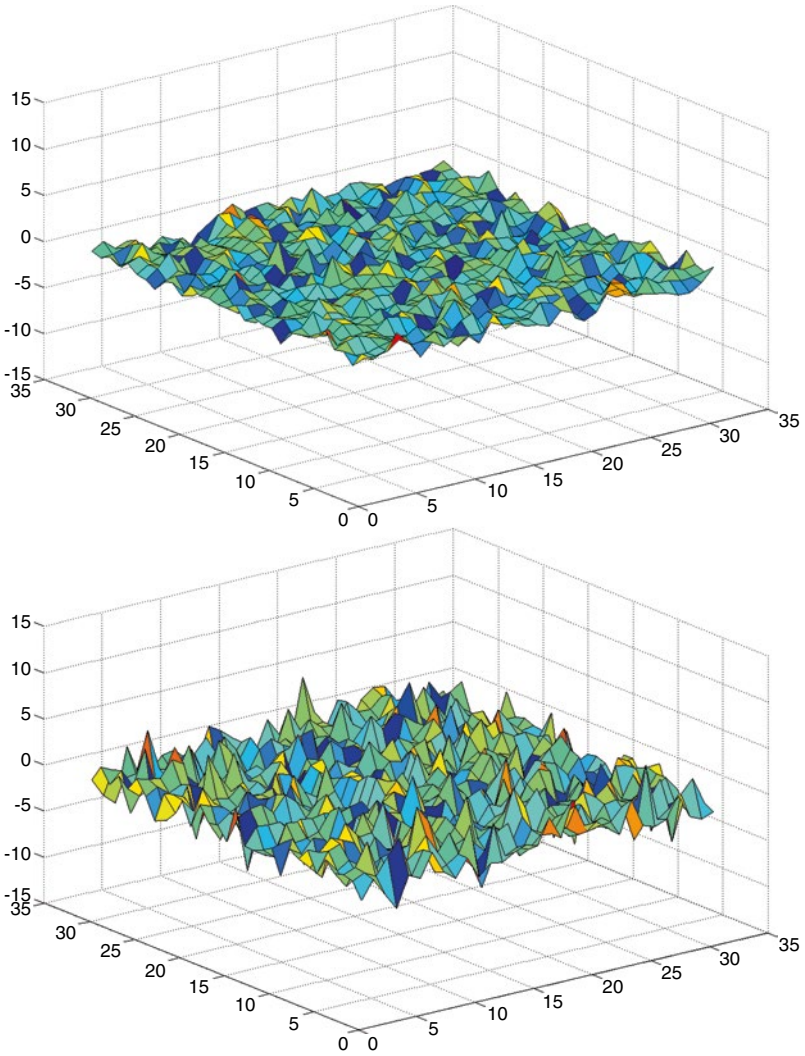

Fig. 6.7 Fractal surfaces based on fractional fractal Brownian surfaces for further design of biodevices. Effect of parameter change: *Upper image* → α=0,8 leading to fractal dimension 2,2. *Lower image* → α=0,2 leading to fractal dimension 2,8

6.3.3 Designs Based on (Evolutive) Kardar–Parisi–Zhang/ Langevin Models

These "evolutive" models, leading to similar results, start from a surface, whose height at every point varies with time ($z(x,y)=z(x,y,t)$), what can be programmed using height matrixes varying step-by-step. Equations governing such evolutions are shown below for both models.

Kardar–Parisi–Zhang model can be written down as:

$$z(t+dt) = z(t) + \frac{\partial z}{\partial t} dt$$

$$\frac{\partial z(\vec{x})}{\partial t} = \mu \nabla^2 z(\vec{x},t) + \lambda (\nabla z(\vec{x},t))^2 + \eta(\vec{x},t)$$

$\eta(\vec{x},t)$: Gaussian white noise.
μ, λ: Control constants.

For this model, two examples are provided in the following pages. Figure 6.8 shows its application starting from a planar surface $z(x,y)=0$, and Fig. 6.9 shows its application starting from a wavy surface $z(x,y)=\text{sen}(x)\cdot\text{sen}(y)$. It can be appreciated that the degree of fractality of irregularity increases with time and the adequate final step for the simulation has to be adapted to the objective of final device. Otherwise too low or too high roughness or inappropriate details could be obtained.

Langevin model can be written down as:

$$z(t+dt) = z(t) + \frac{\partial z}{\partial t} dt$$

$$\gamma \frac{\partial z(x,y)}{\partial t} = -\nabla V(z) + \xi(t)$$

$\xi(t)$: White noise.
γ: Control constants.
$V(z)$: A potential function of $z(x,y)$.

Although these evolutive models can be used for design purposes, their actually more relevant field of application is the modelling of corrosion or wear phenomena, with impact on *in silico* assessing the service life of implantable devices as well as the modelling of biological colonisation processes, in which the surface of an object changes due to the appearance of microorganisms.

6.4 Design Procedure: From Fractal Models to CAD Files

Once the Matlab surfaces have been obtained, using some of the models previously detailed or alternative ones, the related geometrical information can be stored in the form of a [X, Y, Z] matrix and can be further converted into .stl or a similar universal format, so that the surface can be recognised and imported with a CAD programme, for additional design operations (i.e. providing the surface with a thickness different to zero, copying the surface atop a previously designed geometry…).

Figure 6.10 shows the CAD model achieved after importing a fractal surface from Fig. 6.7 with a CAD programme and extruding such surface for obtaining a virtual prototype of a fractal scaffold and a fractal mould for mass production of such scaffolds. The design process, including also advices for serial manufacture, is

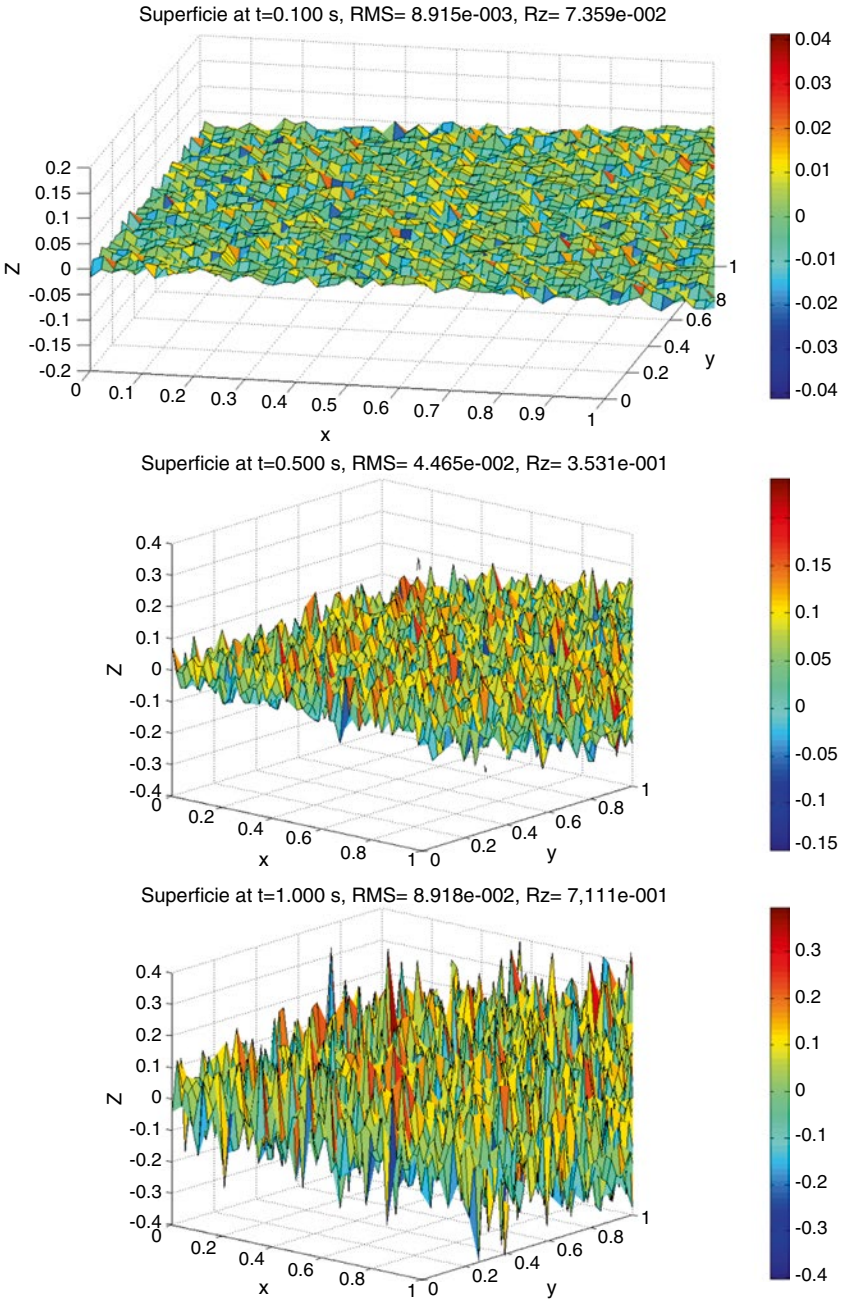

Fig. 6.8 Fractal surfaces based on Kardar–Parisi–Zhang/Langevin models for further design of biodevices. Evolutive design starting from a planar surface: Fractal surfaces obtained after 1, 5 and 10 iterations (iteration step = 0,1 s)

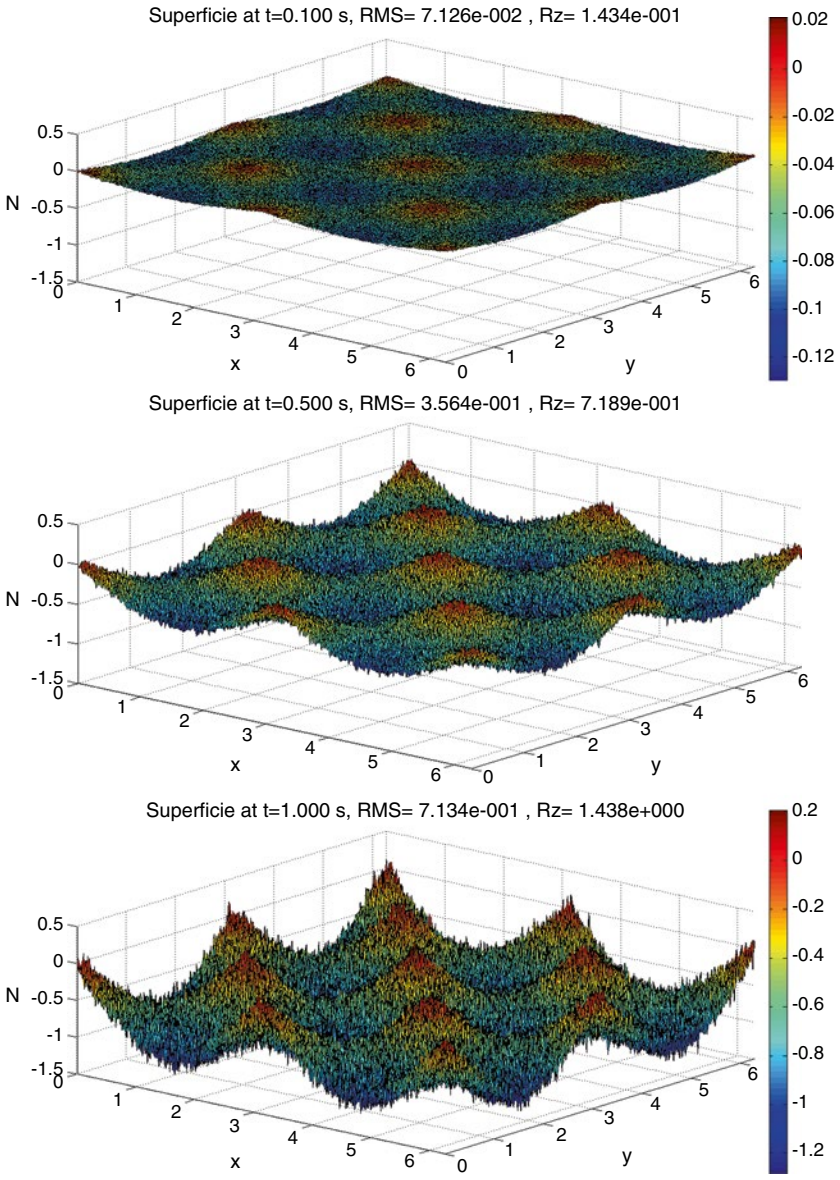

Fig. 6.9 Fractal surfaces based on Kardar–Parisi–Zhang/Langevin models for further design of biodevices. Evolutive design starting from a wavy surface: Fractal surfaces obtained after 1, 5 and 10 iterations (iteration step = 0,1 s)

currently patent pending (Díaz Lantada 2010a, b, and c, Spanish Patent and Trademark Office P201030957 document).

Some additional biodevices based on this process for fractal-based biomimetic design, including scaffolds for cell growth and tissue engineering-related procedures,

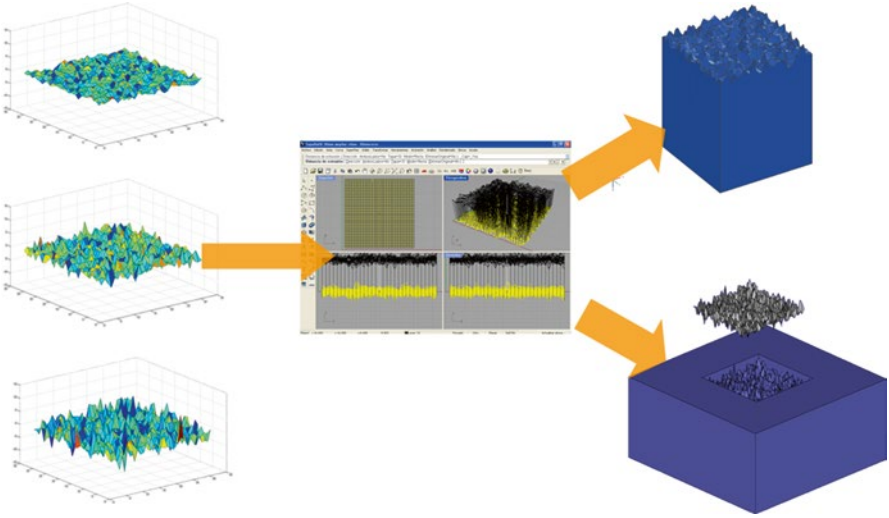

Fig. 6.10 Scheme for fractal-based biomimetic design of biodevices (Patent pending: Spanish Patent and Trademark Office P201030957)

as well as microsystems for studying cell motility can be found in Chaps. 10, 11 and 12, when focusing on the manufacture of biodevices with micro- and even nanofeatures.

Until now the chapter has focused on the design process of biodevices based on fractal surfaces, thus leading to textured devices but with an overall geometry clearly "planar", which may be somehow limited for obtaining three-dimensional implants and prostheses.

Fractal models may also be of help for reproducing the spatial morphology of tissues and organs and for providing a way of controlling aspects such as porosity, surface/volume ratio, stiffness…, which are decisive for promoting some chemical reactions and biological processes.

We would like to introduce here the use of "fractal spheres" or "fractal seeds", whose distribution for filling the 3D space and subsequent Boolean combination with the solid object of a prosthesis, organ or structure can lead to three-dimensional porous structures for being used as support for 3D cell growth, both in tissue engineering and in the novel field of biofabrication.

The process is schematically described in Fig. 6.11 and is based on combining "fractal spheres", which can be defined by the equations detailed below. A fractal sphere, by adapting the definition of fractional Brownian fractal surface, can be defined by an almost randomly changing radius in the form:

$$r(\vec{x}) = r_0 + \sum_{k=1}^{\infty} C_k \bullet \lambda^{-\alpha k} \bullet \sin(\lambda^k \bullet |\vec{x}| + A_k)$$

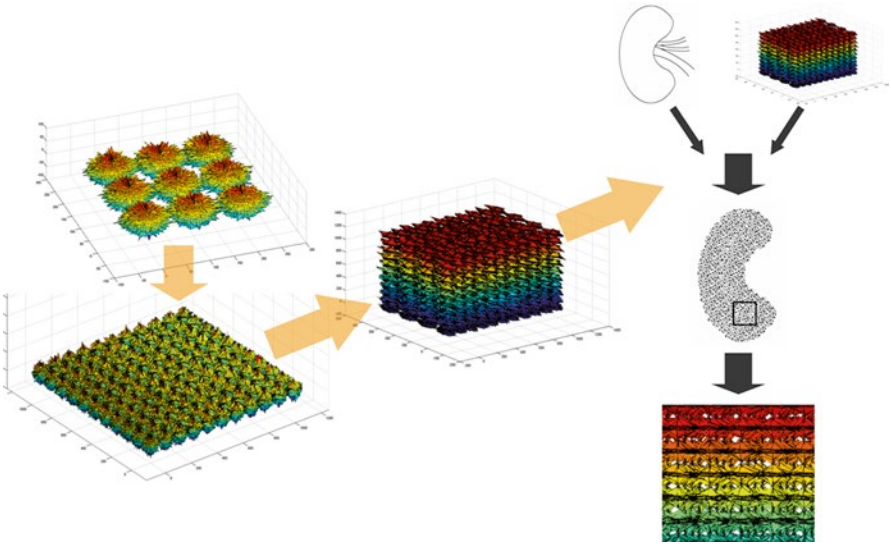

Fig. 6.11 Scheme for fractal-based design of structures for biofabrication (Patented process: Spanish Patent and Trademark Office P201030957)

Such expression describes the fractal sphere radius as a function of the position vector ($\vec{x}$) of each point of an initially regular spherical mesh (as can be obtained for instance with the "sphere" command of Matlab).

Applying the expression to the initially regular sphere, the initial radius r_0 is forced to change by the summatory of terms including random functions (A_k, C_k) and control parameters (α, λ). The summatory must again be limited, so as to avoid an infinite loop, but the approximate fractal sphere obtained may well be of use for several applications.

Additional details on the computation of fractal spheres can be found by having a look at the Matlab (The Mathworks Inc.) code of the different programmes included in the Annexes of the handbook.

Similar and novel ways of extending the texturisation process, based on fractal biomimetic models, to the external features of several prostheses and to the features of tissue engineering scaffolds may promote interesting biological phenomena. The progressive incorporation as an additional command (i.e. "apply roughness" or "apply fractality") to conventional CAD programmes is also matter of research.

Of course these complex geometries can be even impossible to manufacture with conventional subtractive procedures, due to their inner porosity, irregular features and fractality. Some advices linked to manufacture of fractals and fractal-based designs are provided in the following section.

Alternative uses of such fractal spheres and fractals applied to modifying the surfaces of three-dimensional objects are also linked to conventional prostheses, for instance, for trying to provide additional roughness and increase friction coefficient and for the promotion of primary stability and subsequent osseointegration, and also promoted by textures and edges to which osteoblasts typically attach properly.

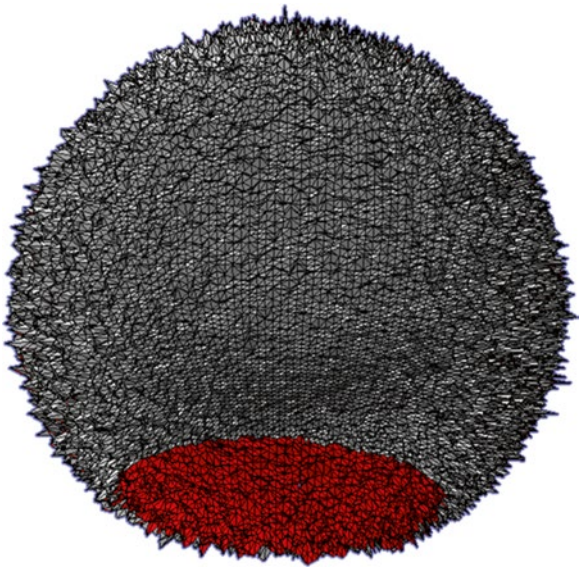

Fig. 6.12 Biomimetic micro-textured fractal-based design of the acetabulum of a hip prosthesis for improved primary stability and osseointegration

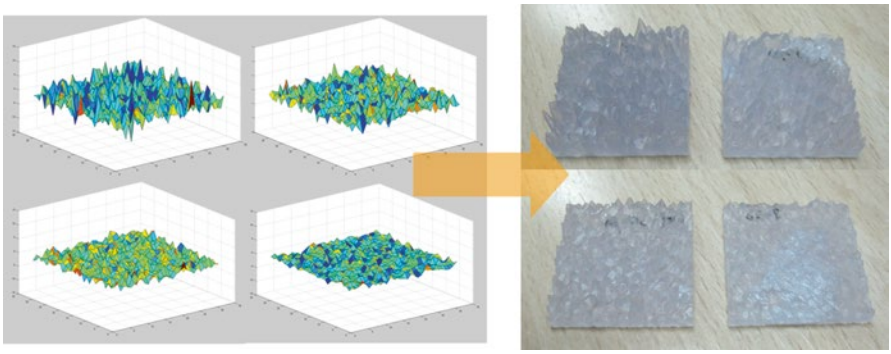

Fig. 6.13 Manufacture of fractional Brownian fractal surfaces, with the help of laser stereolithography (3D Systems), with different fractal dimension

Figure 6.12 provides an additional example linked to the design of the outer surface of the acetabulum of a total hip prosthesis. Inner part of the acetabulum is normally manufactured using UHMWPE (ultra-high molecular weight polyethylene), a polymer with a very low friction coefficient, to promote low friction and wear, when the head of the femoral component slides inside the acetabulum.

However, the outer surface of the acetabulum is in direct contact with patient's bone, and sometimes metallic or ceramic coating or covers are used for helping proper attachment to bone. A possible alternative is depicted in Fig. 6.13, as a fractal

sphere based on fractional Brownian fractal models, whose "spiky" features can promote such anchorage to bone and help with primary stability, when the patient is recovering from surgical intervention.

Some additional possibilities more linked to the biomimetic design of biological systems and structures are provided in Chap. 14, when explaining the importance of biomimetic design inputs for promoting relevant advances in the field of biofabrication.

We have focused here on the use of fractals for the design of irregular complex surfaces and of fractal three-dimensional objects such as spheres, perhaps not having adequately focused on linear fractal models, as they are easier to generate and widely covered in the literature and websites.

In fact fractal paths and related models (diffusion limited aggregation, lattice random walks, random branching processes, among others) can be also helpful for several tasks linked to biomedical engineering and have great potential for the development of microsystems, lab-on-a-chip devices and appliances linked to tissue engineering and cell motility studies (prototypes for electrophoresis, prototypes with controllable capillarity), as further discussed in Chap. 12, when focusing on micro-manufacturing technologies and related photolithographic approaches.

In the near future, biofabrication (see Chap. 14) will also benefit from CAD designs based on fractal paths and similar models (i.e. branching processes for mimicking bronchia and blood capillaries…) as well as from advances on high-precision medical imaging technologies. Probably biomimetic approaches will combine several disciplines, as mathematical modelling, computer-aided design process and reverse engineering technologies (including the combined use of medical imaging and CAD), for providing more versatile solutions.

6.5 Manufacture of Fractal Geometries

We propose the use of the rapid prototyping technologies based on additive manufacturing approaches (see Chap. 10), for directly manufacturing fractal scaffolds and related devices from the previously explained designs. Some enterprises already provide their customers with rapid-prototyped biodevices; however, they are normally designed using conventional CAD design operations (holes, grooves, extrusions), and the related prototypes do not provide the desired complexity, when trying to mimic the features of organs and biostructures.

The design and manufacturing approach proposed here provides additional control tools and helps to obtain biomimetic fractal-based designs, which can be directly manufactured. Figure 6.13 shows an example of physical prototypes of fractal surfaces manufactured through laser stereolithography in epoxy resin (Accura 60, 3D Systems), directly from the CAD file of the part. They have been manufactured using the SLA-3500 machine from 3D Systems which can manufacture details down to around 150 μm. Figure 6.14 shows the topography obtained, in which the "layers" of the additive process can be appreciated.

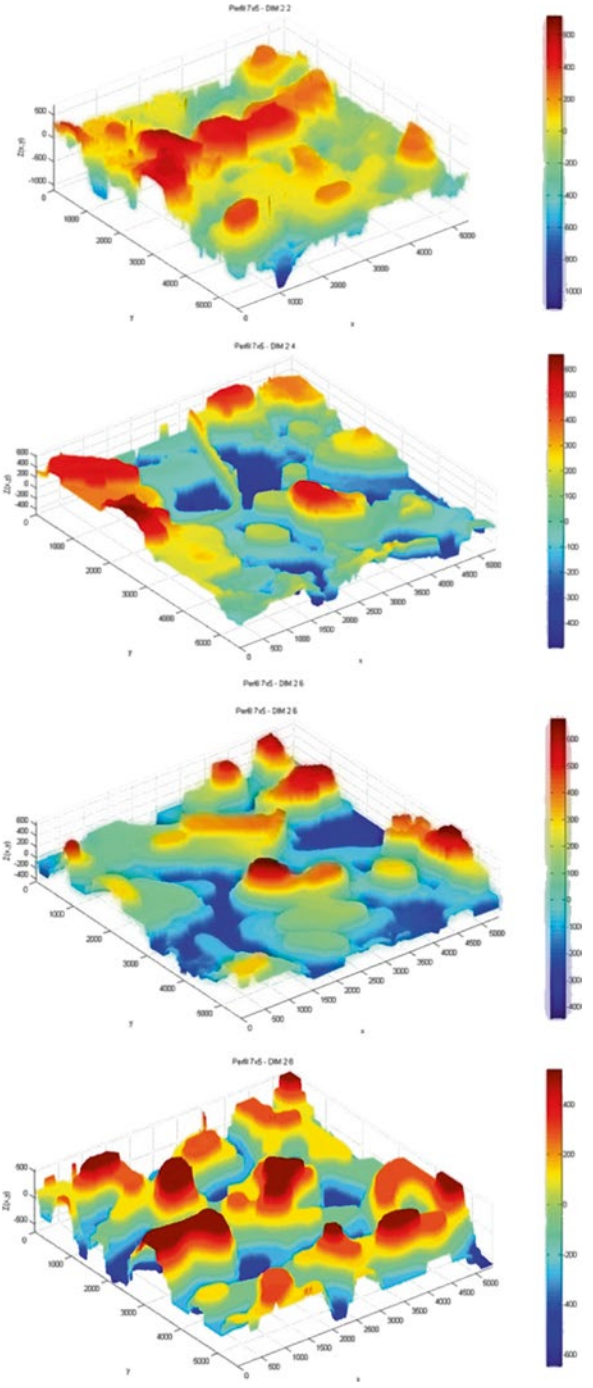

Fig. 6.14 Surface topography of rapid prototypes based on designs with different fractal dimension (From *upper* to *lower image*: 2.2; 2.4; 2.6; 2.8). Area measured 7×5 mm^2, courtesy of Laser Centre at UPM

Although the photopolymerisable epoxy resin used for these prototypes is not a medical grade polymer, and therefore cannot be used for the manufacture of implantable devices, it is important to mention some recent advances in the development of biocompatible photopolymerisable resins for several additive manufacturing processes, whose accuracy is also noteworthy (even down to 0,1 μm), as well as the possibility of using rapid-form copying processes replicating these geometries in biomaterials. All these possibilities are covered in depth in Chaps. 10, 11 and 12, providing examples or real biodevices with fractal-based designs.

It is important to note that using a layer manufacturing technology allows the obtaining of very complex geometries, even with inner details and porosity, even unable to be manufactured using other processes. Aspects like roughness, waviness, skewness or fractal dimension can be precisely controlled from the design stage and adapted in a personalised way to the requirements of the application.

6.6 Main Conclusions and Future Research

The possibility of designing parts with surfaces mimicking those from natural organisms, thanks to the incorporation of fractal models to the design procedure (see Fig. 6.15 below), can prove to be of great value for incorporating advanced contact phenomena into devices for several industries, thus promoting interactions with surrounding elements (if the part is integrated within a complex device) or tissues or organs (in the case of an implant).

Among most promising applications, we would propose to focus in the near future on the design of implants with optimised biocompatibility, devices with self-cleaning properties, devices with ad hoc improved hydrophobicity or

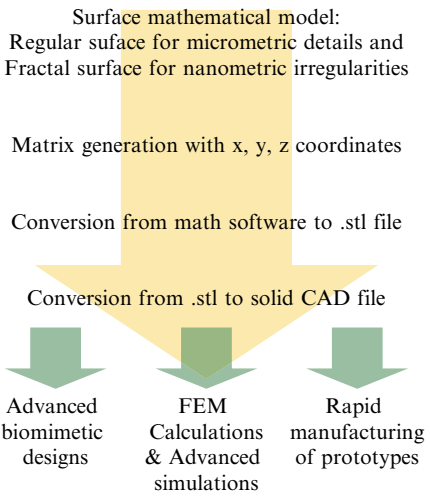

Fig. 6.15 Process scheme of biomimetic design based on fractal surfaces (Spanish patent document OEPM P20103947)

hydrophilicity, scaffolds for cell and tissue growth and prototypes for research linked to tribological phenomena, including adhesion, lubrication, friction and wear. Some of these examples are further studied and validated in forthcoming chapters.

In addition, combining novel advances in micro-CT and medical imaging software (i.e. Mimics, Materialise NV) for obtaining precise CAD data of organs and biostructures (Shi et al. 2008; Guo et al. 2010), with the possibility of incorporating even nanometric, can be of great help for research, not only linked to the enhanced modelling of biosystems but also to the final development of implants with highly relevant special features.

In some cases, a combination of regular surfaces, for describing the micrometric structure, and an additional fractal component, for providing the final nanometric details, can be used for multilevel biomímesis of biological systems and of the devices designed to interacting with them.

Regarding the manufacture of fractal surfaces, our previous research has helped to validate the use of rapid prototyping for obtaining physical prototypes with details in the range of 0.3–4 mm (Díaz Lantada 2010a, b, and c; Díaz Lantada et al. 2012a, b); a couple of examples have been treated here and some additional ones are included along the handbook. The manufacture of more precise geometries can be accomplished by using some of the additive manufacturing technologies described in Chap. 10, which also includes some additional examples with details in the range of 25–100 μm.

The different fractal surfaces and spheres described in this chapter serve as a basis for designing several biodevices and microsystems for studying cell-scaffold interactions, analysing micro-fluidic effects and developing lab-on-a-chip devices, among other direct applications.

However, further research efforts have to focus on the application of these fractal geometries upon all kinds of 3D surfaces. It would be very beneficial to incorporate, in conventional CAD resources, a new "fractal" command, capable of applying a desired roughness to the surface of an already designed 3D geometry or aimed at controlling its final fractal dimension.

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[1]On fractals with demonstrations.

On Euclidean and non-Euclidean geometries:[2]

http://mathworld.wolfram.com/EuclideanGeometry.html. Accessed Mar 2013
http://mathworld.wolfram.com/Non-EuclideanGeometry.html. Accessed Mar 2013

[2] 2 For using some Matlab (The Mathworks Inc.) programmes for constructing fractal surfaces and fractal spheres, please have a look at the Annexes of the handbook.

Chapter 7
Porous and Lattice Structures for Biodevices with Advanced Properties

Andrés Díaz Lantada and Juan Carlos Álvarez Elipe

Abstract During their development, biological systems have to continuously work with a limited amount of energy, and, therefore, their own materials and structures are built trying to maximise the resistance-weight relationship, which leads to finally obtaining porous or hollow materials and structures.

Biomimetic design of medical appliances and biodevices can be promoted by using conventional or novel computer-aided design software, staring from solid models and systematically eliminating material from such solid parts, for instance, using Boolean subtractive operations with 3D sphere matrixes or cubes. Hollow biomimetic structures can be also designed in an additive way, firstly by obtaining a lattice cell unit, repeating such cell unit for filling the space and using Boolean intersections using solids with the desired final part external geometry.

Using the mentioned approach, materials and structures can even be tailored ad hoc for final application, including precise control of density, Young modulus, Poisson ratio (even with negative values by using auxetic structures) and others, with results very adequate for designing prostheses with mechanical features adapted to those of human body, in order to limit negative phenomena like stress shielding and bone resorption.

This chapter provides examples of both approaches, linked to prostheses design and tissue engineering, comparing the advantages and disadvantages of porous, lattice and auxetic structures and discussing main additional resources for simplifying the whole process. Production of these complex porous, hollow and lattice structures is also discussed, as it would have been thought impossible just a couple of decades ago. Novel advances on "layer by layer" or "additive manufacturing technologies" can be used for its automated production, as additionally explained in forthcoming chapters.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_7,

7.1 Brief Introduction to Porous and Lattice Materials and Structures (Metamaterials) in Bioengineering

Metamaterials are artificial materials engineered to have properties that may not be found in nature or only in strange and expensive materials. Metamaterials usually gain their properties from structure rather than composition, using small inhomogeneities or usually based on the periodic repetition of a unit cell, to create special macroscopic behaviours (Capolino 2009a).

Most current applications of metamaterials are oriented to the development of devices for controlling electromagnetic waves in the fields of optoelectronics and electronic engineering. Photonic crystals, plasmonic structures and sensors, superlenses, light cloaks and frequency selective surfaces, among other applications, benefit from ad hoc designed or engineered metamaterials, whose performance depends on the designed periodic structure, much more than on their chemical composition (Capolino 2009b).

In more traditional engineering fields, such as mechanical and aeronautical engineering as well as architecture, metamaterials are used for improving mechanical characteristics, by adequately designing and manufacturing porous or lattice structures, with results that are also highly beneficial for the development of several biodevices linked to biomedical engineering, as the present chapter details.

For example, the use of porous materials for product design and the use of lattice structures in architecture are normally aimed at obtaining much lighter structures, with remarkable relationships between Young modulus and overall density and between resistance and weight, either for less energy consumption during performance or for enhancing long-term performance.

In a similar way, biological systems, as they have to manufacture their own materials and structures and subsequently endure their weight, both tasks being highly expensive in energetic terms tend to optimise the relationship between resistance and weight, and porous materials structures (trabecular bone, natural foams) and lattice structures (supporting skeletons or exoskeletons) provide very often optimal solutions.

Novel advances in computer-aided design and engineering (covered in Chaps. 4 and 8) and in solid free-form fabrication (detailed in Chap. 10) offer designers and engineers the possibility of constructing a wide set of cell units for subsequent periodical reproduction, so as to obtain all kinds of imaginable metamaterials, with mechanical properties tailored to the requirements of final applications.

In the field of biomedical engineering, the use of metamaterials is relevant for developing novel scaffolds and cell sheets for tissue engineering (for instance, based on auxetic geometries for avoiding wrinkles when stressed), for obtaining light (porous or lattice) prostheses with improved resistance-weight relationship, for developing minimally implantable devices (with the help of lattice auxetic geometries), among other highly innovative solutions, as explained in the next sections including some case studies.

7.2 Design of Porous and Lattice Structures for Biodevices: Boolean Operations and Special Resources

The design of porous and lattice structures with the help of CAD resources is in fact simple and rapid, once a couple of operations are adequately combined. In fact the introductory examples provided in the present handbook as a way of showing the capabilities of CAD programs (see Sect. 4.4) are linked to porous and lattice structures.

The process, for lattice structures, normally includes combination of solid operations (cylinders, piles, etc.) for obtaining a unit cell and pattern or periodic replication of such solids and unit cells. Intersecting the obtained lattice with a solid implant leads to final device. In the case of porous structures, the process instead of additive is subtractive. It normally begins with a cube, from which smaller spheres and cubes are usually subtracted. The porous structure (or metamaterial) obtained can additionally be intersected with the geometry of a solid prosthesis, for finally obtaining a porous implant. Both processes are schematised in Fig. 7.1 included below.

Even though all conventional CAD programs already commented (Solid Edge, NX-8.0, Catia v.5, Solid Works, Autodesk-Inventor, etc.) include several operations for designing unit cells and replicating them, for applying pores to solid objects and Boolean operations for applying an outer geometry to a lattice structure, novel CAD resources are being specifically developed for promoting the application of metamaterials to product development.

Among ad hoc CAD software oriented to the design of lattice and porous structures, for improved control of aspects such as density, stiffness and resistance of final geometries, we would like to cite "Within" (www.within-lab.com) and also "Netfabb" (www.netfabb.com), as the most advance ones and with direct application in biomedical engineering.

Recent advances in topological optimisation, a mathematical approach that optimises material layout within a given design space, for a given set of loads and boundary conditions, are also helpful for deriving into lattice and porous structures and progressively being incorporated to conventional CAD resources (Bendsoe and Sigmund 2003; Schramm and Zhou 2006).

Figure 7.2 provides some examples of cubic lattice structures with different density and stiffness due to different geometrical configurations. They have been designed with the help of a NetFabb 30-day trial version available at www.netfabb.com. From the different available software for designing lattice structures, surely NetFabb offers the best quality/price relationship, with the licence from its basic

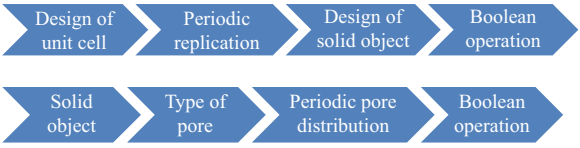

Fig. 7.1 Schematic processes for designing biodevices with lattice and porous structures

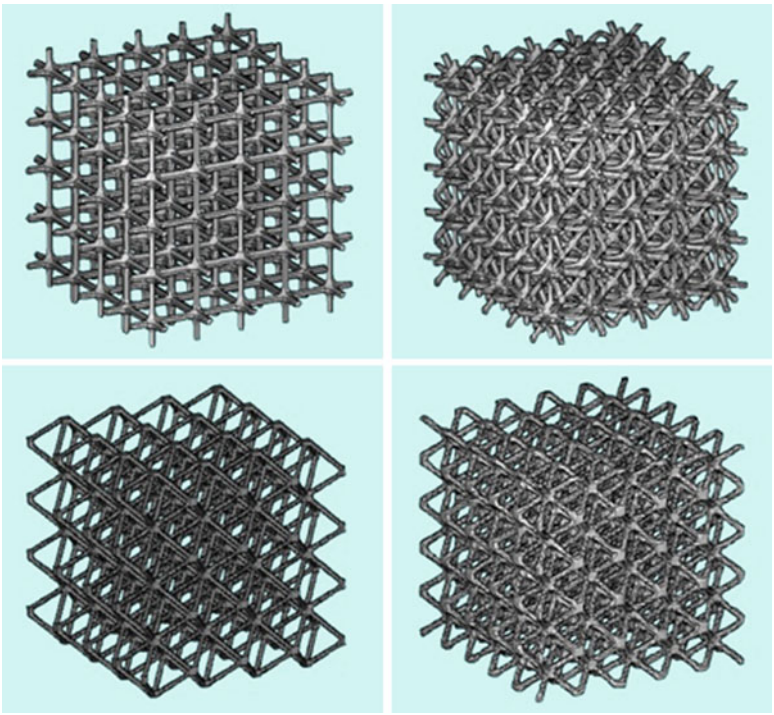

Fig. 7.2 Example of bidimensional and three-dimensional auxetic structures

product "NetFabb Studio" starting from 699€. Such a competitive price can indeed be strategic for their software being used as support for teaching-learning tasks in universities and research centres. Their website includes support for research projects and services for converting solid .stl files into lattice structures and also subsequent 3D printing of prototypes.

A main alternative, also ad hoc oriented to the development of lattice structures, Within (www.within-lab.com) is also useful for designing implants with improved stiffness versus density, although basic licence starts from £3.000 and a licence with FEM simulation capabilities is around £20.000, going up to £30.000 if geometrical optimisation is included. Less specific but much more versatile and widespread, CAD–CAE software, such as NX-8.0 Siemens PLM Solutions, offer complete design and simulation resources (including static, dynamic, thermal and fluidic simulations) for less than 4.000€.

After the three-dimensional space is filled with the lattice or porous structure of a metamaterial, with adequately engineered properties for final application, the use of Boolean operations (in this case intersection) with the CAD design of a solid prosthesis can lead to special implants as those shown in Fig. 7.3.

The use of FEM (finite element method)-based simulations (as detailed in Chap. 8) helps to predict *in silico* how a biodevice will behave in vivo, which has several

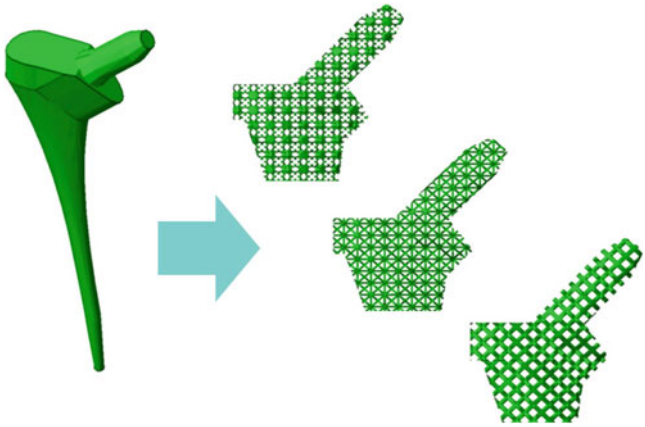

Fig. 7.3 Example of bidimensional and three-dimensional auxetic structures

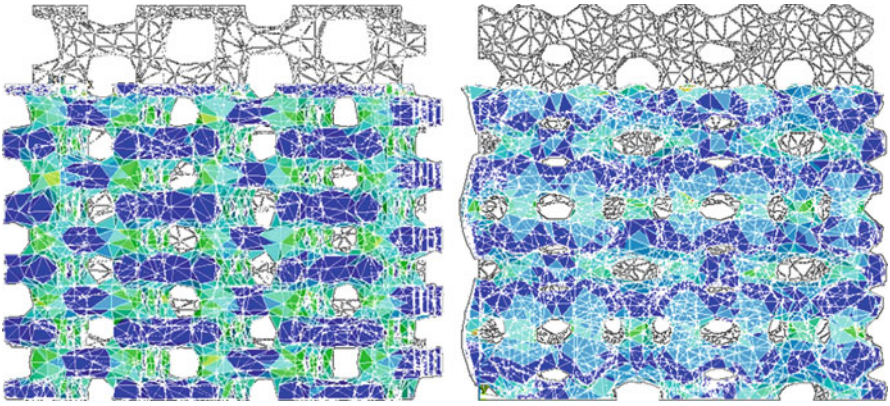

Fig. 7.4 Examples of FEM-based simulations for analysing the stress, strain and displacement fields in different lattice structures under service loads

advantages including schedule and cost optimisation and a very relevant reduction of the number of trials using animal models required for placing a novel implant into market. Such simulations, among other studies, can help to assess the mechanical stiffness of different geometrical configurations, in this case different lattice structures, so as to assess those most adequate for mimicking the properties of bone or related organs or biostructures that will interact with the implant.

Figure 7.4 provides a brief comparison between two lattice/porous structures, showing the results of stress fields, mapped on the deformed structures, after loading them uniaxially. In both cases the maximum stresses obtained under the applied loads would be in the range of 10–15 MPa, what would not suppose any problem for a conventional polymeric material, as has been here selected.

The apparent stiffness of such lattice structures can be also obtained and the different structures represented in form of Ashby's diagrams showing, for instance, adimensional apparent Young modulus (effective Young modulus/Young modulus of the bulk material) versus adimensional apparent density (effective density/density of the bulk material).

Such graphics or diagrams (grouping materials by families and subfamilies) provide a very useful tool for material selection processes, in parallel to the whole product development, helping to consider different factor to be optimised, such as stiffness, resistance, weight, cost and manufacturability, among others (Ashby and Jones 1996, 1998; Ashby 2005).

It is also relevant to cite the development of material selection software based on the Ashby's methodology for helping engineers and designers to handle these information and graphics in an easier way. The mentioned software is commercialised under the name "CES Selector" by Granta (www.grantadesign.com), and several teaching resources and professional packages oriented to different industries, including the medical device industry, are offered.

The combination of CES Selector with more specific databases of material properties, for example, "CampusPlastics" (www.campusplastics.com) for polymer technology, can be a source of valuable information for novel product development projects, even though quality control and verification through personal trials that the materials provided by the suppliers fulfil specifications is always a very advisable procedure.

In many cases, in projects linked to medical devices, novel or special functionalities are provided by the use of recently discovered biomaterials, what normally requires special attention to characterisation tasks for obtaining the valuable information needed for the design process.

7.3 Design of Lattice Auxetic Structures and Devices: Application to Expandable Devices

When a material is stretched, there is normally an accompanying reduction in width, normally linked to mass conservation. A measure of this dimensional change can be defined by Poisson's ratio, $\nu = -d\varepsilon_{trans}/d\varepsilon_{axial}$, being ε_{trans} and ε_{axial} the transverse and axial strains when the material is stretched or compressed in the axial direction. In a more general case, ν_{ij} is the Poisson ratio that corresponds to a contraction in direction "j" when an extension is applied in direction "i".

For most materials this value is positive and reflects a need to conserve volume. Auxetic materials (or metamaterials) are those with a negative Poisson ratio (NPR) and display the unexpected property of lateral expansion when stretched, as well as an equal and opposing densification when compressed (Lakes 1987; Evans 1991; He et al. 2005; Liu and Hu 2010). Natural (some minerals, skins, etc.) and man-made (foams, Gore-Tex®, polymeric foams) auxetics have been described, and

very special attention is being paid to the development of auxetic structures designed and controlled on a molecular scale (Griffin et al. 2005).

Auxetic geometries are being progressively employed in the development of novel products, especially in the fields of intelligent expandable actuators, shape morphing structures and minimally invasive implantable devices. Regarding smart actuators based on an auxetic structure, it is important to cite some recent progress linked to auxetic shape-memory alloys (SMA) for developing deployable satellite antennas (Scarpa et al. 2010) and some research on the characterisation of polyurethane foams with shape-memory behaviour and auxetic properties, promoted thanks to several post-processing stages (Bianchi et al. 2010).

In the area of medical devices, recent research has also assessed the behaviour of a few auxetic geometries for implementing expandable stents (Tan et al. 2011), and their application to other implantable biodevices is clearly a matter of research.

The use of auxetic devices in the biomedical field is started to be assessed as useful for the following possibilities:

- Adapting the stiffness of prostheses to that of tissues and organs with which the biodevice will interact, for promoting more adequate contact phenomena and minimising stress shielding and related aspects as bone resorption
- Improving implantability of biodevices and promoting minimally invasive surgical procedures, as explained towards the end of present section
- Obtaining sheet structures for cell growth that do not let wrinkles appear when stressed, helping implanted tissue to progressively grow and adapt

Figure 7.5 provides a brief extract from a CAD library recently developed by our team, aimed at providing auxetic cell units for complementing future design innovation tasks linked to their application to implantable devices and scaffolds for tissue engineering (Álvarez Elipe and Díaz Lantada 2012; Álvarez Elipe 2012). Some examples of 2D and 3D auxetic structures or metamaterials are provided.

Based on the computer-aided design files, structural calculations using the FEM method can allow us to estimate the Poisson modules and compression ratios of the auxetic structures, even from the design stage. Aspects such as stiffness and density can also be assessed rapidly.

Additional information regarding the FEM-based simulation (elements used, loads and boundary conditions applied) of these and several more structures, together with a comparative study considering stiffness, density, maximum compression ratio and Poisson ratio, can be found at our more specific report on auxetic geometries (Álvarez Elipe and Díaz Lantada 2012; Álvarez Elipe 2012), even though it is not so aimed at medical devices as present section.

Once obtained, CAD files can be also manufactured for carrying out in vitro and in vivo trials, following the approach mentioned in Sect. 7.4.

As previously introduced, these auxetic structures have also remarkable potential for the development of implants and medical devices for promoting minimally invasive surgical procedures. A minimally invasive medical procedure is defined as one that is carried out by entering the body through the skin or through a body cavity or anatomical opening, but with the smallest damage possible to these structures. The

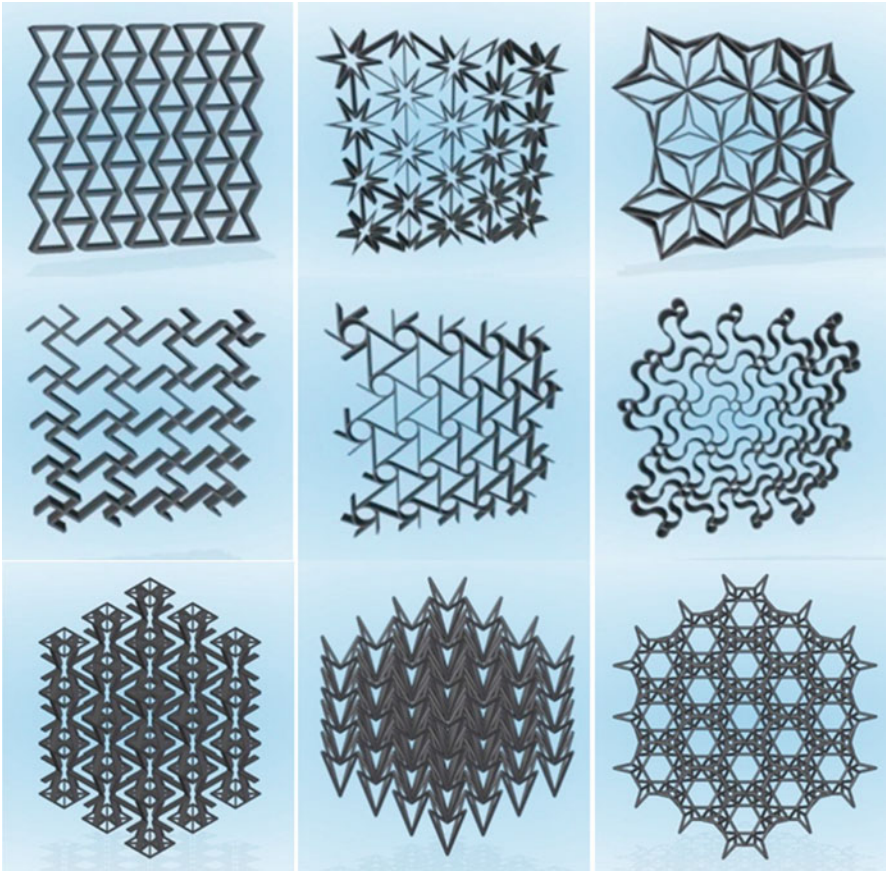

Fig. 7.5 Example of bidimensional and three-dimensional auxetic structures

benefits are very relevant, as patients suffer less during the intervention and recover much more rapidly and with a lower risk of postsurgical complications.

However, for promoting such procedures, implantable medical devices have to be adapted to them, what often involves designs with bistable (open/closed, compressed/expanded) structural configurations or designs including some kind of actuator for introducing and placing the device (laparoscopy, arthroscopy, other catheter based techniques, etc.), near to the organ or biological structure under repair, and subsequent deployment for final attachment.

Many of these minimally invasive surgical solutions incorporate or are based on the use of "intelligent" or active materials, capable of responding to external stimuli in a controlled way by changing some of their properties, appearance or geometry.

For example, some materials such as shape-memory alloys respond with structural modifications to temperature changes, what has been applied to the development of auto-expandable stents, devices for treating some septal defects (problems

in the walls dividing right and left heart cavities), intelligent catheter tips or even artificial prostheses for heart valve treatment or replacement, among other interesting examples, all of them promoting minimally invasive surgical procedures (Díaz Lantada 2012).

Similar solutions can be also combined with the advances provided by auxetic geometries, and it would be interesting to study the use of shape-memory materials auxetically structured for obtaining morphing structures and deployable actuators with thermal activation.

Explained below is the design process of two implantable devices, an annuloplasty ring for treating mitral valve insufficiency and an expandable stent for cardiovascular pathologies, both of them based on an auxetic structure that simplifies the training process for obtaining a reduced geometry for easier implantation. In conventional devices, such process for obtaining a reduced geometry requires simultaneous actuations in different directions, normally by means of additional workbenches and tools.

However, by using an auxetic structure, the size reduction process is simplified, as just by applying a uniaxial compressive force, geometric reductions in different directions are obtained.

For the annuloplasty ring a 3D auxetic structure has been used, and for the stent a 2D auxetic structure, rolled over itself, has been applied. The design process and the use of FEM simulations for *in silico* validating this kind of applications are detailed further on.

Figure 7.6 shows the design process followed to obtain an auxetic annuloplasty ring. The process begins with the design of a solid annuloplasty ring, in a similar way to those exposed in Chaps. 4 and 5. A spline can be constructed as basis for the solid ring, either "point by point" or "through table". After the mentioned spline is obtained, a point of the spline is selected, and a reference plane, normal to the spline and containing such point, is constructed.

A 2,5-mm circumference contained in the reference plane and with centre on the intersection point between plane and spline is then drafted. By using the "sweep" command, the circle is made to follow the whole spline, hence leading to final solid annuloplasty ring.

In parallel, a 3D auxetic is constructed (based on the auxetic design from the middle image of the bottom row of Fig. 7.5) filling a cube with dimensions exceeding those from the annuloplasty ring. An intersection is carried out between the solid annuloplasty ring and the auxetic structure for leading to final part with auxetic lattice structure. Figure 7.6 represents different views of the mentioned prosthesis. Future studies will be linked to its manufacture by means of solid free-form fabrication (additive manufacturing), so as to validate the auxetic behaviour.

Included below, Fig. 7.7 shows the design of an auxetic stent based on chiral geometries similar to those of middle row of Fig. 7.5. In this case a bended unit cell was designed and replicated by means of translations and circular patterns for obtaining final 3D part. Also included in Figs. 7.7 and 7.8 are the results of FEM simulations used *in silico* validating the auxetic behaviour (more details about this kind of simulations can be found in Chap. 8).

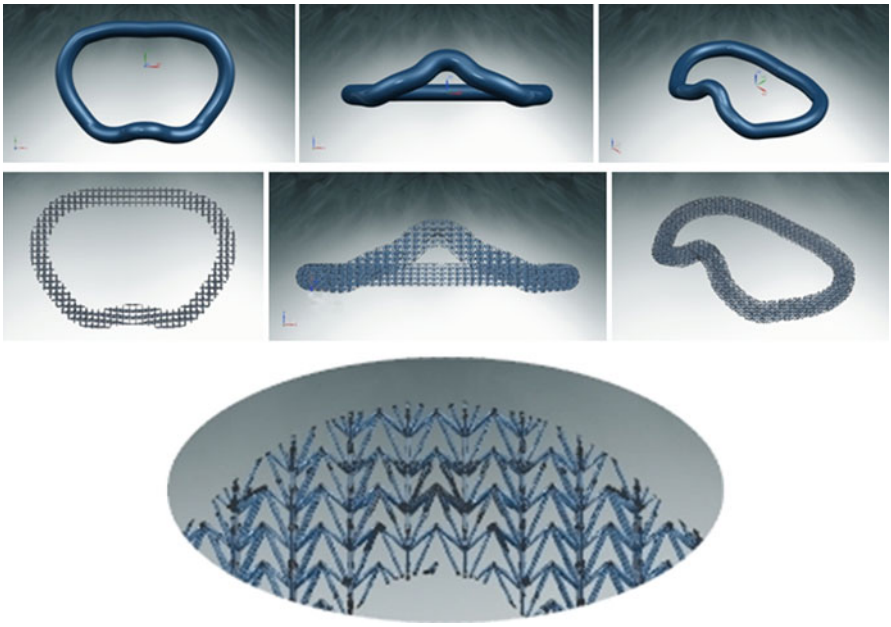

Fig. 7.6 Application of Boolean CAD operations for obtaining an implantable device with auxetic geometry starting from an original solid model. The example is linked to the development process of an annuloplasty ring for mitral valve with enhanced implantability, thanks to the auxetic properties of its structure

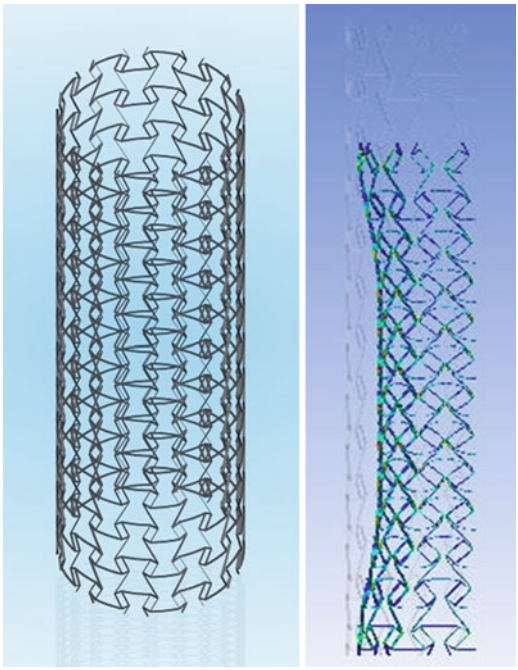

Fig. 7.7 Auxetic stent: CAD design and finite element method simulation of uniaxial compression for obtaining a reduced size with enhanced implantability

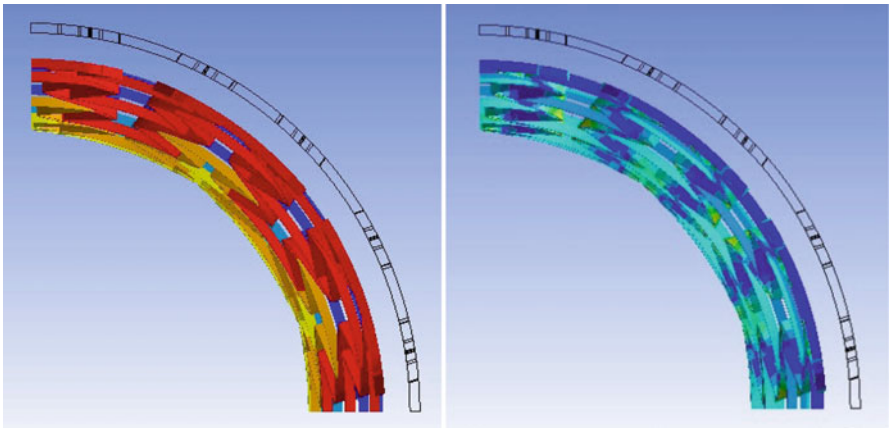

Fig. 7.8 Results from FEM simulations: strains (*left*) and stresses (*right*) linked to radial displacements when the auxetic stent is compressed longitudinally

In this simulation example, a polymeric material has been selected and the geometry has been meshes with 10-node 3D tetrahedrons. Vertical displacement has been restricted in the base of the stent, and progressive vertical ("-z" direction) displacements have been imposed on the upper part of the stent, so as to analyse the effects of uniaxial compression. The results show a clear auxetic behaviour, as the prosthesis deforms in radial direction towards a reduced geometry. The stresses obtained are at every moment below 5 MPa, which according to the simulations provides a safety coefficient of around 3–5.

This *in silico* validation through FEM-based simulations constitutes the first validation step towards obtaining finally implantable devices. The whole process is explained in more detail in Chaps. 15 and 17. In short, simulations are a great help with design validation, but the continued use of prototypes along the whole development process is even more useful, especially since rapid prototyping technologies, based usually on additive manufacturing approaches and directly linked to CAD programs, provide a very easy an rapid way of obtaining several prototypes for systematic trials.

Next section provides some introductory aspects linked to the manufacture of complex geometries and its application to auxetics, as well as some indications for carrying out in vitro trials for validating the auxetic behaviour and for helping to reproduce the ideal boundary conditions used in the FEM-based simulations (i.e. restriction of the longitudinal displacements at the base of the stent, while the displacements in transversal directions are completely free) in a real workbench. The mentioned complete freedom of some freedom degrees is sometimes difficult indeed to obtain, which can reduce the success of some designs that would work very properly in ideal conditions.

Therefore, the continued use of prototypes helps to analyse the important design decisions in conditions more similar to those in service, under which final device has to develop its mission.

7.4 Manufacture of Three-Dimensional Complex Structures Based on Metamaterials

The complexity of metamaterials, including porous and lattice structures, as well as auxetics, prevents them from being obtained by conventional subtractive manufacturing methods. Instead additive "layer-by-layer" processes are advisable for complex geometries, typical of the bioengineering field, as Chap. 10 discusses in depth. Figure 7.9 shows, as example, the application of additive manufacturing to the manufacture of complex 2D and 3D auxetic geometries, what can be applied to many of the porous and lattice structure previously analysed.

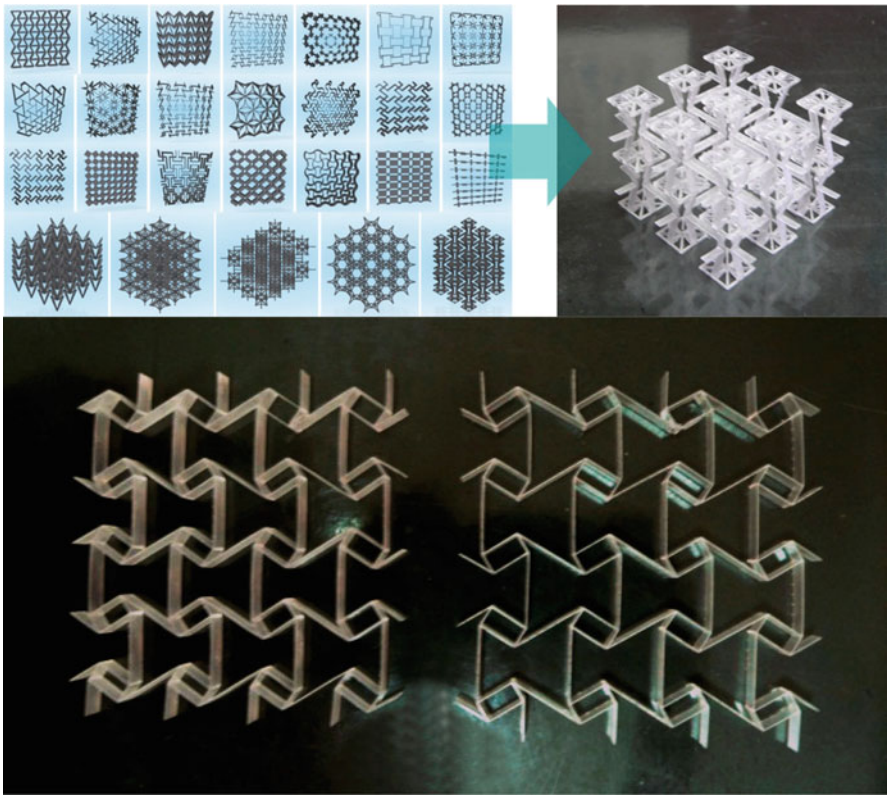

Fig. 7.9 Brief CAD library of 2D and 3D auxetic geometries and automated direct manufacture of prototypes of auxetics by additive manufacturing, in this case using laser stereolithography (SLA-3500 from 3D Systems) with epoxy resin

Table 7.1 Properties of the material used for prototype manufacture

Accura® 60 epoxy resin	
Density	1.21 g/cm^3
Tensile strength	58–68 MPa
Glass transition temperature	58–62 °C
Young's modulus below glass transition	2,690–3,100 MPa
Hardness-Shore D scale	86

For beginning with the manufacture, the .stl files with the 3D virtual CAD geometry of different auxetic designs were transferred to the laser stereolithography SLA-3500 (3D Systems, 333 Three D Systems Circle, Rock Hill, SC 29730 USA) machine with the help of 3D Lightyear TM for subsequent direct manufacture. Different prototypes for further validation of the simulated auxetic behaviour have been manufactured. The SLA-3500 system mentioned, which is available at the UPM Product Development Laboratory, allows us to manufacture details down to around 150 μm, although more recent studies linked to the development and progressive precision enhancement of micro-stereolithography are reaching features of around 10–30 μm size (Varadan et al. 2001; Stampfl et al. 2008), which could promote similar developments of auxetics-based implants and auxetic-based actuators oriented to the MEMS industry.

The prototyping process by stereolithography can be briefly described as follows. Laser stereolithography is an additive manufacturing process using a vat of liquid UV-curable photopolymer or "resin" and a UV laser to build parts layer by layer in an additive way. On each layer, the laser beam traces a cross-sectional part pattern on the surface of the liquid resin. Exposure to the UV laser cures (and solidifies) the pattern traced on the resin, causing it to adhere to the layer below.

After a pattern has been traced, the SLA's elevator platform descends a single layer thickness, typically 0.05–0.15 mm. Then, a resin-filled blade sweeps across the cross section of the part, recoating it with fresh material. On this new liquid surface, the subsequent layer pattern is traced and adheres to the previous layer. A complete 3D part is formed by repeated iterations of this process. After manufacture, parts are cleaned by immersion in a chemical bath (normally 1–2 min in isopropyl alcohol or acetone) and finally post-cured to improve their mechanical properties in a UV oven for around 10–20 min, depending on the resin's specifications (Wohlers 2010).

In this case, as in several trials along the handbook, epoxy resin Accura® 60 (3D Systems, 333 Three D Systems Circle, Rock Hill, SC 29730 USA) was used as base material for the auxetic structures, due to restrictions of the additive laser stereolithography prototyping process also used. Isopropyl alcohol was used for cleaning the prototypes once obtained. Detailed properties are included in Table 7.1, which have also been used for the aforementioned simulations.

Alternative additive manufacturing procedures may start from powder or solid materials that, instead of being photopolymerised, can be sintered or fused layer by layer obtaining a final part. The versatility of the approach is remarkable.

7.5 Main Conclusions and Future Research

During their development, biological systems have to continuously work with a limited amount of energy, and, therefore, their own materials and structures are built trying to maximise the resistance-weight relationship, which leads to finally obtaining porous or hollow materials and structures. The design of prostheses, following biomimetic principles, can also benefit from geometries similar to those employed by biological organisms, and providing design procedures and resources with such biomimetic objective in mind is highly relevant.

Metamaterials based on porous and lattice structures can be tailored ad hoc for final applications linked to the development of novel products with special features, including precise control of density, Young modulus and Poisson ratio (even with negative values by using auxetic structures). Such property control results very adequate for designing prostheses with mechanical features adapted to those of human body, in order to limit negative phenomena like stress shielding and bone resorption as well as to benefit from improved mechanical features and reduced weight.

This chapter has provided examples of both approaches, linked to prostheses design and tissue engineering, compared the advantages and disadvantages of porous, lattice and auxetic structures and discussed main additional resources for simplifying the whole process.

Production of these complex porous, hollow and lattice structures has been also discussed, as it has not been possible until just a couple of decades ago. Novel advances on "layer by layer" or "additive manufacturing technologies" can be used for its automated production, as has also been discussed and is additionally explained in forthcoming chapters.

The case studies provided, linked to hip prostheses, annuloplasty rings and expandable stents, cover applications linked to soft and hard tissue replacement and give some indications linked to the use of metamaterials for obtaining improved relationship between stiffness and for helping with recent surgical advances linked to minimally invasive procedures.

More recent research has also been linked to obtaining pentamodes or fluidlike solid structures (based on the periodic repetition of a special cell unit, being thus metamaterials) (Kadic et al. 2012), whose applications in the bioengineering field should be further studied.

High-precision additive manufacturing technologies, including direct laser writing or 3D nanolithography (i.e. NanoScribe GmbH), are already providing excellent results, when obtaining metamaterials with unit cells sizes even below 1 μm^3 and features (wall thicknesses, diameter of trusses, etc.) in the range of 100 nm, what will prove especially beneficial in applications aimed at interacting at a cellular level, mainly in the fields of tissue engineering and biofabrication.

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Chapter 8
Computer-Aided Engineering Resources and FEM for Biodevices

Andrés Díaz Lantada

Abstract Computer-aided engineering (CAE) refers to the general use of software to aid in engineering tasks, in its broadest sense even including computer-aided design and computer-aided manufacturing; although in product design, CAD is perceived as the starting point for designing a part, CAE involves the simulations carried out upon a CAD part in order to verify geometries and materials, and CAM is linked to the simulations realized upon a CAD part to prepare manufacturing processes and to the automated control of machine tools during production.

Although CAE can involve the use of all kinds of software and computer-aided calculations, in product development and linked to computer-aided design, such calculations are normally carried out by application of the finite element method (FEM), whose generalization in the final decades of the twentieth century has been essential for promoting the incorporation of CAE analysis tools together with CAD software packages.

Such method allows solving complex engineering problems by using a mesh discretization of a continuous domain into a set of discrete elements (connected by nodes) and by transforming initial partial differential equations as well as integral equations into an approximate system of ordinary differential equations (forced to be valid in the nodes) for final numerical integration. This method is especially well suited for solving partial differential equations over complicated domain or geometries, when the domain changes during the whole simulation, when the desired precision varies over the system under study, or when the solution lacks smoothness.

This chapter provides an overall introduction to the possibilities of CAE tools and gives several examples of FEM simulations of different phenomena (including mechanic, dynamic, thermal, and fluidic cases) for studying its effects on organs and biostructures, medical appliances and biodevices in general, as well as the interactions between implants and organism.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_8,

8.1 Introduction to Computer-Aided Engineering (CAE) and to the Finite Element Method (FEM)

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The foundations of the FEM method are out of the scope of present handbook and are well detailed in pioneer works elsewhere (Zienkiewicz et al. 2005). Being a matrix-based calculation method, it is very adequate for programming, and most engineers using FEM simulations resort to commercial software; although for research tasks, it is also common that researchers themselves develop ad hoc programs for their particular problems. In any case, through present handbook, we will be using NX-8.0 (Siemens PLM Solutions) for design and FEM-based simulation tasks.

When using software resources for FEM-based simulations, it is necessary to understand the working methodology, divided into preprocessing, analysis, and post-processing, as detailed below:

Preprocessing. Is the stage focused on preparing the model, normally starting from a previous CAD geometry. During this stage, the geometry is discretized into elements and nodes (meshing), and the material and physical properties, as well as the loads and boundary conditions, are applied.

Analysis solver. Is the real computational stage, oriented to verifying the prepared model and to developing the calculations (frequently iterative) and finally storing the results from stresses, strains, displacements, temperatures, flows, velocities….

Post-processing. Allows users to represent and study the solutions obtained, which are normally represented upon the geometries of interest in form of colormaps, each color showing a different level of stress, strain, displacement, flow, temperature, velocity, among other results.

It is very relevant to note that "red" colors do not mean that a part is breaking and "green" colors do not mean that a part is properly prepared for service. The colormaps are just visual helps, and the actual values, for instance, of stress have to be adequately compared to the values the material is capable to resist, so as to verify which part is prone to failure in such simulated conditions, simulations which must be somehow validated or verified.

Therefore, it is always very advisable to have a preliminary estimation of final simulation results, possibly carried out analytically using simplified geometries, so as to help verification during the post-processing stage (Díaz Lantada and Lafont Morgado 2012).

Further detailed validation of simulation results, with the help of real trials carried out using rapid prototypes and different characterization resources, is an excellent way of increasing our confidence in simulation results and of helping with optimization tasks.

It is also very necessary to note the importance of using a coherent units system during the preprocessing stage, so that calculation leads to adequate results. In many cases, when the post-processing stage represents "impossible" results, the actual cause is linked to an incorrect use of units.

In the last decades, thanks to the progressive advances on CAD tools and to the continuous incorporation of novel simulation features for helping designers, many CAD–CAE software offer very comprehensive FEM-based resources for studying different physical fields (Lorenzo Yustos et al. 2010), as detailed in the following section.

8.2 Conventional CAE Software Modules and Tools

The different modules of conventional CAE software are oriented to solving the most typical problems of engineering, normally linked to evaluating the mechanical performance of a system, thermal, and fluidic phenomena that may occur during service life, failure prevention, and overall optimization.

Stress calculation modules are the most used for solving static problems, as loads (forces, pressures, accelerations) and boundary conditions (clamped, fixed displacements, fixed rotations) can be defined and final results provide information on stress

and strain fields, displacements, and even security factors if materials yield strength is defined properly.

Dynamic response calculations are also possible, as most FEM-based simulation software include modules for studying natural vibration modes and related frequencies of parts and structures, so as to analyze which kinds of cyclic loads may promote resonance phenomena and improve service life of structures and mechanical systems.

Thermal phenomena can also be studied with the help of the finite element method, what is highly useful for analyzing the in-service behavior of mechanical systems and structures and predicting the steady-state temperature field they can develop, due to the heat coming from motors, installations, inner or outer phenomena, fluids and other systems from the environment… as well as the transitory evolutions of such heatings. Heat transmission through conduction, convection, and radiation can be analyzed and normal results are temperature fields and thermal fluxes. The temperature maps obtained can be also connected to mechanical simulation modules, so as to analyze the mechanical effects of temperature changes.

Fluid simulations generally allow obtaining velocity fields, pressure fields, and convection coefficients along a system, from previously defined inlet and outlet fluids entering and exiting the control volume. Coupled thermal–fluid simulations can also be carried out. Normally these modules help also to optimize geometries by realizing aerodynamic/hydrodynamic-related considerations.

Other more specific modules include impact and fatigue calculations, for assessing part life and unexpected phenomena; topological optimization tools, for optimizing geometries; electromagnetic simulations, more linked to telecommunications and electronics; and some additional resources focused on micro- and nanotechnologies. Figure 8.1 shows a couple of examples of mechanical and thermal simulations of different mechanical components, including a beam, a gear, a rod, a prosthesis, an injection molds, and a microprocessor on an electronic plate.

8.3 Simulating the Behavior of Artificial Prostheses

In biomedical engineering, the use of FEM-based simulations helps greatly along the completed product development process, for analyzing different physical phenomena and interactions. Normally there are three main application fields of FEM in biomedical engineering, covered, respectively, in Sects. 8.3–8.5.

First of all, FEM-based simulations are used to assess in silico the performance of medical devices, especially artificial prostheses, so as to validate or optimize the CAD design. Secondly, FEM-based simulations are used to study the behavior of organs and biological structures, so as to increase our knowledge about how different mechanical, thermal, or fluidic phenomena affect them, aiming also at the discovery of novel diagnostic or therapeutic alternatives. Finally FEM-based simulations are very useful to analyze the interaction between prostheses and living tissues, so as to predict their effects on patients once implanted. We aim to provide

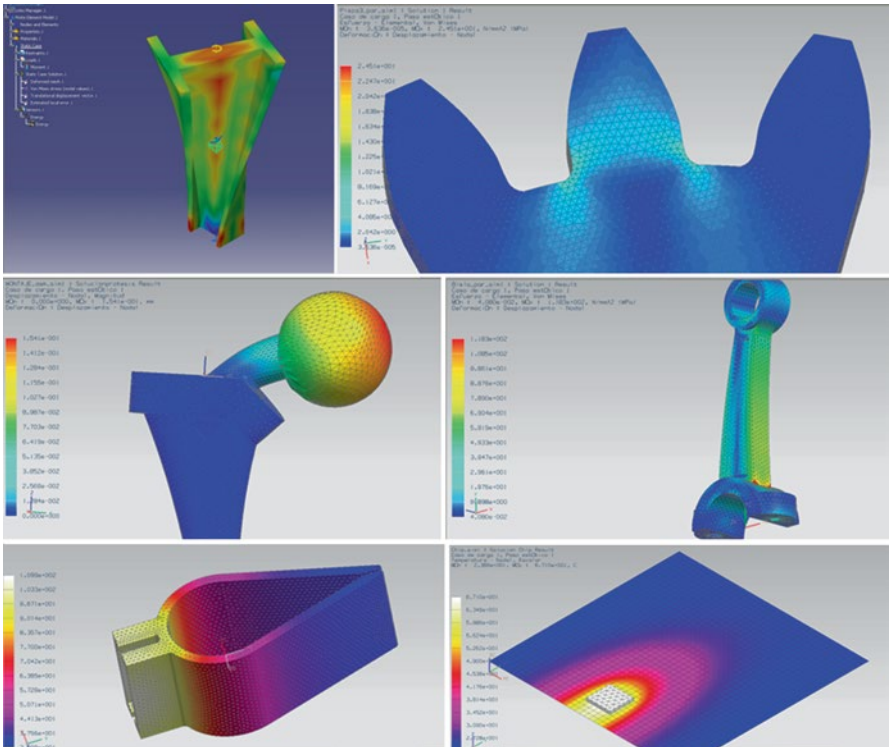

Fig. 8.1 Examples of static, dynamic and thermal simulations

some representative examples of these applications in present and forthcoming sections, hoping they may be of help for researchers beginning to tackle similar questions.

8.3.1 Case Study: Mechanical Static Behavior of Knee Prosthesis

Knee replacement, or knee arthroplasty, is a surgical procedure to replace the weight-bearing surfaces of the knee joint, so as to relieve the pain and disability of osteoarthritis. It may also be performed for other knee diseases including rheumatoid arthritis and psoriatic arthritis. In patients with severe deformity from very advanced rheumatoid arthritis, trauma, or long standing osteoarthritis, the surgery may be more complicated and risky. On the other hand, osteoporosis does not typically cause such severe knee pain, deformity, or inflammations and is not a reason to perform knee replacement. Other major causes of debilitating pain include meniscus wear and tears, cartilage defects, and ligament damage.

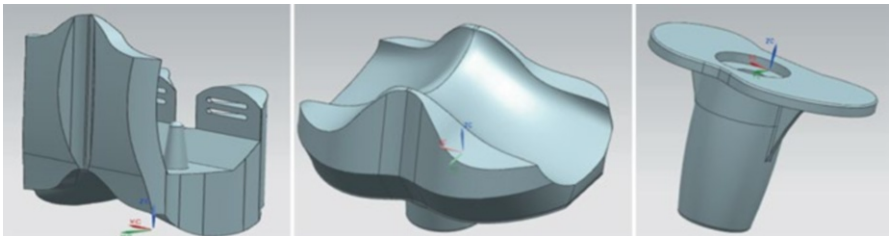

Fig. 8.2 CAD design of knee prosthesis: femoral component, sliding plate, and tibial component (Design by P. Gómez based on patent WO2010/001010 A1)

Knee replacement surgery can be performed as a partial or a total knee replacement. In general, the surgery consists of replacing the diseased or damaged joint surfaces of the knee with metal and plastic components shaped to allow continued motion of the knee. The use of FEM-based simulations can help to optimize the designs of knee prostheses, as detailed below.

Figure 8.2 shows the CAD design of knee prosthesis, including the femoral component, the sliding plate, and the tibial component, as designed by P. Gómez, within UPM bioengineering subject (please see Chap. 18), based on patent WO2010/001010 A1. Figure 8.3 shows the results from FEM simulation of the tibial component of such knee prosthesis under load: 10-node tetrahedrons have been used for meshing; Ti-alloy has been selected as material; upper surface has been loaded with 1,200 N, a typical value used in assessment of prosthesis performance; and lower surface has been fixed, as boundary condition. The stress field included shows a maximum value of around 80 MPa, meaning that the prosthesis withstands the applied load adequately.

8.3.2 Case Study: Mechanical Dynamic Behavior of Artificial Hip Prosthesis

Just as a brief revision, hip replacement is a surgical procedure in which the hip of the patient is replaced by a prosthetic hip. Such joint replacement orthopaedic surgery is generally conducted to relieve arthritis and related pain or to fix severe physical joint damage as part of hip fracture treatment. A total hip replacement (total hip arthroplasty) consists of replacing both the acetabulum and the femoral head, while hemi-(or half) arthroplasty generally only replaces the femoral head.

The prosthesis used in hip replacement consists of different parts, the acetabular cup, the femoral component, in which this case study focuses, and the articular interface. The femoral component is designed to fit in the femur, normally by removing a part of the bone and shaping the remaining part to accept the prosthetic component. There are two main types of femoral components: cemented, based on adhesive fixation between prosthesis and bone, and uncemented, based on friction

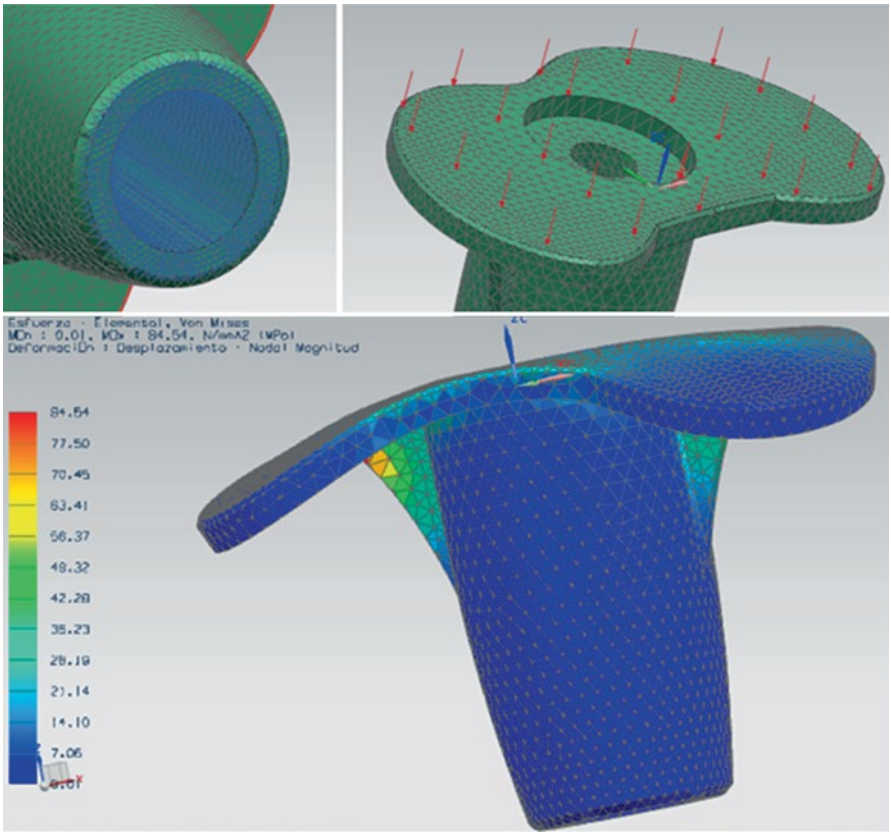

Fig. 8.3 FEM simulation of knee prosthesis under load. Boundary conditions, loads applied, and stress result

for promoting stability. Final prosthesis type selection depends on several factors, including age of the patient, mechanical strength of the bone, as assessed with the help of medical imaging, life expectancy, among others.

Previous case study was linked to a static structural analysis on a knee prosthesis, while this case study is aimed at showing other alternatives of FEM-based mechanical analyses, such as the study of vibration mode shapes, and related frequencies. We use as starting point the CAD design of the personalized hip prosthesis from Sect. 5.4 (see Figs. 5.4 and 5.5), obtained by using the information from medical imaging (Osuna 2008; Ojeda 2009). Prosthesis has been meshed using 10-node tetrahedron elements and Ti-alloy has been used as material. No loads or boundary conditions have been applied as we carry out this preliminary approach focusing on the natural vibration modes and frequencies of the free structure.

Figure 8.4 shows FEM simulation results, including the shapes of the first four modes for the personalized hip prosthesis, which appear at frequencies of 1,380, 2,330, 4,200, and 6,440 Hz, respectively, corresponding to different bending modes.

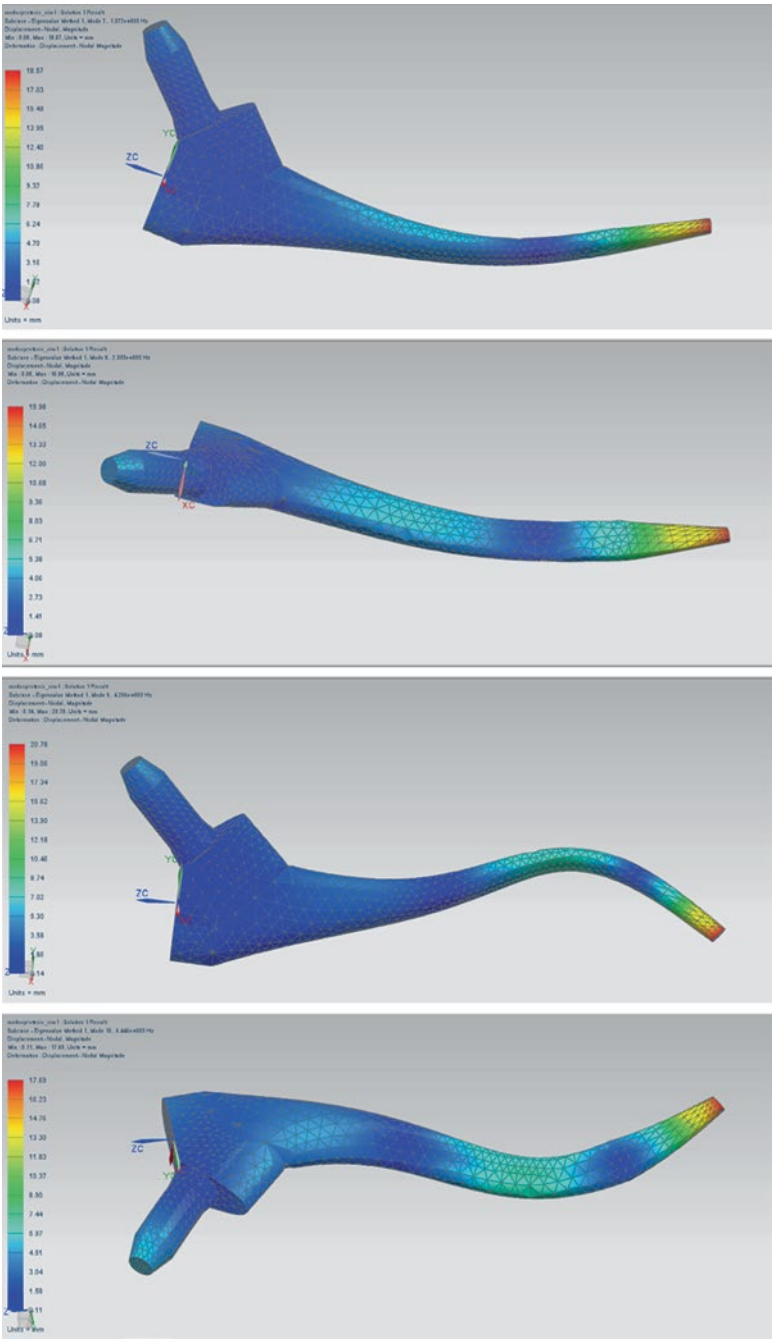

Fig. 8.4 FEM simulation of natural vibration modes of hip prosthesis

From the design perspective, it is interesting to understand that cyclic loads applied to the patient, with frequencies near to the natural frequencies of corporal structures (or related prostheses), may produce resonance phenomena and increase wear rate, disturb, and, in the case of implants, produce their loosening or disadjustment. In this case, such high frequencies show that the prosthesis would not suffer any special dynamic problem; as in conventional activities, cyclic loads do not reach such frequencies. In fact only if driving super motorbikes would it be perhaps possible to reach such high frequencies, so static calculations would be sufficient. More complete studies can also focus on the interaction between prosthesis and bone and on the possible effects of cement (in cemented prosthesis) on final response to vibrations (Tan et al. 2004). Normally cement will be more elastic than the prosthesis, and, consequently, final natural frequencies of the set bone–cement–prosthesis can be much lower than the values provided in Fig. 8.4 and even promote some undesirable vibratory phenomena when driving car or seating in a bus, what must be considered from the design stage.

8.3.3 Case Study: Mechanical Behavior of Scaffold for Tissue Repair

As already detailed, a key element involved in tissue engineering processes is the matrix or scaffold which serves as substrate or framework for cell growth, aggregation, and tissue formation. These scaffolds must be porous so as to allow cell migration during the colonization process as well as the transport of nutrients and waste to and from cells, but they have to be also resistant enough to withstand possible mechanical demands and long-term stresses, especially if final implantation is desired.

Aspects such as porosity, pore size, and surface micro-texture promote cell adherence, migration, and proliferation within the scaffold, for subsequent differentiation into relevant cell types. Thus, the scaffold plays a fundamental role in most tissue engineering strategies.

In addition mechanical stability of the scaffold is critical, as porous structures tend to be more fragile and as adequately mimicking the related tissue stiffness is essential for promoting the desired cell differentiation into expected tissue. The use of FEM simulations for analyzing if a porous material, with potential of being used as a scaffold, might provide a satisfactory solution, depending also on the organ or biostructure to replace, is very remarkable.

The case study here provided is linked to the in silico assessment of poly(HIPE) foams as scaffolding material. Poly(HIPE)s (HIPE meaning high internal phase emulsion) are open-cell or closed-cell foams, and they are used as scaffolds in tissue engineering due to its high porosity. Poly(HIPE)s are usually synthesized through free radical polymerization, and they include both hydrophobic polymers

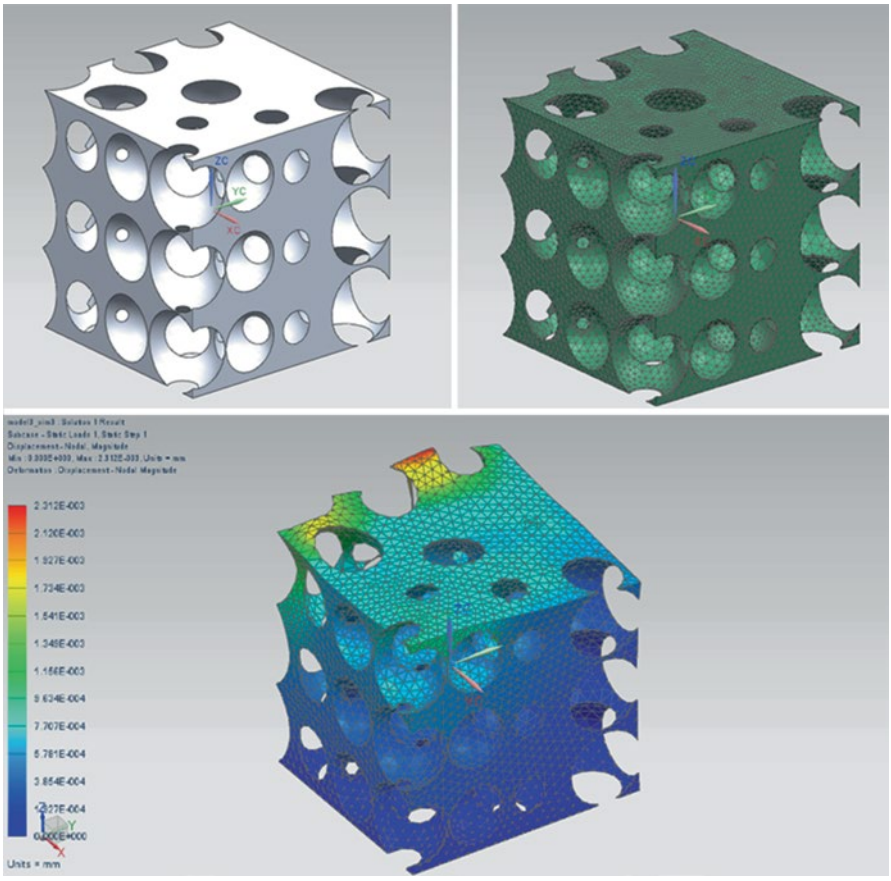

Fig. 8.5 FEM simulation of scaffold (polyHIPE) for tissue engineering

synthesized within water-in-oil (W/O) emulsions and hydrophilic polymers synthesized within oil-in-water (O/W) emulsions.

The preparation of the poly(HIPE)s is performed with the curing of the HIPEs and the subsequent washing and drying. At first polystyrene and another nondegradable materials were used in the preparation of the polyHIPEs, but nowadays poly(lactic acid) (PLA) or polycaprolactone (PCL) are more used, which are biodegradable. Additional information about the synthesis, processing, and characterization can be found elsewhere (Fernández Cid 2012).

Figure 8.5 represents a computer-aided design of a porous structure trying to mimic that of a porous polymer, the FEM model developed, and the results from a traction trial, so as to compare simulation results with those obtained in the working bench (Fernández Cid 2012).

The porous structure designed includes pores from 30 to 100 μm distributed randomly. Again 10-node tetrahedron elements with a characteristic size of around

5 μm were used, lower surface of the material was fixed, and upper surface was submitted to progressively increasing loads, so as to reach 0.8–1 MPa of simulated stress in the inner features of the poly(HIPE). As characterized yield strength is around 1 MPa, higher load values would produce failure, and the material would begin to behave nonlinearly.

Simulation results shown in Fig. 8.5, the displacement field, which together with part dimensions and load applied, allow for the final calculation of the equivalent Young modulus of the poly(HIPE), providing a value of $E \approx 200$ MPa, similar to the value obtained in the trials, so the designed CAD unit cell is validated as a representative geometry for simulating poly(HIPE)s.

However, it is also a fact that the pore distribution of the cell provided in Fig. 8.4 is not as homogeneous as that from the original material. Currently we are concentrating on using fractal spheres for obtaining more adequate results (forthcoming Master Thesis of B. Pareja Sánchez, UPM).

8.3.4 Case Study: Mechanical Behavior of Active Prostheses

A very special feature of FEM simulations is the possibility of studying different parts simultaneously and of simulating their interactions, for example, the different components of a machine, the different subsystems and components of a prosthesis…, just by defining the adequate contact (in mechanical simulations) or coupling (in thermal simulations) boundary conditions.

The linkage with CAD resources is especially useful, as complex assemblies including different parts and constraints can be directly imported to the CAE FEM-based simulation module and the application of boundary conditions is sometimes automated.

In biomedical engineering, the possibility of simultaneously analyzing the interactions between different geometries is very relevant, both for studying the effects of prostheses on corporal tissues (as Sect. 8.5 details) and also for evaluating the design of active implantable devices, in which an active component typically forces the displacement of other parts of the implant for adapting them to the surrounding tissues.

For instance, the design of a compressed stent mounted on a balloon and FEM-based simulations of the effects of inflating the balloon and the consequent stent expansion to the desired implanted diameter have already provided results similar to those obtained in vivo (Díaz Lantada 2012).

In a similar way, the effect of the balloon on the adaptation of Amplatzer devices, for treating atrial and ventricular septal defects (St Jude Medical) and B-shaped stents, a coronary sinus implanted stent more adequate for patients with refractory angina who are not candidates for conventional revascularization procedures (Banai et al. 2007, Neovasc Ltd.), is also possible.

The case study exposed further on is precisely linked to the simulation of a B-shape stent, although the geometry and boundary conditions applied can be easily changed to simulate and Amplatzer device.

Figure 8.6 shows the FEM model of the B-shaped stent originally mounted on the balloon in a reduced geometry. Both the balloon and the stent have been meshed using 10-node tetrahedron elements; boundary conditions fix the radial displacements of the extremes and central part of the stent and define the contact between outer part of the balloon and inner part of the stent; applied load is just a pressure inside the balloon, with increasing values, so as to analyze the most adequate inflation pressure.

Results from simulations show an adequate 14 mm radial displacement of the balloon, and the stent and stress results provide a maximum stress of 0,2 MPa for the balloon and of 0,1 MPa for the stent, so the prosthesis design can be considered adequate, even though in vitro trials with prototypes should be carried out for additional validation.

Including in the CAD design, the coronary sinus would also help to simulate the final effects of implant on the surrounding tissue and would be interesting indeed, even though simulation time, due to the incorporation of additional contact boundary conditions, would surely increase importantly.

8.4 Simulating the Behavior of Corporal Geometries and Tissues

Medical imaging technologies, together with CAD-linked software, for the virtual reconstruction of corporal geometries, organs, and structures, are a great help for biomedical designers, as prostheses can be personalized.

They also constitute a continuous source of information and inspiration for researchers linked to the fields of biomechanics and physiology, as they provide in silico replicas of complex biological systems, whose feature can be analyzed in depth by a repeated use of FEM-based simulations, as some case studies provided here try to highlight.

8.4.1 Case Study: Mechanical Simulation of an Aneurysm

An aneurysm (from Greek *aneurusma* or dilation) is a localized blood-filled balloon-like bulge in the wall of a blood vessel. Aneurysms can commonly appear in arteries at the base of the brain (the circle of Willis) and in the aorta, the main artery carrying blood from the left ventricle of the heart. When the size of an aneurysm increases, there is a significant risk of rupture, resulting in severe hemorrhage, other

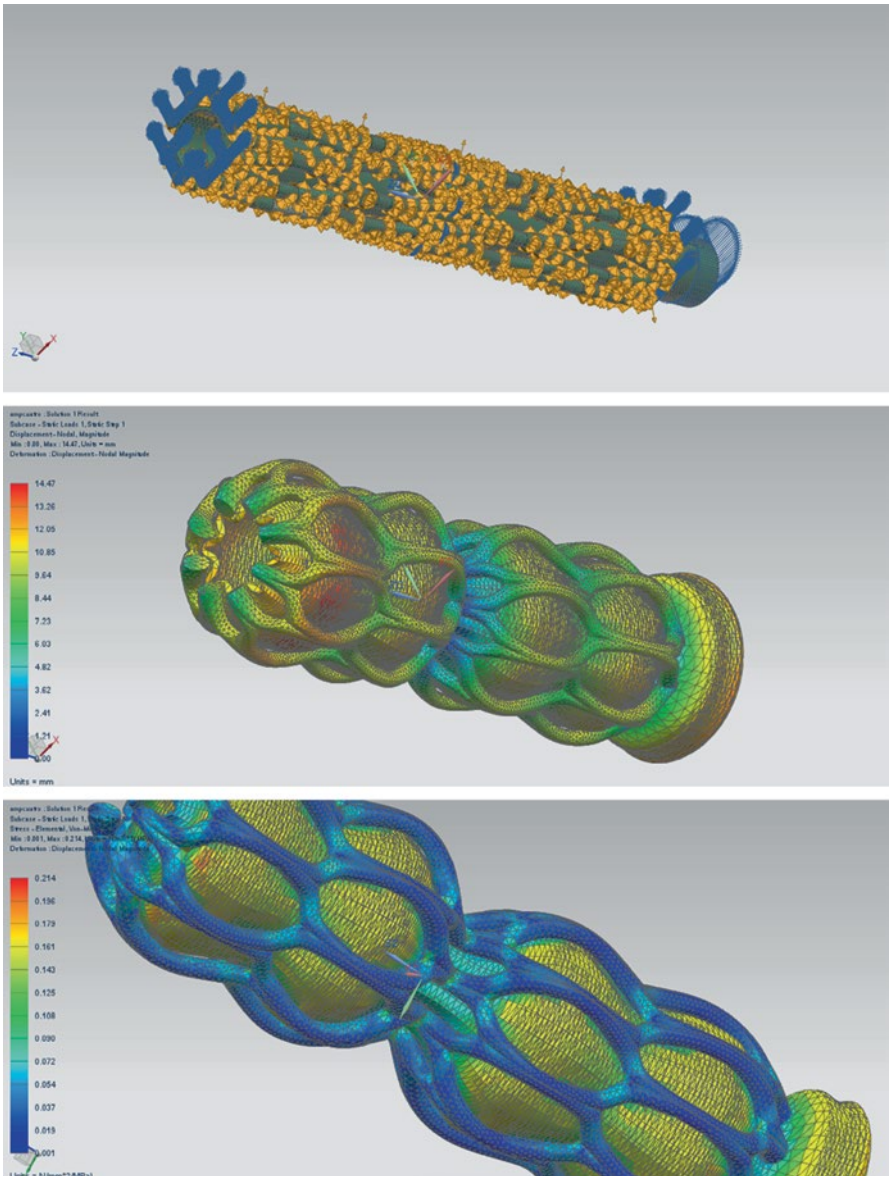

Fig. 8.6 FEM simulation of B-shape stent for coronary sinus. Loads and boundary conditions, displacements, and stress results

complications, or death. Aneurysms can be hereditary or caused by disease, both of which cause the wall of the blood vessel to weaken, as we simulate further on.

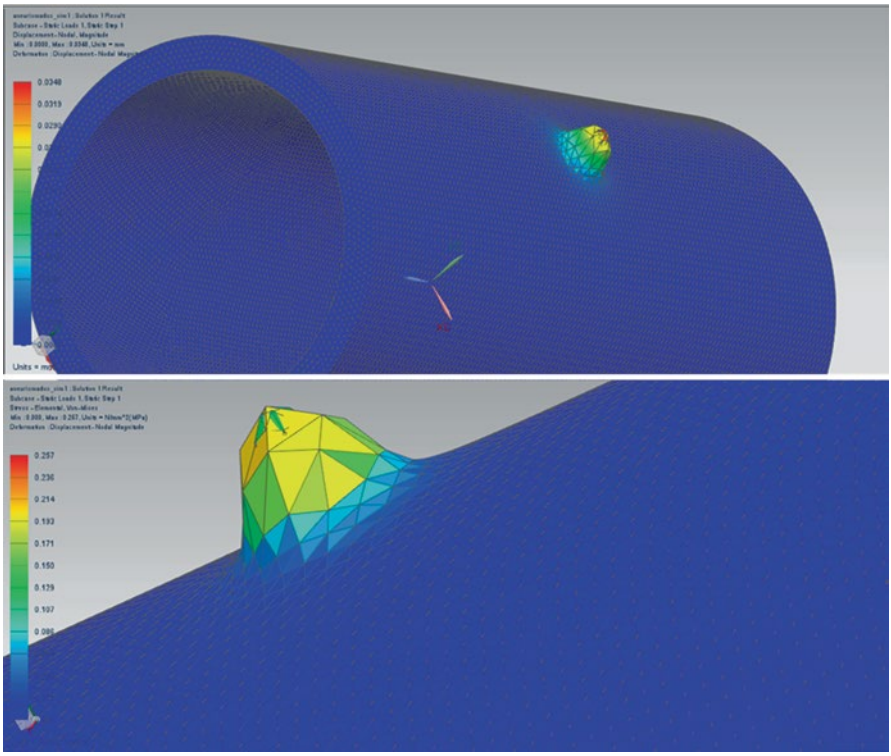

Fig. 8.7 FEM simulation of aneurysm formation. Displacements and stress results

Intracranial aneurisms are typically treated by clipping or endovascular coiling, while for aortic aneurisms bypassing the weaken section of the artery with a graft or using a stent are the common solutions.

Once diagnosed, the patient is commonly given date for surgery, depending on the existing waiting list and on the possibility of rupture in the short term. FEM-based simulations can support diagnoses and help to detect those cases with high risk of rupture, so as to force urgent surgical measures be taken. From the medical images, it is easy to reconstruct the aneurysm geometry and to analyze the stress and strains, to which the surrounding tissues are being submitted.

The study carried out here, whose results are shown in Fig. 8.7, is based on a portion of cylindrical artery designed with CAD, in which inner wall, a reduced conical feature, has been subtracted, so as to reduce wall thickness in a localized place. Ten-node tetrahedron elements have been used for meshing; the extremes of the artery have been fixed; and an inner systolic pressure of 120 mmHg has been applied.

Simulation results show a deformed structure (scaled) very similar to that from real aneurysms when they are beginning to expand, with maximum radial

displacement of 0,05 mm and maximum stress of 0,25 MPa. Such displacement and stress values are of course not critical, as critical values can even reach values of 5–20 cm and yield strength of arterial tissue is around 30 MPa, so in this case, thickness is still sufficient. The effect of further reducing wall thickness could be additionally analyzed.

More precise simulations should consider the three layers of the artery wall (intima, media, and adventitia), as well as their mechanical characteristics and aspects such as stress rigidization of corporal tissues.

8.4.2 Case Study: Mechanical Dynamic Behavior in Femur

In a similar way as that related for the femoral component of the artificial hip prosthesis studied in Sect. 8.3.2, we concentrate here on the femur itself, so as to analyze possible undesired vibratory effects, due to the loss of stiffness produced during surgery by cutting its head.

We use as starting point the CAD design of the femur from Sect. 5.4, reconstructed from medical imaging information (Fig. 5.5). The femur has been meshed using 10-node tetrahedron elements and bone (11 GPa) has been used as material. No loads or boundary conditions have been applied as we carry out this preliminary approach focusing on the natural vibration modes and frequencies of the free structure. Figure 8.8 shows FEM simulation results, including the shapes of the first four modes for the femur, which appear at frequencies of 1,700, 2,460, 4,290, and 4,600 Hz, respectively, corresponding to different bending and torsion modes. Again the values are high for conventional cyclic loads, and therefore most relevant calculations can be carried out statically.

8.4.3 Case Study: Vibratory Phenomena in Senses, Effects on Sight, and Hearing

FEM-based simulations are also proving to be a very appropriate resource for further learning the properties and behavior of our senses, including sight and hearing, as well as for producing improved solutions for their treatment, as the simulation of the related organs (eye and inner ear) and of the effects of associated prostheses also helps with the design of novel devices (treatment of glaucoma, eardrum replacement…).

Here we present two simplified cases of study linked to studying vibratory effects on the eye and on the eardrum.

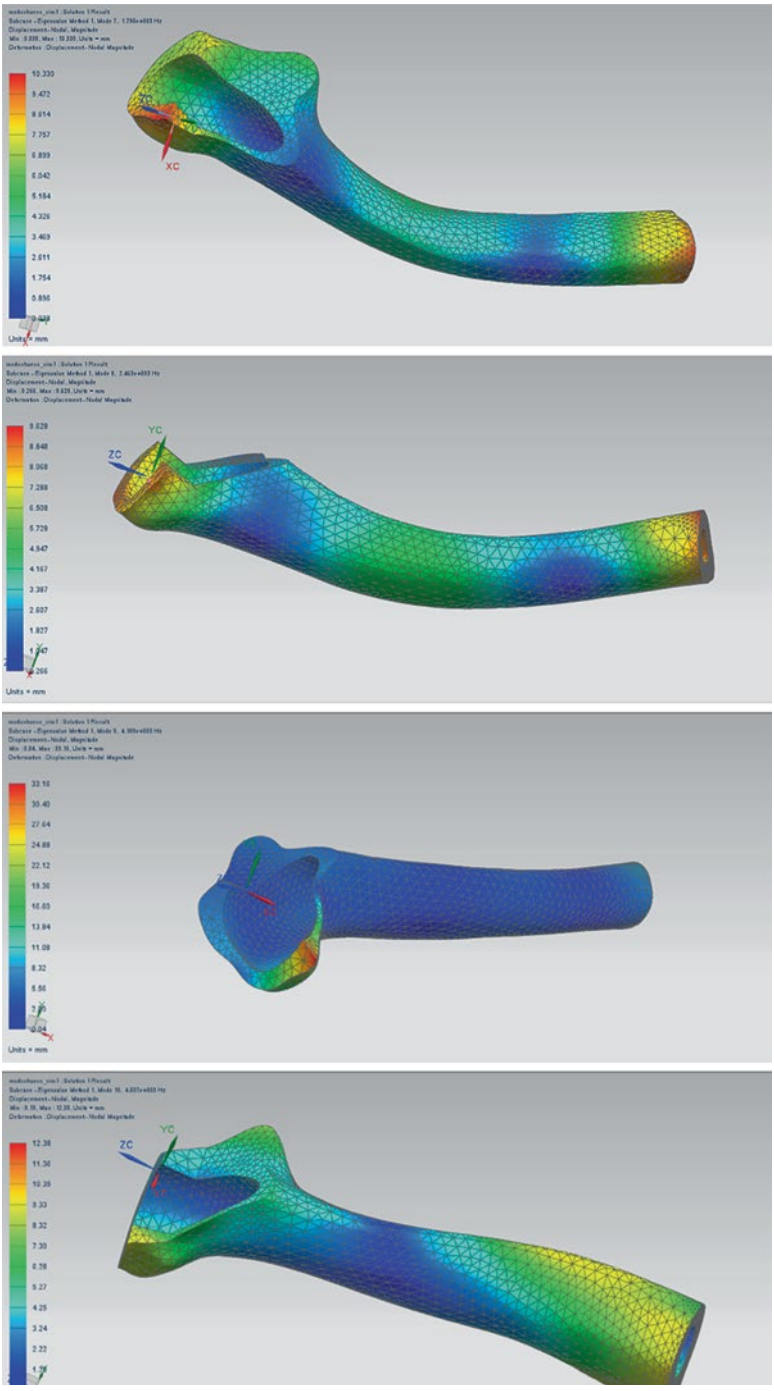

Fig. 8.8 FEM simulation of natural vibration modes of a femur

8.4.3.1 Vibratory Effects on the Eye

Figure 8.9 shows a structure representing ocular globe and four main muscles responsible for its motion. The globe is represented by an outer more rigid part (cornea) simulated with a Young modulus of 0,6 MPa and an inner sphere much more viscous and soft simulated with a Young modulus of 0,01 MPa, while the muscles have been simulated with a Young modulus of 0,1 MPa. Ten-node tetrahedron elements have been used for meshing; contact boundary conditions have been applied to the contact cornea muscles and cornea viscous inner part; and the extreme part of the muscles has been fixed.

After solving the results show the first nine natural vibration modes and related frequencies, with values starting at around 6–8 Hz for the first modes and with several resonant values just around 40 Hz, a value typically considered when designing seats for cars and motorbikes, due to the negative effects that vibrations near 40 Hz produce on driver's sight.

8.4.3.2 Vibratory Effects on the Eardrum

Figure 8.10 represents a FEM model of an eardrum and simulation results for several vibration modes and related frequencies. It has been modeled as a 6 mm circumference (even though it is in fact a conic membrane), with a thickness of 120 μm and a Young modulus of 30 MPa.

We have chosen representative values of geometry and mechanical properties, taken from mechanical characterization and values used in FEM simulations from previous research (Nakao 2000; Fay et al. 2006; Lu et al. 2007). The simulations detailed here are based on some simplified assumptions (circular membrane, instead of conic; constant Young modulus, instead including tensional rigidization; constant Young modulus with frequency; homogeneous thickness), as we just want to provide a basic example and highlight some general aspects, which can indeed be perceived with approximate simulations. More precise simulations, requiring also more specific FEM tools, such as ANSYS, Comsol, Abaqus…, can be based on medical imaging combined with CAD–CAE tools (Coleman 2011).

According to simulations, first resonances already appear at a few hundreds of Hz. In fact, the model serves also to verify that at frequencies above 3 kHz, the tympanic membrane vibrates chaotically (Fay et al. 2006).

It seems that by having many resonances, the eardrum can transmit the broadest possible bandwidth of sound with optimal sensitivity. In essence, the eardrum works best through discord (Fay et al. 2006).

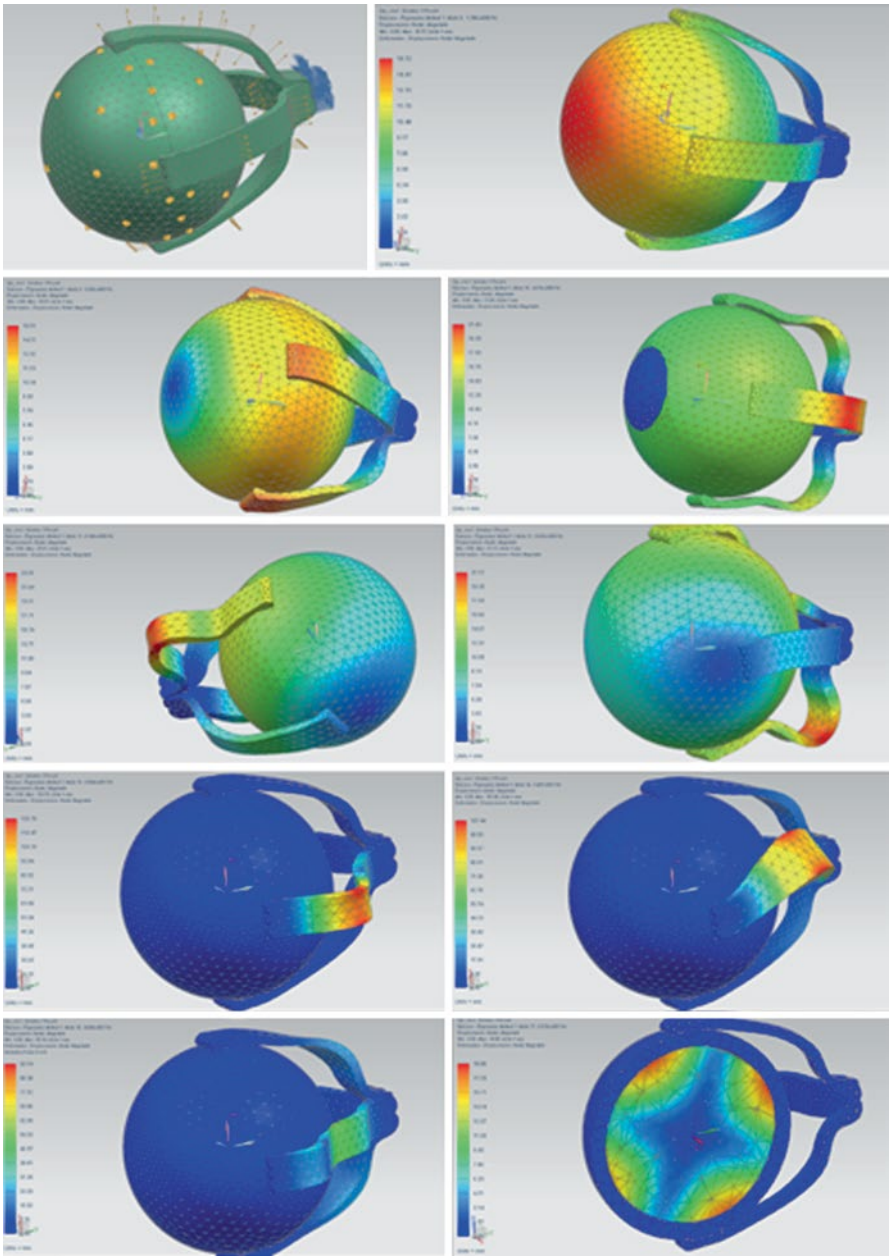

Fig. 8.9 FEM simulation of natural vibration modes of ocular structure

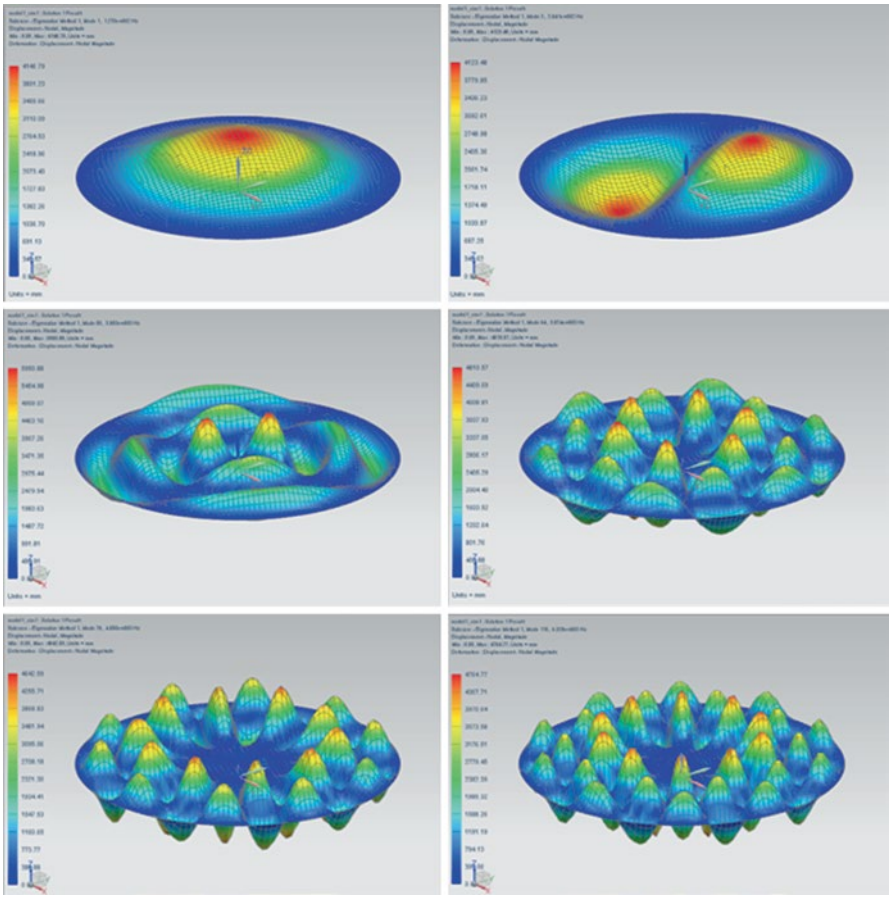

Fig. 8.10 FEM simulation of natural vibration modes of tympanic membrane

8.4.4 Case Study: Fluidic Behavior of Arterial Bifurcation

Fluid mechanics and its application to biology and medicine is also greatly supported by the use of FEM-based simulations, as related analytical equations involve complex terms, only in some cases with analytical solution.

Several biological systems benefit from being studied under such approaches, although in the case of human body, most direct application of fluidic FEM-based simulation is the study of cardiovascular flow and the effects of pathologies and implantable devices on deteriorating or improving such flow.

The case study shown in Fig. 8.11 is linked to an arterial bifurcation, which has been designed by using CAD resources and further simulated for obtaining velocity and pressure fields, as results from initially known inlet and outlet flows.

The computer-aided design of the arterial bifurcation is based in Murray's law, (Murray 1926a, b), which states that for "*n*" daughter branches arising from a common parent branch, the following relationship should be considered:

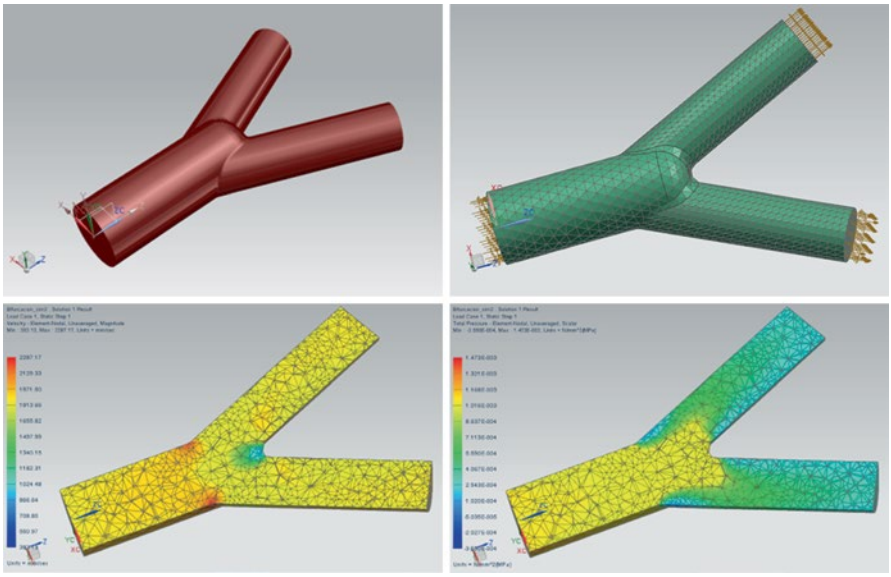

Fig. 8.11 FEM simulation of flow through arterial bifurcation. CAD model, FEM model with mesh, boundary conditions, velocity, and pressure results

$$R_p^{\ 3} = R_{d1}^{\ 3} + R_{d2}^{\ 3} + \quad + R_{dn}^{\ 3},$$

being R_p the radius of the parent branch and R_{di} the radii of the daughter branches from $i = 1 \ldots n$.

Other design alternatives for more bifurcations using parametric fractal models by Lindenmayer are also useful (Zamir 2001) and have been also used for computer-aided additive manufacture of biostructures, linked to the novel field of biofabrication (Yasar et al. 2007); see Chaps. 10 and 14 on additive manufacturing for medical devices and biofabrication.

The CAD design has been subsequently meshed using 10-node tetrahedron elements; a liquid with the viscosity and density of blood has been used; and inlet and outlet velocities of 2 m/s have been applied. Results from the simulation show a remarkable speed reduction near the bifurcation as well as an expected pressure reduction when the blood bifurcates.

Similar studies can be used to analyze the pressure reduction in aneurysms and the effect of atheroma layers, deposited on the wall, on the flow. Figure 8.12 shows again an arterial bifurcation but with an aneurysm and a deposition of atheroma, so as to detail the influence of such pathologies on blood flow and behavior.

Similar modeling and boundary conditions have been used and the model has been solved using the "flow" solver of NX-8.0. Results show lower pressures and velocities inside the aneurysm and behind the atheroma layer. The speed reduction is especially noteworthy in the case of the aneurysm, what constitutes a relevant

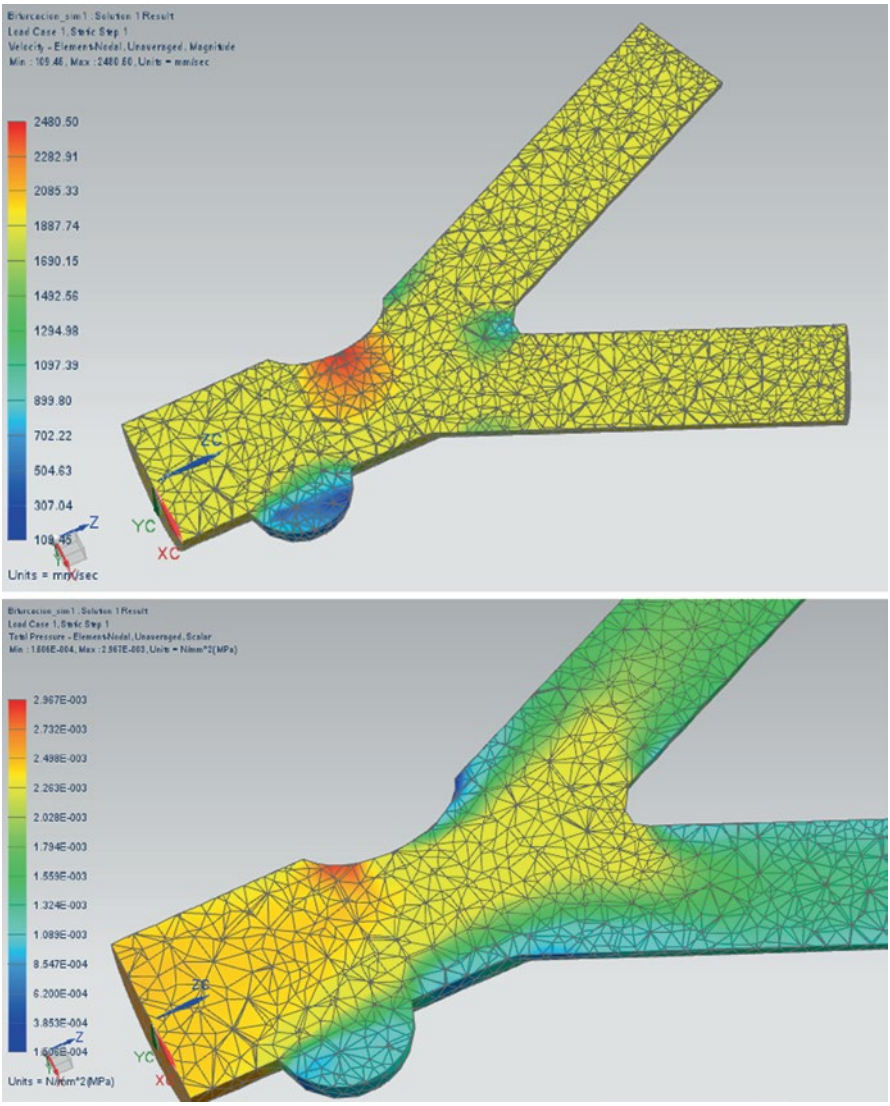

Fig. 8.12 FEM simulation of flow through stenotic arterial bifurcation with aneurysm. Velocity and pressure results

problem, due to the thixotropic behavior of blood, which tends to coagulate at lower velocities and to form thrombus, whose effects are dramatic.

Again these cases of study are just examples upon which more complex and detailed simulations can be constructed. In the field of fluid mechanics, it is relevant to cite other more specific FEM-based resources, such as Fluent (ANSYS-Fluent).

8.4.5 Case Study: Effects on Tissue Submitted to Thermal Ablation

Thermal simulations are also highly interesting, as some surgical procedures involve the application of high temperatures and some active implantable devices could potentially affect the temperature of surrounding tissues. Therefore, related thermal simulations can help with surgical planning and also with risk assessment of some specific active implantable devices (Díaz Lantada 2009).

Here we provide a case study linked to the thermal ablation of the mitral valve tissue, as an alternative way to annuloplasty (previously discussed in Chaps. 4 and 5), when trying to improve the mechanical stiffness of patient's muscular mitral valve annulus. Localized thermal ablation can lead to small areas of more stiff tissue, but the whole surgery has to be especially controlled, so as not to damage greater zones than expected. In this case, the steady state is not so important, what is indeed relevant to simulate is the transitory heating process, in order to obtain an idea of how long the activation of the device for thermal ablation should be applied.

The CAD structure resembling the left atrioventricular union has been taken from my Ph.D. thesis. It is a 2 mm width trunk cone and has been meshed using 10-node tetrahedron elements. Density is similar to that from soft tissue, a specific heat $c_p = 3{,}500$ J/(kg·K) (Huang and Wilber 2000) and a thermal conductivity $k = 0{,}6$ W(m·K) (Koncan et al. 2000) have been used. A heat convection coefficient $h = 500$ W/(m^2·K), for taking into account the heat transfer to the surrounding fluids at 37°C, has been considered.

In any case, it is important to note the complex measurement of heat convection coefficient in the surroundings from mitral valve. Several different values have been found in other research (Tangwongsan et al. 2004; Shah et al. 2006), so here we have just selected a mean value and simulation can initially just be considered as estimation. Only empirical results from in vitro/in vivo trials can help to further adjust such coefficients.

A localized heating load of 2 W has been applied to the zone of the mitral valve annulus. During the transitory heating, tissue should reach between 50 °C and 100 °C (Williams et al. 2002), and studying the transitory is indeed interesting, as it provides useful information for the surgical intervention (although prior to that adequate in vitro and in vivo trials in animal models should be made).

After solving, using the thermal flow solver from NX-8.0, post-processing (Fig. 8.13) provides temperature results for $t = 1$ s, $t = 5$ s, $t = 10$ s, and $t = 15$ s to assess and prepare the typical surgical treatment. In just 15 s, temperatures above 90 °C are reached, what is in consonance with results and advice from previous research (Huang and Wilber 2000).

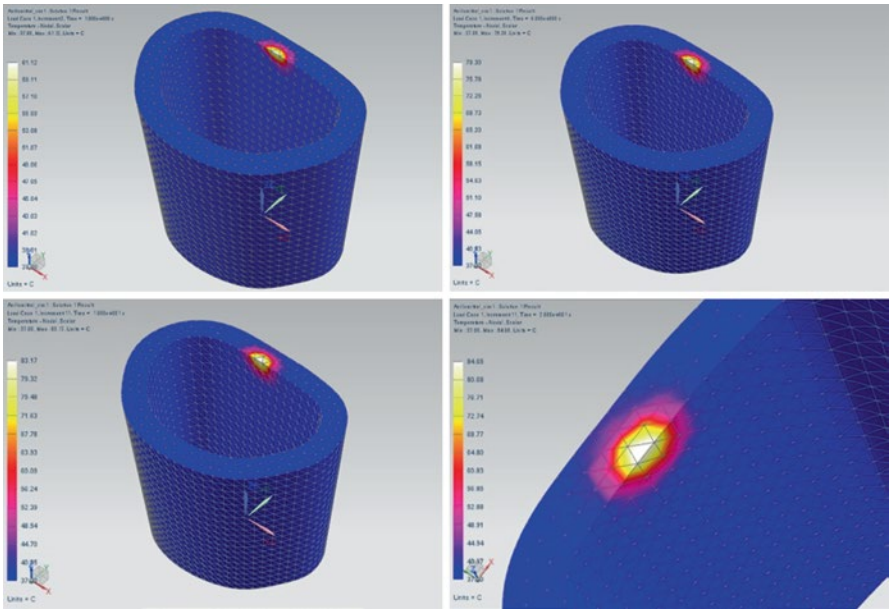

Fig. 8.13 FEM simulation of cardiac tissue heating during thermal ablation process for treating mitral valve insufficiency and different aneurysms. Temperature results for $t = 1$ s, $t = 5$ s, $t = 10$ s, and $t = 15$ s to assess and prepare the typical surgical treatment

8.5 Simulating the Interaction Between Prostheses and Biological Tissues

8.5.1 Case Study: Interaction Between Artificial Prosthesis and Hard Tissue

The prosthesis and femur already analyzed in Sects. 8.3.2 and 8.4.2 are now assembled and analyzed together under static loading. It is relevant to carry out this kind of studies, especially in the case of personalized prostheses, as in some cases, the remaining bones or biological structures can extremely suffer, when the prostheses are loaded. Also common is the stress-shielding phenomenon, based on the different stiffness between prosthesis and bone, which promotes nonuniform loading of the bone and resorption in the less-loaded parts (Ojeda Diaz et al. 2009).

Figure 8.14 shows the FEM model of the assembly, similar to previous ones, just including a contact boundary condition between bone and prosthesis and a load of 1,200 N. Results from displacements and stresses are also included. It is relevant to note that the contact between prosthesis and bone is not homogeneously loaded, which can promote stress shielding, even though the maximum stress of 80 MPa in the prosthesis and 30 MPa in the bone are, in principle, adequate.

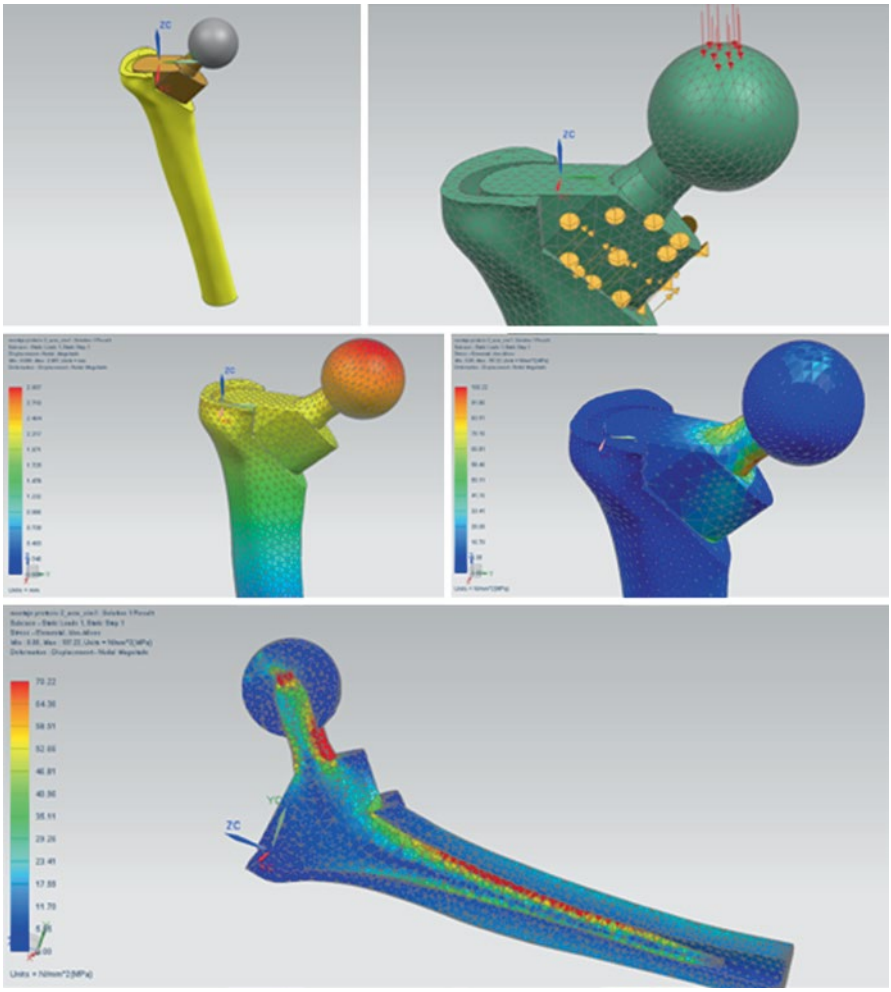

Fig. 8.14 FEM simulation of interaction between hip prosthesis and femur. Personalized CAD design, FEM model, displacement, and stress results

8.5.2 Case Study: Interaction Between Artificial Prosthesis and Soft Tissue

The interaction between soft tissues and prostheses can also be assessed by means of FEM-based simulations. Here we focus on assessing the mechanical performance of different designs of annuloplasty rings, which are loaded due to the effect of heart pumping and to the deformation of the cardiac tissue to which they are attached. It helps also to show in more detail the relevance of inserting such kind of prosthetic

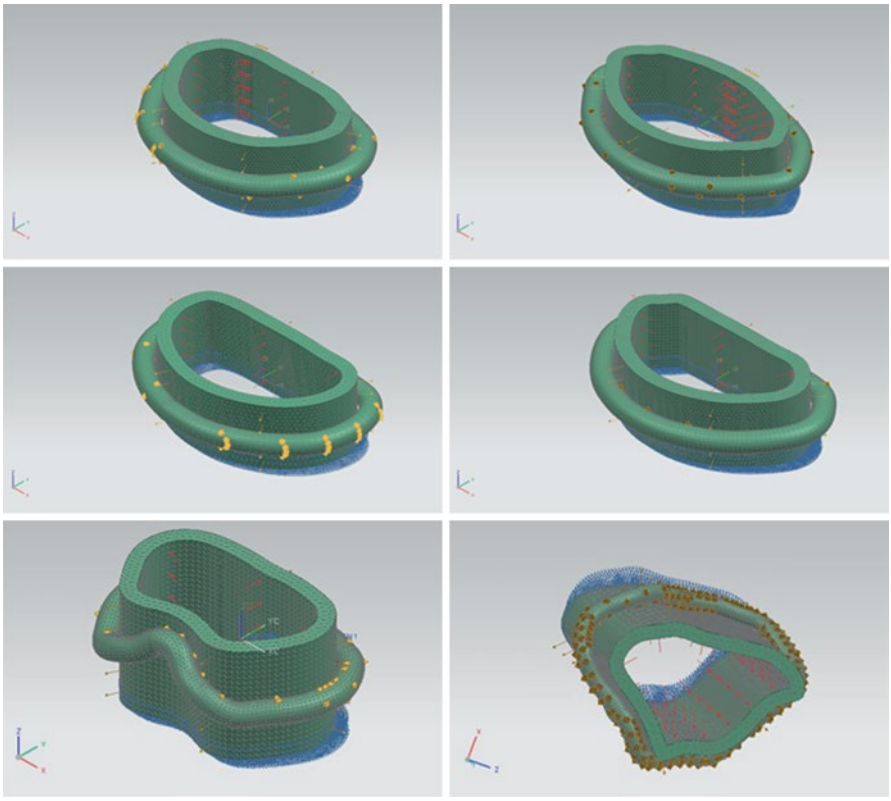

Fig. 8.15 FEM models of different annuloplasty rings attached to cardiac tissue for studying their mechanical performance

rings, for providing additional structural support to the typically loosened tissue of an insufficient mitral valve.

Figure 8.15 shows the different FEM models, using 10-node tetrahedron elements for meshing; 85 kPa as Young modulus for heart tissue (even though values from other research differ from 60 kPa to 1 MPa, Mirsky et al. 1974; Dagum et al. 2001; Choi and Zheng 2005); 1,750 MPa as Young modulus for the prosthetic ring; 120 mmHg as inner systolic pressure; and contact boundary conditions for simulating the union between rings and tissues. Lower part of the geometry representing the atrioventricular union is fixed, representing more rigid structures than the loosened mitral tissue in the case of insufficiency.

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After solving, post-processing results are shown in Fig. 8.16. The stress contours help to verify that the expansions of soft tissues are limited by the different rings, which become stressed. In the most critical parts of the different geometries, rings reach around 4 MPa, while yield strength is around 20 MPa, what helps to confirm the validity of the different designs, based on commercial ones, each of them

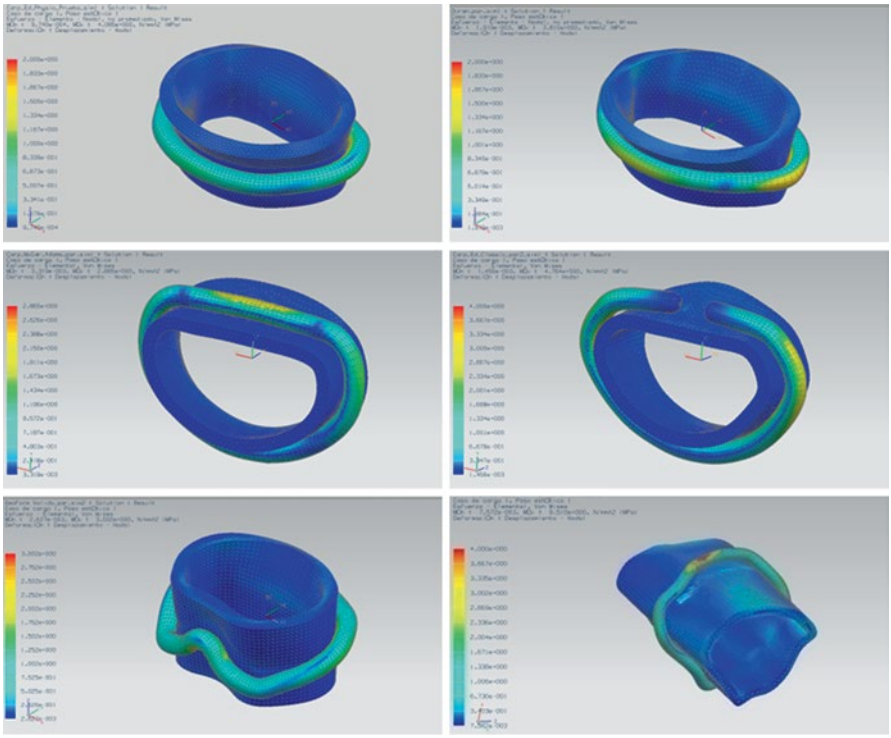

Fig. 8.16 FEM simulation of the mechanical performance of different annuloplasty rings during cardiac cycle: stress results

selected depending on patients' morphology and surgeons' personal tastes or experience (Díaz Lantada et al. 2010).

Even though each of the aforementioned case studies could cover at least a whole chapter and even a whole handbook, or even a book series, could be arranged focusing on FEM-based simulations for biomedical engineering, we hope to have provided here a brief summary of the possibilities for simulating the behavior of prostheses, of biological systems and tissues, and of the interactions between synthetic biodevices and biological structures.

8.6 Main Conclusions and Future Research

Computer-aided engineering (CAE), as already detailed, refers to the general use of software to aid in engineering tasks, in its broadest sense even including computer-aided design and computer-aided manufacturing; although in product design, CAD is perceived as the starting point for designing a part, CAE involves the simulations carried out upon a CAD part in order to verify geometries and materials, and CAM

is linked to the simulations realized upon a CAD part to prepare manufacturing processes and to the automated control of machine tools during production. Although CAE can involve the use of all kinds of software and computer-aided calculations, in product development and linked to computer-aided design, such calculations are normally carried out by application of the finite element method (FEM), whose generalization in the final decades of the twentieth century has been essential for promoting the incorporation of CAE analysis tools together with CAD software packages.

Such method allows solving complex engineering problems by using a mesh discretization of a continuous domain into a set of discrete elements (connected by nodes) and by transforming initial partial differential equations as well as integral equations, into an approximate system of ordinary differential equations (forced to be valid in the nodes) for final numerical integration. This method is especially well suited for solving partial differential equations over complicated domain or geometries, when the domain changes during the whole simulation, when the desired precision varies over the system under study, or when the solution lacks smoothness.

This chapter has provided an overall introduction to the possibilities of CAE tools, focusing on main applications in the biomedical engineering field, revised further on. First of all, FEM-based simulations are used to assess in silico the performance of medical devices, especially artificial prostheses, so as to validate or optimize the CAD design. Secondly, FEM-based simulations are used to study the behavior of organs and biological structures, so as to increase our knowledge about how different mechanical, thermal, or fluidic phenomena affect them, aiming also at the discovery of novel diagnostic or therapeutic alternatives. Finally FEM-based simulations are very useful to analyze the interaction between prostheses and living tissues, so as to predict their effects on patients once implanted.

Several examples of FEM simulations of different phenomena (including mechanic, dynamic, thermal, and fluidic cases) for studying its effects on organs and biostructures, medical appliances, and biodevices in general, as well as the interactions between implants and organism, have been provided for covering main application fields previously detailed.

A final remark is linked to the need of validating simulation results by using in vitro, ex vivo, or in vivo trials. The use of prototypes for such validations is further described in Chaps. 10 and 11 and some additional indications on trials are given in Chap. 15.

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[1] On computer-Aided Design and Engineering Resources:

[2] More linked to design tasks:

Chapter 9
Computer-Aided Manufacturing (CAM) of Biodevices

Andrés Díaz Lantada, Pilar Lafont Morgado, and Carlos Jahel Ojeda Díaz

Abstract Computer-aided manufacturing (CAM) is the use of software to prepare part manufacture and to control machine tools and related machinery during part or product fabrication. A more advanced and complete approach includes also all the computer-based simulation tools for preparing and adequately managing a whole production plant and its manufacturing processes.

Initially it was mainly linked to preparing and controlling numerical control machining, in most cases starting from the information provided by a computer-aided design of the part to be produced. Progressively, more complex procedures, such as high-speed machining, multifunction machining, and 5-axis machining, among others, have benefited from CAM resources, and final integration into the product life cycle management (PLM) is now also much more direct.

Nowadays the simulation of other relevant industrial manufacturing processes, such as plastic injection molding, metal injection molding, extrusion, lamination, and stamping, is also common, and final parts benefit from quality improvements, being final production also optimized.

This chapter introduces CAM technologies and its main applications, especially focusing on the biomedical industry and related products. Case studies of a couple of medical appliances are provided, showing manufacturing simulations and also subsequent automated manufacture in the case study linked to CNC machining.

The simulation of other more novel manufacturing processes is also discussed, together with an analysis of present challenges and future directions, many of them connected with the additive manufacturing technologies and approaches explained in forthcoming chapters.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_9,

9.1 Introduction to Computer-Aided Manufacturing (CAM)

Computer-aided manufacturing is the use of computer software to prepare part manufacture and to control machine tools and related machinery during part or product fabrication.

Traditionally CAM has been directly associated to computer numerical control machining, aimed at the direct generation of a code to drive the machine tool, starting from the information included in the 2D or 3D CAD part geometries. The whole machining process is aided and aspects such as tool velocity, precision required, and tool change, among others, can be defined and automated, what normally involves processes such as roughing (from raw material to a rough shape of the part), semi-finishing (further working on the rough part), finishing (based on much slower passes across the surface for increased accuracy), and contour milling (optional final accuracy improvement by moving the part to make the features of the part tangent to the cutting edges, only in special machines), each of them requiring different parameters and tools.

A more advanced and complete approach includes also all the computer-based simulation tools for preparing and adequately managing a whole production plant and its manufacturing processes. Therefore, novel simulation resources and modules are progressively being included in CAM software for helping with tasks as diverse as manufacturing plant planning; management of energy, materials, processes, information, and products in the whole plant; control of resources; and estimation of costs and deadlines.

Nowadays CAM is integrated together with CAD-CAE within the umbrella of product life cycle management (PLM) (i.e., Siemens PLM Solutions), aimed at the global definition of all aspects involved in the product development, including design of parts and components, definition of materials and commercial pieces, preparation of manufacturing and production-related processes, definition of maintenance strategy, and global management of information, including inputs from suppliers and clients.

In any case, the collaboration between the mechanical engineers, normally focused on the design; the production engineers, normally focused on manufacture; the NC programmers; and the machinists is still essential for obtaining adequate results. In fact, the traditional role from the NC programmers is being progressively acquired by the machinists, whose expertise in computer resources and manufacturing technologies is highly demanded and essential for the success of novel product development projects.

More recent additive manufacturing technologies (AMT), working on a "layer-by-layer" approach, as detailed in Chap. 10, also benefit from specific CAM resources, as each AMT process has its own special details and the automated manufacture has to be also prepared with the help of software (i.e., 3D Lightyear™ file preparation software). Other mass production processes such as plastic injection molding (Moldflow, Autodesk Inc.) and metal injection molding (Magmasoft®) also benefit from CAM resources, as a help for production-oriented design.

9.2 Computer-Aided Manufacturing in Bioengineering

In Biomedical Engineering, personalization is usually pursued for providing a remarkable solution for an especially unconventional and complex pathology, for promoting diagnostic or therapeutic capabilities of a device by a better adaptation to patient's morphology, and for supplying enhanced technical helps designed by a more detailed application of ergonomic principles. In such a field, personalization is in most cases a relevant need, not just a luxury, and its social impact justifies carrying out continued research for its promotion.

The combination of medical imaging-based computer-aided design approaches, as explained in Chap. 5, with the progressive advances in computer-aided manufacturing is promoting prosthesis personalization. Next section provides an example of hip prosthesis personalization, although the most common sector in which personalized implants are widely being obtained by computer-aided manufacturing is dentistry.

In such field, implants are not so invasive or linked to vital organs and have also a relevant aesthetic component, which is perhaps also connected with the desire of dentists of promoting marketing through innovative processes. Placing dental implants into market is quite easier than facing the production of total hip or knee replacements, artificial heart valves, and pacemakers, among others, whose production is controlled by multinationals, sometimes also linked to marking standardization directions, usually promoting the appearance of oligopolies.

The collaboration between dental clinics and prosthetics laboratories is very common and most laboratories nowadays include digital scanners for teeth reconstruction, computer-aided design resources for design operations, and CNC-driven compact milling machines for directly manufacturing personalized implants in zirconia and other biomimetic materials with enhanced aesthetic features. Besides, the computer-aided manufacturing of personalized splints, for helping with dental surgical procedures, is also widely used.

Companies such as Materialise HQ offer their CAD-CAM services for providing customers with such personalized splints for surgical aid, sold under the name "Surgi Guide" (http://biomedical.materialise.com), and a similar business model is expanding.

In any case, relevant research efforts have been devoted in the last decades to extending these procedures to all kinds of prostheses, such as knee replacements (Riechmann et al. 1991), hip prostheses (Osuna 2008; Ojeda 2009), and annuloplasty rings (Díaz Lantada et al. 2010) among other biodevices.

Such research is worth of attention, even if the final implantation is not achieved (as related regulatory affairs usually require a devoted team of jurists for handling all the procedures, what can only be afforded by the bigger enterprises). Similar processes and resources can be of help for alternative developments and for promoting novel personalized biodevices.

9.3 Simulating Machining Processes

Preparing automated subtractive machining processes has been the traditional core of computer-aided manufacturing. In this section we provide a case study linked to the real development of a personalized hip prosthesis, including design personalization, with input from medical images, and CNC machining for final prototype manufacture.

The example has been provided by Prof. Dr. Carlos Ojeda, current leader of the Bioengineering Research Group at the University of Piura, Peru, and we would like to thank his contribution.

Figure 9.1 shows schematically the personalized design of a femoral prosthesis, adapted to the femur of the patient. The usual procedure for carrying out a customized examination with a view to using a prosthetic device usually begins by taking either a computerized tomography (CT) or a nuclear magnetic resonance (MRI/NMRI) of the patient needing the prosthesis.

Then, with the aid of .dicom or .dcm (Digital Communications in Medicine) format, the information from the CT or MRI can be transferred to a program such as "Mimics," so that it can be displayed in 3D. These programs usually include modules that allow selecting part of the patient's bone geometry and storing it in .stl or .igs formats that can be read by other CAD programs, for ad hoc design operations, after processing the images "slice by slice."

Additional information, linked to a similar reconstruction and personalized design, can be found in Chap. 5 (Ojeda Díaz et al. 2009).

Once the CAD solid model of desired prosthesis is obtained, the CAM resources of the CAD-CAE-CAM software allow for manufacture preparation and simulation, including the possibility of precisely defining tool velocity, precision required, and tool change operations, among other aspects, linked to the roughing, semifinishing, finishing, and contour milling processes involved. Figure 9.2 shows different images describing the whole automated CNC machining process of the personalized prosthesis, using different tools and advance and spindle speeds for the different processes.

Figure 9.3 shows the "MAHO MH 600 C" CNC universal milling machine, which was used for the prosthesis manufacture, as well as the beginning of the roughing process starting from a block of raw material. Figure 9.4 details how the roughing process continues and provides an image of the femoral component of the final artificial hip prosthesis obtained.

After manufacture some final post-processes can be applied, including physical and chemical vapor deposition (PVD and CVD) processes for improving several mechanical and tribological properties, as well as corrosion resistance and final biocompatibility, as Chap. 13 details (please see Figs. 13.1–13.3 for some additional examples).

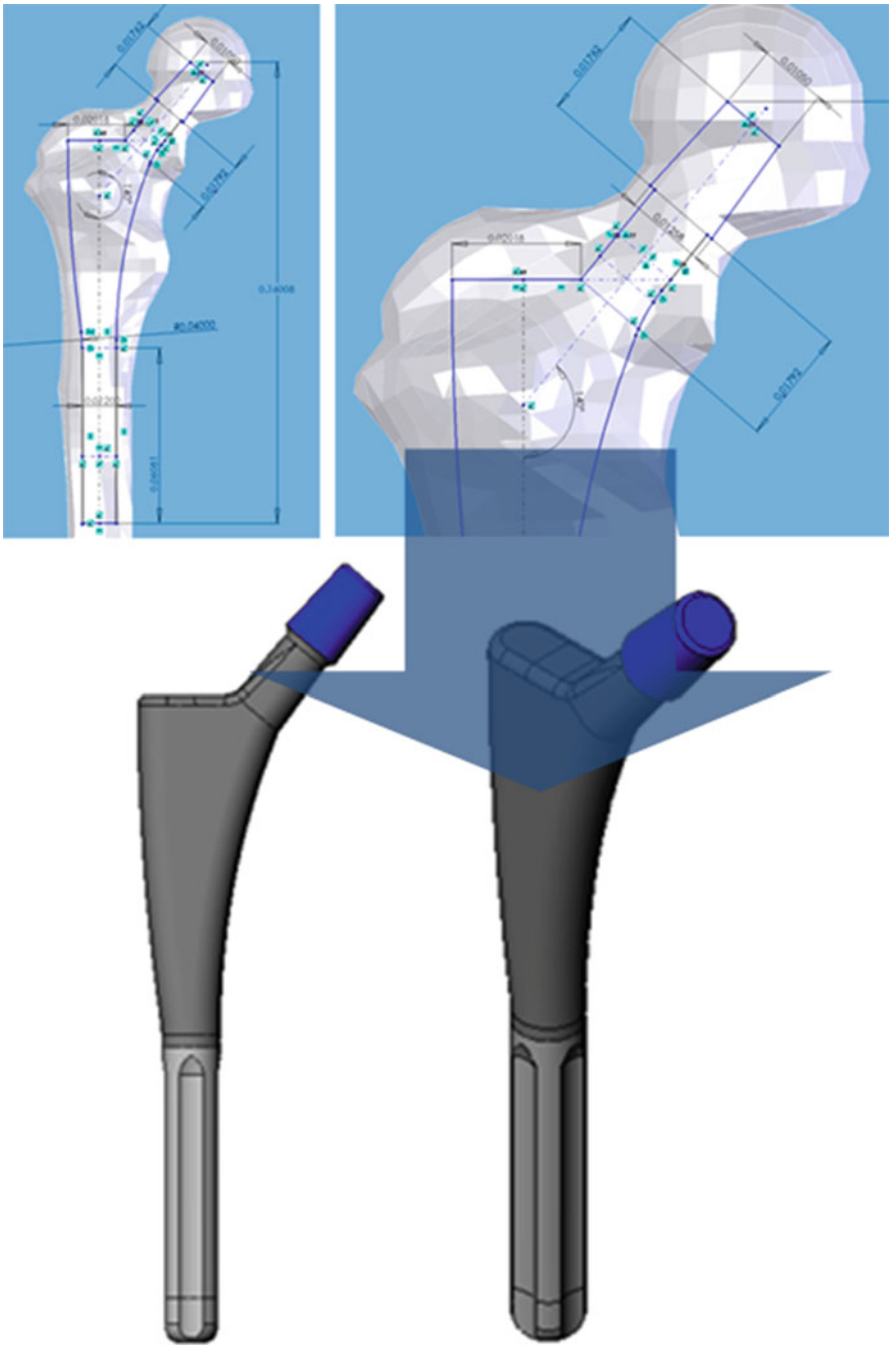

Fig. 9.1 Personalized CAD design of artificial hip prosthesis

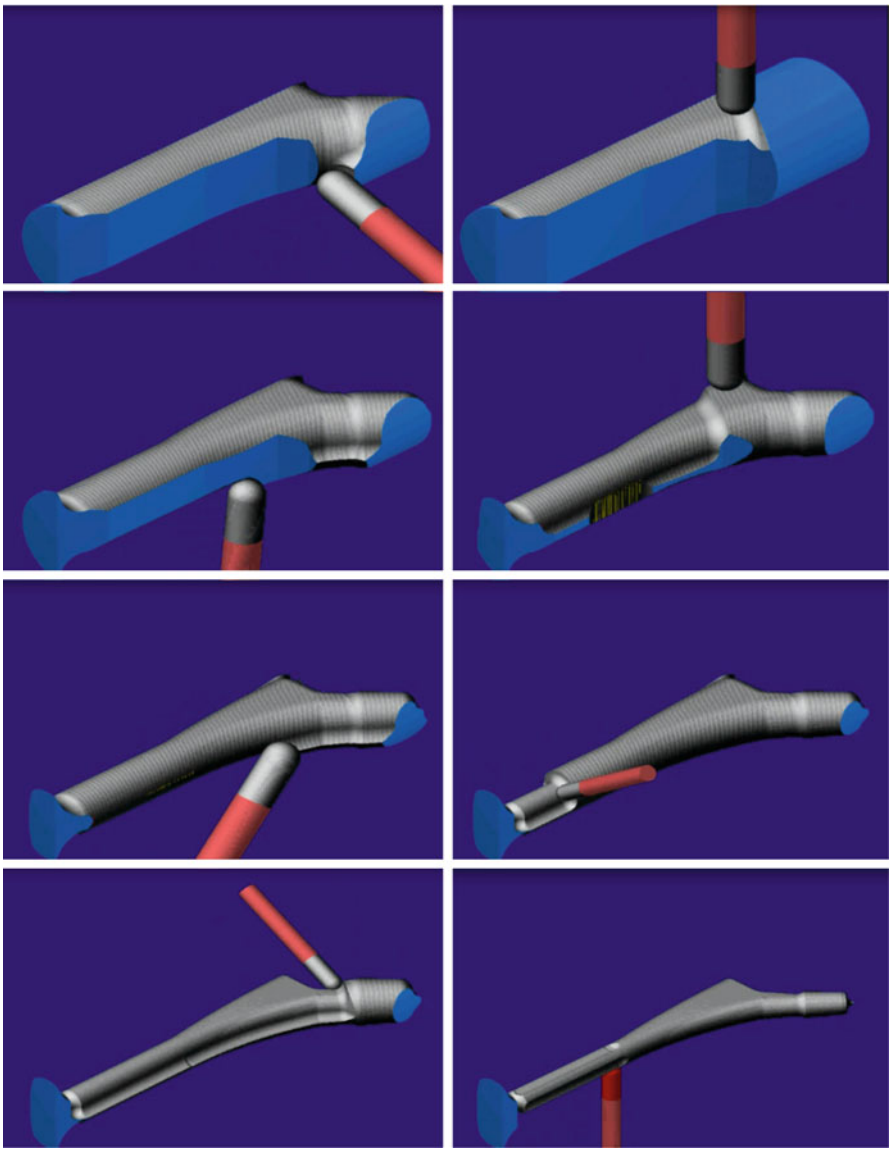

Fig. 9.2 CAM: simulation of the machining process of personalized artificial hip prosthesis for preparing production

9.4 Simulating Injection-Molding Processes

Several recent advances of the Biomedical Engineering field are directly connected to progresses on Materials Science and, very especially, to the evolution of polymers and their synthesis and transformation processes during the last 20–30 years.

Fig. 9.3 CAM-assisted CNC machining of artificial hip prosthesis

Polymeric materials, based on the polymerization of some basic units called monomers, have several advantages for their continuously increasing application to conventional product development, including:

- They can be mass-produced and shaped into complex geometries, thanks to the use of the injection-molding process.
- Final products are very cheap, thanks to such mass production enabled by the injection-molding process.
- They are electrical, acoustical, and thermal insulators, what promotes many special applications.
- The use of a vast number of formulations and additives helps to adapt their properties to requirements almost “a la carte.”

Fig. 9.4 CAM-assisted CNC machining of artificial hip prosthesis

Regarding products for the biomedical field, there are some additional relevant properties that we would like to highlight:

- Their chemical stability allows polymers to resist the aggressive biological environment and to withstand corrosion and degradation better than most metals and alloys.
- Their mechanical properties and densities are near those from many tissues and biological materials in general, what constitutes an advantage for the design of biodevices.
- Several biopolymers can be processed using conventional methods, such as injection molding, or even using novel additive technologies (see Chap. 10), for obtaining implants with improved biocompatibility. Examples include PVA, PLLA, PCL, and PLGA, among others.

- Their low densities provide lighter final implantable devices, what is also advisable if mechanical requirements are not too high.

Of course there are also some disadvantages linked to the extensive use of these polymeric materials, such as:

- Their properties are influenced by temperature changes and mechanical stresses, what complicates the design process and requires exhaustive characterization.
- Adequate experience is needed for promoting designs oriented to the final manufacturing process, typically injection molding.
- Many polymers are toxic or environmentally harmful, as they are oil-derived materials.

However, some of these difficulties can be tackled by engaging good designers in the development process, by using complete databases with detailed properties (www.campusplastics.com), and by devoting researchers to the synthesis of new formulations with biological origin, instead as based on oil chemistry.

In addition, other relevant related difficulties can be solved by the use of ad hoc developed computer-based design, engineering, and manufacturing tools. Linked to the topics of this chapter, it is important to mention the extended use, in the polymer industry, of computer-aided manufacturing resources for helping part and mold designers to obtain more adequate designs.

Most renowned software for in silico assessment of injection-molding processes is Moldflow (currently Autodesk Moldflow, which is also included within the Autodesk Suite for product design, directly connected with Autodesk Inventor). Details can be found in the website: http://usa.autodesk.com/moldflow.

Moldflow provides tools to help designers validate plastic part, mold, and tool designs before manufacturing begins. Using a digital prototype to simulate the plastic injection-molding process helps to reduce the number of physical (rapid) prototypes required to optimize a plastic design and get the products into market faster.

Such software helps with material and injection machine selection, provides information linked to injection cycle time, gives an idea of final part quality, and helps to improve the design and optimize production by changing the injection points, by using multicavity approaches, and by changing materials and machine parameters, among other possibilities. Related teaching applications are also very remarkable in the field of product design (Díaz Lantada et al. 2007; Lorenzo Yustos et al. 2010).

Figure 9.5 shows the computer-aided design and the rapid prototypes obtained by additive manufacturing (see Chap. 10) of a "gerotor"-type internal gear pump, development carried out in 2005 to provide a teaching example of complete product development process, oriented to polymers, for the subject "Design and manufacturing with polymers" (Díaz Lantada 2005). The prototype serves to validate the assembly process, as well as to carry out some validation trials.

In order to finally adapt the design for promoting injection molding and predesigning mold structure, Fig. 9.6 shows some simulation results linked to the

Fig. 9.5 Computer-aided design and rapid prototype of "gerotor"-type internal gear pump (i.e., for extracorporal pumping)

evaluation of fill time and part quality in a multicavity mold aimed at part production optimization.

Simulations, based on similar software resources, can be used for analyzing transformation processes involving the flow or deformation of plastic materials, including plastic injection molding, metal injection molding, forging, and compression molding, among others.

9.5 Main Conclusions and Future Research

Computer-aided manufacturing, as already detailed, is the use of software to prepare part manufacture and to control machine tools and related machinery during part or product fabrication. A more advanced and complete approach includes also all the computer-based simulation tools for preparing and adequately managing a whole production plant and its manufacturing processes.

This chapter has introduced computer-aided manufacturing technologies and its main applications, especially focusing on the biomedical industry and related products. Case studies of a couple of medical appliances have been provided, one linked

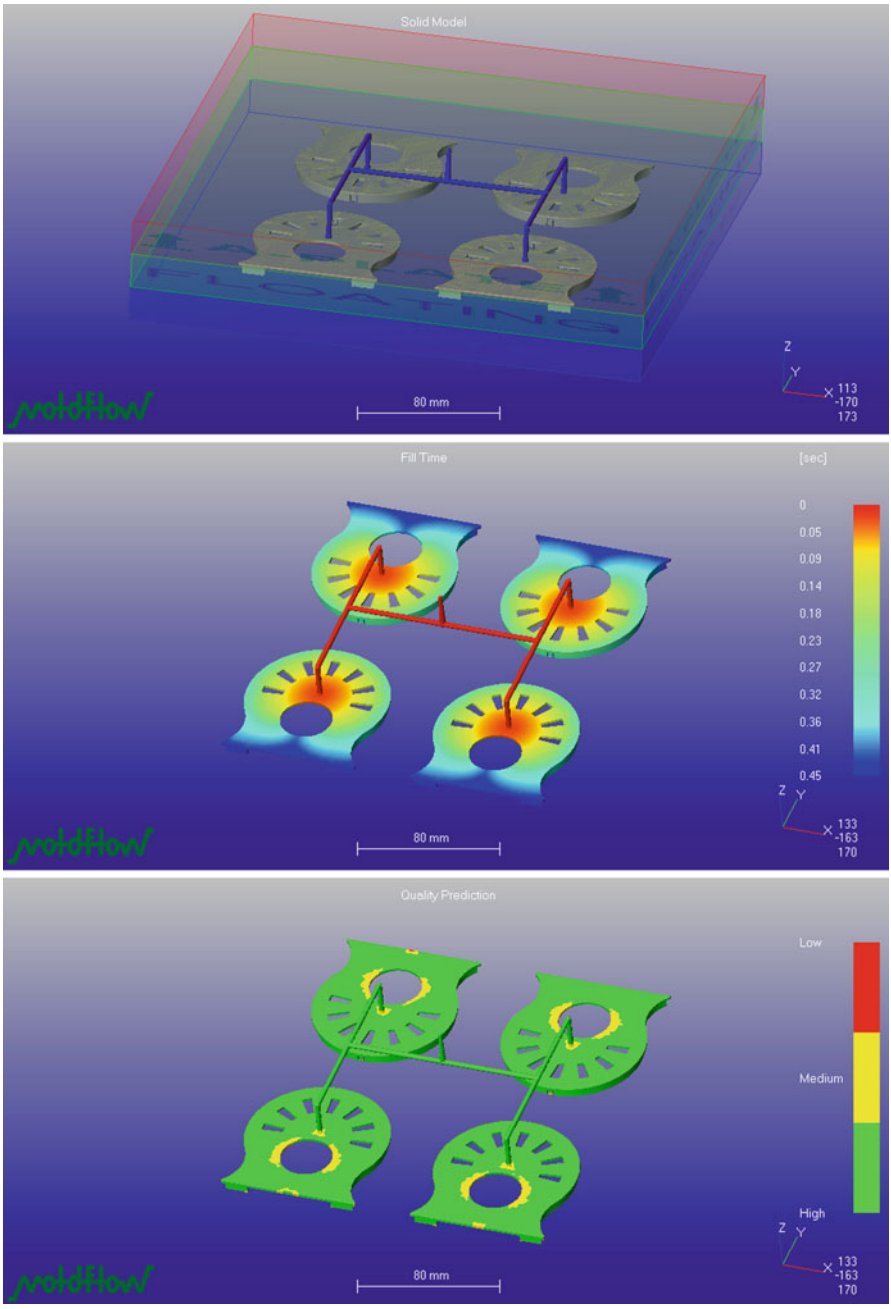

Fig. 9.6 FEM-based simulation of serial production using the injection-molding process. Predictions of mold fill time and part quality

to an implantable hip prosthesis, the other detailing a gear pump for handling several fluids. Both examples have provided manufacturing simulations and also subsequent details on final automated manufacture, in the case study linked to CNC machining of the hip prosthesis.

The simulation of other more novel manufacturing processes is also discussed, together with an analysis of present challenges and future directions, many of them connected with the additive manufacturing technologies and approaches explained in forthcoming chapters.

Computer-aided manufacturing resources are also linked to improving overall security in plants and industrial installations, as the whole manufacturing process, including stock management, machine and robotic movements, transportation, and all necessary operations can be integrally simulated, so as to verify secure zones for operary movements.

Additional incorporation of interesting features for analyzing the influence of the manufacturing process and its conditions, not only on final part geometry and quality, but also on expectable mechanical properties, for subsequent linkage to computer-aided engineering resources for FEM-based calculations on final performance, would be desirable.

Finally, it is important to note that computer-aided manufacturing is also linked to several automated additive manufacturing technologies, covered in Chap. 10, which, instead of working on a subtractive approach, allow for solid freeform fabrication of complex geometries in several materials.

Several of the technologies also described in Chaps. 12–14, when focusing on micro- and nano-manufacturing technologies and on recent advances linked to biofabrication, are also connected to computer-aided manufacturing, as they work in an autonomous way based on computer-aided designs, after adequate manufacture preparation with help of more specific CAM software.

Progressive format universalization, for easier information exchange between CAD resources and aiming at a more direct and automated control of the machines carrying out manufacturing, with less intermediate conversions and preparation steps, will surely be linked to the progressive expansion of "factory at home" approaches and to research topics aimed at deciding the most adequate processes for the "factories of the future."

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Chapter 10
Additive Manufacturing Technologies for Enhancing the Development Process of Biodevices

Andrés Díaz Lantada, Pilar Lafont Morgado, and Jürgen Stampfl

Abstract A new set of manufacturing techniques and technologies has appeared in the last two decades to address market requirements in an ever more customized way and to provide support for research work where physical models (or prototypes) are needed for tests and trials. These new techniques and technologies go by the name of "rapid prototyping and manufacturing technologies." They are usually based on "additive manufacturing processes" and also called "layer manufacturing technologies," which are covered in this chapter.

The different technologies available allow prototypes to be obtained in a wide range of metallic, ceramic, or polymeric materials with remarkable precision. These technologies enable physical parts to be manufactured in a short time (hours or a few days) directly from the designs made with the help of computer-aided design, calculation and manufacturing programs, or "CAD-CAE-CAM technologies." They greatly help to optimize design iterations, contribute to early error detection, and speed up production start-up.

In spite of their being rapidly incorporated into product development methodologies, these new types of technologies are still in their initial stages of development and their applications in bioengineering are continuously evolving. The global biodevice development process, from validating conceptual designs to carrying out in vitro and in vivo trials, can be especially helped by the use of such tools, due to the several specific problems related to interacting with biological systems and the need of validating each design decision, as discussed here by means of several case studies.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_10,

Other rapid prototyping technologies, including rapid shape-copying processes or based on subtractive manufacturing processes (such as in high-speed numerical control machining), are also covered in previous and forthcoming chapters.

10.1 Introduction to Additive Manufacturing and Rapid Product Development

Rapid prototyping and manufacturing technologies allow researchers to obtain physical parts in a short period (hours or days), directly from the designs created with the help of computers using computer-aided design, engineering, and manufacturing "CAD-CAE-CAM" programs, as has already been mentioned in some previous chapters.

Such technologies significantly help to optimize the design iterations, allowing for the early detection of errors and speeding up the whole development process. They are generally based on automatic additive or layer-by-layer manufacturing processes (and they are also referred as layer manufacturing technologies or "LMT"). In some cases, very fast manufacturing processes involving material removal, such as high-speed numerical control machining, are also included within the concept of rapid prototyping, or "RP," although the term is normally linked to additive processes.

As the operation principle is based on deposition processes or layered manufacturing, the creation of very complex geometries, including inner details, can be carried out directly from the associated CAD files, and currently the geometrical limitations are more linked to the designers' ability, than to the manufacturing process.

Almost all departments involved in the overall process of launching a new product benefit from the systematic use of these RP technologies. A previous prototype is a physical communication tool that reduces the risk of possible misinterpretation, as may occur if only CAD designs or plans are used, and allows subjective features (aesthetics, ergonomics) to be analyzed.

They can also be used to perform tests of assembly and interference, so as to check the designs. In addition, functional prototypes can also be obtained to verify the performance of parts and products, although sometimes with certain mechanical limitations, depending on the materials and technologies used. They dramatically assist the relationship between customers and suppliers, helping to avoid communication problems, and often help to promote improvements both in the design and in the production process.

More recently (Wohlers 2010), the accuracy and the mechanical performance obtained by some of the rapid prototyping processes, operating on an additive manufacturing approach (i.e., selective laser melting, laser cusing), allow for the direct manufacture of final parts, whose mechanical properties are similar, or even better, than those from the parts obtained using more conventional production processes (including CNC machining).

Rapid prototyping technologies and the related prototypes also allow for customized approaches, especially due to the development of new combinations of technologies and materials, which is of great interest to the biomedical industry as analyzed in forthcoming sections.

A historical perspective of the beginnings and evolution of additive manufacturing is described in detail elsewhere (Walters and Thirkel 2007; Bourell et al. 2009). We have included some preliminary approaches in Fig. 10.1 showing the Blanther's process for layered topographic maps, Di Matteo's process for constructing 3D surfaces and bodies, Baese's process for reproducing plastic parts, and Munz's layered photopolymerization process, whose ideas, adequately combined with advances in automation and laser technologies, among others, led to many of the currently available processes.

10.2 Overview of Additive Manufacturing Processes with Impact on the Biomedical Field

The various technologies available can operate and manufacture prototypes using a wide range of metals, ceramics, or polymers, both with synthetic and biological origin and with outstanding precision (see scheme of Fig. 10.2).

Remarkable technologies (and associated materials) with a significant impact on the evolution of the rapid prototyping industry include laser stereolithography (photosensitive polymers), selective laser sintering (polymer powder, usually nylon, or ceramic powder), 3D printing (powder with binder, liquid resins), fused deposition modelling (thermoplastics), digital light processing (photopolymers, biophotopolymers), or direct laser writing (photopolymers, ceramics, ormocere, biomaterials), these last two very linked to the manufacture of micrometric objects (see Chap. 12).

There are other more recent technologies with an optimized precision of a few micrometers or even hundreds of nanometers also capable of using materials for specific applications in biomedical engineering, such as obtaining implantable devices or manufacturing scaffolds for tissue engineering processes, as will be discussed in forthcoming sections.

Certain "rapid tooling" technologies within rapid manufacturing are also noteworthy, as they can produce tools and parts for injection molds quickly and economically, either by reproducing the geometry of physical models, through shape-copying processes (copying the geometries from rapid prototypes), or by directly manufacturing such tools and parts in an additive way. These "rapid tooling technologies" and "rapid form-/shape-copying processes" are described in more detail in Chap. 11, although Fig. 10.3 includes a brief schematic description of the different connections between rapid prototyping and rapid tooling, thus covering main processes in the field of rapid manufacturing.

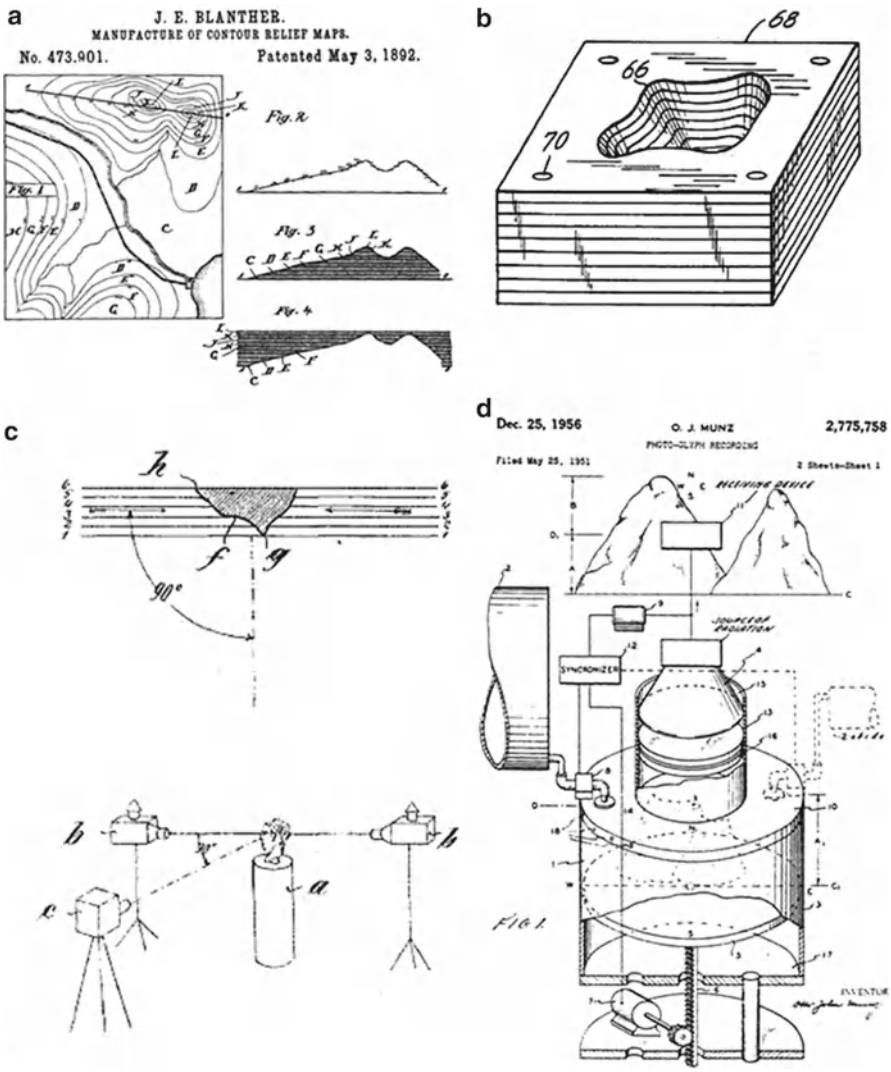

Fig. 10.1 Images from several patents related to processes in different fields as forerunners for present additive manufacturing technologies: (**a**) Blanther's process for layered topographic maps (1892). (**b**) Di Matteo's process for constructing 3D surfaces and bodies (1977). (**c**) Baese's process for reproducing plastic parts (1904). (**d**) Munz's layered photopolymerization process (1956)

Present chapter focuses on first-phase technologies, especially on those operating on an additive basis, which due to last years' technological advances are even providing final parts (and implantable devices), while second-phase technologies, normally linked to the use of more special materials, are covered in depth in Chap. 11. The global panorama of rapid manufacturing was already introduced in Chap. 3, although the additional

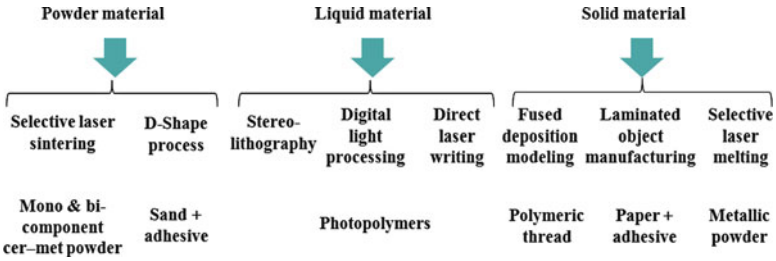

Fig. 10.2 Overview of remarkable additive manufacturing technologies and of the materials they use for building the prototypes

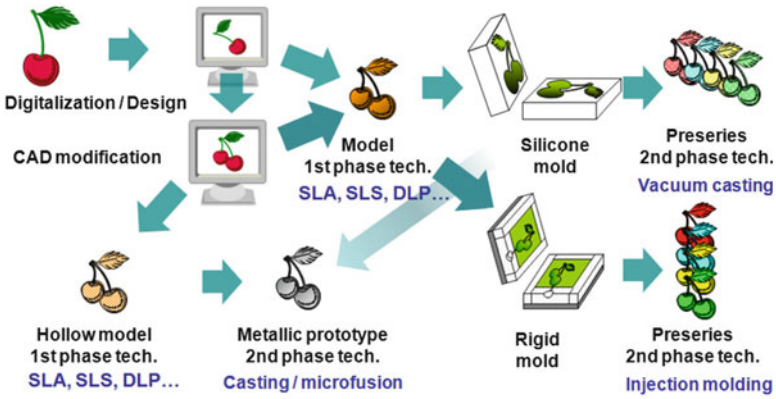

Fig. 10.3 Scheme of different rapid manufacturing technologies (Adapted from H. Lorenzo and P. Lafont, Product Development Laboratory, Universidad Politécnica de Madrid)

summary provided here serves as a reminder, showing the usual inputs and outputs of additive manufacturing technologies, in a complex development process.

Most typical areas of application of additive rapid prototyping are in the field of "traditional" engineering, including mechanical, naval, and aeronautical engineering as well as in the field of electrical engineering (providing protective cases, frame works, structural support, etc.), although novel advances in technologies and processable materials are promoting very remarkable novel applications in biomedical engineering. They are also enormously helping active research linked to materials science, including the area of active or "intelligent" materials for promoting their integration in new devices with improved sensing or actuation capabilities (Díaz Lantada 2012).

Next section provides an overview of applications of additive manufacturing processes for the biomedical field, before focusing on more specific case studies linked to the development of biodevices for in vitro/in vivo trials, of biodevices with complex geometries for special interactions and of biodevices with improved biocompatibility.

10.3 Overview of Applications of Additive Manufacturing Processes for the Biomedical Field

The present relevance of additive manufacturing for supporting the advances of biomedical engineering has already been subject of comprehensive reviews and detailed roadmaps (Choi and Cheung 2009; Iwami and Umeda 2011; Díaz Lantada 2012; Díaz Lantada and Lafont Morgado 2012; Díaz Lantada et al. 2009), although here is presented actualized and revised, including novel topics.

Main areas of application of additive manufacturing, within biomedical engineering, can be summarized according to the types of biodevices and biosystems they help to develop, improve, or replace, including:

- Biomodels for diagnosis. These models are usually customized, according to the patient or field of study, in order to assist pathology diagnosis and subsequent decisions regarding surgery or pharmaceutical treatment. In many cases, it is particularly useful to have physical prototypes that reproduce the morphology of certain internal organs of patients, in order to consider later actions, as they often provide information that is more valuable and easier to interpret than images produced by conventional medical imaging technologies (Court et al. 2010; Erdelt and Lamper 2010).
- Biomodels for surgical training and planning. The rapid manufacture of biological and anatomical models greatly helps to support surgical training and planning tasks, as well as the development of prototypes to simplify surgical procedures (Jacobs et al. 2008; Hananouchi et al. 2008). In some cases, rapid customized prototyping acts as a support or complement to virtual 3D reconstruction technologies, by helping to implement physical test benches for surgical training or for detailed validation of novel medical devices (see Chap. 15).
- Implantable devices for hard tissue replacement. Together with the development of models for surgical training and planning, the direct manufacture of customized implantable medical devices has been, in the last two decades, the main bioengineering area at which rapid prototyping technologies have been aimed (Gittard et al. 2009; Kocacikli et al. 2010). In these cases, rapid prototyping technologies such as electro-beam melting or laser fusion are used to directly obtain meshes, structural supports, or complete implants made of Ti or of Cr-Co alloys. Also technologies that work on ceramic materials, normally selective laser sintering, are employed to produce prototypes with properties more similar to those of the bones to be replaced.
- Implantable devices for soft tissue replacement. Improvements in imaging systems and in design software based on information from medical images have also led to promising experiments related to the development of implants, adapted to soft tissues, even though the adaptation to hard tissue is still simpler and more direct (as detailed in Chap. 5, Díaz Lantada et al. 2010d).
- Orthotic devices and technical helps for improving human performance. Some of the earliest applications of rapid prototyping in bioengineering were in the field

of ergonomics and orthotics and included the development of individualized devices and consumer products designed ad hoc, taking account of the anatomy of patients with reduced mobility or anatomical problems. As these customizations concern non-implantable conventional devices (toys, kitchen utensils, orthoses, to name a few appliances), they involve far less risk to patients and, therefore, require fewer controls before being placed on the market (Gerrits et al. 2006; Pandremenos and Chrussolouris 2009).

- Biodevices based on active or "intelligent" materials. Rapid prototyping technologies also promote and assist the integration of "smart" materials in complex devices, many of them with application in the biomedical field as they allow for novel diagnostic and therapeutic approaches. The validation of these new approaches, based on unconventional transducers, is thus promoted by the multidisciplinary nature of additive manufacturing, here applied on the frontier between materials science and bioengineering (Díaz Lantada 2012).
- Biodevices for tissue engineering. Rapid prototyping, in combination with medical imaging and CAD-CAE software, is proving to be a powerful tool in the design and manufacture of scaffolds, as it allows complex geometries to be obtained, normally in an additive way, using a wide range of materials. Several scaffolds with controlled microstructures have already been manufactured using different RP technologies (Li et al. 2009).
- Direct additive manufacture of tissues and organs (the near future). The progressive adaptation of several additive manufacturing technologies to the layer-by-layer or drop-by-drop deposition of biological materials, biogels, and even living cells and nutrients opens new horizons and can even completely reshape medicine in the next decades (see Chap. 14, Mironov et al. 2009).

The following sections concentrate on several case studies and applications, among the previously mentioned areas, including implantable devices, extracorporeal appliances, and devices for diagnostic and in vitro trials, many of them linked to tissue engineering.

Some other examples, of the application of additive manufacturing to the development of different prostheses for hard and soft tissue replacement, can directly be based on previously described designs (Chaps. 5–7), and additional case studies are provided in forthcoming chapters (Chaps. 11, 12, and 14).

10.4 Case Studies: Additive Manufacture of Conventional Biodevices for In Vitro or In Vivo Trials

The different prototypes shown in this chapter as case studies have been manufactured, either by using laser stereolithography (3D Systems Inc.) in epoxy resin or by using digital light processing (EnvisionTec GmbH) in acrylic resin. As these are not medical grade materials, most of these prototypes have been used as visual models, for validating design concepts, for assembly verifications, and for different in vitro

Fig. 10.4 *Left image*: prototype of stent in shape-memory epoxy. *Right image*: prototype of annuloplasty ring in shape-memory epoxy (Manufactured using laser stereolithography: SLA-3500 Machine 3D Systems)

trials. Additional discussion on the direct additive manufacture of prototypes using biomaterials and strategies for reaching final biocompatible devices is discussed towards the end of the present chapter and along the whole handbook.

Figure 10.4 shows two models obtained in epoxy resin by laser stereolithography. Left image includes a prototype of a stent, whose design process was explained in Sect. 4.5 (Fig. 4.5), and right image includes a prototype of a personalized annuloplasty ring, whose design was explained in Sect. 5.5 (Figs. 5.6 and 5.7). Both of them are developed as proof of concept devices for analyzing the possible advantages of using shape-memory polymers for promoting minimally invasive surgical procedures.

The designs are adapted to desired implanted geometry, and adequately "training" the shape-memory effect, trough heating above the polymer activation temperature, followed by compression and cooldown, temporary reduced geometries for promoting implantation can be obtained. The reduced geometries promote catheter-based delivery approaches, and once the implants are located next to the organ or tissue under repair, further heating above activation temperature produces the return of the temporary "frozen" geometries to the initial ones, adequate for final implantation. Additional details can be found in documents included in the reference section (Díaz Lantada 2009; Díaz Lantada et al. 2010, 2012).

In many cases, rapid prototypes are needed as housings for a device or machine or as support elements for connecting different components (motors, bearings, gears, axes, etc.). Figure 10.5 shows the CAD designs of different volumetric pumps, for example, for drug delivery, due to their reduced dimensions, although similar principles can be used also for larger flow ratios. In any case, volumetric pumps help to precisely control the amount of fluid delivered, as a fixed quantity is delivered in every revolution.

Left images from Fig. 10.5 show a "gerotor"-type micropump, similar to some commercialized by Micropump, IDEX Corp. (www.micropump.com), or HNP Mikrosysteme GmbH (www.hnp-mikrosysteme.de). Right images show a more conventional peristaltic pump, in this case, based on the smallest ball bearings supplied by SKF (www.skf.com). Both are designed to provide 5–10 ml/min.

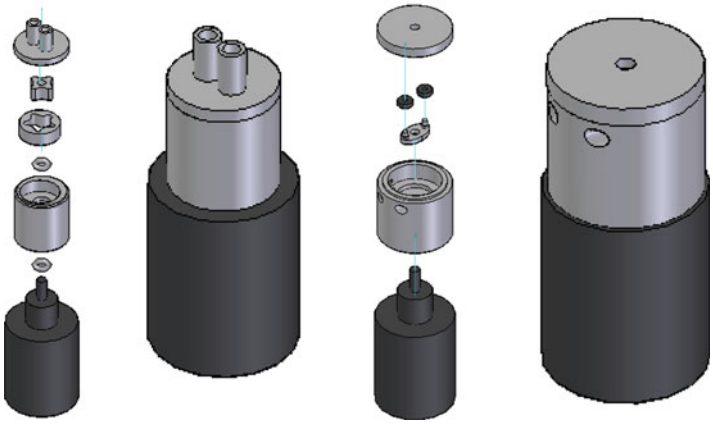

Fig. 10.5 Designs of different volumetric pumps for drug delivery. *Left images*: "gerotor"-type gear micropump. *Right images*: peristaltic micropump activated by roller bearings

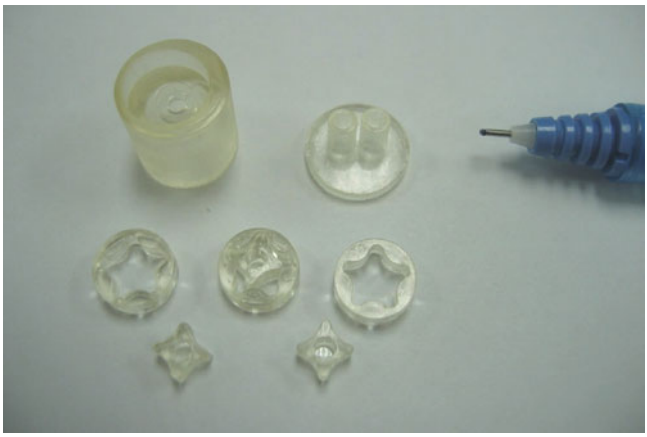

Fig. 10.6 "Gerotor"-type micropump: prototypes of cases and gears for analyzing the tolerances achieved, the assembly process, and the pumping process (Manufactured using laser stereolithography: SLA-3500 Machine 3D Systems)

Figures 10.6 and 10.7 show the rapid prototypes of different housings and components manufactured by laser stereolithography, together with commercial components for assembly validation and for analyzing the tolerances achieved as well as for carrying out some limited functional trials. We have to note the hygroscopic behavior of epoxy resin, what affects the dimensions of prototypes when maintained inside of water for several hours, although for short validation trials dimensions are not dramatically affected.

In other cases, the whole device is rapid prototyped in a unique part, as the examples already provided in Fig. 10.4 and those included in Figs. 10.8, 10.9, 10.11, and 10.12. Even though the great potential of additive manufacturing is better

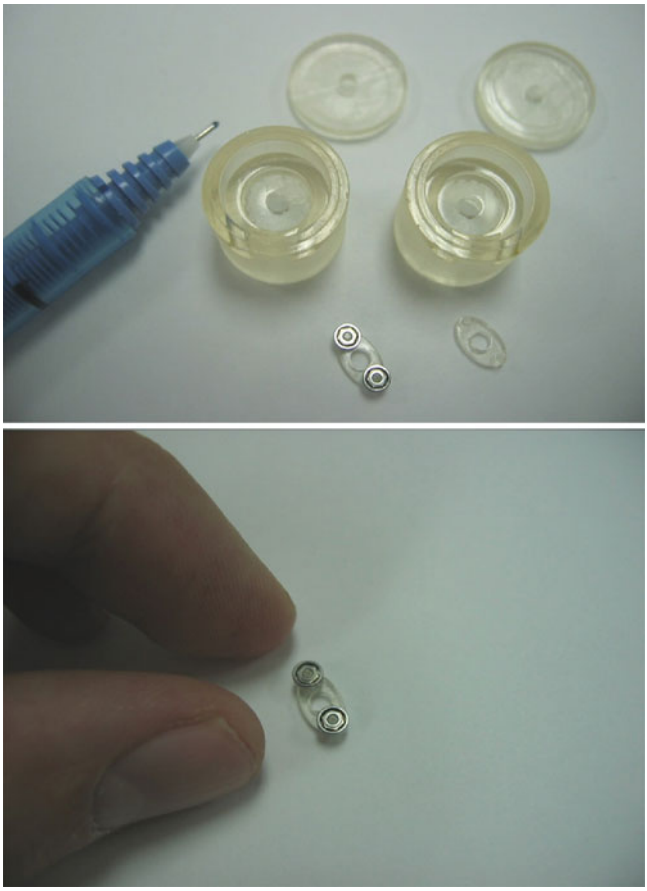

Fig. 10.7 Peristaltic micropump: prototypes of cases and supports for analyzing the tolerances achieved, the assembly process, and the pumping process (Manufactured using laser stereolithography: SLA-3500 Machine 3D Systems). Micro roller bearing from SKF with 3 mm external diameter

perceived when we are developing devices with complex geometries, the fact is that in many cases very simple geometries also provide highly adequate solutions. The rapid design of biodevices, by combination of straightforward operations (pads, holes, grooves, etc.) and the use of patterns and Boolean commands, has already been discussed in Chap. 4, especially providing case studies linked to the design of scaffolds for tissue engineering.

Here we focus on the rapid additive manufacture of designs with some common features to those described in Chap. 4. Here we have also tried to verify the actual manufacturing precision of more conventional technologies such as laser stereolithography and digital light processing, so as to assess their possibilities for

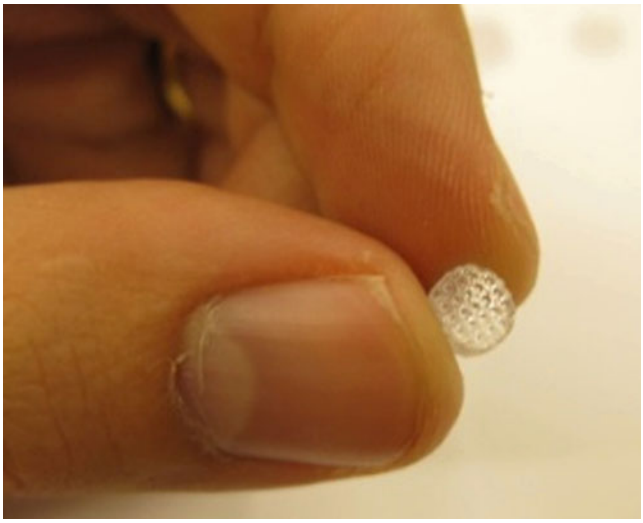

Fig. 10.8 Scaffold with microholes (diameter, 250 μm) for cell culture (Manufactured using laser stereolithography: SLA-3500 Machine 3D Systems)

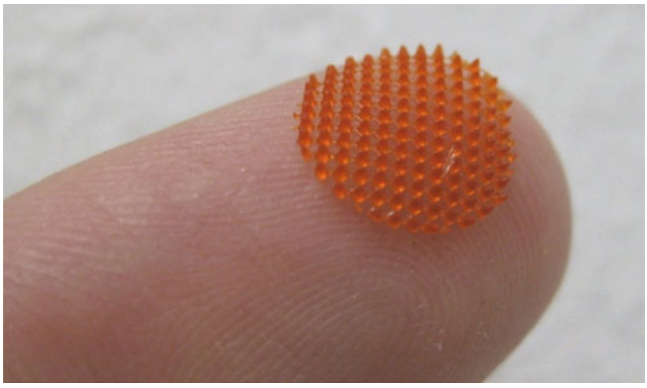

Fig. 10.9 Scaffold based on way microstructures for cell culture (Manufactured using digital light processing: Perfactory (EnvisionTec GmbH))

micro-manufacturing tasks (see also Chaps. 11 and 12) in the biomedical field, currently usually connected to cell-related studies.

Figure 10.8 shows a multi-well plate for lab-on-a-chip studies manufactured in epoxy resins using laser stereolithography, which has been adequate for obtaining 250 μm-diameter holes. Even though the toxicity of this material would not allow for ex vivo trial, rapid form-/shape-copying strategies commented in the next chapter provide, as well as those mentioned in Sect. 10.6, adequate solutions. A similar development is shown in Fig. 10.9, in this case linked to a wavy scaffold

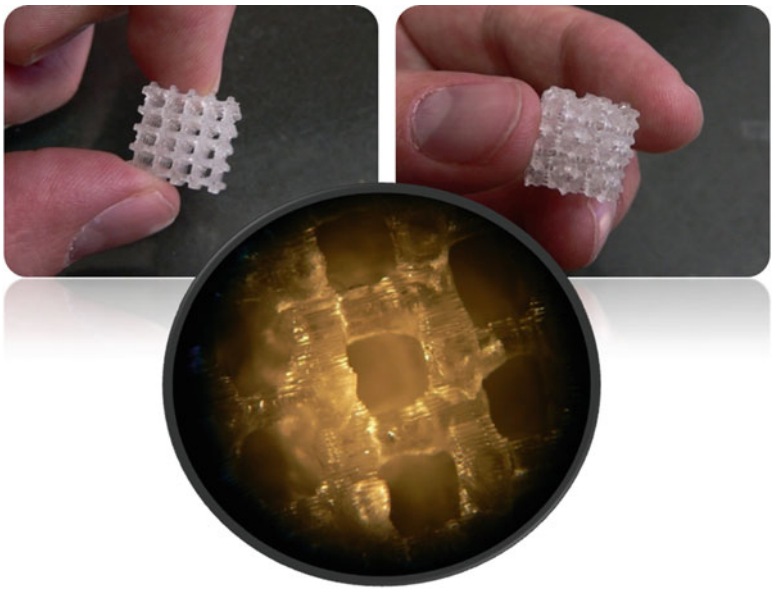

Fig. 10.10 Prototypes of hollow structures based on the CAD designs from Chap. 7 (Sect. 7.2 and Figs. 7.2–7.4). Used to validate mechanical models (see Chap. 15) (Manufactured using laser stereolithography: SLA-3500 Machine 3D Systems)

manufactured through digital light processing in acrylic resin, for which similar considerations to those detailed for epoxy resin can be useful.

Chapter 7 also detailed the potential of additive manufacturing for promoting novel developments based on the use of metamaterials, based normally on hollow and porous structures, for different fields, from optics and electronics to the development of special biodevices. Most medical applications are connected to the promotion of minimally invasive surgical procedures, by means of ultraflexible structures (even with negative Poisson ratio), as well as to advances in tissue engineering, as scaffolds are normally porous, so as to allow cell growth, access to nutrients, and throw-out of debris.

Figure 10.10 includes a couple of prototypes of hollow structures, based on some designs from Sect. 7.2 (Figs. 7.2–7.4), manufactured by laser stereolithography. It is important to note that woodpile structures with pile diameters of around 400 μm are easily manufactured and final prototypes are perfectly porous and mechanically consistent, as can be further perceived by consulting the related in vitro compression trials from Chap. 15. In fact more than 100 kg loading is needed to produce the collapse of a tiny scaffold as those shown below.

Using a conventional digital light processing system, higher precision can be obtained than by means of laser stereolithography, as Figs. 10.11 and 10.12 show. In these cases, for the different woodpile structures designed, pile diameters of

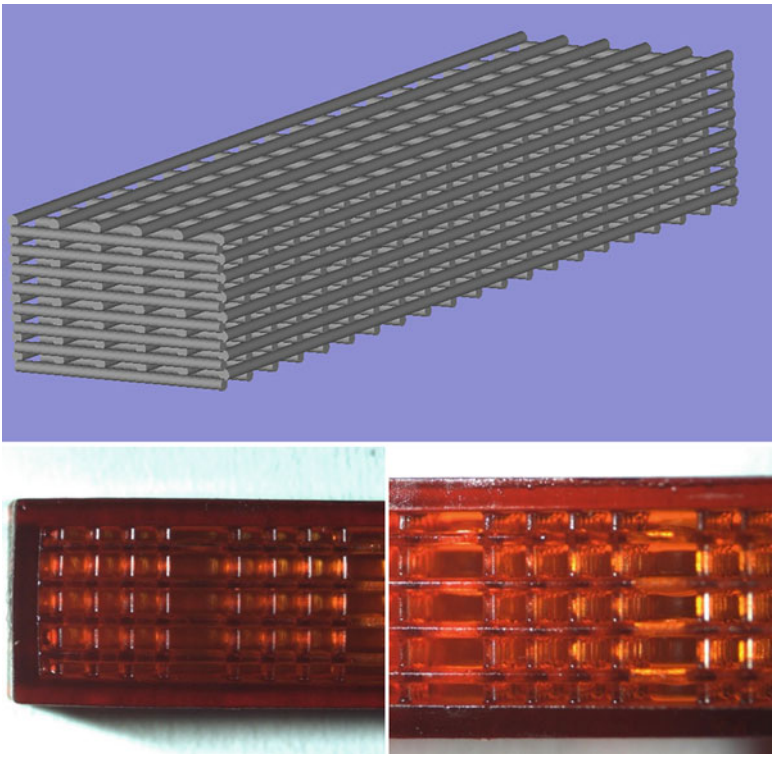

Fig. 10.11 3D scaffold for tissue engineering based on conventional woodpile structure designed with help of a CAD program. Scale: diameter of cylinders, 200 μm. Complete scaffold, $20 \times 5 \times 3$ mm^3 (Manufactured using digital light processing: Perfactory (EnvisionTec GmbH))

around 200 μm can be obtained, although normally some unpolymerized resin remains between piles and layers, what requires additional post-processes. In the case of laser stereolithography, UV post-curing of around 10–20 min is common. In the case of the structures from Figs. 10.11 and 10.12, an additional cleaning by compressed air was needed to extract the uncured material and obtain final porous structures, as due to capillarity the liquid uncured material could not properly flow out of the structure.

Unfortunately, these prototypes are not adequate for biomedical trials, and in the case of multilayered hollow or porous structures, we cannot either resort to the use of rapid form/shape-copying process, for obtaining rapid molds and casting biomaterials, as described in Chap. 11, due to the great number of undercuts.

However, the use of some novel additive manufacturing machines (bioplotters and 3D printers capable of handling biomaterials, see Chap. 14) and the use of especially synthesized materials, as Sect. 10.6 explains, provide very adequate and promising alternatives for further research.

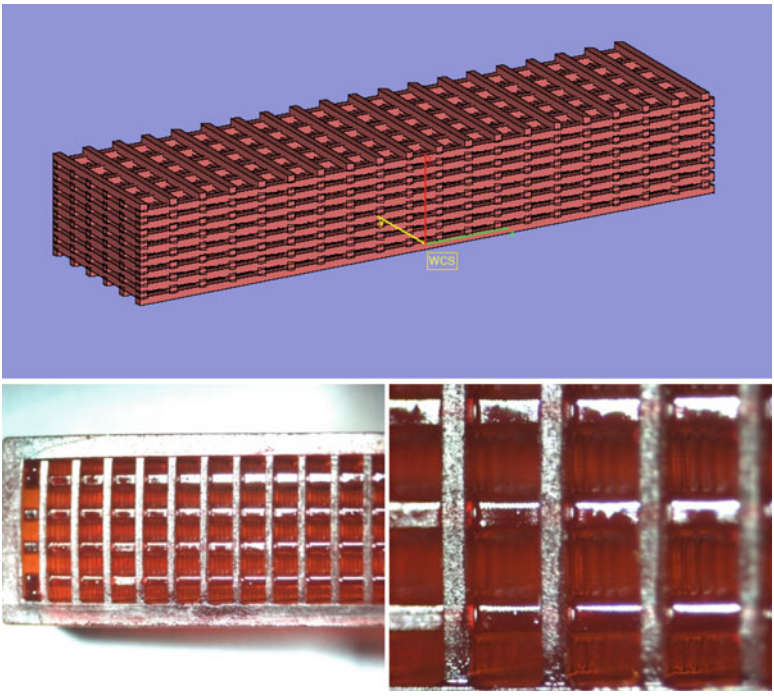

Fig. 10.12 3D scaffold for tissue engineering based on conventional woodpile structure designed with help of a CAD program. Scale: square section prisms, 200 μm^2. Complete scaffold, 20×5×3 mm^3 (Manufactured using digital light processing: Perfactory (EnvisionTec GmbH))

10.5 Case Studies: Additive Manufacture of Biodevices with Fractal Features for Cell Growth and Cell Interaction

The complex geometries described in Chap. 6, based on the use of non-Euclidean fractal models, for controlling from the design stage aspects, such as device microtexture, topography, porosity, surface/volume ratio, and overall morphology, can promote biomimetic design approaches and enhance several contact phenomena and cell-material interactions, linked to osseointegration, and final device biocompatibility, among other effects. However, such geometries are difficult to obtain, using conventional subtractive manufacturing approaches, and even impossible to attain, if the fractals are three-dimensionally structured.

The use of additive manufacturing for obtaining fractal-based prototypes was already discussed as the most adequate possibility for these complex geometries and validated in Sect. 6.5 (see Figs. 6.12 and 6.13). In present section, we focus on biodevices, enhanced by the incorporation of fractal features, for some more specific purposes. As we have concentrated on studying the effects, on cell growth and differentiation, of different fractal patterns and microtextures, the prototypes

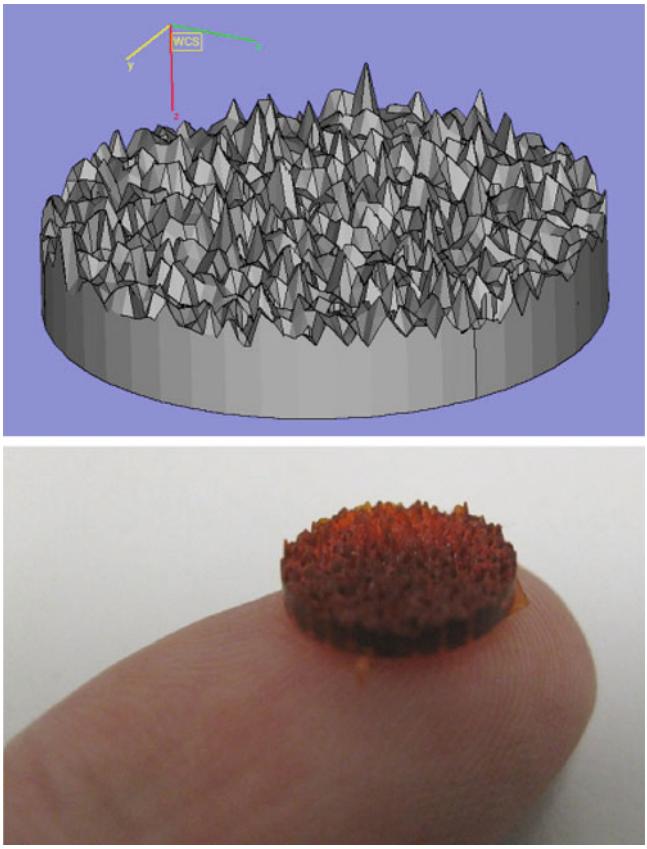

Fig. 10.13 CAD design and prototype of fractal scaffolds according to the design procedure described in Chap. 6 (Sect. 6.4, Fig. 6.10). Validation of the additive manufacture of fractional Brownian fractal surfaces (Manufactured using digital light processing: Perfactory (EnvisionTec GmbH))

detailed here have been manufactured by means of digital light processing, more precise than laser stereolithography, with which so fine details cannot be obtained (Fig. 10.13).

The prototypes from Figs. 10.14–10.16 are based on the use of fractional Brownian fractal surfaces, according to the design procedure described in Chap. 6 (Sect. 6.4, Fig. 6.10). Figure 10.14 shows an example of the design and rapid prototype of a fractal scaffold, with a remarkable level of precision. By controlling parameter "α," from the design stage (related Matlab program is included also in the Annexes of the handbook), the fractal dimension of the prototype can be controlled (given by 3 – α), what has a relevant influence on aspects such as roughness and surface/volume ratio and affects cell behavior in a very remarkable way.

For further studying the influence of such fractal dimension on tissue engineering procedures, special microsystems have been designed and manufactured, as

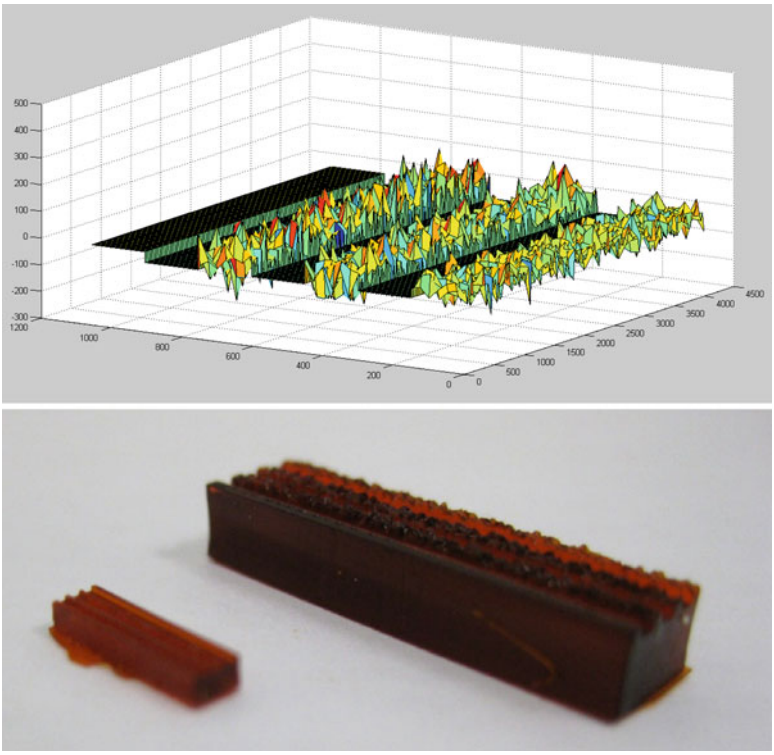

Fig. 10.14 CAD design and prototypes of microsystems with fractal channels for cell motility studies, according to the design procedure based on fractional Brownian fractal surfaces, as described in Chap. 6 (see Sect. 6.4, Fig. 6.10). Each channel has a different fractal dimension: 2, 2.1, 2.5, and 2.9. Additive manufacture at different scales (10 and 30 mm long) (Manufactured using digital light processing: Perfactory (EnvisionTec GmbH))

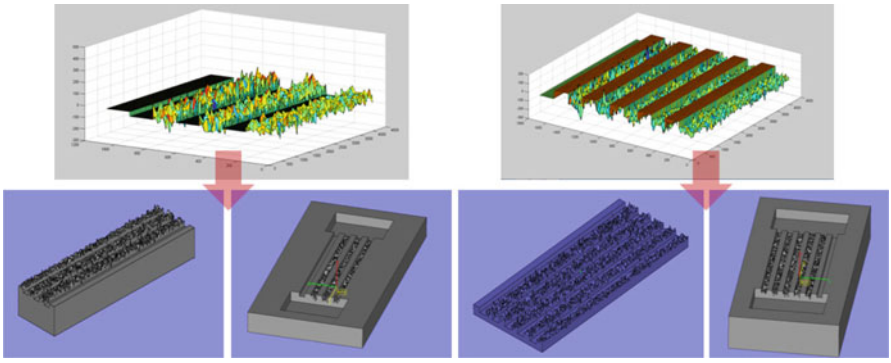

Fig. 10.15 CAD designs of microsystems with fractal channels for cell motility studies, according to the design procedure described in Chap. 6 (see Sect. 6.4, Fig. 6.10). Each channel has a different fractal dimension: 2, 2.1, 2.5, and 2.9 for the four-channel microsystem and 2, 2.1, 2.3, 2.5, 2,7, and 2.9 for the six-channel microsystem

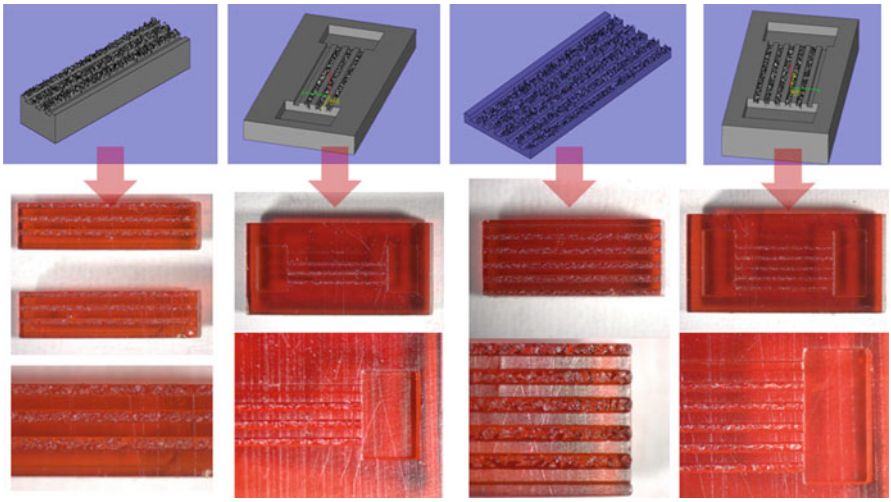

Fig. 10.16 Additive manufactured rapid prototypes of the different microsystems from Fig. 10.15. Each channel has a width of 200 μm. Validation of the additive manufacture of different microsystems for studying cell motility based on using fractional Brownian fractal surfaces for the channels (Manufactured using digital light processing: Perfactory (EnvisionTec GmbH))

shown in Figs. 10.14–10.16. Such microsystems include different channels with different fractal dimensions for further analyzing how cell crawls along them and which dimension is more adequate for their spreading process, growth, and differentiation into relevant tissues.

Designs and prototypes from Fig. 10.14 serve as validation and for assessing the manufacturing precision, while designs and prototypes from Figs. 10.15 and 10.16 are already optimized. In these optimized designs and prototypes, each channel has a different fractal dimension: 2, 2.1, 2.5, and 2.9 for the four-channel microsystems and 2, 2.1, 2.3, 2.5, 2,7, and 2.9 for the six-channel microsystems.

In any case, additional post-processes or alternative solutions are needed for the ex vivo trials with living cells, including those detailed in Sect. 10.6 and in Chaps. 11, 12, and 14.

Chapter 6 also detailed a versatile design approach (see also related Matlab program included in the Annexes of the handbook) based on the use of fractal spheres as "seeds" for obtaining three-dimensional structures and biodevices, with the possibility of controlling roughness, porosity, surface/volume ratio, density, and stiffness, from the design stage. For designing devices based on such spheres, first of all, a fractal semisphere is obtained in matrix form and subsequently converted into .stl format, for further design tasks. Figure 10.17 shows a design including fractal spheres (obtained after converting the surface into a solid by means of Boolean operations) with different sizes, so as to analyze to minimum viable size attainable by additive manufacture (in this case, DLP). Fractal spheres of 500 μm diameter are easily obtained, with remarkable fractality, as shown below.

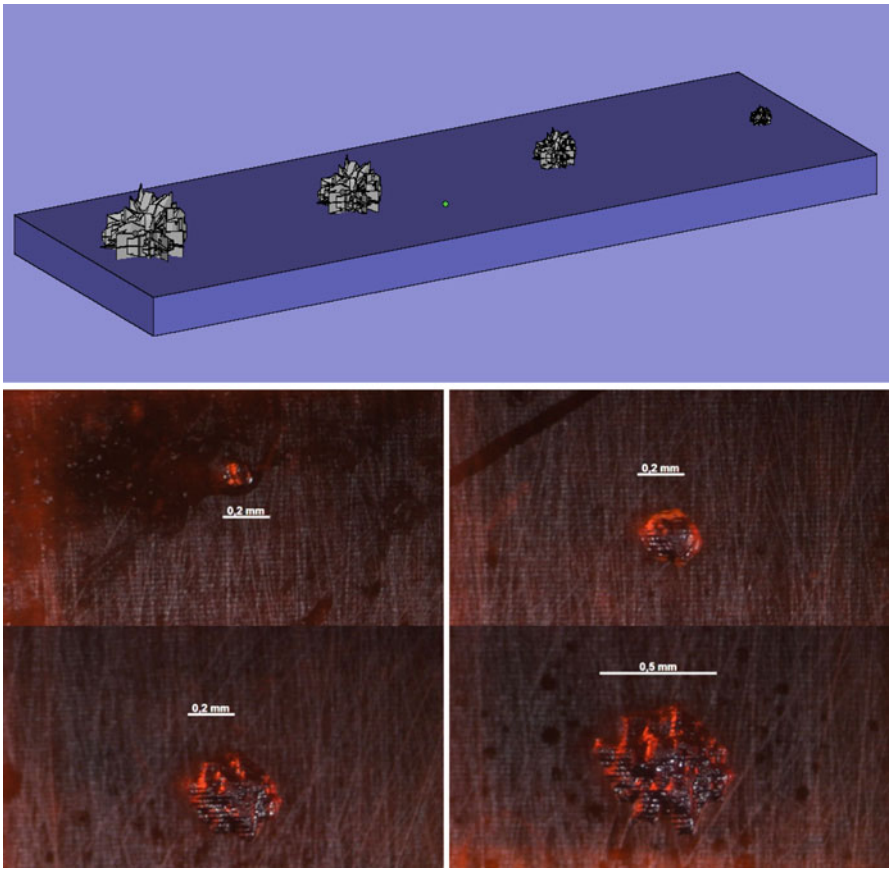

Fig. 10.17 CAD design of part with four fractal semispheres of different sizes, according to the design procedure described in Chap. 6 (see Sect. 6.4, Fig. 6.11), aimed at assessing the precision of the manufacturing system (Manufactured using digital light processing: Perfactory (EnvisionTec GmbH))

After an adequate assessment of the size of fractal spheres attainable, designs of more complex devices can be accomplished and manufactured, at least for a visual validation, as final ex vivo/in vivo trials would require their manufacture using alternative procedures, as already highlighted.

Figure 10.18 shows the CAD design of fractal scaffold based on Boolean operations using fractal spheres, according to the design procedure described in Chap. 6 (see Sect. 6.4, Fig. 6.11). In this case, the three different layers of fractal spheres we joined weakly and only the first layer could be adequately obtained, as shown below. In any case, the microtexture obtained corresponds to fractal semispheres and seems to be highly interesting for promoting cell adhesion and

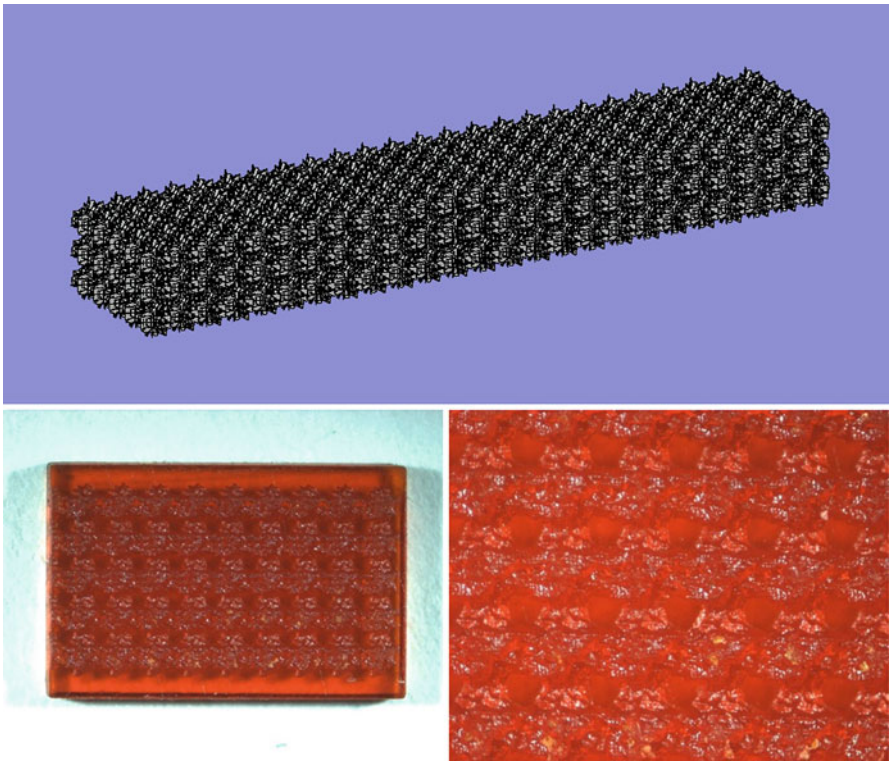

Fig. 10.18 CAD design of fractal scaffold based on Boolean operations using fractal spheres, according to the design procedure described in Chap. 6 (see Sect. 6.4, Fig. 6.11). Length of prototype, 8 mm (Manufactured using digital light processing: Perfactory (EnvisionTec GmbH))

"crawl," according to studies carried out with copies of these prototypes in more satisfactory biomaterials.

Figure 10.19 includes the CAD design of stent-like 3D structure, based on Boolean operations using fractal spheres, according again to the design procedure described in Chap. 6 (see Sect. 6.4, Fig. 6.11). External diameter is around 11 mm and its length reaches 9 mm, while the average diameter of the fractal spheres is around 3 mm. Of course such a stent, if not adequately drilled and polished in its inner surface, would be thrombogenic, but perhaps the microtextured external surface could lead to a more adequate fixation or be of help for drug delivery.

The application of such kind of textures to the surfaces of implants and all kinds of biodevices is of course matter of research, and several in vitro studies, currently being carried out, will provide additional information surely useful as design input.

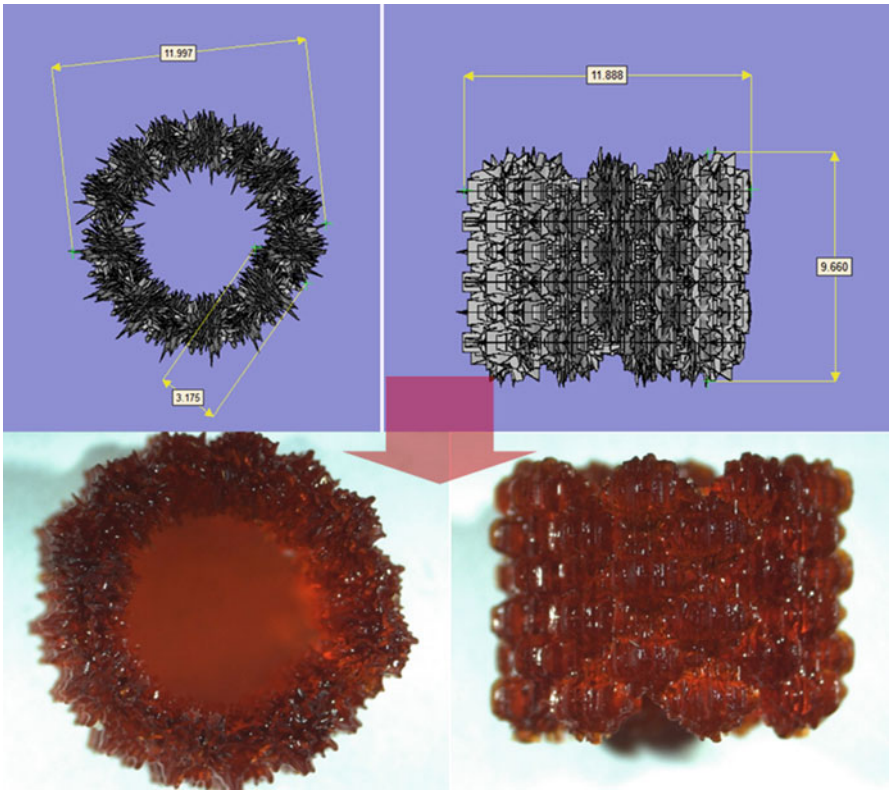

Fig. 10.19 CAD design of stent-like 3D structure, based on Boolean operations using fractal spheres, according to the design procedure described in Chap. 6 (see Sect. 6.4, Fig. 6.11). Length of fractal stent, 9 mm (Manufactured using digital light processing: Perfactory (EnvisionTec GmbH))

10.6 Case Studies: Additive Manufacture of Scaffolds for Tissue Repair Using Biopolymers and Polymers with PVD/CVD Biocoatings for Enhanced Biological Response

Many technologies working on the basis of photopolymerization processes (laser stereolithography, digital light processing, polyjet, etc.) usually work more properly with materials such as epoxy or acrylic resins, which are not adequate for final biodevices, due to their toxicity. In other cases, some technologies include a powder material (ceramic, polymeric, metallic, or even biological, including wood powder) and a second gluing material, as happens with conventional three-dimensional printing, what typically leads to non-biocompatible parts, due to the toxic effects of the gluing agent.

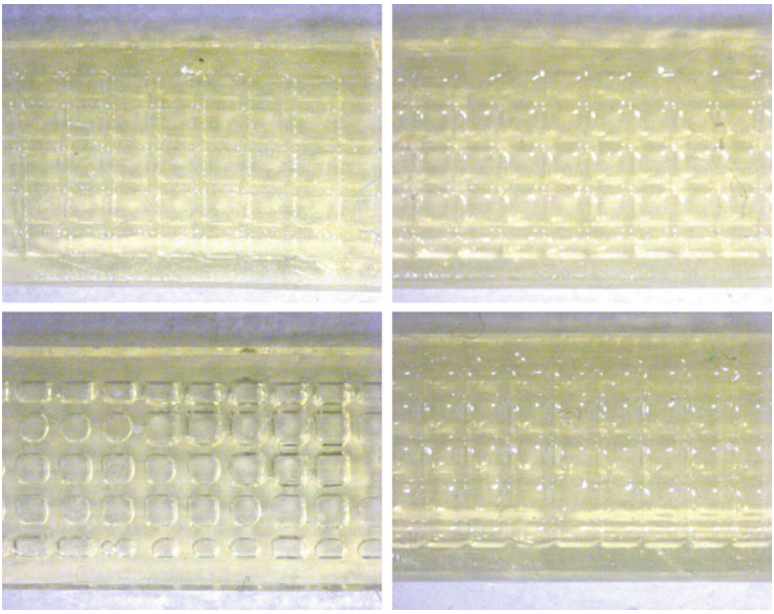

Fig. 10.20 Manufacture of scaffolds based on woodpile structures using a bio-photopolymer (poly(dimethacrylate of urethane)). *Upper left*: 100 mg curcumin/15 g prepolymer, 30 s exposure/layer. *Upper right*: 100 mg curcumin/15 g prepolymer, 50 s exposure/layer. *Lower left*: 50 mg curcumin/15 g prepolymer, 30 s exposure/layer. *Lower right*: 50 mg curcumin/15 g prepolymer, 50 s exposure/layer (Manufactured using digital light processing: Perfactory (EnvisionTec GmbH))

The use of alternative materials to those provided by the machine manufacturers can damage the prototyping machine and always goes at the researcher's own risk, as machine's guarantee does not cover such kind of "personalizations," being usually an expensive, although also a highly interesting strategy.

Of course some companies are aiming at broadening their materials portfolio and trying to include at least nontoxic materials for some research tasks linked to biomedical engineering. However, most relevant advances linked to the 3D structuring of biomaterials are still carried out by researchers at universities; some examples are included in the reference section (Stampfl et al. 2004, 2008; Manjubala et al. 2005; Infür et al. 2007; Schuster et al. 2007a, b).

The prototypes included in Fig. 10.20 are also result from exploring such directions. Our intention was to obtain woodpile structures, similar to those from Fig. 10.12, but using bio-photopolymers. The material synthesized for that purpose was a poly(dimethacrylate of urethane), whose synthesis, characterization, and proposals of application had been previously assessed (Baudis et al. 2009, 2010).

Biodevices such as vascular grafts and compact implants can be obtained, as well as cellular structures (with pores and inner details) for tissue engineering. A difficulty encountered during this research was linked to the difficulty of structuring inner details through digital light processing if the base material is almost

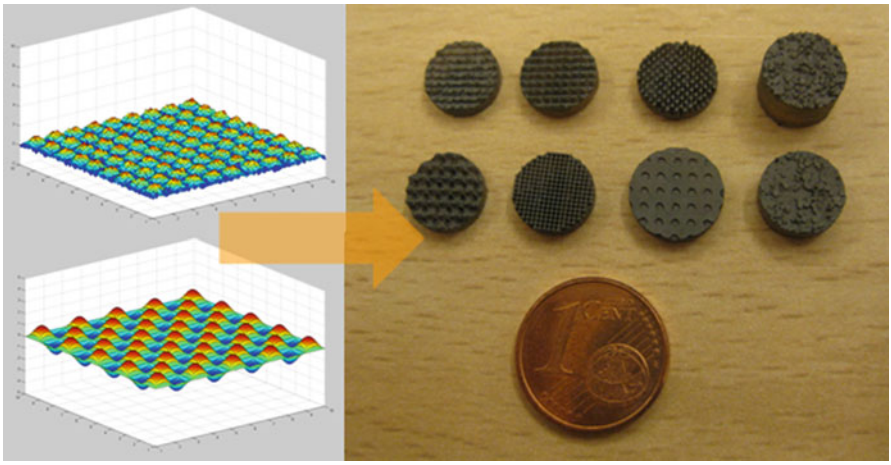

Fig. 10.21 Different Matlab-based CAD designs of microtextured scaffolds and prototypes manufactured in epoxy resin using laser stereolithography and final diamond-like carbon coating for improving biocompatibility. See Chap. 15 for ex vivo trial of h-MSC upon these scaffolds (Additional details: (Díaz Lantada et al. 2012))

transparent. In such case, light penetrates easily through the material and several layers can be polymerized at a time, thus eliminating the pores and inner details included in the CAD design. In order to limit light penetration and improve precision, organic colorants can be used, such as curcuma.

Figure 10.12 shows the effect of different proportions of colorant and exposure times on final woodpile structure. It can be seen that the manufacture of patterned thin sheets for cell growth studies is possible, even though structuring larger and more complex parts needs further research. Anyway superposition of thin sheets can also lead to final 3D structures, and if the sheets are previously patterned with cells and nutrients and added to each other, when cells are already growing, some interesting results connected with the field of biofabrication might be obtained.

Another possibility, if the biodevices or scaffolds are not aimed at final long-term implantation, is the use of a protective coating upon more conventional rapid prototyping materials, such as epoxy or acrylic resins. Such bio-coating, normally obtained by physical or chemical vapor deposition (see Chap. 13), can help with ex vivo trials for assessing the effect of microtextures, pore sizes, and overall scaffold morphology on cell growth and subsequent differentiation into relevant tissues.

However, if implanted, progressive deterioration or delamination of the coating (due to combined mechanical and chemical effects) could possibly lead to the basis material being in contact with corporal tissues and producing undesirable effects.

Figure 10.21 shows different Matlab-based CAD designs of microtextured scaffolds and the rapid prototypes manufactured in epoxy resin using laser stereolithography, which here benefit from a final diamond-like carbon (DLC) coating for improving biocompatibility. Compact coatings were obtained, with thickness of around 100 nm, by deposition at room temperature using the vacuum filter cathodic

arc technique. Remarkable adhesion and film conformity were obtained in all of the deposition trials.

In any case, these trials have helped also to verify the viability of successfully protecting rapid-prototyped epoxy parts with diamond-like carbon coatings, which are highly biocompatible as previously reported in the literature (Salgueiredo et al. 2008; Endrino et al. 2008).

In fact final results with h-MSC (Díaz Lantada 2012, see Chap. 15 also) have proved that the influence of the coating on cell-scaffold interactions is indeed very relevant and can be a useful option if the prototypes cannot be directly obtained by structuring of biomaterials.

More alternatives for obtaining final biocompatible biodevices, in many cases by using preliminary rapid prototypes as basis for different processes (form/shape copying, mold making, casting, coating, among others), are discussed in Chaps. 11–14.

10.7 Main Conclusions and Future Research

Rapid prototyping and manufacturing technologies allow researchers to obtain physical parts in a short period (hours or days), directly from the designs created with the help of computers using computer-aided design, engineering, and manufacturing "CAD-CAE-CAM" programs. Such technologies significantly help to optimize the design iterations, allowing for the early detection of errors. They are generally based on automatic additive or layer-by-layer manufacturing processes, what helps to manufacture very complex geometries with inner details.

This chapter has provided an introduction to these technologies and their applications, especially focusing on the different areas of applications within biomedical engineering, including the direct development of biomodels for diagnosis, of biomodels for surgical training, of implants for hard and soft tissue replacement, of orthotic biodevices, of biodevices based on smart materials, and of biodevices for tissue engineering, as well as novel approaches linked to the area of biofabrication.

Several case studies and applications, of additive manufacturing in biomedical engineering, have also been detailed and discussed, including implantable devices, extracorporeal appliances, and devices for diagnostic and in vitro trials, many of them linked to tissue engineering, explaining also some related current limitations and research challenges.

Main desirable advances for an even more direct application of additive manufacturing in biomedical engineering are currently linked to improvements in processable materials and to precision enhancement for larger parts (as some technologies are already providing more than enough precision, although in parts around 1–10 mm^3, useful only for some very specific applications). Some of the topics detailed in Chap. 11, on "rapid tooling"; on Chap. 12, on micro-manufacturing; on Chap. 13, on nano-manufacturing; and on Chap. 14, on "biofabrication," are also connected with possible improvements on the biocompatibility of final rapid-prototyped devices.

In any case, the industrial impact of these additive manufacturing technologies and their more extended application to research tasks, especially in fields such as

biomedical engineering and materials science, can be remarkably promoted by the development of more accessible technologies (cheaper and easier to handle and manipulate) as well as by the collaboration between researchers and institutions worldwide (development of standards, establishment of roadmaps, etc.).

It is important to mention the "RepRap" project (reprap.org), a collaborative wiki-based project focused on the development of very economic, "do-it-yourself," and "self-replicating" additive manufacturing machines, as one of the most remarkable initiatives trying to promote easier access (from researchers to hobbyists) to these technologies. Such collaborative platforms can be of great help for solving many of current research challenges in the field of additive manufacturing.

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Chapter 11
Rapid Form Copying and Rapid Mould-Making Systems for Biodevices

Andrés Díaz Lantada, Pilar Lafont Morgado, and Pedro Ortego García

Abstract Previous chapters have focused on different technologies for automated rapid prototyping of parts for validation trials and also final production parts, with two main approaches, in the one side high-speed CNC machining and in the other side "AMT" or "layer by layer" based.

In some cases, CNC machining is not able to provide some complex biomimetic geometries, and in other cases, additive manufacturing does not always work with proper biomaterials. A versatile alternative for producing rapid prototypes, in a wide set of materials and oriented to the production of short and medium series for more systematic pre-production trials, is the use of rapid form copying processes, normally aiming at direct texture/pattern replication or at the rapid manufacture of moulds for subsequent casting of more adequate materials.

Such rapid form copying processes normally use master models, obtained by high-speed CNC machining or by additive manufacturing methods, whose outer geometry is copied using silicone or PDMS for creating a soft mould, in which many types of (bio)materials can be later casted for obtaining more advanced or adequate prototypes for trials. In some cases more rigid moulds can be obtained by using resins with metallic additives instead of silicone, normally oriented to the manufacture of medium series by laboratory injection moulding.

This chapter provides an introduction to these rapid form/shape copying and rapid mould-making systems, including case studies linked to direct form replication by sol–gel processes, direct form/shape replication for obtaining silicone or PDMS sheets, rapid soft mould manufacture and casting of biomaterials in rapid moulds. A brief additional discussion on future directions and challenges and on present difficulties is also provided, as an introduction for next chapter's topics.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_11,

11.1 Introduction to Rapid Form Copying and Rapid Tooling

The present chapter focuses, within the field of rapid manufacturing, on second-phase technologies, normally linked to the use of rapid moulds obtained by copying the geometries of prototypes obtained by first-phase technologies (see Chap. 10), for obtaining final parts in more specific materials. The global panorama of rapid manufacturing was already introduced in Chap. 3, although the additional introduction provided here serves as a reminder. It is important to reintroduce some definitions, nowadays very common in the product development industry and progressively expanding into the biomedical field (Díaz Lantada and Lafont Morgado 2012).

Rapid Form/Shape Copying. Consists of using a master model or "green part" usually obtained by a rapid prototyping approach, based on additive manufacturing or on high-speed numerical control machining, as a pattern to create a replica very rapidly, by casting, vacuum casting, injection or even stamping or hot embossing, in a more adequate material for the final purpose of the geometry being copied. In many cases the "green part" is designed with final geometry, and the rapid form copying process leads to a mould (see "rapid tooling" below), in which pre-series can be obtained. In other cases the rapid copying process leads directly to a final part, in which case the master model has to be designed as the negative geometry of the desired part.

Rapid Tooling. Is typically used to describe a process which either uses a rapid prototyping model as a pattern or master to create a mould easily, rapidly and in a very economic way or uses a rapid prototyping process directly to fabricate a tool or mould cavity for a limited volume of prototypes. Tooling time is then much shorter (tools can be typically obtained in less than a week) and cost is also much less than for conventional tools (i.e. in steel by electrodischarge machining), although tool life is considerably lower than for conventional tools and tolerances are also wider.

Many of the most used rapid tooling processes are based on rapid form/shape copying approaches. Using a rapid-prototyped model, the cavities of a mould can be obtained by placing the model in the middle of a case and filling the case with a pre-polymer, a pre-polymer with ceramic charge or a pre-polymer with metallic charge, so as to obtain a block of solid material. Final cutting and model extraction lead to the mould cavities (or tools) for further casting, vacuum casting or injection of more adequate materials for the second-phase prototypes. In some cases, when the tooling material is especially hard, cutting is not an option and cavities are obtained by filling the case just to the partition line, although two steps are then needed.

In other cases, the mould cavity or tool can be directly obtained by using rapid prototyping facilities such as selective laser sintering and selective laser melting, among others, typically working with metal powders for obtaining hard and highly resistant pieces.

For laboratory experiences even RP technologies working with polymers (normally thermoset polymers) can be useful for obtaining such rapid tools and subsequently stamping or embossing other thermoplastic polymers and low-melting-point biomaterials.

Depending also on the material's hardness and expected life of the rapid tool or cavity obtained, the rapid tooling processes can also be divided in some more groups commented below:

Soft tooling. Makes reference to silicone moulds obtained by rapid form copying processes, which usually allow for the manufacture of short series of 25–50 polymeric parts by casting or vacuum casting, as the mould material progressively deteriorates due to thermal shock when the polymers are casted or thermally cured.

Bridge tooling. Makes reference to harder moulds obtained usually by rapid form copying using low-melting-point alloys or pre-polymers with metallic or ceramic micro-/nanocharges used for increasing hardness, mechanical resistance and cavity service life. Normally short–medium series of 100–1,000 parts can be obtained by conventional injection moulding, once the cavities are arranged as a prototype mould. As the mould material has usually a polymeric matrix, temperature cycles produce continuous relevant mechanical deformations and stresses and the mould deteriorates rapidly.

Hard tooling. Makes reference to rapid moulds obtained in metals aiming to provide the most possible similar results to those from final production injection moulding using steel moulds. Normally the cavities are obtained by easy machinable metals (aluminium alloys, brass, etc.) by high-speed CNC machining or by additive manufacturing technologies capable of working with metals (normally starting from metallic power), such as selective laser sintering, selective laser melting, laser cusing and laser cutting, among others. Much larger series (in many cases for substitution of final production) even up to 100.000–500.000 parts can be obtained.

The aforementioned processes provide a step-by-step validation, increasing the level of detail of final prototypes and their resemblance to mass produced parts, helping to detect and correct possible defects before investing in final steel moulds for mass production. Additional information on these processes and on the different tolerances, expected life of components and typical industrial applications can be found in the references (Lorenzo-Yustos 2008).

The next section provides an overview of applications of rapid form copying and rapid tooling for the biomedical field, before focusing on more specific case studies linked to the development of biodevices for in vitro and in vivo trials using adequate biomaterials.

11.2 Benefits from Using Rapid Form Copying and Rapid Tooling for the Biomedical Field

Rapid prototyping by means of additive manufacturing was already highlighted in Chap. 10 as a powerful set of technologies capable of enormously promoting the optimisation of cost and schedules in conventional product development processes.

Even though every year novel technologies appear and the use of more and more polymeric, metallic, ceramic materials is possible (Wohlers 2010) and some recent advances are even aiming at the manufacture of 3D biodevices by deposition of biological materials (Mironov et al. 2009, see Chap. 14), it is still true that many of the widely available technologies providing the best quality (precision)/cost relationship cannot directly work with materials adequate for in vitro, ex vivo or in vivo trials.

For instance, as already detailed, many technologies working on the basis of photopolymerisation processes (laser stereolithography, digital light processing, polyjet, etc.) usually work more properly with materials such as epoxy or acrylic resins, which are not adequate for final biodevices, due to their toxicity. In other cases, some technologies include a powder material (ceramic, polymeric, metallic or even biological, including wood powder) and a second gluing material, as happens with conventional three-dimensional printing, what typically leads to non-biocompatible parts, due to the toxic effects of the gluing agent.

The use of alternative materials to those provided by the machine manufacturers can damage the prototyping machine and always goes at the researcher's own risk, as machine's guarantee does not cover such kind of "personalisations", being usually an expensive, although also a highly interesting, strategy.

Of course some companies are aiming at broadening their materials portfolio and trying to include at least non-toxic materials for some research tasks linked to biomedical engineering. However, most relevant advances linked to the 3D structuring of biomaterials are still carried out by researchers at universities; some examples are included in the reference section (Stampfl et al. 2004, 2008; Manjubala et al. 2005; Infür et al. 2007; Schuster et al. 2007a, b).

Therefore, rapid tooling still provides several highly remarkable alternatives, for obtaining prototypes in more adequate materials for final purpose, especially if the use of biomaterials is required (as is usually the case in the development process of novel biodevices, when the different in vitro, ex vivo and in vivo trials are required), than most of the currently available rapid prototyping technologies.

In fact many biomaterials are difficult to be structured in an additive way but are indeed very apt to other conformation processes, such as casting, injection moulding stamping or hot embossing, and the use of rapid tools and rapid moulds proves to be very adequate for the rapid manufacture of prototypes for trials, as the case studies included in the following sections detail.

11.3 Case Studies: Manufacture of Biodevices by Vacuum Casting in Rapid-Copied Silicone Moulds

The process of silicone (also polydimethylsiloxane or "PDMS") mould manufacture, based on a master model obtained normally through rapid prototyping, involves some steps described further on. We concentrate on the process aimed at obtaining a two-part mould, as the process for obtaining a single cavity is simpler.

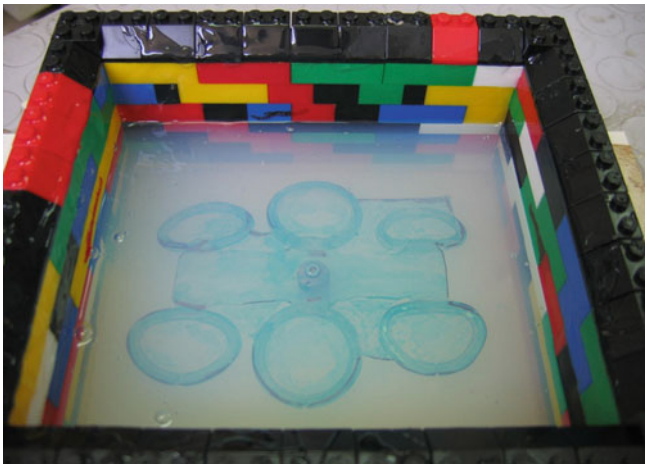

Fig. 11.1 Preparation of a silicone mould. Aspect after degasification

First of all, the partition line is defined, normally by attaching adhesive tape to the lateral part of the master model or by joining the different models together to a central entrance channel (in the case of a multicavity mould, as the following example shows). Then the model(s) is placed in the centre of a cubic cage, levitating thanks to some additional supports (tooth sticks, more adhesive tape, etc.). The bicomponent liquid mixture for producing the silicone is carried out and poured into the mould, until the whole model is covered, while polymerisation is starting. It is advisable to carry out the polymerisation process at low-pressure atmosphere (into a vacuum chamber) so as to allow degasification of the silicone and avoid a final hollow structure. After polymerisation (see Figs. 11.1 and 11.2), the mould has to be cut, following the partition line, for finally extracting the master model and leaving the two cavities ready for closure and casting of new formulations.

Some interesting tutorials can be found at www.makeyourownmolds.com including also references to mould-making kits, materials suppliers and mould-making suppliers and accessories.

Vacuum Casting. By taking prototypes manufactured using rapid prototyping technologies or layer manufacturing technologies, silicon moulds can be made for rapid shape copying to reproduce the geometry of the original model with precision using polymer materials with different kinds of micro- and nanocharges or micro- and nanoforces. These "soft" moulds can be used to make short runs of 25–50 units, usually to make concept samples and verify functions before proceeding to manufacture prototypes with the definitive process.

Vacuum casting makes it easier to fill the mould, improves the final precision and helps to eliminate the bubbles that form during the curing process of many of the dual component polymers usually used for this type of casting. During the mixing process, before casting, the micro- or nanocharges can also be added (like those in

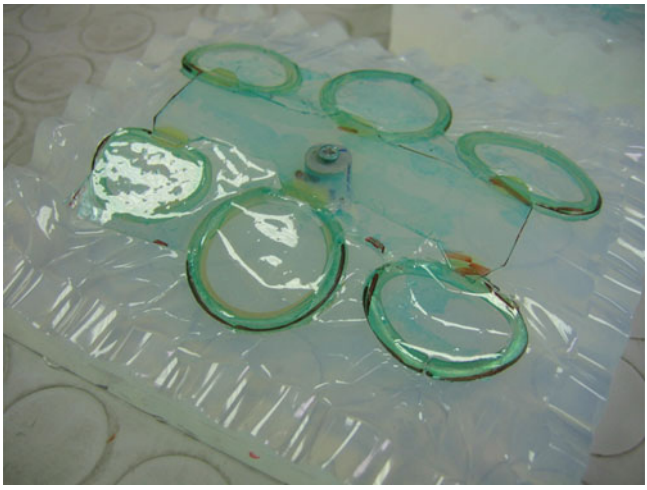

Fig. 11.2 Silicon mould. Aspect after cutting and separation of the two mould cavities, just before extraction of the model for subsequent casting

the image below) using mechanical and ultrasonic agitators to improve the dispersion of the particles and achieve more homogeneous properties.

Vacuum casting in silicone moulds comes under rapid prototyping and rapid tooling technologies called "second-phase technologies", since they require an additional step to obtain the prototypes or equipment required from some initial models. Obtaining physical prototypes is therefore not so direct or rapid (a couple of days are needed instead of a few hours), but the chance to use materials with properties similar to the end parts justifies its use.

Once the mould is obtained and the original models extracted, the mould is closed again, using metallic clips or adhesive tape, and placed in the vacuum casting machine. The polymeric mixture to be casted (normally bicomponent polyurethanes in conventional applications and several biopolymers in biomedical engineering) is prepared and subsequently introduced into the mould through a channel. At the beginning just gravity acts, but once the material begins to fill the mould, further assistance from vacuum in the mould chamber helps to fill the mould completely and to obtain a remarkable level of precision. After polymerisation, the mould is opened again, and final prototypes are extracted for carrying out some last adjustments.

By way of example, Figs. 11.3 and 11.4 show a comparison between active annuloplasty rings produced by using shape-memory polyurethane (white, from MCP Iberia ref. 3115) and shape-memory polyurethane and graphite powder (12 % by weight), to optimise the thermal conductivity and other mechanical properties of the original polymer. Additional details linked to the final application of shape-memory polymer-based biodevices for the production of active implants, with the capability of changing their geometries upon heating, thus producing geometrical changes to adjacent tissues and organs for treating several pathologies, can be found in the reference section (Díaz Lantada 2009, 2012; Díaz Lantada et al. 2009).

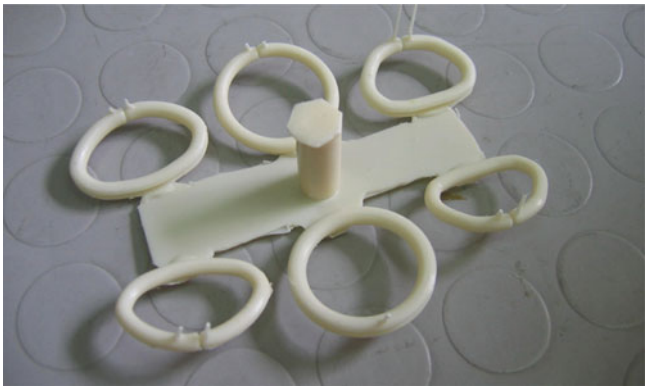

Fig. 11.3 Active annuloplasty rings manufactured by vacuum casting in silicone moulds using shape-memory polyurethane

Fig. 11.4 Active annuloplasty rings manufactured by vacuum casting in silicone mould using shape-memory polyurethane with graphite powder (12 % weight)

As a brief introduction, these kind of active annuloplasty rings are aimed at their being implanted with a temporal geometry adapted to the insufficient valve, and, after the patient is recovered, controlled heating should lead to progressive mitral valve section reduction, thanks to the shape-memory training process.

In any case it is very important to note the possibility of using rapid moulds for casting several (bio)materials, even active or "intelligent" materials for including some additional functions to final biodevice. The possibility of using a mould in repeated occasions is also of great help for analysing the influence of composition or additives in the performance of the different prototypes, as necessary part of the material selection process.

Such additives, especially some changing the optical properties of the base polymer (carbon nanotubes, graphite powder, carbon black, silver or gold nanoparticles, etc.) would dramatically affect a rapid prototyping process by photopolymerisation and probably prevent such comparative studies, while in the case of vacuum casting in rapid moulds, the influence of additives is minor and final prototypes with different properties can be easily obtained.

Next sections provide additional examples more linked to the use of biomaterials, either using sol–gel processes upon rapid-prototyped master models or again by casting in rapid-copied silicone moulds.

11.4 Case Studies: Manufacture of Biodevices by Copying the Geometries of Rapid Prototypes Using Biomaterials

The similar strategy of rapid shape copying for obtaining rapid moulds can be used for manufacturing final prototypes for trials. The process usually involves placing the master models in the bottom of a box or case and, subsequently, casting the desired final material (in a liquid state) upon them. Final solidification, polymerisation or gelation leads to a stable replica that can be cut into small parts or probes. We have used such an approach for obtaining micro-patterned and micro-textured biodevices in PDMS, several gels, beeswax and low-melting-point alloys, among other materials susceptible of biomedical applications. The level of detail is remarkable, and features of around 5–0 μm are simple to replicate if the process is carried out methodically.

The examples included in this section, shown in Figs. 11.5 and 11.6, are linked to sol–gel processes. These sol–gel processes are characterised by their transition from a sol phase to a gel phase, usually by various hydrolysis and poly-condensation reactions, and are used for producing vitreous and ceramic materials. The sol is made up of solid particles (usually around 0.1–1 μm in diameter) dispersed in a liquid, while gel comprises a solid network of macromolecules immersed in a solvent. The conventional stages of the process are additionally described in the references (Brinker and Scherer 1990; Hench 1998; Albella 2003, 2006) and in Sect. 13.5.

Here we focus on the replication of some micro-textured biodevices based on the use of fractal patterns for carrying out cell motility studies. The design and manufacture of the master models were detailed in Sect. 10.5 and in Figs. 10.14–10.16). The main problem of such master models obtained through digital light processing in acrylic resin is their toxicity for ex vivo trials, what has to be solved for carrying out the desired studies. A possibility is replicating such geometries using more adequate biomaterials. In this example, we have used different sol–gel processes based on products from the "Texturas" series by Albert and Ferrán Adriá (www.albertyferranadria.com), directly acquired from their exclusive distributor Solé Graells (www.solegraelss.com). We have used agar (powder obtained from some types of red algae, *gelidium* and *gracilaria*) and gellan (powder from vegetal gum obtained

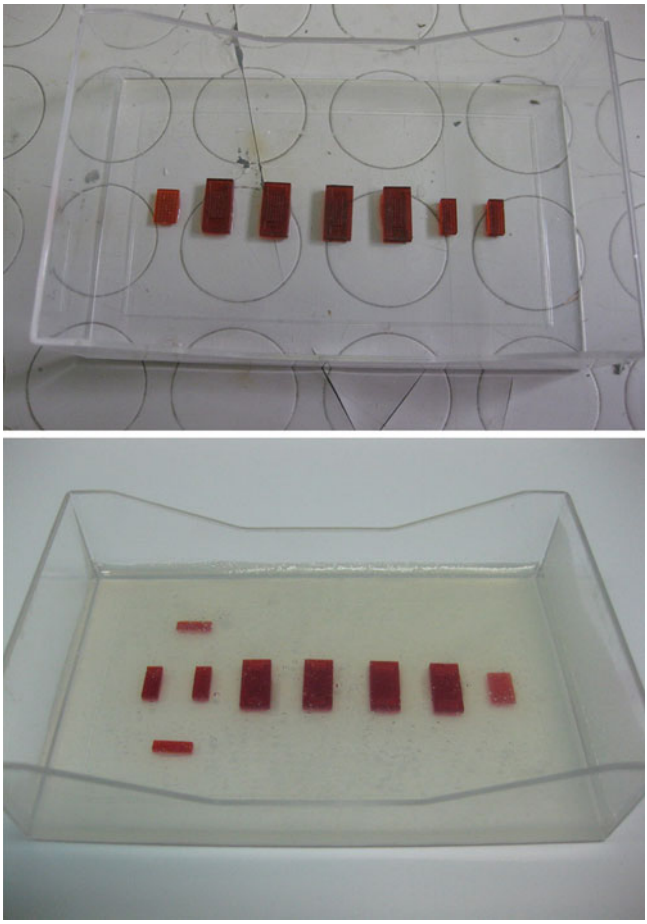

Fig. 11.5 Rapid mould with original models (*scaffolds*), obtained by additive manufacturing, prepared for replication. Agar gel film obtained by sol–gel process

through fermentation of glucose through the action of the bacteria *sphingomonas elodea*).

The sol–gel process involves preparation of the sol by pouring around 5–6 % in weight of the mentioned powders in different water containers and continuous agitation during heating until boiling. Once the sol is boiling, pouring into the box, with the different micro-textured prototypes to replicate, and cooling down leads to gelation (Fig. 11.5). After around 1–2 h in the refrigerator, the gel can be extracted and cut for obtaining final parts (Fig. 11.6). By careful control of the weight ratio of powder used for obtaining the sol, mechanical strength can be tuned to desired applications. Additional information can be found in the specification sheets of the suppliers of these or similar materials.

Fig. 11.6 Details of the micro-textured gel replicas obtained

Main limitations of the gels achieved are linked to long-term mechanical and dimensional stability, as with time, the gel begins to lose water and to suffer deformations. These parts are aimed at carrying out cell motility and cell growth studies, linked to tissue engineering research, so the studies should be started just after the gel is obtained and in a swollen environment, as usual with cell-related studies.

Some post-processes typical from the sol–gel science include supercritical drying for obtaining an aerogel and conventional drying for obtaining a xerogel, in this case based on a biological material. The aerogel should provide a similar geometry to that of the initial gel, but with a porous structure, what has relevant applications in the tissue engineering field. The xerogel can be milled into powder for further sinterisation in moulds for replicating other geometries.

Additional strength and dimensional stability of the final gel can also be obtained by the inclusion of ceramic or metallic nanoparticles, what is commonly

denominated as gelcasting technique, with which final porous solid structures are obtained. Some details of the versatility of gelcasting processes can be obtained in the reference section (Dhara et al. 2002).

Among the advantages of hydrogels for tissue engineering, it is important to cite the possibility of including nutrients and cells onto the hydrogel and subsequently adapting the form of the gel to that of a desired device or scaffold or even obtain 3D structures by drop-by-drop deposition of the gel, for subsequent cell growth and tissue formation. Some notes on the adaptation of 3D printers to 3D biogel printers for biofabrication are provided in Chap. 14.

11.5 Case Studies: Manufacture of Biodevices by Casting Biomaterials in Rapid-Copied Silicone Moulds

As previously mentioned, the main difficulty with the master models (from Sect. 10.5) obtained through digital light processing in acrylic resin is their toxicity for ex vivo trials, what has to be solved for carrying out the desired cell motility and growth studies. We have proposed a possible solution in Sect. 11.4 by means of sol–gel processes using powders from biological origin as gel precursors.

In this Sect. 11.5, we provide an even more versatile approach based again on obtaining silicone moulds, in a similar way as explained in Sect. 11.3, but only needing one part per mould (for the different case studies detailed further on), due to the geometry of the different parts, at which replication we are focusing.

Figure 11.7 details the process of one-part silicon mould making, first by casting the pre-polymerised silicone into the box with the master models to replicate and then by introduction in vacuum chamber for degasification and bubble breakage of the silicon during its polymerisation, so as to obtain a final silicone sheet, part or cavity without pores.

Figure 11.8 shows the silicone mould obtained for further replication of different microsystems for cell motility studies, whose design process and manufacture of master models were already described in Sect. 10.5 (Figs. 10.14–10.18). Even though it is just a one-part mould, the incorporation of different cavities is aimed at a more productive casting process.

For example, in the mould shown below, there are nine cavities, four of them linked to microsystems with “pools” for the cells connected through micro-textured channels with different fractal dimension, four of them linked to parts with micro-textured fractal paths and one of them for replicating a part with a texture based on semi-spherical fractals.

Dimensional verification has to be carried out at different stages, so as to see if the master model reproduces adequately the original CAD design, to evaluate if the silicone mould reproduces correctly the features of the master model and to validate the geometrical characteristics of final casted part and its fidelity to the original design.

Figure 11.9 shows the silicone mould obtained for further replication of different scaffolds for cell growth and tissue engineering-related studies, whose design

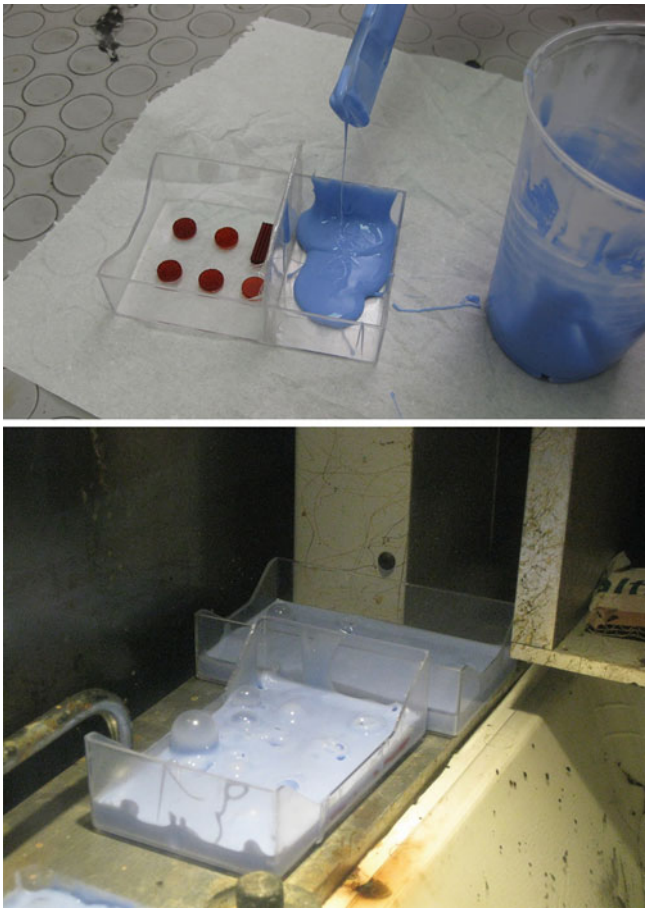

Fig. 11.7 Rapid mould with original models (*scaffolds*), obtained by additive manufacturing, and silicone casting process. Silicone degasification process for enhancing the detail level and avoiding final porous moulds

process and manufacture of master models were already described in Sect. 10.5 (Figs. 10.13 and 10.14). Even though it is just a one-part mould, the incorporation of different cavities is aimed at a more productive casting process.

The five circular cavities include different scaffold with different fractal dimension (2 planar; 2,2; 2,4; 2,6; and 2,8) for assessing the effects of fractal dimension on cell growth, differentiation and final tissue formation. The rectangular cavity includes a part with different fractal paths for studying cell crawl and assessing the impact of fractal dimension on their behaviour.

Figure 11.10 shows final prototypes obtained through beeswax casting using the mould from Fig. 11.8. The wax is heated until melting (just above 64 °C) and then poured into the mould. It is important to preheat the mould at around 70 °C in oven,

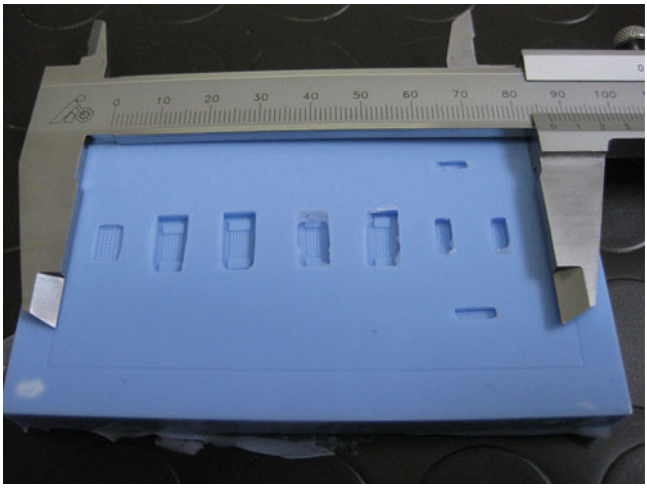

Fig. 11.8 Silicone mould, for subsequent casting of biomaterials. The different cavities reproduce the geometry of microsystems with several channels for studying cell motility

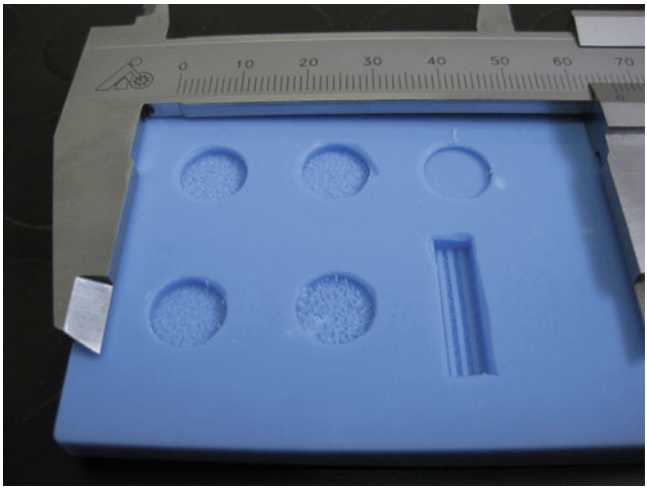

Fig. 11.9 Silicone mould, for subsequent casting of biomaterials. The different cavities reproduce the geometry of scaffolds with fractal surface for promoting cell growth and differentiation

so as to avoid sudden solidification upon contact of the wax with a cold surface, what would prevent the different cavities from filling correctly. The level of detail can be appreciated by having a look at the bottom image of Fig. 11.10.

The possibility of obtaining wax replicas of different rapid prototypes, even through the use of a second-phase process, is remarkable indeed, not just for using wax parts in biomedical applications (as it is a biomaterial) but also for obtaining metallic parts/prototypes. For improved production, a wax tree, to

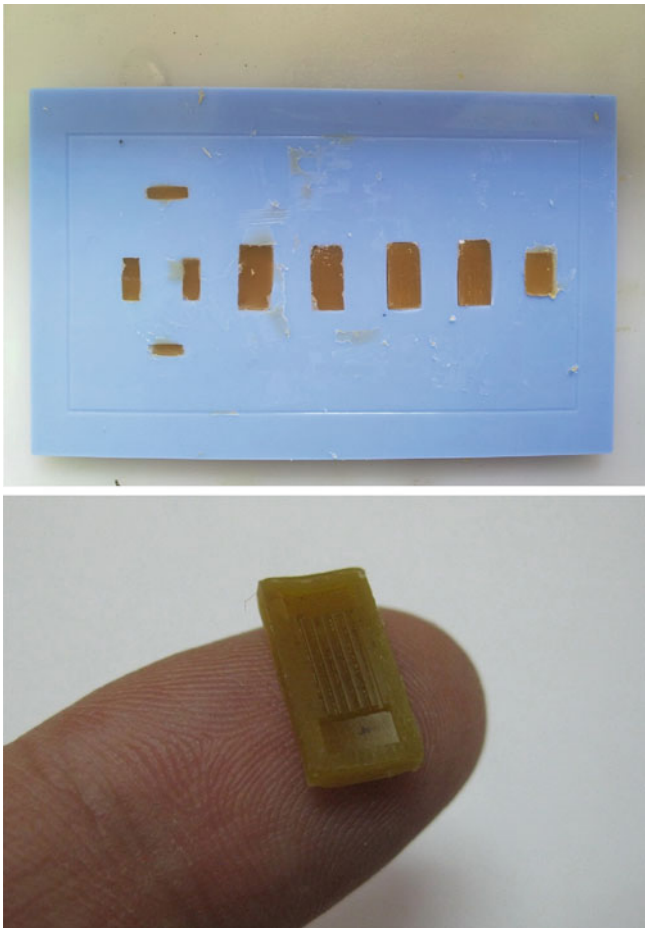

Fig. 11.10 Microfluidic device for cell motility. Replicas obtained by casting of beeswax, after wax melting above 64 °C

which different wax replicas are attached, can be constructed, as a basis for obtaining a ceramic mould and final casting of several metals and alloys by the lost-wax casting process.

Final metal part is obtained through a third-phase process (first rapid prototype, second silicone mould and wax replica, third ceramic mould and metal replica), although the use of special geometries allows the direct achievement of a ceramic mould upon a polymeric master model ("quickcast" process, Lorenzo-Yustos 2008), hence reducing one stage.

Some rapid prototyping technologies, working on an additive approach, also allow the direct manufacture with metals and alloys, although through the lost-wax casting process, a greater range of metallic materials (even though some relevant ones for the biomedical industry as titanium and titanium alloys do not cast properly, as they tend to explode) can be used for obtaining the final prototypes.

Technologies based on the lost-wax casting process, such as microfusion from MCP, carry out the metal casting process on a low-pressure chamber with inert atmosphere, hence promoting final quality and precision.

In any case most metallic prostheses and implants, especially Ti and Ti alloys, are currently, depending on size and geometry, CNC machined, laser machined or micro-machined, wrought or conformed in their plastic state (superplastic forming) (Klose et al. 2008), although relevant studies also focus on their solid free-form fabrication through more recent AMT such as electron beam melting (Thomsen et al. 2008).

The different alternatives complement each other, and further research may lead to highly interesting connection between very different manufacturing approaches, either if final metallic part is directly obtained or if several stages are required. In some cases time schedules will be more important than cost; in others the availability of a technology will account for final decision, therefore the establishment of collaborative research consortia, placing at the different partners' disposal the set of technologies available, is proving of great importance (see Chap. 12).

We just wanted to precise that, although rapid form/shape copying and "soft" tooling (in the biomedical field) are usually more connected with the manufacture of prototypes using biopolymers, biogels and biomaterials in general, there is also the possibility of finally obtaining prototypes using metals and alloys, what may also be of great interest for several applications linked to biomedical and tissue engineering.

11.6 Main Conclusions and Future Research

Apart from being used as technologies to allow speeding up new product production start-up, as they greatly help to optimise costs and timescales, rapid prototyping and rapid tooling technologies also serve to promote several research tasks in the field of biomedical engineering. Their use as a support for researchers and scientists trying to incorporate biomaterials and functionalities, based on the use of special materials, as the integral parts of more complex biodevices is becoming particularly relevant.

This chapter has provided an introduction to these rapid form copying processes and rapid mould-making procedures, including case studies linked to direct form/shape replication by sol–gel processes, direct form/shape replication for obtaining silicone or PDMS sheets, rapid soft mould manufacture and casting of biomaterials in rapid moulds.

The possibility of using rapid moulds in repeated occasions is also of great help for analysing the influence of composition or additives in the performance of different prototypes, as a necessary part of the material selection process. Such additives, especially some changing the optical properties of the base (bio)polymers (including carbon nanotubes, graphite powder, carbon black, silver or gold nanoparticles), would dramatically affect a rapid prototyping process by photopolymerisation and probably prevent such comparative studies, while in the case of casting or vacuum casting in

rapid moulds, the influence of additives is minor and final prototypes with different properties can be easily obtained. Therefore, the impact of these technologies on research in the materials science field is also highly remarkable.

As the case studies described here are linked to laboratory experiences at our UPM Product Development Laboratory, normally requiring only short series for validation, we have just focused on the "soft tooling" sector of the "rapid tooling" area, as the use of silicone moulds and parts is very appropriate for the studies commented. Further experiences linked to more conventional product developments, aimed at mass production by injection moulding, which typically benefit from more specific validations through "bridge and hard tooling", can be found in the reference section.

Some of the processes and techniques detailed in the present chapter, whose replication precision is in the range of a few microns, are directly connected with the field of micro-manufacturing, which is covered in depth in Chap. 12, so in this chapter has also served as an introduction to some aspects of micro-manufacturing technologies. Additional relevant information for more in-depth studies can be found in the reference section.

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11.6.1 Some Interesting Related Websites

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Chapter 12
Micro-manufacturing Technologies for Biodevices: Interacting at a Cellular Scale

Andrés Díaz Lantada, Pilar Lafont Morgado, and Pedro Ortego García

Abstract Micro-manufacturing technologies started in the late 1950s mainly linked to the electronic industry, for producing circuits with improved performance, without a dramatic increase of final device size. Such beginning was very connected to the properties of silicon, which can be easily micromachined using chemical attacks through specially designed patterns or masks.

The progressive adaptation of these techniques for micromachining alternative materials, including metals, ceramics, and polymers, and the introduction of novel manufacturing technologies, including laser micro-manufacturing, electron-/ion-beam milling, micro-replication tools, and high-precision additive manufacturing, have greatly promoted final quality of the obtained microsystems, as well as the incorporation of additional features and the combination of materials, in many cases using thin-film technologies for special contact phenomena.

The applications of microsystems in the biomedical field are indeed remarkable and continuously evolving thanks to progresses in the aforementioned micro-technologies, as explained in detail in this chapter. As living organisms are made up of cells, whose dimensions typically range from 10 to 100 μm, micro-manufactured devices (with details precisely in that range) are very well suited to interacting at a cellular level for promoting innovative diagnostic and therapeutic approaches.

Main fields of application of microsystems in Biomedical Engineering are also discussed and several examples provided, as a basis for discussion on future trends, present knowledge, and technical challenges. Connections with the following chapter, about nano-manufacturing, are also established by paying attention to relevant new tools working between the "micro" and the "nano" world.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_12,

12.1 Introduction to Micro-manufacturing Technologies

Micro-manufacturing technologies, capable of manufacturing devices with details in the typical range of 1–500 μm, started in the late 1950s mainly linked to the electronic industry, for producing circuits with improved performance, without a dramatic increase of final device size. Such beginning was very connected to the properties of silicon, which can be easily micromachined using chemical attacks through specially designed patterns or masks.

The lecture "There's plenty of room at the bottom," given at Caltech in 1959 by Richard P. Feynman (reprinted 1992, revised 1993), focused on the possibility of improving and expanding the use of micro- and even nano-manufacturing technologies for obtaining more efficient, multifunctional, and scalable systems and made researchers aware of the related socioeconomical importance.

The progressive adaptation of micro-techniques for micromachining alternative materials, including metals, ceramics, and polymers, and the introduction of novel manufacturing technologies, including laser micro-manufacturing, electron-/ion-beam milling, micro-replication tools, and high-precision additive manufacturing, have since the 1960s greatly promoted final quality of the obtained microsystems, as well as the incorporation of additional features and the combination of materials, in many cases using thin-film technologies for special contact phenomena.

The applications of microsystems in the biomedical field are indeed remarkable and continuously evolving thanks to progresses in the aforementioned micro-technologies, as explained in detail in this chapter. As living organisms are made up of cells, whose dimensions typically range from 10 to 100 μm, micro-manufactured devices (with details precisely in that range) are very well suited to interacting at a cellular level for promoting innovative diagnostic and therapeutic approaches.

Figure 12.1 provides an overview of micro-manufacturing technologies with special application to the development of micro-medical devices, technologies that will be covered in depth in the following sections. As a brief introduction, we have divided here the field of micro-manufacturing in the following main fields:

- Subtractive micromachining. Some of these technologies are based on processes similar to those used in conventional manufacturing (milling, drilling, lathing, etc.) although with much more precise tools and capable of reaching detail levels in the range of a few microns. Other even more precise technologies also eliminate material from a substrate by using focused highly energetic beams from different sources, including lasers, electron beams, ion beams, X-rays, or even water.
- Chemical micromachining. Initially linked to the electronic industry, although nowadays it has greatly evolved and can be applied to several materials including polymers, ceramics, metals, and semimetals, chemical micromachining is used to engrave substrates by chemical attacks (using acids or bases), after some parts have been protected by a mask.
- Manufacture of microporous structures. Focused at the manufacture of solutions usually for the field of Tissue Engineering, these technologies are based on phase-separation process, foaming procedures, or even additive processes.

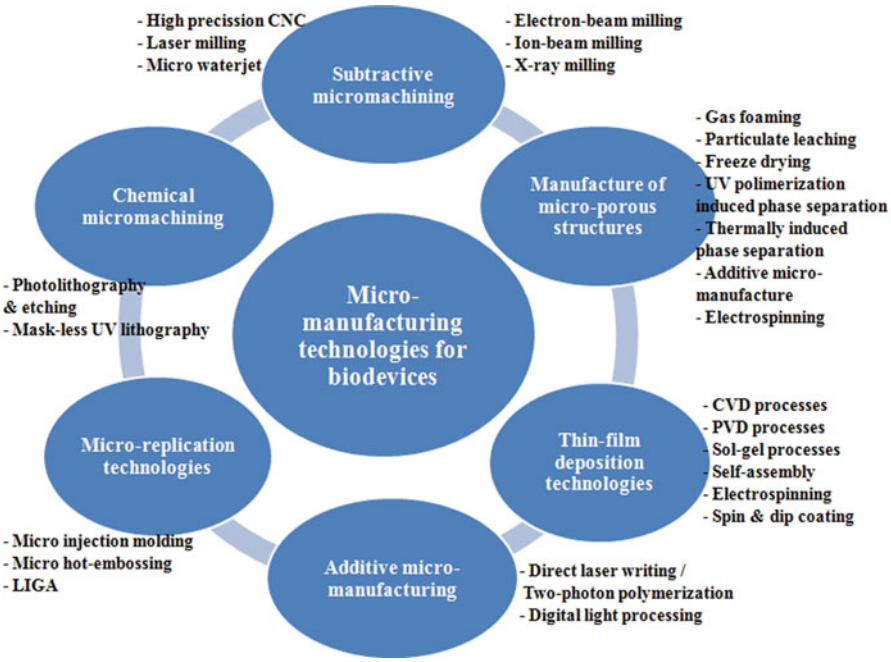

Fig. 12.1 Overview of micro-manufacturing technologies for biodevices

- Micro-replication technologies. Aimed at the fabrication of large series of parts, normally using polymers, due to their plasticity, microstructured by hot embossing, stamping, or microinjection molding.
- Thin-film deposition technologies. Allow the deposition of micrometric polymeric, metallic, or ceramic films by means of chemical-vapor deposition, physical vapor deposition, sol–gel processes, electrospinning, spin and dip coating, and even self-assembly. Applications are normally aimed at providing special properties to a biodevice (biocidal properties, enhanced biocompatibility, etc.) or as support for subsequent chemical micromachining processes.
- Additive micro-manufacturing. Uses similar principles as the additive manufacturing technologies discussed in Chap. 10, but with a higher precision due to the use of special materials and machines.

12.2 Overview of Applications for the Biomedical Sector

A search carried out with the help of Thomson Reuters' "Web of Knowledge" resources in June 2012, using "microsystem" and "biomedical engineering" as search topics, provided 51 indexed documents of interest. Alternative topics such as "MEMS (microelectromechanical systems)," "micro-devices," "medicine,"

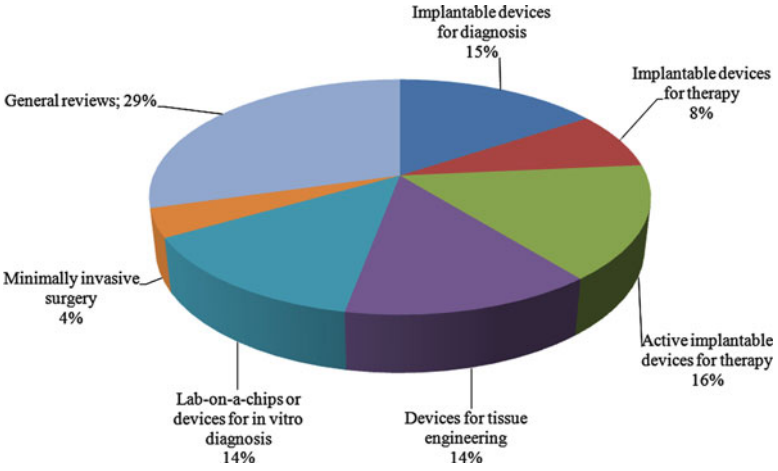

Fig. 12.2 Main current fields of application of microsystems in Biomedical Engineering

"bioengineering," or "biophysics" may provide different results but we consider the mentioned 51 documents as a relevant sample for further study.

Figure 12.2 shows the result from dividing the mentioned documents in some more specific fields of application, so as to provide an overview of typical applications of microsystems in the biomedical sector. Most articles have been linked to topical reviews centered on describing general technologies, procedures, or applications of microsystems and MEMS and their potential impact on Medicine and Health, together with discussions on forthcoming applications.

There are four additional specific and remarkable fields of application of microsystems in Biomedical Engineering, including the development of micro-implantable devices for diagnosis, the development of micro-implantable active devices for therapy, the promotion of tissue engineering activities, with micro-devices interacting at a cellular scale, and the development of highly efficient in vitro diagnostic tools or "lab-on-a-chips," also including several direct interactions with cells. Some documents also describe passive implantable devices (lenses, bone fixations, among others) as well as tools for minimally invasive surgery.

The next sections detail some of the most used technologies for the micro-medical device sector and provide some case studies linked to the aforementioned fields.

12.3 Subtractive Micromachining for Biodevices

Subtractive micromachining technologies are based on processes similar to those used in conventional manufacturing (milling, drilling, lathing, etc.) although with much more precise tools and capable of reaching detail levels in the range of a few microns. Other even more precise technologies also eliminate material from a

substrate by using focused highly energetic beams from different sources, including lasers, electron beams, ion beams, X-rays, or even water.

Almost all of them are controlled via PC through the CAM modules of CAD software, so automation is promoted, as well as repeatability of results. Normally several of these technologies work on **a** 2D ½ approach, that is, they are aimed at obtaining micropatterns on top of substrates of different materials, for instance, for the development of microsystems for microfluidic studies (capillarity, blood flow, studying biomimetic fluids), microsystems for cell motility and related studies (electrophoresis, dielectrophoresis), "lab-on-a-chip" solutions, and even "life-on-a-chip"/"body-on-a-chip" or micro-devices emulating the principles of a living organism, as an alternative to methods based on UV lithography (Sin et al. 2004; Shuler 2012, see Sect. 12.4).

Such "lab-on-a-chip" and "body-on-a-chip" devices integrate various laboratory functions in a few square centimeters. They can be used for blood analysis, for DNA sample extraction, in performing antigen-antibody reactions, and others; all of this in the fastest, most controlled, cheapest way. The possibility of mimicking more complex systems, respiratory apparatus, vascular system, etc., by micropatterning of a substrate, promotes the viability of the "body-on-a-chip" concept, linked with emulating in a simplified way the behavior of more complex systems, thus helping to assess the effects of different diagnostic and therapeutic approaches in a much more rapid and cheaper way.

Even though several technologies allow for the micromanufacture of 2D ½ and 3D geometries for biodevices, perhaps the most subtractive micromachining technology is based on laser ablation (or laser machining/drilling), as it can work with a wide range of materials and help to obtain complex geometries. Among the main advantages of the process, it is important to highlight the chemical-free process, the simple automation, the minimal heating and damage to surrounding zones of the material (very important for polymers and composites and also relevant for metals → the lower the heat-affected zone or "HAZ", the higher the quality, as less phase changes are promoted), and the complex geometries attainable.

Several devices such as auto-expandable stents, normally made of Nitinol, and many "lab-on-a-chip" solutions are manufactured by means of laser ablation or micromachining (Queste et al. 2010). Some examples are detailed further on, thanks to the courtesy of Oxford Lasers Ltd.

Figure 12.3 shows as example a laser micromachining system and some of its applications, which have been provided with courtesy by Oxford Lasers. Oxford Lasers came out of the Physics Department of Oxford University some 32 years ago, initially to exploit the development of new laser sources. As an enterprise, not only does it still manufacture lasers but also integrates these laser and others into flexible laser micromachining systems. This gives them the benefit of not only understanding the integration of such systems, but a deep insight into lasers and laser characteristics.

Oxford Lasers has been selling laser micromachining systems and providing micromachining Services for the last 20 years, having processed many thousands of orders from customers with materials ranging from metals and ceramics and silicon, through to polymers and glasses. Oxford Lasers use lasers predominantly with pulse widths in the

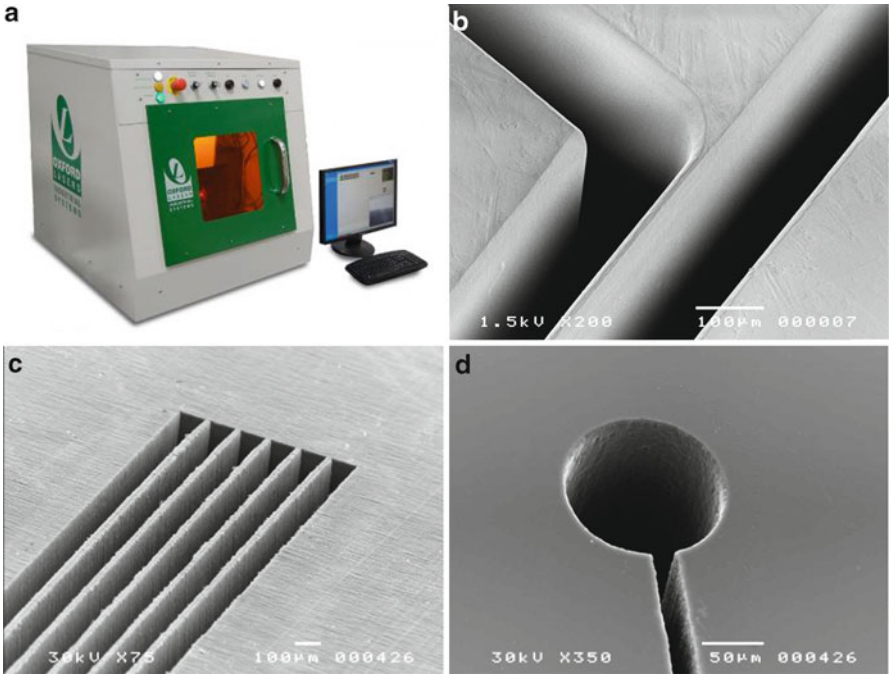

Fig. 12.3 (**a**) Laser micromachining: Oxford Lasers' ultracompact Alpha system. (**b**) 150 µm channels in sapphire. (**c**) 100 µm channels in polyimide. (**d**) Hole and channel in glass. Geometries suitable for microfluidic biodevices and even for "lab-on-a-chip"/"body-on-a-chip"/"life-on-a-chip" development projects (Images courtesy of Oxford Lasers Ltd. [www.oxfordlasers.com])

nanosecond, picosecond, and femtosecond regimes with wavelengths from 1,064, 532, 355, and 266 nm. The solutions offered can prove highly beneficial for supporting research projects linked to the development of novel micro-medical devices.

12.4 Photolithographic Approaches for 2D ½ Biodevices

Photolithography is a micro-manufacturing process used to selectively remove parts of a thin film or a substrate, for creating textures and channels and obtaining 2D ½ devices. It uses light to transfer a geometric pattern from a photomask to a light-sensitive chemical "photoresist" (normally photopolymerizable resins), on the substrate. A series of chemical treatments then either engrave the exposure pattern into or enable deposition of a new material in the desired pattern upon the material underneath the photo resist (Maluf 2000; Madou 2002; Gad-el-Hak 2003).

These techniques share some fundamental principles with photography, because the pattern in the etching resist is created by exposing it to light, either directly or with a projected image using a physical mask, or even by using a mask-less process (being the mask obtained by software) as the Intelligent Micropatterning LLC SF-100 machine uses (see Fig. 12.4 below).

Fig. 12.4 Intelligent Micropatterning LLC SF-100 machine

This procedure is comparable to a high-precision version of the method used to make printed circuit boards. Subsequent stages in the process have more in common with etching than with lithographic printing. It is used because it can create extremely small patterns (down to hundreds of nanometers in size), it affords exact control over the shape and size of the objects it creates, and because it can create patterns over an entire surface cost-effectively. Its main disadvantages are that it requires a flat substrate to start with, it is not very effective at creating nonplanar or 3D objects, and it can require extremely clean operating conditions.

The 2D ½ approach is, as already mentioned, widely used for the development of microsystems for microfluidic studies (capillarity, blood flow, studying biomimetic fluids), microsystems for cell motility and related studies (electrophoresis, dielectrophoresis), "lab-on-a-chip" solutions, and even "life-on-a-chip"/"body-on-a-chip" or microdevices emulating the principles of living organisms (Sin et al. 2004; Shuler 2012).

Combinations of UV photolithography and chemical etching have allowed us to obtain micro-textured devices for promoting interactions with cells and microorganisms, for obtaining micro-channels for "lab-on-a-chip devices" or even for reducing friction in artificial joint prostheses, what can be highly relevant for promoting service life of final prostheses.

In our prior preliminary validations (De la Guerra Ochoa et al. 2012), we have used copper plates and discs as substrate material due to its easy processability and the need of a lower etching time.

For the manufacture of the micro-textures, we have normally followed several steps including:

- Initial preparation of the copper discs by washing out the possible surface oxides in ultrasonic cube for around 30 min and subsequent drying.

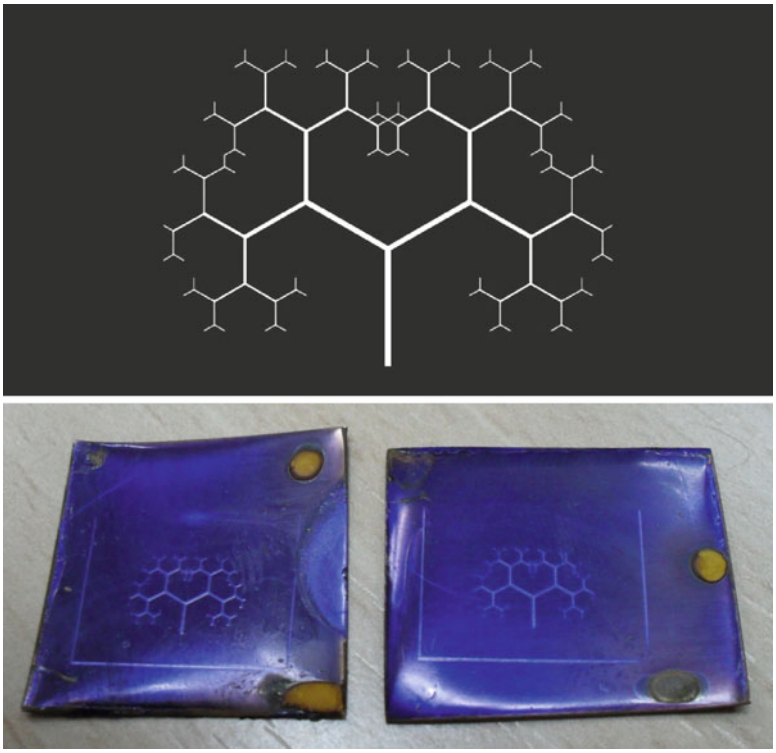

Fig. 12.5 Substrate patterning using a Julia tree geometry for mimicking capillaries and obtaining micro-channels. Mask-less UV lithography with channel width varying from 300 to 50 μm. Using similar procedures micro-devices for controlling cell motion and lab-on-a-chips can be manufactured (With gratitude to MSc. Eng. Vanessa Hernández for her help with the manufacture of the Julia tree)

- Coating of the discs using Dupont Riston PM-100 photoresin.
- Exposure of the photoresin to UV light by means of the SF-100 equipment from Intelligent Micro Patterning LLC. As previously mentioned, this process is known as mask-less photolithography, as the use of programmable light filters prevents from using a physical mask.
- Development, using a Na2CO3 0.85 % w. solution, for eliminating the uncured photoresin in those pattern zones that are going to be chemically etched.
- Chemical etching introducing the substrate in a FeCl3 40 % w. solution for attacking the uncoated pattern zones, hence obtaining the micro-texture.
- Stripping or elimination of the remaining photoresin.
- Washing out debris and drying.
- Final dimensional verification.

Figure 12.5 shows an example of substrate patterning using a Julia tree geometry for mimicking capillaries and obtaining micro-channels for several microfluidic

studies. In this case channel width has been varied from 300 to 50 μm in order to assess the precision attainable. Lower images show the result from developing the photoresin after exposure, thus obtaining a micro-pattern for further substrate etching and final stripping and washing.

Such obtained micro-textured surfaces can be also used for micro-replication activities (complementing the technologies describe in the following section), in a family of processed normally referred to as "soft lithography." The soft stamp can be obtained by casting PDMS onto the metallic micro-textured substrate following a "rapid form copying" procedure (as explained in Chap. 11). Once the soft stamp is obtained, a solution or ink can be applied to the textured PDMS, which is subsequently used as a stamp for transferring the micro- (or even nano-) pattern to other substrates in an automatic replicating process.

The mentioned process is easy to industrialize for producing serial production of microsystems, as the electronic industry has widely shown. Once the process parameters are well analyzed in the laboratory, the different solvents, etchers, concentration of solutions, and time schedules for the steps involved are fixed for producing repetitive results and the operations can be automated. Clean rooms with controlled level of pollution are needed for avoiding contamination of the substrates, as explained in ISO 14644.

12.5 Micro-replication Technologies for Mass Production

Some of the technologies already mentioned, including the combination of UV lithography with chemical etching, can be used for mass production, once the process parameters are adjusted.

In the case of micro-manufacturing with polymers, there are two typical micro-replication processes of special relevance, as they are based on current industrial processes that have enormously promoted the use of polymers for conventional product development. Based on adaptations from conventional injection molding and compression molding, with which large series of low-cost parts are typically obtained, the microinjection molding and the micro-hot-embossing processes aim to manufacture large series of low-cost microsystems, taking advantage from the use of polymers, whose relevant properties for micro-manufacturing, when compared with silicon for instance, include:

- Polymers can be tailored for final application, thanks to the use of additives, and the use of biopolymers is especially noteworthy for biodevices.
- They are much cheaper than silicon, ceramics, or alloys, and final part benefits from their processability at high temperatures.
- They can also be recycled and the progressive use of polymers from biological origin is improving their environmental sustainability.
- Several "intelligent" polymers (piezoelectrics, pyroelectrics, shape-memory polymers, etc.) benefit also from connecting different physical domains and can

be used as transducers for the development of biodevices with improved diagnostic or therapeutic capabilities (Díaz Lantada 2009, 2012).
- Mass production can be achieved even for polymeric microsystems by using microinjection molding and hot embossing.

Microinjection molding is normally connected to the mass production of polymeric parts weighting less than a gram and including micrometric features (patterns, holes, textures, etc.). In many cases, for manufacturing the mold, not just micro-milling or micro-drilling are needed but also processes like micro-electro discharge machining, laser micromachining, or even LIGA (involving X-ray/ion-beam lithography, galvanoforming, and replication). The reduced space available makes it also more complex to include so many sensors for process monitoring, as in conventional injection machines. Therefore, empirical adjustment of the process is necessary and final quality control is indeed relevant. Additional problems include manipulation and packaging of such small pieces. Conventional thermoplastics, engineering polymers including PEEK (highly demanded for the medical industry), and even combinations of several polymers can be used. The complexity of geometries attainable is not as high as using conventional injection molding and molds, but for most microcases, implants, and scaffolds for Tissue Engineering, the microinjection molding is a remarkable technology for large series.

Hot embossing is a technique for imprinting microstructures on a substrate (polymer) using a master mold (silicon or metallic tool). While microinjection molding is aimed at three-dimensional parts, hot embossing works on a 2D ½ approach useful also for many applications (microfluidics, cell motility studies, micro total analysis systems, etc.). During the process the polymer is heated above glass transition and the stamp works also at high temperature, for avoiding rapid cooldown of the polymeric surface. By carefully adjusting the stamp pressure, the pattern can be transferred to the polymer, and after cooling the stamp and the polymer below the glass transition, the tool is de-embossed for obtaining final part.

Industrial hot-embossing machines allow feature sizes of around 1 μm and aspect ratio of around 10, with high productivity and low cost. The process can be also used in the laboratory, with ad hoc built structures even manually operated.

Figure 12.6 shows, as example, a hot-stamped polycaprolactone substrate, using rapid prototyped part as stamp (already described in Sect. 10.5, when referring to prototypes with fractal patterns and features) for obtaining a microfluidic device in final biomaterial for cell growth and motility studies. It is important to note that mass production could not be achieved by using such rapid prototyped polymeric (in this case acrylic resin) parts as stamps, even though for obtaining some prototypes for conceptual validation trials, it provides enough precision.

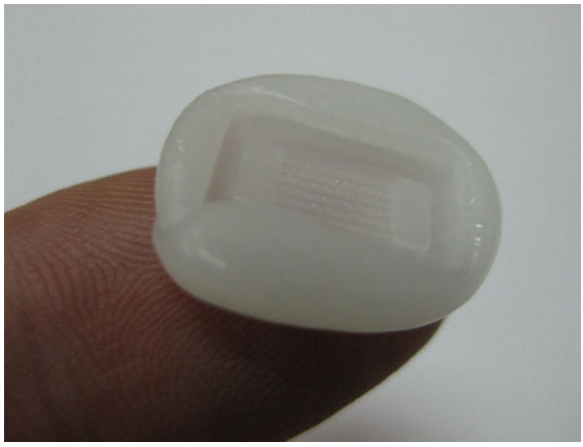

Fig. 12.6 Hot-stamped polycaprolactone substrate, using rapid prototyped part as stamp (see also Fig. 10.16), for obtaining a microfluidic device in final biomaterial for cell growth and motility studies

12.6 Methods for Manufacturing Microporous Structures for Prostheses and Tissue Engineering

Most processes for manufacturing microporous structures involve a combination of materials in some step of the process and finally a phase separation, for obtaining a solid part with distributed small pores. Such structures are relevant in Biomedical Engineering, especially for the development of scaffolds acting as extracellular matrixes for Tissue Engineering procedures. In such scaffolds the pores allow cells to grow, have access to nutrients, and expulse their debris to the environment. The importance of Tissue Engineering has promoted the use of these micro-manufacturing methods and the discovery of novel ones.

Among most extended processes gas-assisted injection molding is an industrial process based on injecting a molten resin or thermoplastic into a mold cavity and then injecting a quantity of pressurized gas into the resin, so as to help to fill out the mold cavity and to create hollows and pores in the polymer. The incorporation of foaming agents as additive to polymers also allows the manufacture of polymeric parts with pores.

The use of porogens is also commonplace. Normally the process involves mixing a liquid prepolymer with solid particles (wax, sugar, salt, etc.). Once polymerization is produced (normally by UV exposure or by heating), a solid structure, formed by a polymeric network with dispersed particles, is obtained. Final porous structure is obtained by dissolving such disperse particles in water and other solvents or by heating. The use of prepolymer-water emulsions is also typical for obtaining a polymerizable mixture that after thermal or UV-based polymerization provides a

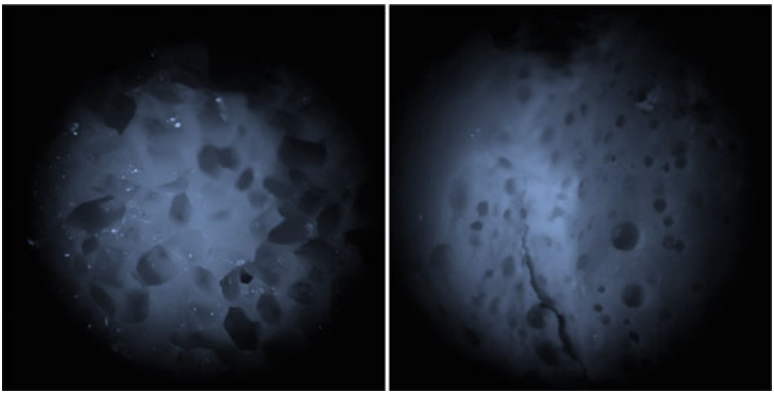

Fig. 12.7 Porous PDMS: *Left image*. PDMS with sugar as porogen after solving sugar. *Right image*. PDMS emulsified with water after thermal curing

polymeric network with pores according to initial water content. Figure 12.7 provides a couple of examples of PDMS porous structures, obtained by using porogens and by thermal polymerization of an emulsion, and Fig. 12.8 shows the results of the photopolymerization of epoxy-water emulsions and foams.

Main alternative, for improving the control of pore size and distribution from the design stage, is the use of micro additive manufacturing technologies (AMT), which are describe in detail in Sect. 12.7. Electrospinning can be also adapted to "layer-by-layer" fabrication and used for obtaining 3D porous structures, even though the process is not as repetitive as the use of micro AMT.

12.7 Additive Micro-manufacturing for Biodevices: Linking Complex 3D Micro- and Nano-manufacturing

The progressive increase in precision of additive manufacturing technologies, together with their improved versatility thanks to a continuously increasing set of materials available for layer-by-layer processing, is greatly promoting applications linked to micro- and even nano-manufacturing of complex 3D geometries for very innovative medical solutions.

Probably the first quantitative leap forward came with the adaptation of conventional stereolithography to micro-stereolithography around a decade ago (Varadan et al. 2001), with which 3D details of around 15–20 μm began to be produced (what nowadays can be achieved with some multipurpose systems, such as the Digital Light Processing from EnvisionTEC, among others). The process was initially based on combining a PC-controlled UV lamp with high-precision optics and positioning systems for enhanced polymerization (integrated harden polymer

Fig. 12.8 Foam and emulsion obtained by mixing photopolymer (epoxy resin) and water. Microstructures obtained after UV polymerization and drying. Foam leads to pore sizes around 300–500 μm (*lower left image*) and emulsion leads to pore sizes around 30–50 μm (*lower right image*)

stereolithography, Ikuta, validated 1992, published, 1993). The process progressively improved thanks to the incorporation of lasers, more sensible photopolymers, and enhanced positioning systems.

Nowadays two-photon lithography or multiphoton lithography provides the most remarkable accuracy. Multiphoton lithography (also known as direct laser lithography, direct laser writing, or 3D laser lithography) of polymer templates has been known for years by the photonic crystal community and is currently spreading to the biomedical field. Similar to standard UV-photolithography techniques, structuring is accomplished by illuminating negative or positive photoresists via light of a well-defined wavelength. The fundamental difference is, however, the avoidance of

physical masks and the change from a 2D ½ approach to a 3D layer-by-layer process. Instead, two-photon absorption is utilized to induce a dramatic change in the solubility of the resist for appropriate developers and high precision is attainable thanks to the use of femtosecond lasers (Ostendorf and Chichkov 2006).

With these high-precision additive manufacturing technologies, not only complex 3D geometries (hollow structures, inner details, etc.) can be achieved but also extraordinary high-aspect-ratio microstructures, many of them with medical application as mentioned further on. Previously, such ultrahigh-aspect-ratio microstructures could only be manufactured through X-ray lithography, ion-beam lithography, and some other micro-manufacturing technologies, whose possibilities of leading to complex 3D structures, with hollows and inner details, with application for instance in the development of novel metamaterials, were indeed limited. The incorporation of bio-photopolymers to the range of materials available for 3D additive micromanufacturing is also promoting final medical applications, especially in the fields of devices for drug delivery, "lab-on-a-chip" solutions for rapid diagnosis and scaffolds for Tissue Engineering (Ikuta and Hirowatari 1993).

Table 12.1 provides a brief comparison of several high-precision manufacturing technologies, including additive and subtractive ones, as well as some conventional procedures as additional reference.

The next pages provide some case studies linked to the rapid manufacture of complex 3D micro- and nano-biodevices, achieved thanks to direct laser writing, courtesy of NanoScribe GmbH (spin-off from Karlsruhe Institute of Technology), which currently offers the most versatile and precise additive manufacturing technology commercially available. An introduction to the company, due to its relevance in the field, is also provided below.

Nanoscribe GmbH (www.nanoscribe.de) was founded in 2007 by scientists in the field of photonics as a spin-off company of the Karlsruhe Institute of Technology (KIT – www.kit.edu). The company is specialized on the innovative technique of 3D laser lithography* and produces compact and easy-to-operate table-top laser lithography systems (Photonic Professional). The systems are designed for the fabrication of true three-dimensional micro- and nanostructures in various photoresists. Carl Zeiss invested in 2008 into this disruptive technology of 3D laser lithography and holds about 40 % of the company's shares.

Additionally to the Photonic Professional systems, Nanoscribe also offers proprietary photoresists and advice in casting 3D polymer templates into metals or semiconductors. Tailor-made, customer-oriented service and fast online support are integral parts of its philosophy. Research institutes and universities in Europe, the USA, China, and Japan utilize successfully Nanoscribe's products. As world market and technology leader in 3D laser lithography, the company secures the highest quality and fast cycles of innovation.

The applications of 3D laser lithography are widely spread, for example, photonics, photonic waveguides and wire bonds, micro-optics, microfluidics, biomimetics, or scaffolds for cell biology, among other directions continuously evolving.

Besides photonics and micro-optics, cell biology is perhaps the most important field of applications of Nanoscribe's 3D laser lithography technology. Typical

Table 12.1 Comparison between high-precision rapid manufacturing processes. Also includes some references to other conventional technologies (Adapted from Díaz Lantada and Lafont Morgado 2012)

Technology	Precision	Materials	Working principle	Reference
Two-photon polymerization	Around 200 nm	Photopolymers, biomaterials	Additive	Infür et al. (2007)
Micro-stereolithography	5–35 μm	Photopolymers	Additive	Varadan et al. (2001)
Digital light processing	25–50 μm	Photopolymers	Additive	Stampfl et al. (2004)
Bioplotter and bioprinters[a]	250–400 μm	Biological materials	Additive	Mironov et al. (2009)
Laser micromachining	15–100 μm	Organic and inorganic	Subtractive	Queste et al. (2010)
X-ray-based microfabrication	100 nm–100 μm	Metals, plastics, glass, ceramics	Subtractive	Gad-el-Hak (2003)
Pressure-assisted microsyringe	10–600 μm	Biopolymers	Additive	Yeong et al. (2004)
Robocasting	100–1,000 μm	Organic ink	Additive	Yeong et al. 2004
Conventional 3D printers	250–400 μm	Waxes, polymers	Additive	Wohlers (2010)
Conventional stereolithography	150–300 μm	Photopolymers	Additive	Díaz Lantada (2009)
Conventional fused deposition modeling	350–500 μm	Wawes, thermoplastics	Additive	Masood et al. (2005)
Conventional CNC machining	50–150 μm	Mainly metals	Subtractive	Several manufacturers

[a] Capable of 3D printing using biomaterials.

topics of interest are the studies of cell migration, stem cell differentiation and customized construction of biomedical parts on the microscale.

*This unique capability is, as previously mentioned, based on the two-photon polymerization process. The laser lithography system exposes predefined paths which after development result in self-supporting structures that are anchored to a substrate. The desired structures can either be designed in any CAD software program that supports the .dxf or .stl file format or they can be implemented directly in Nanoscribe's .gwl scripting language.

Figure 12.9 (top image) shows an ultrahigh-aspect-ratio microneedle together with a light director array. The prototype has helped to validate the possibility of obtaining 1 mm high and 20–5 μm wide micro-hypodermic needles for painless drug delivery. Figure 12.9 (bottom image) includes an array of microneedles that could be used to deliver chemical compounds or actives in an easy and painless way into the skin. The array would thereby work as a semipermanent subcutaneous interface.

Please note that even being a layer-by-layer process, such layers are difficult to observe, even through electronic microscopy, as they are in the range of a hundred

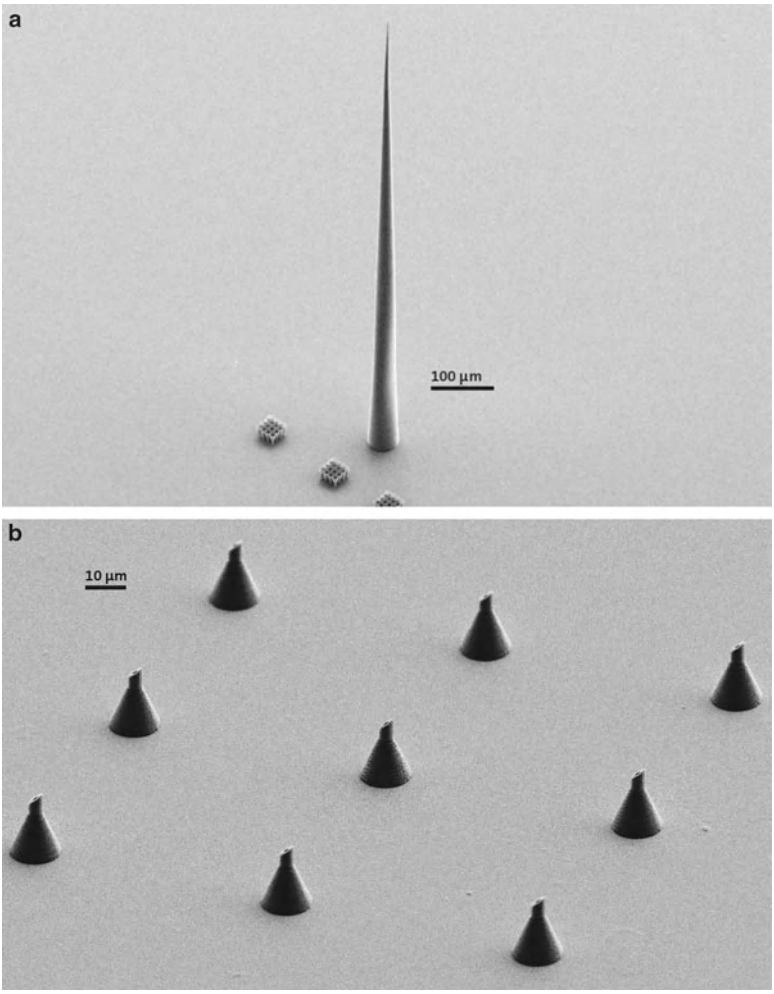

Fig. 12.9 (**a**) Ultrahigh-aspect-ratio microneedle with light detector array. (**b**) Array of microneedles for painless and controlled drug delivery. Courtesy of Nanoscribe GmbH (www.nanoscribe.de)

nanometers, so the gap between micro- and nano-manufacturing is already filled with versatile technologies.

The additional example provided in Fig. 12.10 is linked to a polymeric microstent. Tiny stents could be inserted even in small cerebral arteries for treating aneurysms and strokes. The structure shown here consists of a strong cross-linking polymer, 3D structured via direct laser writing.

The possibility of combining the precision attainable with this technology, together with the relevant improvements to minimally invasive implantable

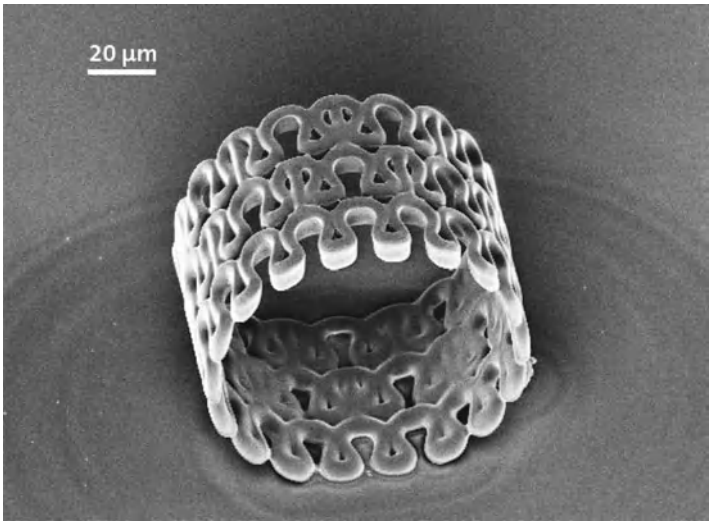

Fig. 12.10 Micro-stent for reduced section arteries. Courtesy of Nanoscribe GmbH (www.nanoscribe.de)

procedures provided by the use of stent designs based on auxetic geometries (please see Sects. 7.3 and 7.4), should be taken into account in future research.

Several biodevices based on the use of metamaterials for promoting special features, as those mentioned in Sect. 7.3 (not only stents but also minimally invasive implantable annuloplasty rings, devices for treating septal defects also minimally invasive, planar auxetic structures for cell growth oriented to limiting the appearance of wrinkles after implantation, among others), would also benefit from micrometric manufacture through direct laser writing.

The prototype included in Fig. 12.11 helps to validate the manufacture of 3D hollow nano-fluidic channels. Such nano-fluidic channels can find many relevant applications in the field of "lab-on-a-chip" systems and micro-devices for rapid diagnosis. Compared with the "lab-on-a-chip" systems made by conventional UV photolithography, they provide many advantages, that is, lower fluid volumes (drugs and expensive reactives) consumption, faster analysis and response times, simple industrial scalability, better process control, etc.

They can potentially contribute to the development of "point-of-care" testing devices, thus making possible in-time disease diagnosis in remote areas and even without the need of highly qualified medical personnel.

Regarding the manufacture of micro-/nano-cantilever structures and micro-/nano-hollow channels present technology provides several advantages, when compared with those attainable by chemical micromachining, by combining UV lithography and etching processes. First of all precision is higher (around 10–20 times

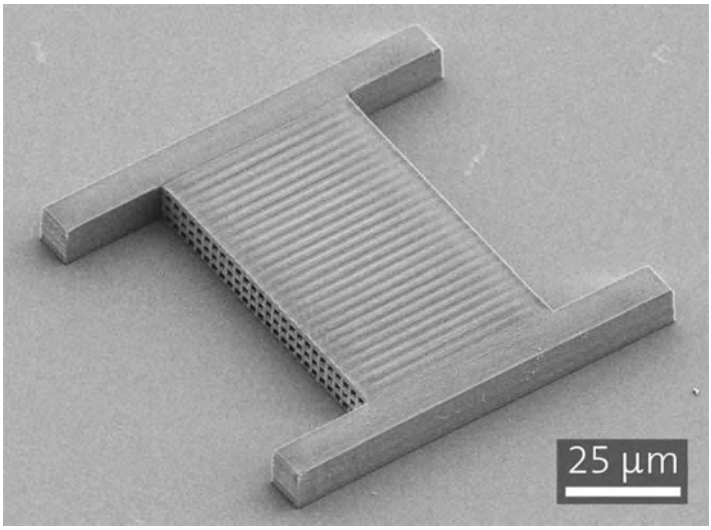

Fig. 12.11 Micro-/nano-fluidic channels by means of 3D laser lithography. Courtesy of Nanoscribe GmbH (www.nanoscribe.de)

higher) and no chemical attacks are needed, thus leading to final devices "cleaner" for bio-applications and with much more homogeneous surfaces and features. In addition this process is almost completely automated, while more conventional micro-manufacturing processes require several steps and extremely well-trained laboratory craftsmen.

Perhaps a limiting factor for some applications is the impossibility of directly processing metals through direct laser writing. However, it is important to note that organic photoresists (like SU-8, IP-L, IP-G), hybrid materials (ormocere) or the amorphous semiconductor As_2S_3 are capable of two-photon polymerization, what provides a wide range of possibilities. In addition to CVD/PVD coating processes (see Chap. 13), final metallization is possible and casting processes can also be used for additional versatility.

The prototypes from Fig. 12.12 show cell scaffolds made of ormocere. The white photographs are SEM images and the black/green ones are 3D reconstructions of LSM confocal image stacks. Mammalian cells were cultured and the images show how scaffold orients their movements. Images courtesy of Klein, F.; Striebel, T.; Jiang, Z.; Franz, C.M.; Von Freymann, G.; Bastmeyer, M.; Karlsruhe Institute of Technology (KIT) (Klein et al. 2010).

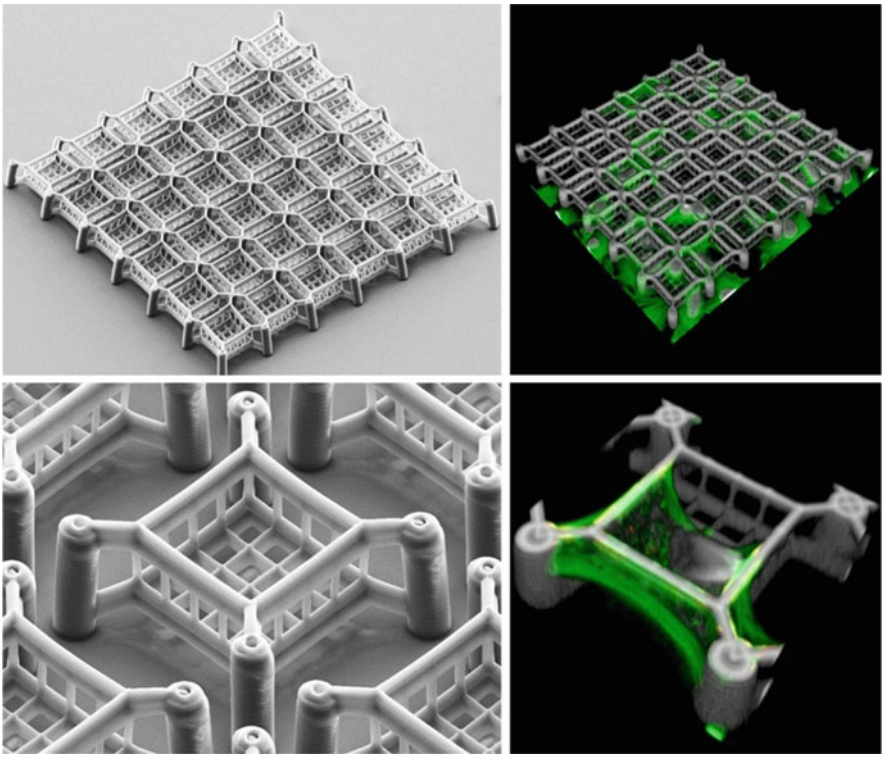

Fig. 12.12 Cell cages for advanced cell culture and cell motility control. 3D tailored scaffold for cell growth, acting as an artificial extracellular matrix. Cell cages: cells have docked at the scaffolds and begun to contract

12.8 Main Conclusions and Future Research

The applications of microsystems in the biomedical field are indeed remarkable and continuously evolving, thanks to progresses in several micro-manufacturing technologies and to the development of novel ones, as has been explained in detail in this chapter. As living organisms are made up of cells, whose dimensions typically range from 10 to 100 μm, micro-manufactured devices (with details precisely in that range) are very well suited to interacting at a cellular level for promoting innovative diagnostic and therapeutic approaches.

Main fields of application of microsystems in Biomedical Engineering have been discussed and several examples provided, as a basis for discussion on future trends,

present knowledge, and technical challenges. Connections with the following chapter, about nano-manufacturing, have also been established, as very recent technologies as direct laser writing promote applications in-between the micro and the nano world.

Even though several of the technologies explained a still unconventional and thus normally very expensive, as happens also with the microscopy facilities needed to assess the effectiveness of these procedures and devices, some relevant international research groups for transnational cooperation in different fields are being established.

We would like to highlight here the actual importance of the "Capabilities Programme" of the "EU Seventh Framework Programme," which is currently funding EU collaborative activities among very relevant partners in many fields, such as micro- and nano-manufacturing for the establishment of long-term collaborative consortia, capable not only of basic research but also focused on technological transfer to society.

Among the aforementioned consortia, due to its special linkage to the topics covered in this chapter, it is necessary to make reference to "EUMINAfab," a European Research Infrastructure offering open access to state of the art of multimaterial micro- and nano-technologies. By combining scientific expertise with technological capabilities, EUMINAfab provides innovative and efficient solutions to challenges in the area of micro- and nano-fabrication of functional structures and devices out of a knowledge-based multimaterials' repertoire. Some of the technologies previously described are accessible (a call for projects opens every year) to researchers presenting highly innovative projects, linked to novel devices and systems, requiring validation through high-precision manufacturing.

Some additional help, especially for design tasks linked to the use of microstructured or nano-structured materials, can be found by collaboration with other relevant consortia, including the "KMM-VIN: Virtual European Institute on Knowledge-based Multifunctional Materials," also linked to the design of novel biodevices based on the important possibilities provided by using metamaterials, functional-gradient materials, and intelligent materials or their combinations.

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Chapter 13
Nano-manufacturing Technologies for Biodevices: Interacting at a Molecular Scale

Andrés Díaz Lantada

Abstract Nanotechnology is the study of manipulating and interacting with matter on an atomic and molecular scale, and related research is connected to the development of novel materials and devices with at least some details including sizes from around units to a few hundreds of nanometres. Research is linked to many fields benefiting each other, as materials science, quantum physics, molecular biology, optics and micro/nano fabrication, among others, and main applications range from medicine and biology to industrial processes, electronics and energy.

The topics and directions of nanotechnology are so diverse, including aspects related to modelling, design, characterisation, novel synthesis and fabrication methods, and integration of components into final systems, among other fields, that trying to cover them in a chapter, or even in a whole handbook, would not be realistic.

Therefore, we focus on providing a brief introduction to nano-manufacturing technologies and on discussing main technologies currently being applied to promoting the performance of commercially available biodevices and in some cases of rapid prototypes.

In the biomedical field, nano-manufacturing processes are already being widely used for improving the mechanical performance, the corrosion resistance, the contact properties, the biocompatibility and biocidal behaviour and even the aesthetics of several implantable devices, as is also detailed further on.

Such manufacturing processes, mainly physical and chemical vapour deposition, thin-film solution-deposition processes and self-assembly and related processes, together with some typical applications, are summarised. Finally some details about present challenges, forthcoming technologies and expectations are also included.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_13,

13.1 Introduction to Nano-manufacturing Technologies

Nanotechnology may be defined as the science that studies the control of matter on an atomic and molecular scale. This means that structures of less than 100 nm, in at least in one of their dimensions, are normally used, which also means developing devices of that size.

Inorganic, organic and biological nanostructured materials have been around in nature ever since the beginning of the evolutionary chain on Earth. This can be seen if the crystallised minerals forming the rocks, the component parts of microorganisms or the particles in suspension in smoke or fog are examined in detail (Schwartz 2006). However, real progress in this discipline and the control of material on a nanoscale began to emerge at the beginning of the 1970s and was closely linked to the developments in electronics and computing, which were continuously seeking circuits with ever tinier connections and sizes, so that more information could be stored in a smaller volume.

During the first decades of development, nanotechnology basically focused on the use of semiconductor materials, particularly silicon, due to the ease and precision that could be attained when processing it with acid attacks, thanks to its peculiar crystallography. From the 1980s, however, attention began to focus on other materials, especially polymers. The intention was to obtain nanosystems that were cheaper to mass-produce and that would be suited to other potential applications, particularly in Health Sciences, because of their good behaviour when in contact with human tissue.

On these very tiny scales, the quantum effects between particles begin to take on considerable importance, and the typical physical, chemical and biological properties of the materials undergo a surprising alteration as their size gets smaller. This means that nanosystems and nanostructures can be obtained with very high mechanical strength, which makes amazingly fast chemical reactions possible, with extraordinary optical and chromic effects, among many other properties, and remarkable responses to external stimuli that can be managed (or controlled) by simple changes to size, shape or the relative geometric layout of the grain forming these materials.

Generally speaking, any material containing fibres, layers, particles or granules of a size less than 100 nm may be considered as a nanostructured material. If, moreover, the material is oriented to exploit some of the remarkable variations in the properties mentioned, depending on the different external stimuli, we can speak of the concept of "nanostructured active material".

Some manufacturing and processing technologies like "CVD" and "PVD" (chemical and physical vapour deposition) techniques, thin-film solution-deposition processes, self-assembly and related processes and even additive rapid manufacturing (as discussed in Chap. 12, Sect. 12.7) have multiple applications for the development of nanostructured materials with a growing impact in the biomedical field.

In fact such capability of structuring materials at the nanoscale helps to improve the mechanical performance, corrosion resistance, long-term biocompatibility and other relevant properties of many medical devices currently commercially available.

This chapter provides a brief introduction to nano-manufacturing technologies and a discussion on main technologies currently being applied to promoting the performance of commercially available biodevices, and in some cases of rapid prototypes.

In most cases these nano-manufacturing technologies are based on the use of thin-film deposition processes, what involves a change of approach, from the conventional "top-down" manufacturing (either by subtractive machining processes or by chemical attacks), to a more versatile "bottom-up" or additive manufacturing approach.

Actually this "bottom-up" manufacturing strategies can be even considered "biomimetic", as Nature itself also constructs its (bio)materials and (bio)structures normally using additive procedures. Some relevant connections can thus be established with the topics covered in Chap. 10, about additive manufacturing; Chap. 11, about rapid-form/shape copying; and Chap. 12, about micro-manufacturing processes.

It is hoped that the inclusion, in the references section, of various excellent texts and handbooks specifically devoted to nanotechnology and nanomaterials (Drexler 1986, 1991, among others) will be of use to any researchers wishing to examine these topics in greater detail than we have been able to do.

The next section details main already validated applications of these nano-manufacturing processes in the biomedical field, which are normally connected to improving the performance of passive biodevices (conventional implants). Even though enormous research efforts are currently focusing on the development of nano-biosensors, nano-biomarkers and nanodevices for improved drug delivery, among other innovative diagnostic and therapeutic approaches, we do not deal here with active implantable nanodevices, as most advances are currently in the conceptual validation stage.

We are confident that the references included at the end of the chapter may also provide relevant additional information on these more specific topics, also linked to the world of "intelligent" materials, systems and structures.

13.2 Overview of Applications for the Biomedical Sector

In spite of the great potential of nanotechnology and nano-manufacturing for biomedical engineering (including enhanced cancer diagnosis, precise detection and location of infectious microorganisms, remote delivery of highly specific drugs and other research lines), we focus here on concrete already successful applications, commercially available and widely used in the manufacture of many kinds of implants.

Nowadays, manufacturing technologies working on the nanoscale are being used, mainly as post-processes upon conventional implants, for some of the following reasons:

- Improving mechanical performance. The use of multilayers allows for a tailored adaptation of hardness and stiffness of implants, aiming in many cases at a more elastic bone-prosthesis contact for avoiding phenomena such as stress shielding, by enhancing a more distributed loading. In other cases ultrahigh hardness is desired, so as to limit wear ratio and improve implants' life.
- Improving corrosion resistance. Human organism is a corrosive environment, as already detailed in Chap. 2, and permanent implantable devices suffer its effects. The use of special coatings (i.e. titanium dioxide) limits corrosion and improves implants' life.
- Improving tribological properties. Multicomponent implants include parts with relative motion and friction effects lead to progressive wear. By using special coatings for promoting very low friction coefficients (i.e. diamond-like carbon), wear ratio can be minimised, thus improving implants' life and patients' comfort.
- Enhancing biocompatibility of final biodevices. Some coatings and thin-films (i.e. diamond-like carbon, hydroxyapatite) are also used as a way of improving final device biocompatibility, either for final implantation, or for promoting in vitro or ex vivo trials (see example of Chap. 15).
- Obtaining biocidal and antimicrobial activity. The incorporation of some inclusions within already mentioned coatings (i.e. diamond-like carbon with Ag or Au nanoparticles) has proven also very useful for obtaining biocidal and antibacterial properties of implants.
- Enhancing aesthetics. In Odontology, implants normally require a tough metallic (titanium or titanium alloys) nucleus, as well as an outer aspect similar to that of remaining teeth, what can also be achieved by means of vapour deposition processes (i.e. zirconia).
- Including novel functionalities. Multilayers can also promote the incorporation of some kind of active material to the surface of an implant, so as to achieve final active implantable devices, for improved diagnosis or even therapy (i.e. piezoelectric coating for enabling pressure monitoring).

The next sections deal with the most demanded nano-manufacturing technologies in the biomedical device industry, currently aimed at the deposition of thin-films for improving the aforementioned characteristics by means of nanostructured multilayered materials.

13.3 Physical Vapour Deposition Processes

In physical vapour deposition processes, the vapour to be deposited and condensed on the substrate to be coated is not the result of a chemical reaction but is generated as a result of the different physical processes conducted on a solid sample of material to be deposited, without involving the chemical formation of novel species. Standard processes that might be mentioned are vapour deposition by evaporation,

electron beam physical vapour deposition, plasma sputtering, pulsed arc-enhanced physical vapour deposition or laser ablation-enhanced physical vapour deposition (Smith 1995; Albella 2006). Materials such as metal alloys, pure elements and composites like tungsten carbide, chrome nitrate or titanium nitrate are usually deposited by these PVD processes (Bunshah 1994; Glocker and Shah 2002).

In general, PVD processes lead to deposits of higher purity, than those obtained by chemical processes, since they start out from solid samples as a source of the material to be deposited and because there is no contamination from other reacting species, as is often the case in CVD techniques. Deposits can also usually be done at a lower temperature using PVD than with CVD, which is important for polymer or biological substrates. However, effects resulting from the directionality of PVD processes usually result in somewhat less homogeneous depositions than by using CVD processes.

The different processes and most suitable materials are dealt in the references mentioned at the end of the chapter and fall outside the scope of the present handbook. Using them depends on the pressures and temperatures admitted by the substrate during processing, as well as the end quality and coating thickness required, among others. However, being able to consult expert suppliers that can be subcontracted to do the coating of a specific device is always very convenient for research teams that require a coating to enhance the properties of a biodevice but who do not have access to the facilities and equipments required.

Most materials deposited using PVD or CVD are oriented towards obtaining very hard wear-resistant surfaces, on highly tough substrates that already show good performance towards vibrations and impacts. In other cases main objective is to minimise the friction coefficient, so as to obtain machine parts or implants with a longer useful life. Besides, these technologies can also be applied to produce active materials with optimised detection or actuation capabilities.

The following examples of Figs. 13.1 and 13.2, courtesy of Ceramed, show different implants benefiting from TiN and TiNbN PVD coatings, which present several advantages in surgical instruments and medical devices. Figure 13.1 includes different components of an artificial hip prosthesis and Fig. 13.2 a part (similar to a slide bearing) of a knee prosthesis.

This PVD process from Ceramed attributes a high toughness along with a low shear coefficient, giving the instrument a higher cut attribute, a high density, which makes it an excellent barrier to any aggressive chemical environment, and an excellent biocompatibility, presenting a low or inexistent diffusion rate, preventing the appearance of prosthesis material in the surrounding tissues.

In some cases Ceramed uses also anodisation as an alternative to PVD. Due to its properties of flexion resistance and fatigue resistance, Ti is used in biomedical application in mechanical support, orthopaedic and dental and in pacemakers. The oxidation of titanium and its alloys in the implants surface is responsible for the corrosion resistance increase and therefore its stability in vivo. These properties improve its behaviour when implanted. The anodisation process accelerates the formation of the oxide layer under controlled conditions to provide the desired result. An example of anodised Ti implant is provided in Fig. 13.3.

Fig. 13.1 PVD coating on different components of total artificial hip prosthesis (Images courtesy of Ceramed Medical Coatings [www.ceramed.pt])

Fig. 13.2 PVD coating on component of knee prosthesis (Image courtesy of Ceramed Medical Coatings [www.ceramed.pt])

Fig. 13.3 Result from implant after anodisation process for promoting the formation of titanium oxide and consequently helping against corrosion (Image courtesy of Ceramed Medical Coatings [www.ceramed.pt])

13.4 Chemical Vapour Deposition Processes

A standard chemical vapour deposition process obtains a coating through the deposition on a substrate of a chemical product generated from a gaseous reaction. Other volatile by-products are usually produced in this reaction and are removed from the reaction chamber. On other occasions the chemical reaction between the gases introduced into the chamber and the substrate material is encouraged, so that the product of reaction can be then condensed on that surface (Smith 1995; Albella et al. 2003; Albella 2006).

By using these processes, thin layer deposits of micrometric thicknesses (and even nanometric) can be obtained, including details of microcrystalline, polycrystalline, amorphous and epitaxial structures. A wide range of materials are usually deposited in this way, such as silicon, fibres, nanofibres and carbon nanotubes, silicon dioxide, tungsten carbide and various oxides and nitrates with a high surface hardness.

However, the consistency and adherence of the thin layer depends to a large extent on the compatibility of the substrate and the surface deposit. To encourage this compatibility, multilayer structures are often used in which the transition from substrate to the required final coating includes several intermediate layers for a better transition with fewer residual stresses that can cause the appearance of cracks in many thin coatings (Bunshah 1994; Glocker and Shah 2002).

Operating pressures for standard CVD equipment range from atmospheric (APCVD) to high vacuum (UHVCVD) and on occasions aerosols and plasmas are used, so as to favour the chemical reaction or to focus it on the substrate zone for a more effective process. All this increases the complexity of the related systems whose installation and maintenance costs are usually high.

Although the CVD and PVD systems mentioned are expensive, there are many different suppliers who offer the chance to subcontract their thin-film deposition services for coating different materials, including metallic, ceramic and polymeric substrates. This can be very convenient in projects linked to the development of a novel implant or of a special material for medical applications, in case it might be interesting to compare the mechanical, chemical and biological behaviour of possible surface coatings, before choosing the most suitable substrate-coating combination for the end application.

A good association (and related website) for locating different services and information on technological supply and demand in the surface coating sector is "The Society of Vacuum Coaters" (www.svc.org) website. There is also detailed information on teaching resources, seminars and specific conferences and congresses, where specialised information on these tools can be found. It has free resources on vacuum generation techniques, surface and thin-film characterisation and matters related to the preparation of substrate, deposition using different technologies and the major surface coating and multilayer structure applications.

13.5 Solution-Deposition Processes

Several techniques for coating biodevices with different adequate thin-films, for adapting or enhancing their performance, start from a solution or are carried out in a wet environment. These technologies stand out for their versatility, especially when trying to deposit biomaterials upon a substrate, and the most relevant are detailed below.

Sol–gel. These sol–gel processes are characterised by their transition from a sol phase to a gel phase, usually by various hydrolysis and polycondensation reactions, and are used for producing vitreous and ceramic materials.

The sol is made up of solid particles (usually around 0.1–1 μm in diameter) dispersed in a liquid, while gel comprises a solid network of macromolecules immersed in a solvent. The conventional stages of the process (Brinker and Scherer 1990; Hench 1998; Albella 2006) include:

(a) Dispersion of particles in a liquid to form the sol material comprising the initial chemical solution. Metal alkoxides are usually used as precursor particles (R-O-M, where R is a radical, O an oxygen atom and M a metal atom) and metal chlorides. Using particles of materials like SiO_2 as precursors and organic additive, modified silica glass with multiple applications can be produced.
(b) Deposition of a thin layer of sol on the substrate to be coated, normally by centrifuging or spin coating, by immersion–extraction or "dip coating" or by spraying. Different technologies, such as Langmuir–Blodgett deposition and other methods to prepare self-assembled monolayers are enabling even thinner thicknesses to be attained and more flexible films that can adapt to the geometries of more complex devices (see below).
(c) Polymerisation of sol particles by volatilisation of the stabilisers and the formation of the three-dimensional solid network that constitutes the gel. The alkoxides react rapidly in the presence of water (hydrolysis) to form R-OH and M-OH species molecules that can be then linked together by polycondensation to form OR-M-O-M-OR species three-dimensional networks with M-O-M bonds and remnants of H_2O and R-OH. The vaporisation of these H_2O and R-OH subproducts results in the required gel.
(d) Final thermal processing to obtain an amorphous or crystalline coating that is stable over time.

Of the different addition stages that can be achieved by sol–gel processes, depending on processing conditions and the end properties sought, we can cite the following:

- Xerogel. By gelation of the sol and conventional drying of the gel.
- Aerogel. By gelation of the sol and supercritical drying of the gel. Very porous solids are thus produced with an extremely high volume/mass ratio and are very useful for packaging.
- Dense ceramic. By sintering the dust from a milled xerogel or aerogel.

- Thin compact layer. By deposition of a thin layer of the sol on a substrate and subsequent polymerisation and drying.
- Fibres. By stretching the sol, followed by polymerisation and drying.

It should be mentioned that supercritical drying to obtain aerogels causes the fluid to reach supercritical conditions and a subsequent quasi-isothermal depressurisation is produced, thereby preventing the effects of contraction. It also prevents the effects of the surface tension produced on the surrounding solid structures by the appearance of liquid, which endows this supercritical process with numerous applications for the manufacture of MEMS (microelectromechanical systems) and NEMS (nanoelectromechanical systems).

Some of the many advantages of sol–gel processes for thin layer deposition are the wide ranges of attainable thicknesses (from tens of nm to several mm), the excellent adhesion between the substrate and the coating, low operating temperatures and the economical process. From a research point of view, what is exceptional is the ability to widely vary the end properties by making simple changes to parameters like initial concentration, precursor size, working temperature and initial sol viscosity. Some examples linked to sol–gel processes have already been detailed in Sect. 11.4.

Spin coating. This process is used to deposit dissolved polymer thin-films (using solvents like chloroform or trichloroethylene) or even liquid state monomer layers, in order to then activate the polymerisation reaction using heat or UV light, for instance by using massless UV lithography (see Sect. 12.4). It can also be used to complement deposition in the sol phase of sol–gel processes as different substrates can be used. If the process is repeatedly performed, homogeneous multilayers of different materials can be obtained.

The process consists in supplying a liquid resin or dissolved polymer drop-by-drop on to the substrate that will be centrifuged. The centrifuge or spinner is then switched on and the material spreads over the substrate to form the film and is then left to dry. It is sometimes also subjected to heating at different temperatures to evaporate the volatile elements and cure the film (soft bake and hard bake processes).

The greater the viscosity of the liquid or resin supplied to the spinner, the greater the thicknesses attained. High rotation speeds lead to thinner layers. The process can be used to obtain varied samples with very different properties in very short times, which for research is major added value.

In the biomedical filed simple planar geometries can benefit from this approach, such as “lab-on-a-chip” devices and scaffolds for Tissue Engineering.

Dip coating. The process consists in immersing a film vertically into a tank containing the polymer to be deposited in solution form, as liquid state monomers or in sol phase with dispersed particles. The film is then extracted at constant speed to achieve constant thickness (Newtonian fluid) and is left to dry.

At the end, thermal processing can be applied to finally cure the polymer. Greater viscosities and higher extraction speeds (due to the short time the fluid has to become arranged and compact), give rise to thicker layers.

It is mainly used to deposit dissolved polymer film or liquid state monomer layers to then activate the polymerisation reaction through heat or UV light, as is the case with spin coating. The immersion or dip-coating process can also be used for sol-phase deposition in a sol–gel process and various metallic, ceramic or polymeric substrates can be used.

Electrolytic/electrochemical deposition. The basic principle of electrolytic or electrochemical deposition processes for obtaining coatings consists in converting the metal of the anode into metallic ions that are distributed in the solution. These ions are deposited on the cathode (device, part or substrate to be coated) forming a metal layer on its surface. The different coating properties as well as the most suitable fields of application depend on the type of crystalline structure of the metal deposited.

The electrolytic coating of the parts is produced almost entirely through immersion in a bath. For this purpose the parts are immersed in the tanks of electrolyte, current is applied as a cathode and they are then coated and dried. When the parts are removed from the bath some of the electrolyte becomes attached to the surface of the parts. This surface film is then eliminated by a washing process so that it will not interfere in any subsequent operations and will have the required finish.

Deposition using Langmuir–Blodgett technology. This is a very exact deposition technology (performed by the superposition of monolayers) using different organic coatings, such as fatty acids, phospholipids and polymers with long lateral hydrophobic chains. Nanostructures can be produced with molecular alignment and controllable roughness and thickness and are widely used for producing biosensors. Their high precision means that the materials obtained can either be microstructured or nanostructured.

It can also be used for surface micro-engraving that can be combined with other CVD or PVD technologies to produce electrodes with special geometries or patterned biodevices (i.e. for cell motility studies). New research proposes using them to produce multilayers with ferroelectric polymers for non-volatile RAM memories and mass storage devices. By means of this technology extremely thin layers of ferroelectric polymer have been deposited, PVDF as well as various copolymers, attaining thicknesses of 10 Å with properties similar to those of thicker multilayers but showing additional phase changes, what also promotes the development of self-sensing biodevices.

13.6 Self-Assembly and Related Processes

Ionic self-assembled monolayering techniques. Developed by Decher and Hong (1991) for polyelectrolytes and then extended to the production of multilayer structures with many electroactive polymers, fullerenes and other materials. Layers can be deposited on a substrate by consecutively alternating the adsorption of cationic and ionic species. It is a relatively cheap and simple technology for controlling the molecular structure of materials and influencing their macroscopic properties.

It has recently been used to obtain multilayer structures by bonding very different materials like polyelectrolytes, metal colloids, biological molecules, conductive polymers and light emitting polymers (Decher et al. 1992).

The process begins by taking a clean substrate with a negative surface charge. This material is submerged in a solution with polymer molecules dissolved in it that have functional groups bonded to a polymer chain with a net positive charge. These molecules are attracted to the surface of the substrate, which is left coated with a layer that is neutral as a whole, but with a positive charge on its upper surface. When this cationic layer has been deposited, the external charge then incites the deposit of another anionic layer, and in this way a multilayer structure can be produced.

By adding appropriate functional groups to the substrate or using surface patterns, deposition can be encouraged in certain zones. By adjusting immersion times, solute concentration and dissolution temperature, 3D structures can be obtained by depositing material layers of controlled thickness that generally have more stable properties than those obtained by Langmuir–Blodgett technology (Madou 2002). It can then be subjected to chemical attack to eliminate zones of unwanted deposits.

This technology together with the production of multilayer deposits with electroactive polymers has succeeded in optimising the performance of light-emitting diodes (LEDs), as well as enhancing the stability of luminescent organic pigments compared to films obtained by spin coating (Bar-Cohen 2004). Medical applications based on active material substrates are also promising, as this process can also be used to functionalise substrates for biosensors and for improving the biocompatibility of active implantable devices (Saliterman 2006).

In fact ionic self-assembled monolayered techniques somehow resemble some processes carried out by Nature itself to produce its (bio)materials and (bio)structures. Self-assembly processes, by directing the deposition of molecules through charge-based mechanisms are common. Further research in the field and the use of biomimetic design principles will surely lead to more and more precise additive manufacturing machines for even constructing molecule by molecule or atom by atom.

Laser ablation. Laser ablation consists in eliminating the surface material of a substrate, usually solid, using a laser beam to produce evaporation and sublimation or to convert the zone exposed to the beam into a plasma. The process is performed by laser pulses (that last from milliseconds to femtoseconds), which means the elimination of material is so precisely focused that the rest of the substrate remains practically unaltered.

It is therefore an extremely suitable technology for changing the surface of materials that cannot be subjected to high temperature processes (generally polymers and organic matter), as the heat-affected zone "HAZ" in conventionally extremely reduced.

This process has also been used to produce carbon nanotubes and as a support for PVD processes in which a laser acts on the substance to be deposited and the plasma generated is projected on to the substrate to be coated (Phillips 2006).

Ion implantation. The process consists in coating a substrate with the ions of another material, in order to change the physical properties of the substrate. This has

numerous applications in the electronics industry for manufacturing semiconductive devices but also in the biomedical field. For this process an ion source is required, together with an accelerator to project the ions into a chamber, where the substrate to be implanted has previously been placed (Rimini 1995).

With regard to active materials for medical devices, ion implantation is usually used to make the surface of different polymers become locally conductive. This avoids the deposition of electrodes that cover the whole surface of the substrate, as this is usually accompanied by an unwanted stiffening effect, which limits the capacity for deformation and the activation capabilities of microstructured polymer actuators (Díaz Lantada 2012). This technology is an alternative to mask or maskless photolithography when micro-manufacturing electrodes with complex patterns or geometric shapes.

Many additional nano-manufacturing technologies can be used or adapted to the performance enhancement of biodevices, although we believe to have provided here an overview of the most relevant ones. Additional combinations with 3D solid free-form fabrication approaches, by using the most precise additive manufacturing technologies currently available (3D laser writing/two-photon lithography, high precision UV-lithography, etc.), can be very useful for improved solutions in many areas, such as Tissue Engineering and micro-/nano-implants.

13.7 Main Conclusions and Future Research

This chapter has focused on providing a brief introduction to nano-manufacturing technologies and on discussing main technologies currently being applied to promoting the performance of commercially available biodevices and in some cases of rapid prototypes.

Main applications of nano-manufacturing technologies for the biomedical field have been summarised. Mainly, nano-manufacturing processes are already being widely used for improving the mechanical performance, the corrosion resistance, the contact properties, the biocompatibility and the biocidal behaviour and even the aesthetics of several implantable devices, as has been detailed.

Such manufacturing processes, mainly physical and chemical vapour deposition, thin-film solution-deposition processes and self-assembly and related processes, together with some typical applications have also been introduced and links to associations and manufacturers also provided.

In most cases the use of thin-film deposition technologies involves a change of approach, from the conventional “top-down” manufacturing (either by subtractive machining processes or by chemical attacks) to a more versatile “bottom-up” or additive approach. In fact this “bottom-up” manufacturing strategies can be even considered “biomimetic”, as nature itself also constructs normally using additive procedures.

Some relevant connections can thus be established with the topics covered in Chap. 10, about additive manufacturing, and Chap. 12, about micro-manufacturing

processes. The 3D laser nano-lithography (or direct laser writing) process, already cited in Chap. 12, was introduced as a bottom-up process with typical precisions in-between those from micro- and nano-manufacturing, what provides a relevant bridge between both worlds, whose impact is beginning to be assessed.

Further exploring the possibilities of combining theses advanced manufacturing resources, with those provided by novel nano-CAD tools, by more adequate biomaterials and by the use of "intelligent" materials as transducers, can prove to be of great help for finding more efficient diagnostic and therapeutic solutions for the medical industry of the twenty-first century.

The interesting references included in the next section provide additional information about medical appliances already benefiting from the manufacturing techniques described here and more in-depth aspects linked to the application of nanotechnology for the development of biosensors and bioactuators, capable of providing highly innovative diagnostic and therapeutic procedures.

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Chapter 14
Biofabrication: Main Advances and Challenges

Andrés Díaz Lantada

Abstract The artificial production, in laboratories, of organs and biological structures, by adequately placing and combining ex vivo cells, synthetically produced tissue patches, and supporting biomaterials, is no more a matter of science fiction but a present relevant research challenge already providing promising results, included under an innovative area called "biofabrication."

If organs could be artificially produced, patients would benefit from more rapid surgical interventions; compatibility would be highly promoted, as they would be produced ex vivo from the own patient's cells; and aspects such as organ piracy would be limited (nowadays around 10 % of organs used for transplantation worldwide comes from illegal activities).

The socio-economical impact of synthetic organ production is comparable to that of the whole pharmaceutical industry, what explains the interest it has arisen in the last decade, with several new companies aiming at improving state-of-the-art tissue engineering procedures for starting 3D tissue construction.

In addition, novel scientific journals are being devoted to these advances, and it is just a matter of time that related concepts and techniques are included in the syllabuses of teaching programs at universities, what would be very positive for the evolution of this area.

This chapter provides a brief introduction to this field of research, discussing most relevant advances on materials science, design tools, and manufacturing technologies that are working for making biofabrication a viable alternative to conventional therapeutic procedures. Main present difficulties and research challenges are also discussed.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_14,

14.1 Introduction: The Manufacture of Biological Systems

We have seen that in the context of medical device development and the biomedical industry, one of the major areas of application for these rapid prototyping technologies is tissue engineering. Since the 1980s, outstanding researchers like Eugene Bell and Robert S. Langer, both professors at the MIT, began looking at how to produce scaffolds with materials and geometries that were suitable for cell culture and tissue growth and could be used in surgical operations (Langer and Vacanti 1993).

The gradual progress in the field of biodegradable polymers together with the advances in more flexible rapid manufacturing technologies means that at present, complex geometry scaffolds can be obtained to which living cells with growth factors adhere and multiply until they cover the scaffold. Having reached this stage, the set (scaffold + coating) is implanted into the damaged parts of the body. After being implanted, the cells adapt to their environment and reproduce the functions of the surrounding tissue, while the scaffold is gradually reabsorbed (Hollister 2005; Gómez Ribelles et al. 2010). All this has led to changes in the approach to solving many surgical problems.

It is hoped to continue work on this progress with a view to obtaining three-dimensional biological structures that will 1 day lead to the additive fabrication of human organs. The firm EnvisionTec GmbH has already developed the Bioplotter® (see Sect. 14.5) with which small three-dimensional structures are being obtained by the "layer-by-layer" deposit of cells together with biocompatible material, and the initial use of the concept of a "bioprinter" looks promising.

A larger number of printing technologies based on appropriately modified conventional RP technologies are being sought, which are progressively leading to more affordable machines (DigiLab Inc., Sect. 14.5).

This progress may open up new horizons to the treatment of many diseases by combining synthetic and biological materials to produce veins, capillaries, arteries, bones, and soft organs, or at least part of them. By using machines with several heads that can deposit different materials, biological tissue could be directly obtained with synthetic implants pre-integrated into them. This would endow the newly generated tissue with mechanical consistency.

However, there is still a long way to go, not only regarding the precision of these "bioprinters" and the biological and biomedical materials they are capable of depositing but also regarding the manufacture of structures larger than $1 cm^3$. It would appear that the development of a capillary network to provide the newly generated three-dimensional cell structures with nutrients is currently one of the major limitations (Mironov et al. 2009; Bartolo and Bidanda 2008, 2009).

There is also an important need for further progress in the design field, so as to obtain more adequate biomimetic CAD files, for subsequent manufacture of biostructures. Relevant progresses in the field of high-precision medical imaging, together with software for handling such medical images as design inputs, are proving to be very relevant.

Organizing specific work sessions to facilitate information exchange among researchers is a particularly useful idea, usually within a framework of bioengineering congresses, where rapid prototyping applications in the medical sector, especially those oriented to biofabrication, can be discussed, and people can join forces to go forward together.

Worth mentioning are the "World Bioprinting Congresses," the "International Workshop on Bioprinting and Biopatterning," and the "International Conferences on Biomedical Electronics and Devices" – Biodevices 2008, 2009, 2010, 2011, and 2012. Relevant journals in the field include "Bioinspiration and Biomimetics" and "Biofabrication."

This chapter provides a brief introduction to these topics, after discussing main applications of biofabrication for the biomedical field in next section.

14.2 Overview of Applications for the Biomedical Sector

The final objective of research in the biofabrication area is the artificial production of organs and biological structures in laboratories, by adequately placing and combining ex vivo cells, synthetically produced tissue patches, and supporting biomaterials. If organs could be artificially produced, patients would benefit from more rapid surgical interventions; compatibility would be highly promoted, as they would be produced ex vivo from the own patient's cells; and aspects such as organ piracy would be limited. The applications in medicine, if this final objective is achieved, are endless; however, partial results, in the way to final achievement, are already providing interesting applications briefly discussed here.

Advances in the field of biofabrication are actually improving tasks and procedures linked to tissue engineering, as novel machines allow for the combined manufacture of biosubstrates with incorporated living cells and nutrients, hence enhancing cell growth and tissue formation for transplantation (Jakab et al. 2010).

Some biodevices for surgical interventions, such as sutures, are being seeded with cells (normally hMSCs) with the help of 3D printers designed ad hoc, thus accelerating tissue repair and recovery from surgical procedures (Kanani 2012).

New materials and biomaterials are continuously being discovered, in the search for more adequate substrates and supports for cell growth, and special attention is being paid to unconventional biomaterials as candidates for tissue engineering, as well as for other fields of technology, such as secretions from animals and plants (spider silk, plant resins) (Lenaghan et al. 2011).

In addition, progresses on imaging technologies, aimed initially at improving diagnosis, if adequately combined with design and modeling tools, are also being of help for promoting biomimetic designs but also for replicating the structures of novel bio- and meta-materials and *in silico* assessing their behavior, as detailed in next section.

14.3 Advances and Challenges Linked to Biomaterials

Materials science has devoted great efforts in the last decades of twentieth century to the development (mainly synthesis/extraction and processing) of new materials and material families (such as polymers, polymer-matrix composites, metallic foams, superalloys), and main advances during the first decade of the twenty-first century focus also on that direction (artificial muscles, biopolymers, materials from natural origin). These advances have completely changed the engineering world and reshaped the whole product development process, with outstanding impact in several fields including automotion, aeronautics, architecture, design, electronics, information and communication technologies, energy, and biosciences.

Parallel advances in design and simulation tools are providing very adequate resources for modeling such novel and often complex materials, whose behavior is in many cases not yet fully characterized or understood. Therefore, besides the continued search for new materials capable of producing biocompatible devices, additional challenges linked to characterization and precise simulation are also needed for promoting the global biodevice development process.

Some relevant characterization tools (both oriented to biomaterials and to more specific biodevices) are covered in Chap. 15 and are normally oriented to an assessment of overall long-term mechanical performance and stability. More linked to modeling tasks are advances in medical imaging technologies, especially micro-CT, whose current precision, reaching around 25–50 μm, is high enough for the detailed reconstruction of most corporal structures (Shi et al. 2008; Guo et al. 2010).

Figure 14.1 includes some application examples of the use of micro-CT technology to the 3D reconstruction of complex materials (and biomaterials) for subsequent modeling and simulation linked to studies in the field of materials science. Once reconstructed, they can also be used, thanks to Boolean operations (see Sects. 7.2 and 7.3), for designing the inner structure of several biomimetic biodevices and prostheses. The linkage between medical imaging, CAD programs, and FEM-based simulation modules can be a great help for assessing the adequate performance of a biomimetic structure, once adapted to the geometry of novel prostheses and biodevices, before the investing in the manufacture of prototypes for preproduction validation trials.

The examples provided in Fig. 14.1, courtesy of SkyScan company, show reconstructions of the glass fibers of a composite material, of a nickel foam, and of a porous wood. Similar results can be obtained from micro-CT of polymers, ceramics, biopolymers, and other biomaterials such as bone, as well as biostructures, which can help to design biomimetic scaffolds for tissue engineering.

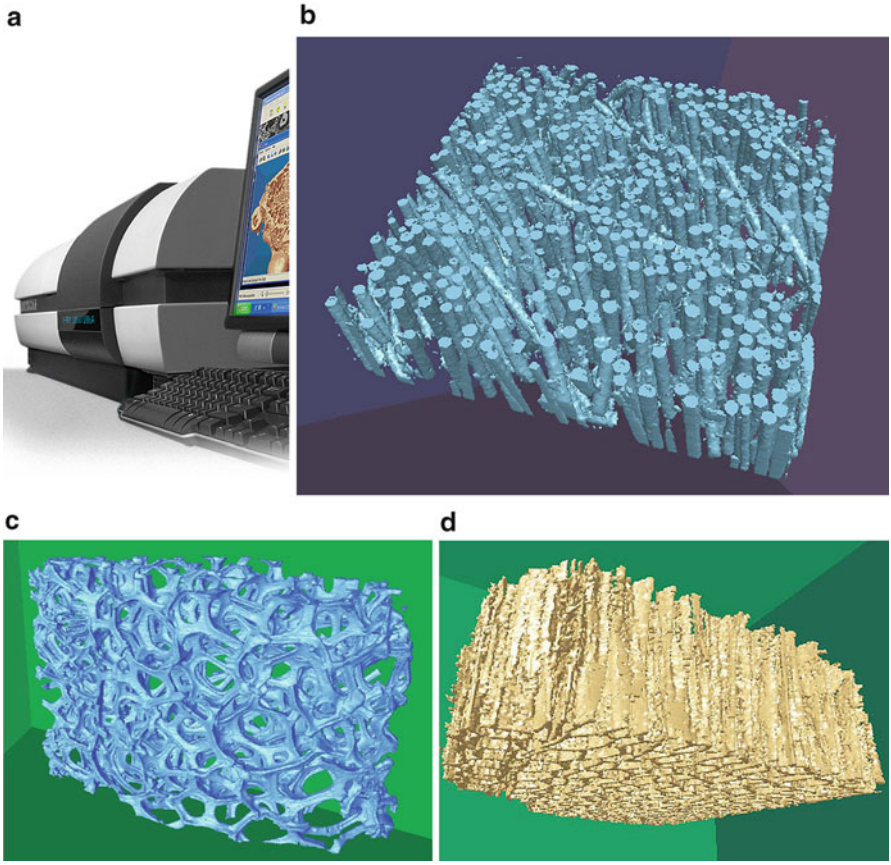

Fig. 14.1 Examples from the SkyScan micro-CT series. (**a**) SkyScan 1172 high-resolution micro-CT scanner. (**b**) Glass fibers of composite material. (**c**) Hollow walls of Ni foam, rendering of internal micro-architecture for subsequent CAD modeling. (**d**) Application to the reconstruction of wood. Applications linked to the reconstruction of biomaterials for further use in biomimetic designs and materials science (Images courtesy of SkyScan company [www.skyscan.be])

14.4 Advances and Challenges Linked to Biodesign Tools

Advances for promoting biofabrication approaches are not only linked to finding more adequate materials and processing technologies compatible with cell deposition but also to additionally exploring design processes capable of providing alternative approaches or complementary solutions, to those based on medical imaging-based reconstructions.

The term "biomimesis" (from Greek "bios" (life) and "mimesis" (imitation)) is linked to the study of nature's models, principles, designs, and processes to imitate them or find new inspiration for solving human problems (Benyus 2002). Main applications of biomimesis are aimed at finding new ways of producing food or

energy, novel methods of manufacture, innovative therapeutic solutions, and overall management of mankind and its relations. In this handbook (mainly in Chaps. 5, 6, 10, 11, 12, and 14), we have focused on summarizing and providing methods for designing special biodevices, with features trying to imitate those from human organs, tissues, and structures, for enhancing final performance.

In this section we reintroduce two important possibilities for promoting the development of biomimetic devices, one based on multi-scale mathematical modeling of biostructures and the other based on medical imaging-based reconstructions, for additionally highlighting the possibility of combining or alternating such methods.

Chapter 6 already introduced the possibility of using fractal models for the design of biodevices with controlled surface properties or geometries imitating those from the body. Here we provide an additional example of the use of such models, more linked to biomimetics and to the modeling of (bio)materials, than to the design of a final biodevice. We have focused on imitating the lotus flower leaves, whose microstructure is famous for providing self-cleaning properties (Barthlott and Neinhuis 1997).

In the mathematical model included below, final multi-scale surface $z(x,y)$ can be considered as the sum of two different surfaces ($z_m(x, y)$ and $z_n(x, y)$), each providing a relevant component at a different scale level. In our case, the microscopic bump–like behavior of the lotus flower leaves can be approximated by using a regular surface defined by $z_m(x, y)$, for obtaining 10 μm size details. For introducing an additional level of precision (irregularities in the range of hundreds of nanometers), $z_n(x, y)$ proves to give positive results if based on fractal models. The following equations give the height "z" of the surface, when assessing the function over a grid of points given by their (x, y) coordinates.

The model uses several random functions (A_k, B_k, C_k) and several control constants (λ, α, k), and an initial height function "z_0" can also be introduced. According to the model, fractal dimension "D" of the generated surface can be obtained from the expression "$D=3-\alpha$," for having an indication on how completely the fractal appears to fill space. Related Matlab program can be found in the annexes of the handbook. Figure 14.2 shows the result of the biomimetic design:

$$z(x,y) = z_m(x,y) + z_n(x,y)$$

$$z_m(x,y) = z_0 + 10 \bullet \left|\sin(\pi x/10) \bullet \sin(\pi y/10)\right|$$

$$z_n(x,y) = \sum_{k=1}^{\infty} C_k \bullet \lambda^{-\alpha k} \bullet \sin\left(\lambda^k [x \bullet \cos(B_k) + y \bullet \sin(B_k) + A_k]\right)/10$$

Further incorporation of different scale terms can lead to more precise control of final geometry or for imitating other biological structures, as shown in Fig. 14.3, which includes some additional micrometric bumps.

Final prostheses, designed on the basis of such fractal models, for controlling roughness, skewness, and surface/volume ratio, aiming at improving biocompatibility and long-term stability, are also possible. Figure 14.4 shows a fractal cylinder, which could be adapted to designing the tubular parts of knee or hip prostheses,

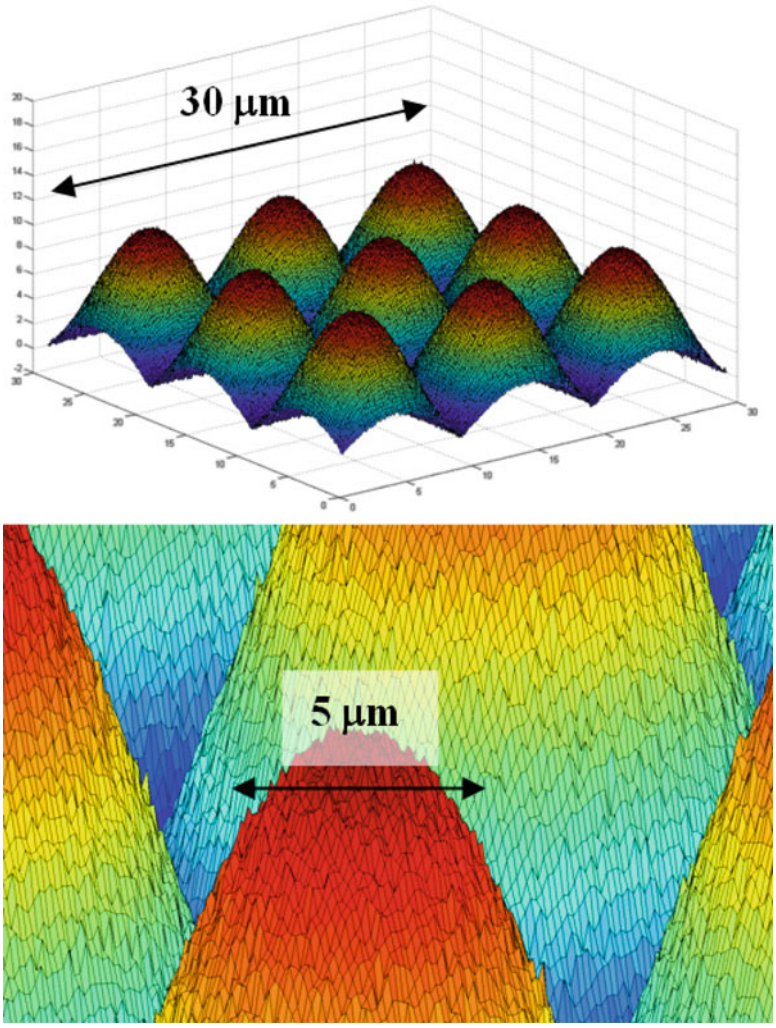

Fig. 14.2 Example of multi-level biomimetic CAD design based on the lotus flower leaves' surface for producing special contact phenomena (Adapted from A. Díaz Lantada et al. Biodevices 2012)

among other biodevices. They can also be manufactured following additive and subtractive procedures (Díaz Lantada et al. 2012; De la Guerra Ochoa et al. 2012).

Figure 14.5 shows the alternative approach, based on digitalization, instead of on analytical modeling. It provides, courtesy of SkyScan company, examples of high-resolution reconstructions of biological structures, such as the capillaries of a mouse lung, the whole reconstruction of a mouse knee, or the inner micro-architecture of a frog femur. The process can also be used for corporal structures, although it requires larger appliances.

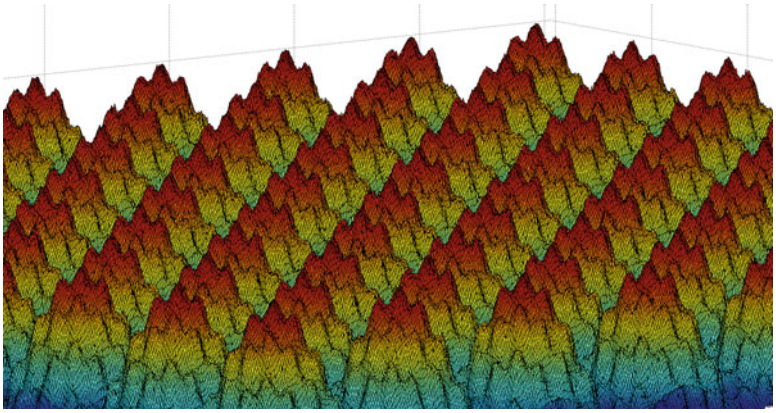

Fig. 14.3 Biomimetic multi-scale design based on combining conventional and fractal geometries, according to proposals from Chap. 6

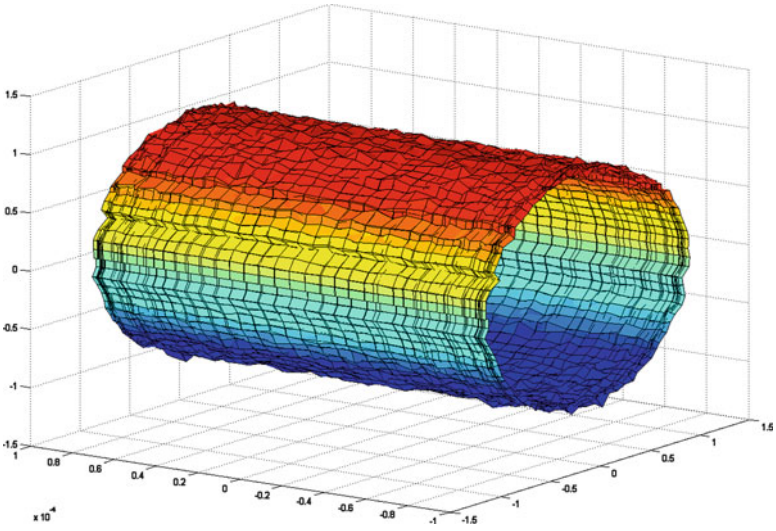

Fig. 14.4 Fractal cylinder based on fractional Brownian fractal model for the control of micro-textured biomimetic cylindrical or conical prostheses

It is necessary to note that, thanks to advances in the linkage between medical imaging technologies and CAD-CAE-CAM resource, once more versatile and effective 3D bioprinters are developed (capable of manufacturing whole implantable organs), the reconstructions will probably be carried out on the basis of original information taken from the patient's body, similar to those shown below, so as to provide personalized solutions.

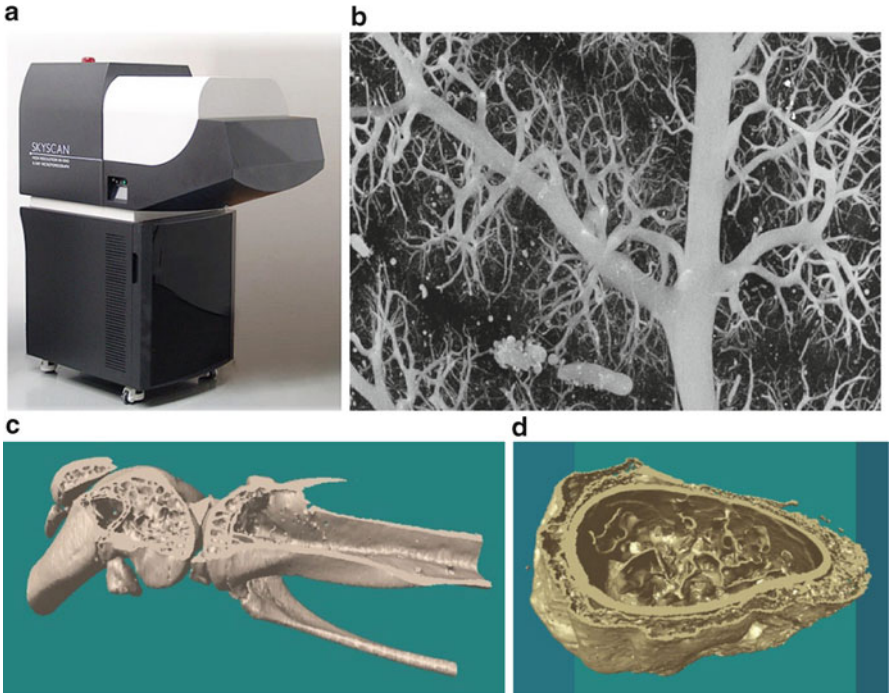

Fig. 14.5 Examples from the SkyScan micro-CT series. (**a**) SkyScan 1,176 high-performance in vivo micro-CT scanner. (**b**) Mouse lung sample. (**c**) Application to the reconstruction of a mouse knee (in vivo scanning). (**d**) Frog femur, rendering of internal micro-architecture (CTan and CTvol programs). Applications linked to the reconstruction of corporal structures for subsequent personalized design of implantable medical devices (Images courtesy of SkyScan company [www.skyscan.be])

14.5 Advances and Challenges Linked to Biomanufacturing Technologies

Conventional desktop printers deposit microbubbles of ink, with remarkable precision, for writing documents, and state-of-the-art very simple 3D printers (see information provided by the wiki of the "RepRap" project) are also capable of extruding fused polymers, gels, and even molten chocolate, for obtaining three-dimensional prototypes with complex geometries in different materials.

Therefore, the technology for depositing cells, coming within a liquid or gel-like matrix, and further constructing sheets and three-dimensional tissues, already exists. A simple combination of already available resources and additional research, focused on supporting such cell growth, through an adequate vascularization and nutrient supply, is making biofabrication a reality.

Relevant recent results have already been obtained by using alternative methods, such as laser printing of cells into 3D scaffolds, which uses the propulsive force

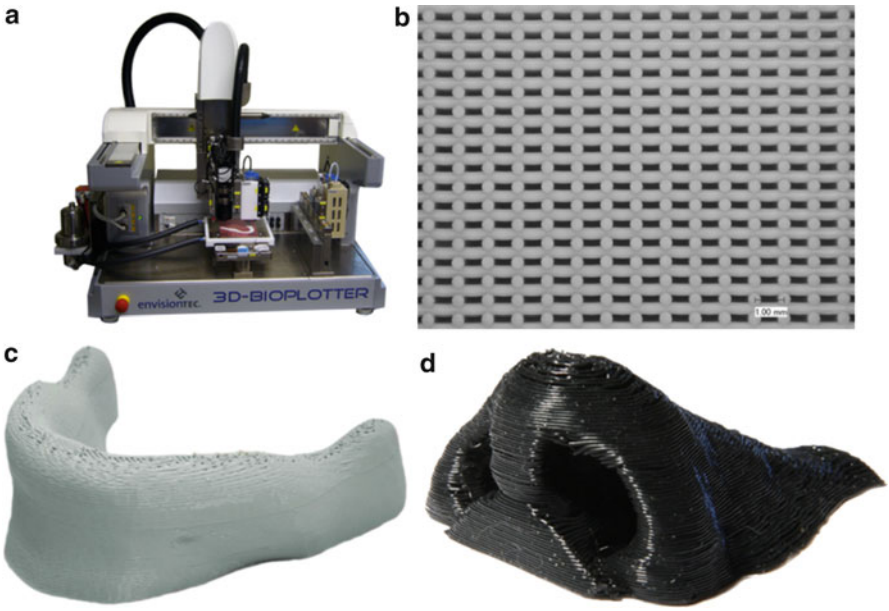

Fig. 14.6 (**a**) Envisiontec 3D-BioplotterTM fourth generation machine. (**b**) Vertical cut trough a bioplotted scaffold (conventional woodpile structure). (**c**) Bioplotted jaw. (**d**) Bioplotted nose (Images courtesy of envision TEC GmbH [www.envisiontec.de])

from laser-induced shock wave to propel cells gently into a substrate (Ovsianikov et al. 2010) or layer-by-layer extrusion of gelatin/alginate with seeded stem cells, for bioprinting small 3D biostructures (Norotte et al. 2009; Li et al. 2009; Marga et al. 2012). The use of concurrent additive manufacture of scaffolding structures based on biodegradable thermoplastics and cells suspended in gels (different extruders would print different materials, as support, and provide also cells and nutrients) has also been proposed (Melchels et al. 2012).

In fact some commercially available resources already exist, which are already providing excellent support to research tasks linked to further advances in these directions, as detailed further on.

In Europe, EnvisionTec GmbH provides its "3D-Bioplotter™" (already in its fourth generation) (see Fig. 14.6) which also includes some examples of attainable devices, including a scaffold for tissue engineering, a bioplotted biomimetic jaw, and bioplotted biomimetic nose.

The "3D-Bioplotter™" stands out for its versatility, as it can build parts by combining up to five materials with automated tool change, for its fast plotting speed, while maintaining appropriate accuracy, and for the possibility of printing up to five types of cells per object.

Actually the "3D-Bioplotter™" has the capacity of fabricating scaffolds using the widest range of materials of any singular rapid prototyping machine, from soft hydrogels and biomaterials (agar, alginate, fibrin, chitosan, collagen, gelatin), over

polymer melts (PLLA, PCL, PLGA), up to hard ceramics (hydroxyapatite, tricalcium phosphate) and metals (titanium), although these last harder materials require a sintering post-process.

In the United States, Digilab Inc. offers its "Cell Jet Cell Printer," which stands out for its special focus on gentle cell deposition and for handling and delivering cell suspensions. Some tailoring to final application is also affordable. The current and potential uses of the cell printer include, but are not limited to:

- Delivering cell suspensions into micro-fluidic chips/high-throughput cell-based assay platforms
- Dispensing cell suspensions in customized patterns to form microarrays on standard or custom microscope slides (or other substances), most commonly for developing/performing cell-based assays
- Delivering cell suspensions (in cell culture media or hydrogels) at defined locations in 2 and 3 dimensions onto preformed scaffolds (such as biological sutures/tissue construct scaffold), in order to populate the scaffold
- Dispensing cell suspensions in custom patterns on a surface, for migrational studies or to study interaction of cells among each other or with growth factors
- Delivering cell suspensions to micro-wells in a various diagnostic/research devices made of silicon, PDMS, or other substances, where manual delivery of sample is difficult, time consuming, or simply impossible
- Dispensing other reagents or growth factors or biologically relevant substances in a suspension, in addition to cells, to targeted locations/patterns in a similar manner
- De novo biofabrication of relatively simple tissue constructs

Next, Figs. 14.7 and 14.8 include some results from the highly interesting Ph.D thesis from Christian Kanani, focused on improving the processes of seeding cells onto biological scaffolds (Kanani 2012).

Figure 14.7 shows a prototype of the Digilab's "Cell Jet Cell Printer," with different reservoirs for dispensing cells and the dispensing tip on action. Two or four dispensing tips can be also used. Lower images shows an image of a 96-well plate seeded with hMSCs using the cell printer. Cytoplasms of live cells show a bright green calcein signal and nuclei of dead cells show a red ethidium homodimer-1 signal. All nuclei show a blue Hoechst 33,342 signal, so the Digilab is perfectly useful for cell seeding upon different types of scaffolds and structures.

Figure 14.8 shows a more demanding task, linked to seeding a surgical suture with hMSCs for promoting final biocompatibility and helping faster tissue repair and recovery from surgery. Upper image shows the cell printer's suspending tip positioned over the thread bundle (biological suture made of fibrin) ready to begin dispensing hMSC suspension. Lower image shows a thread bundle after seeding hMSC suspension with help of the cell printer. Green = phalloidin (F-actin filaments of cytoplasm of seeded hMSCs). Red = ethidium homodimer-1.

Such ex vivo trial helps to validate the approach, and similar procedures can become generally used for promoting the efficiency of surgical interventions, once these cell printers are more widely available.

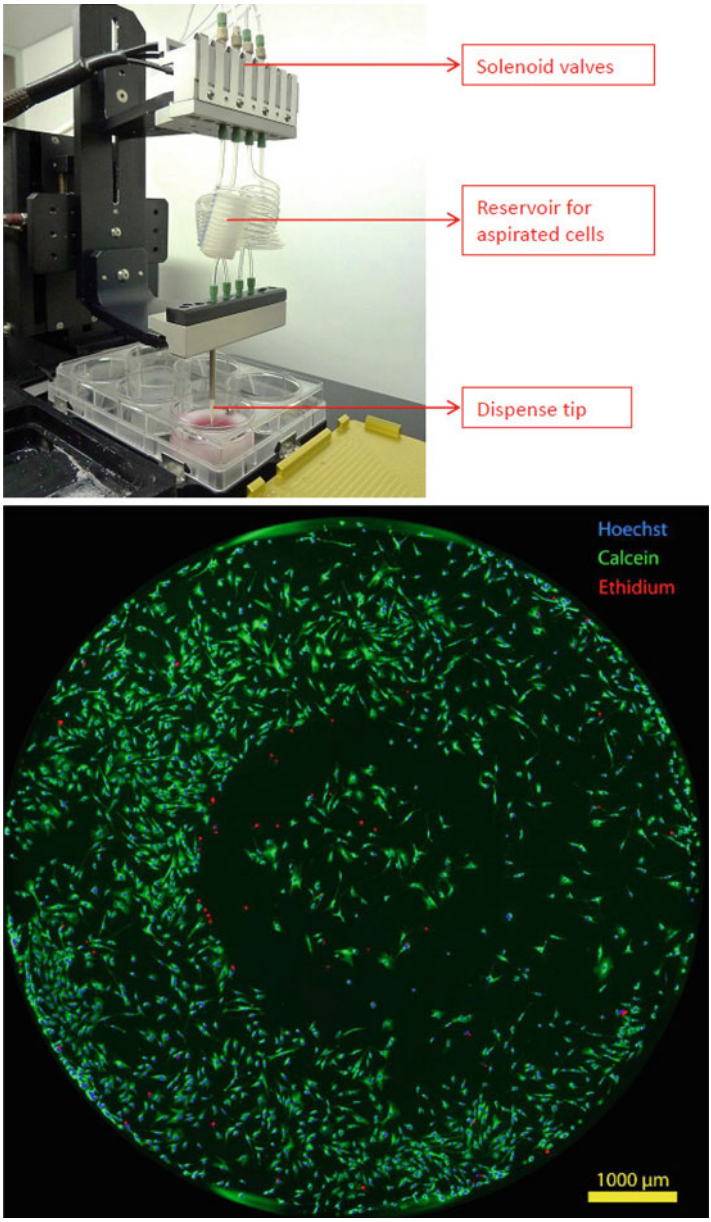

Fig. 14.7 *Upper image*: Prototype of the Digilab's "Cell Jet Cell Printer". *Lower image*: Representative image of a 96-well plate seeded with hMSCs using the cell printer. Cytoplasms of live cells show a *bright green* calcein signal. Nuclei of dead cells show a *red* ethidium homodimer-1 signal. All nuclei show a *blue* Hoechst 33,342 signal (Images courtesy of Digilab Inc. taken from C. Kanani Thesis. [www.digilabglobal.com and www.digilabglobal.com/celljet])

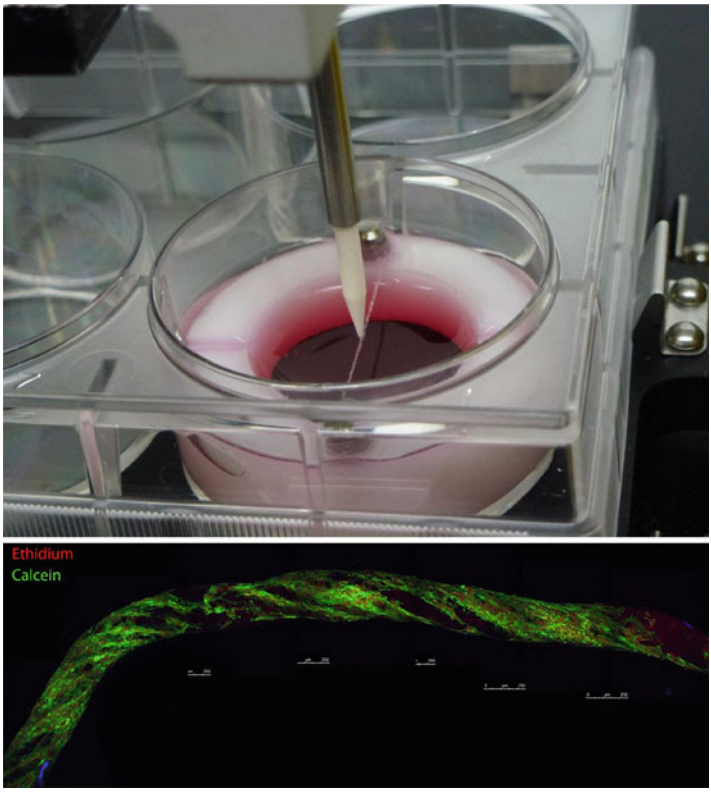

Fig. 14.8 *Upper image*: Cell printer's tip positioned over the thread bundle (biological suture made of fibrin) ready to begin dispensing hMSC suspension. *Lower image*: Image of a thread bundle after seeding hMSC suspension with help of the cell printer. *Green* = phalloidin (F-actin filaments of cytoplasm of seeded hMSCs). *Red* = ethidium homodimer-1 (Images courtesy of Digilab Inc. taken from C. Kanani thesis. [www.digilabglobal.com and www.digilabglobal.com/celljet])

Researchers wishing to obtain additional information on related advances may wish to visit Digilab's website (www.digilabglobal.com) and have a more detailed look at the conference papers and publications linked to the use of the "Cell Jet Cell Printer" and related "synQUAD Technology" (capable of dispensing drop by drop down to 20 nL and up to several microliters of fluids).

Main challenges of bioplotters and cell printers are still linked to constructing more complex and bigger tissue constructs mimicking the complex structures of complete organs (Melchels et al. 2012). Combined advances in medical imaging, design technologies, and materials science will surely find solutions to such challenges, as the "hardware" (automated biomanufacturing machines) for biofabrication is already working properly and providing effective solutions, as Figs. 14.6, 14.7, and 14.8 have shown.

14.6 Main Conclusions and Future Research

The artificial production, in laboratories, of organs and biological structures, by adequately placing and combining ex vivo cells, synthetically produced tissue patches, and supporting biomaterials, is no more a matter of science fiction but a present relevant research challenge already providing promising results, included under an innovative area called "biofabrication."

If organs could be artificially produced, patients would benefit from more rapid surgical interventions; compatibility would be highly promoted, as they would be produced ex vivo from the own patient's cells; and aspects such as organ piracy would be limited. The actual socio-economical impact of synthetic organ production is even comparable to that of the whole pharmaceutical industry, what clearly explains the interest it has arisen in the last decade, with several new companies aiming at improving state-of-the-art tissue engineering procedures for starting 3D tissue construction.

This chapter has aimed to provide a brief introduction to this field of research, discussing some relevant advances on materials science, design tools (either based on analytical modeling or on digital reconstruction), and manufacturing technologies that are currently working for making biofabrication a viable alternative to conventional therapeutic procedures.

Even though main challenges of bioplotters and cell printers are still linked to constructing more complex and bigger tissue constructs, mimicking the complex structures of complete organs, combined advances in medical imaging, design technologies, and materials science are already providing interesting solutions, and the "biomanufacturing machines" are already commercial and effective. Final whole organ printing is just a matter of time.

The promotion of collaboration between researchers may prove essential for reaching final objectives of biofabrication in perhaps a couple of decades, for instance, following the example of the "RepRap" project collaborative wiki, which is encouraging many researchers to introduce additive manufacture as an additional support for their research. These kinds of "do-it-yourself" rapid prototyping machines can also be adapted to 3D printing of biomaterials and cells, as an easy and affordable way of obtaining resources for conceptual validations linked to tissue engineering and biofabrication.

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Chapter 15
In Silico, In Vitro and In Vivo Testing of Biodevices

Andrés Díaz Lantada

Abstract Design validation is a complex process in all kinds of industries but especially in the biomedical field due to the potential risks of using devices for interacting with organs and biological structures. The rapid manufacture of prototypes is an enormous help for carrying out validation trials; however, reaching preproduction stage in the case of biodevices is still complicated, as the normative environment is also multifaceted and several steps have to be followed.

As already explained, systematic validations throughout the whole development process, by using simulations and computer-aided engineering resources for in silico testing, rapid prototypes with increasing level of detail for in vitro trials and (only when working principles and safety have been verified) in vivo trials with animal models, are essential for reaching the preproduction stage.

In this chapter, we introduce the different kinds of procedures used for testing biodevices, providing examples of in silico, in vitro and in vivo testing and trying to detail some novel resources for more adequate validations, from workbenches and automated test systems to physical biomimetic models and virtual reality (VR) haptic devices.

Some commercial systems from relevant enterprises in their respective sectors are provided, as a help for researchers seeking novel, improved and secure ways of probing their biodevices and medical appliances, without directly resorting to the use of animal models. Important advices can also be obtained by consulting the most relevant related standards, which are also discussed. It is necessary to highlight again the importance of multidisciplinary teams in projects linked to the development of novel biodevices as, also for the different kinds of trials, abilities from physicians, surgeons, engineers and scientists are needed.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_15,

15.1 Introduction to the Testing of Biodevices: The Challenge of Introducing a Biomedical Product into the Market

Medical implantable devices must be tested thoroughly during their development process, including tests in living systems, either ex vivo (for laboratory aimed scaffolds and lab-on-a-chip devices) or in vivo (for implants), in order for them to be approved by the EU, by the Food and Drug Administration and by main national administrations connected to biodevices, before final clinical trials and subsequent production and marketing.

In general, the biodevice should undergo design validation in silico, with the help of models and simulations; performance validation, with the help of material probes and prototypes for in vitro testing, carried out by using workbenches, test equipments, anatomical models and even tissues from dead animals; ex vivo testing for analysing the biological behaviour, including aspects such as cytotoxicity, sensitization, reactivity, systemic toxicity and genotoxicity, that is normally carried out by using living cells or small living tissue patches extracted from living organisms; and final in vivo testing by implantation on adequate animal models for assessing aspects like chronic toxicity, carcinogenicity and biodegradation.

The progressive use of more analytic validation procedures, through systematic study of similar devices and materials, through FEM-based simulations and through exhaustive in vitro trials in workbenches and even in ad hoc designed machines, leads to a remarkable reduction in the number of animals used for preclinical in vivo trials, thus increasing overall sustainability of the whole biodevice development process. We hope to provide some advances linked to that direction in the following sections.

A very comprehensive introduction to preclinical research in the framework of FDA is provided by Dr. James Swick (in Kuklick 2006). Main European directives linked to the commercialization of medical devices and main ISO test procedures for design validation, as well as for biocompatibility assessment, have been summarised in Chap. 2 (see also the Reference section of this chapter). Here we provide a brief overview of the different testing stages necessary, always depending on biodevice's class, which is related to its potential harm, and on country's regulatory affairs, for reaching clinical trials.

Main standards providing additional information are also included, as well as several links to research centres and laboratories devoted to in vitro, ex vivo and in vivo testing of biomedical devices, as a help for researchers aiming to reach the clinical trials of novel biodevices and final production.

15.2 The Importance of In Silico Testing

In silico testing refers to the use of computation tools for simulating the performance of products and devices, normally before the manufacture of prototypes, or as an additional help for optimising the design, once results from trials with prototypes are available.

The advances in FEM-based simulation and its much more direct connection to computer-aided design programmes, especially during last two decades, have greatly promoted the use of in silico testing in all kinds of industrial sectors. In the biomedical sector, such expansion is very relevant indeed, as it enables more analytical validation processes, which greatly reduce the number of prototypes required for in vitro/ex vivo/in vivo testing and, what is much more important, the number of animals used for preclinical in vivo trials.

A comprehensive description of different types of FEM-based simulations (linked to static loading, to dynamic response, to thermal behaviour and to fluidic and contact phenomena) with several cases of study has been provided in Chap. 8, and some additional examples are also included in Chap. 7, when describing the mechanical performance of metamaterials, porous and lattice structures.

Computer-aided design resources provide additional tools for in silico evaluation of a design, such as assembly modules for detecting possible collisions during service life, movement simulation tools for studying dynamic effects and some remarkable parametric anthropometric models for ergonomic assessment of novel devices. Figure 15.1 provides an example of in silico validation of the ergonomical features of a splint for aided tracheotomy (see the whole device in Fig. 16.5).

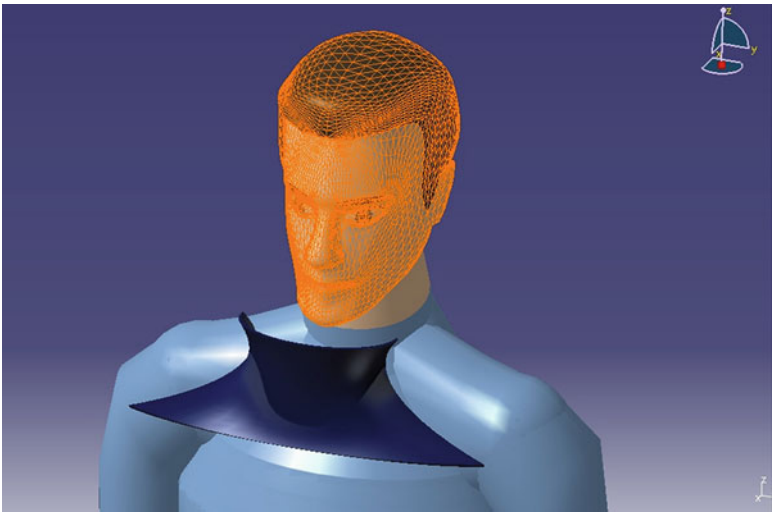

Fig. 15.1 Parametric anthropometric model for in silico validation of the ergonomical features of a splint for aided tracheotomy (See the whole device in Fig. 16.5)

The "ergonomics" module of Catia v.5 has been used, which is a very useful tool for design shape validation.

Additional simulation tools for assessing very relevant aspects, highly connected to conventional biocompatibility ex vivo/in vivo evaluation, such as (bio-)degradation, corrosion, wear, among other issues linked to service life, are already beginning to provide interesting results (Erkizia et al. 2010), with remarkable potential for finally helping to reduce the number of biological trials. Surely it is just a matter of time that main CAD-CAE resources start to incorporate such kind of simulations for a more integral perspective of product lifecycle.

Next section details several approaches to in vitro testing, including testing of raw materials for enhanced characterization, testing of final devices for a more detailed performance assessment, helped by the use of biological/anatomical models and by specific workbenches and virtual reality tools.

In many cases such in vitro trials help to adjust and validate our models and simulations, which (once systematically validated) can then be used with more confidence for optimising the whole design process and reducing the number of prototypes required for trials, thus helping to reduce overall development cost and time.

15.3 The Importance of In Vitro Testing

In biomedical engineering, many improved diagnostic or therapeutic solutions are based on the use of novel biomaterials, sometimes not fully characterised for providing all the relevant information needed in the design process. In many cases the suppliers of such materials do not provide (or do not want to provide) detailed information charts, so carrying out personal characterization trials is in many cases necessary and always advisable, as quality control measure.

Adequate mechanical characterization is also needed for obtaining inputs for carrying out simulations and systematic in silico assessment of the influence of the different design parameters. On the one hand, it is relevant to obtain information from raw materials, for analysing its potential use for developing novel devices; on the other hand, characterizations carried out on prototypes and final biodevices are also relevant. This section describes some typically interesting characterization trials, as well as some remarkable related systems for property and performance assessment. Linked to final biodevice validation, it is also interesting to note the use of anatomical models for complementing in vitro trials, as commented towards the end of this section.

Listed below are some typical tests which provide useful information for design tasks and for predicting the behaviour of a material or device under different loading conditions and environmental circumstances.

- Static loading – Traction and compression tests, creep, stress relaxation, hardness tests, torsion trials
- Dynamic loading – Cyclic loading, vibration tests, aleatory vibration tests

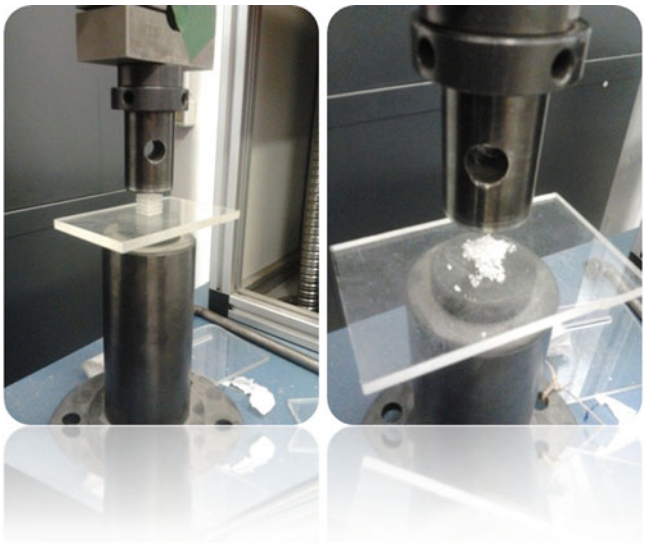

Fig. 15.2 Destructive compression trial of a rapid prototyped scaffold for tissue engineering. 1,100 N applied led to final collapse (See the whole device in Fig. 10.10)

- Impact – Charpy and Izod tests
- Thermal analyses – Thermogravimetric analyses, differential scanning calorimetries
- Thermomechanical analyses – Dynamic mechanical thermal analyses

Figure 15.2 includes a couple of images of the compression test of a rapid prototyped scaffold for tissue engineering. The trial procedure is destructive, as can be seen by comparing left and right images. Figure 15.3 includes the results of a couple of compression tests carried out upon different scaffold models, shown in Fig. 10.10. Both prototypes withstand loads of more than 1,000 N, and the information from trials can be used for obtaining the equivalent Young modulus of such lattice structures, relevant for FEM-based simulations aimed at predicting the behaviour of more complex devices based on similar structures.

Several manufacturers provide such equipments and many of them can also be easily constructed in laboratory. However, more specific designs of testing equipments, oriented to biomaterials and biodevices, can greatly enhance the biodevice development process and allow for a more systematic and automated verification of the fulfilment of related standards.

We would like to mention the products of ***BOSE***® ElectroForce®, a wide set of testing equipments based on Bose′s more than 40 years expertise in power electronics, controls and linear electromagnetic actuators. Their ElectroForce® linear motor, core of several of their testing equipments, provides an attractive alternative to traditional motion and force control because of its simple, durable, moving-magnet design. Their proprietary motor utilises a friction-free, flexure suspension in order

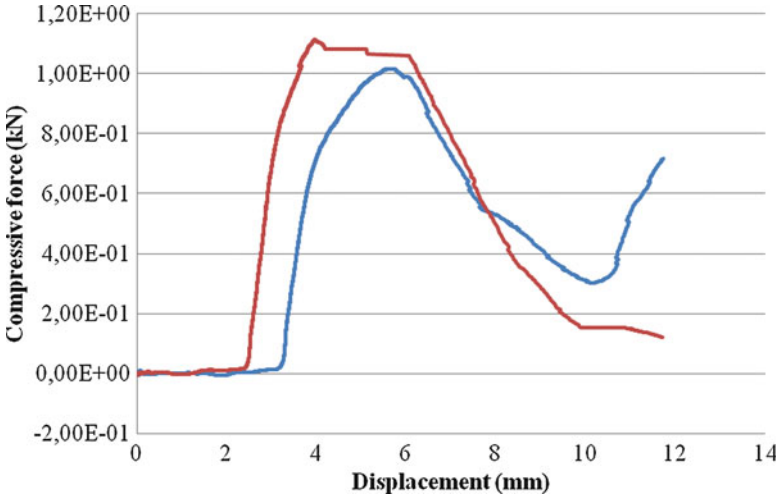

Fig. 15.3 Compressive test of scaffolds for tissue engineering *Red line*: structure with spherical holes. *Blue line*: Structure with cubic holes (See the prototypes in detail in Fig. 10.10)

to achieve exceptional fidelity and precision. In addition, the motor is quiet, energy efficient and clean. Such technology is scalable to fit a wide variety of applications that require superior performance attributes, including large dynamic force and a broad frequency range requiring high accelerations and velocities. With no wear surfaces or friction, these motors have proven to be very reliable, as they have been tested for over a billion cycles and can provide nearly infinite life for a variety of applications.

The ElectroForce® linear motor has been already successfully deployed in several applications including biomedical device testing, component testing and a wide variety of materials testing applications (see http://worldwide.bose.com).

Figure 15.4 shows as example a system from the ElectroForce® 3200 Series II whose test instruments feature a 225 N (450 N optional) maximum force. With the versatility of static to 200 Hz frequency response, the tabletop configuration is adaptable to a variety of biomedical research and engineered materials test applications, including torsion testing, creep under dynamic loading and special environments (hot and cold chambers). Testing of the most advanced biomaterials can easily be carried out, and even in vivo conditions can be mimicked, by using the sterilisable BioDynamic® chambers for live tissue characterization, a very remarkable special feature of these systems.

Linked to in vitro performance evaluation of prototypes and final biodevices, ***BOSE***® ElectroForce® system has also allowed for the development of ad hoc testing equipments. Figure 15.5 shows the Bose® ElectroForce® 9110 stent/graft test system, which accelerates stent testing and provides multibillion cycle reliability, accelerating time to market with the possibility of simultaneously testing several devices.

Fig. 15.4 ***BOSE***® ElectroForce® 3200 series II test instruments (Image courtesy of ***BOSE***® – Bose ElectroForce® products. [http://worldwide.bose.com/electroforce/en/web/home/page.html])

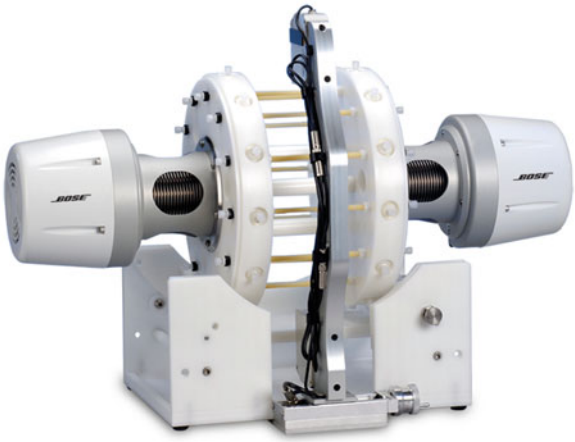

Fig. 15.5 ***BOSE***® ElectroForce® 9110 stent/graft test (SGT) (Image courtesy of ***BOSE***® – Bose ElectroForce® products. [http://worldwide.bose.com/electroforce/en/web/home/page.html])

Additional remarkable test systems benefiting from ***BOSE***® ElectroForce® technology include instruments for dental wear assessment, for the evaluation of intervertebral disc and of orthopaedic applications and for the characterisation of tissues and biomaterials. These equipments are designed to generate specific test

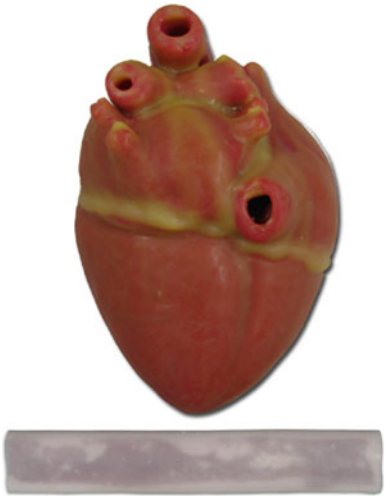

Fig. 15.6 *Upper image*: "Heart model" biomimetic replica. *Lower image*: "Double-layered intestine" biomimetic replica (Images courtesy of Simulab Corporation. [www.simulab.com])

cycles, which are always relevant in testing systems for enabling verifications of the fulfilment of several standards.

For instance, several testing cycles are clearly defined in some remarkable ISO and ASTM standards, as those described in ISO14801 linked to dental implants, ISO 18192 about intervertebral discs, ISO 7206, ASTM F1440 or ASTM F1612 for hip implants, ASTM F1800 for knee replacements, ASTM F382, F384, F1264 or F1541 for bone fixations, among others, which typically provide recommendations for evaluation of traction, bending and fatigue resistance.

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As an additional help for in vitro prototype and biodevice validation, it is very important to remark the possibility of using anatomical models, such as those detailed further on, which in many cases provide adequate biomimetic geometries and mechanical features, even better than those attainable by using dead tissues and organs, typically acquired at the butcher shop (even though these butcher shop models are sometimes very useful, see Fig. 15.10, Díaz Lantada 2009).

We would like to remark some very interesting models of organs and tissues commercialised by Simulab Corporation (www.simulab.com). Figure 15.6 shows their "heart model" and their "double-layered intestine" biomimetic replicas.

In some cases, more complex biostructures and systems can be built, normally for anatomical studies, surgical training and planning, which can also be used for in vitro evaluating a biodevice. Surgical implantation can be mimicked normally aimed at studying if a particular geometry is implantable, if a minimally invasive approach is possible, if different designs of a biodevice behave in a similar way or not or even if active implantable devices based on intelligent materials work as predicted in the CAD design stage.

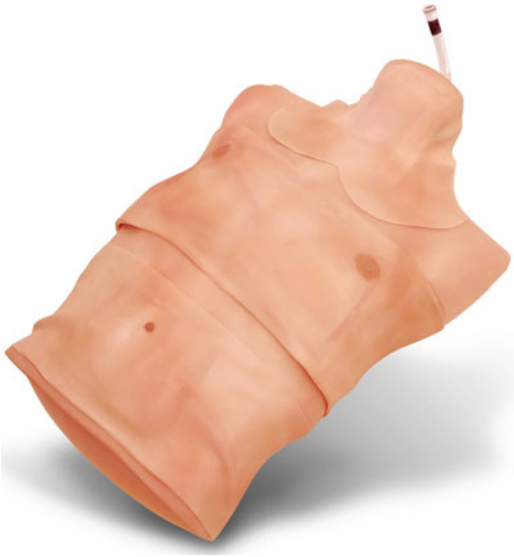

Fig. 15.7 TraumaMan system for in vitro surgical training, high-precision anatomical model of the whole thorax and inner organs and biostructures (Image courtesy of Simulab Corporation. [www.simulab.com])

Figure 15.6 shows, again courtesy of Simulab Corporation, the "TraumaMan" system for in vitro surgical training (and even in vitro biodevice validation), an anatomical model of the whole thorax with inner organs and biostructures. More solutions, linked to several organs and biostructures, can be found by looking at their website (www.simulab.com) (Fig. 15.7).

During last decade, very remarkable research efforts have been devoted to the development of surgical training systems, which may also be very useful for the evaluation of novel biodevices, before tackling preclinical in vivo validations in animal models. Advances in several areas briefly described below, from haptic actuation to virtual reality, are already being combined for obtaining very realistic simulators, which in many cases also benefit from very precise anatomical models that provide the working environment.

Teleoperators are operators that control tools remotely, and in these cases the contact resistance forces need to return to the teleoperator, so as to enable a more adequate interaction with the remote system.

This is called "haptic teleoperation". When these haptic devices are user-operated by means of computer-guided simulation, it is important to provide the return force that could be felt in real operations. As the objects being handled do not exist in reality, the haptic forces generated (by the computer) as "contact" forces must provide the feeling of the environment (in guided-surgery tissues and organs). Haptic simulators are currently widely used for training several surgical operations. They are useful when attempting to minimise damage caused by the use of invasive procedures and even let operations be performed remotely.

Virtual reality (VR) is the combination of technological resources for creating computer-generated worlds or immersive environments, which people can explore

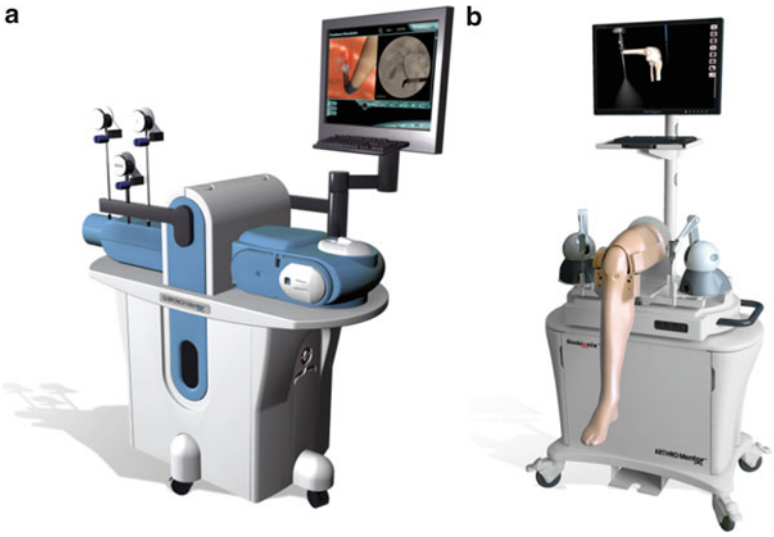

Fig. 15.8 (**a**) GI-BRONCH Mentor VR training simulator for endoscopy and flexible bronchoscopy. (**b**) ARTHRO Mentor VR training simulator for arthroscopic surgery (Images courtesy of Simbionix USA Corporation [http://simbionix.com])

and, in many cases, interact with. Benefiting from advances in imaging technologies, computer graphics, CAD resources, geographic information systems, among others, virtual reality produces a set of data which is then used to develop new models, training methods, communication and interaction, with applications linked to defence (military training), aeronautics and automotion (driving and flight simulators), teaching and surgery (surgical training and planning), among other examples.

These advances are also used, combined or alone, for the development of very remarkable surgical training systems, with application for in vitro trying new biodevices, as those detailed in Figs. 15.8 and 15.9.

Figure 15.8 shows, courtesy of Simbionix USA Corporation, the "GI-BRONCH Mentor" VR training simulator for endoscopy and flexible bronchoscopy and the "ARTHRO Mentor" VR training simulator for arthroscopic surgery.

The "ARTHRO Mentor" simulator features a line of simulated procedures, combining fibreglass anatomical models (shoulder and knee) with 3D images and haptic sensation, to allow users to learn key aspects of the procedures. Simulated procedures are performed utilising a realistic set of tools as used in the operating room, including the arthroscopic camera, which allow the trainee to acquire a true-to-life hands-on experience.

The "GI-BRONCH Mentor" also incorporates force feedback and allows for the training of several different procedures, thanks to a VR environment. In addition, a physical syringe enables realistic fluid delivery, while a physical master tool simulates a wide variety of bronchoscopic tools, such as biopsy forceps, cytology brush, aspirating needle, balloon, electrocautery probes and more.

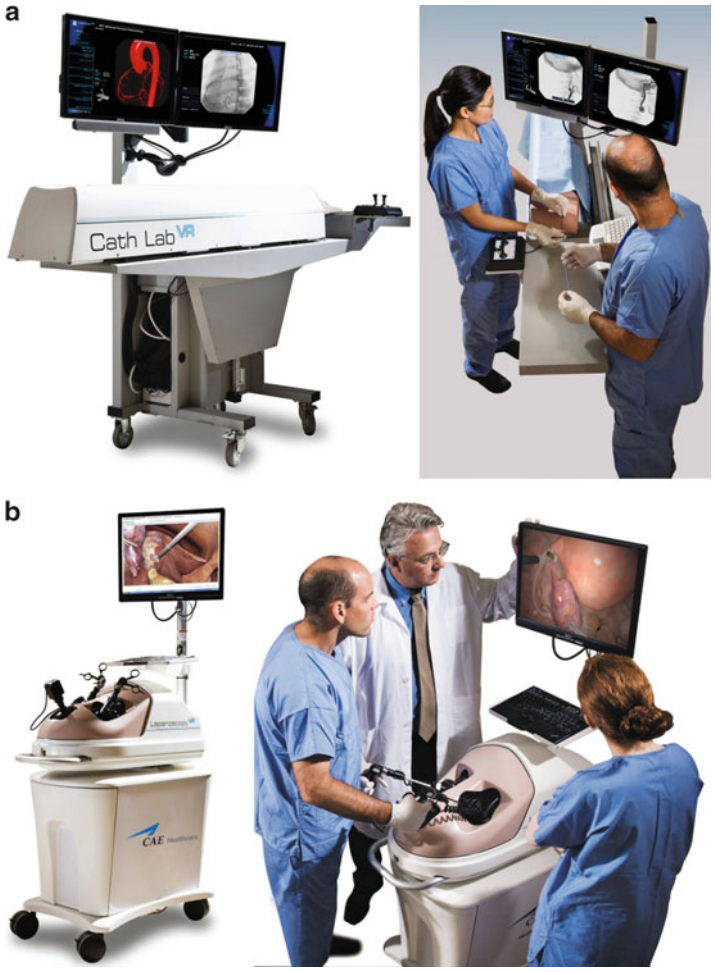

Fig. 15.9 (**a**) CathLabVR Simulator for endovascular surgery training. (**b**) CAE Laparoscopy VR simulator for training laparoscopic procedures (Images courtesy of CAE Healthcare ©2012 CAE Healthcare. [www.cae.com/en/healthcare/home.asp])

For additional information, please visit website (http://simbionix.com).

Figure 15.9 shows, courtesy of CAE Healthcare, the "CathLabVR Simulator" for endovascular surgery training and the "CAE Laparoscopy VR Simulator" for training laparoscopic procedures.

Such systems benefit from multisensory feedback, including visual, audio and tactile, based on haptic force feedback, responses. The trainee is immersed in a virtual reality environment mimicking with high level of detail the different body organs and structures of interest for the surgical intervention.

It is important to highlight that the "CathLabVR Simulator" allows surgical training and planning with real implantable stents (both autoexpandable and

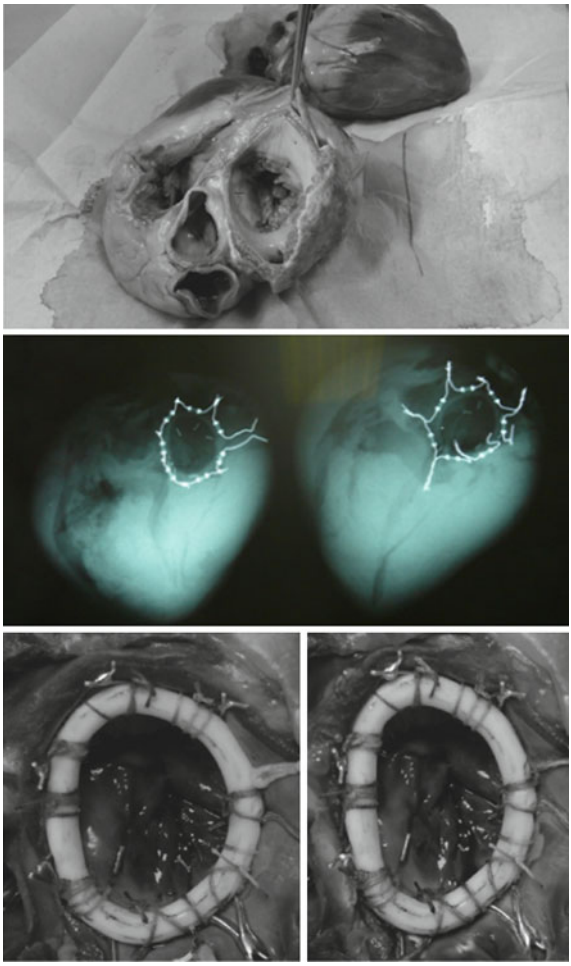

Fig. 15.10 In vitro trials of shape-memory polymer annuloplasty ring for progressive treatment of mitral valve insufficiency. Porcine heart used as animal model due to its similarity to human heart. Results from geometrical changes due to actuation of the active prosthesis, aimed at the reduction of mitral valve section

mounted on balloon and pharmaceutically enhanced or not), for comparing the performance of different available solutions and for validating novel geometries or actuation principles.

The different approaches to the development of simulators, either those based on acting on physical prototypes of biological models, those combining force feedback with virtual reality or those using mixed approaches, including force feedback and images obtained from physical biological models, complement each other, and all of them provide different advantages for in vitro validating surgical procedures in which novel biodevices may be involved, thus helping to reduce the number of animals used for preclinical in vivo trials (Fig. 15.10).

15.4 The Importance of Ex Vivo/In Vivo Testing

Before carrying out any in vivo trials, as working with animals is a privilege and should be taken very seriously, exhaustive in silico and in vitro testing is necessary and, if adequately performed, leads to fewer in vivo trials needed.

In addition, biocompatibility of the biodevice has to be adequately assessed, not only with the in vivo trials in animal models in perspective, but as it will provide also necessary information required for the clinical trials and final production. Of course evaluating the biocompatibility of a device is aimed at protecting patient safety, trying to minimise risks and maximise benefits to patients.

Most adequate document for understanding biocompatibility and trials needed is the ISO 10993 standard on "biological evaluation of medical devices". Such document provides the "biocompatibility matrix", which, depending on device category, linked to the grade of contact with corporal tissues, to the duration of such contact, to the organs involved, and details the types of test to perform. More or less tests will be needed if data from previous assessments are available, if data from suppliers of materials are used or if analytical (exhaustive simulations somehow validated in vivo) or clinical data exist.

In any case, most devices with significant tissue contact will require some kind of chemical and biological testing. Among such tests, it is important to cite cytotoxicity, sensitization, irritation, systemic toxicity, genotoxicity, hemocompatibility, carcinogenicity and biodegradation. Several advices on how to perform them are also provided in the mentioned standard. In many occasions, some probes of the material are seeded with cells, and cell behaviour is evaluated after a determined period, as Fig. 15.11 (linked to ex vivo assessment of a scaffold′s cytotoxicity by using hMSCs) shows (Díaz Lantada et al. 2012).

Once biocompatibility is positively assessed, in vivo trials in animal models can be carried with more confidence, always taking into account the principles of Helsinki Declaration and knowing that such experimentation cannot be taken lightly. The best advice is to require the help of experienced laboratories, with a multidisciplinary team of researchers (surgeons, veterinaries, physicians, biologists), whose experience will also help to select the most adequate animal model, sometimes to induce a special pathology to the animal, to carry out the surgical intervention and to study the postsurgical recovery. In Spain, most renowned centre for in vivo trials in animal models is the Minimally Invasive Surgery Center, also linked to the development of biodevices (www.ccmijesususon.com).

Final in vivo clinical trials in humans require special approval by each country′s competent authorities. Depending on the type of product and the stage of its development, investigators enrol healthy volunteers or patients into small pilot studies initially, followed by larger scale studies in patients that often compare the new product with the currently prescribed treatment. The whole process is complex and highly expensive.

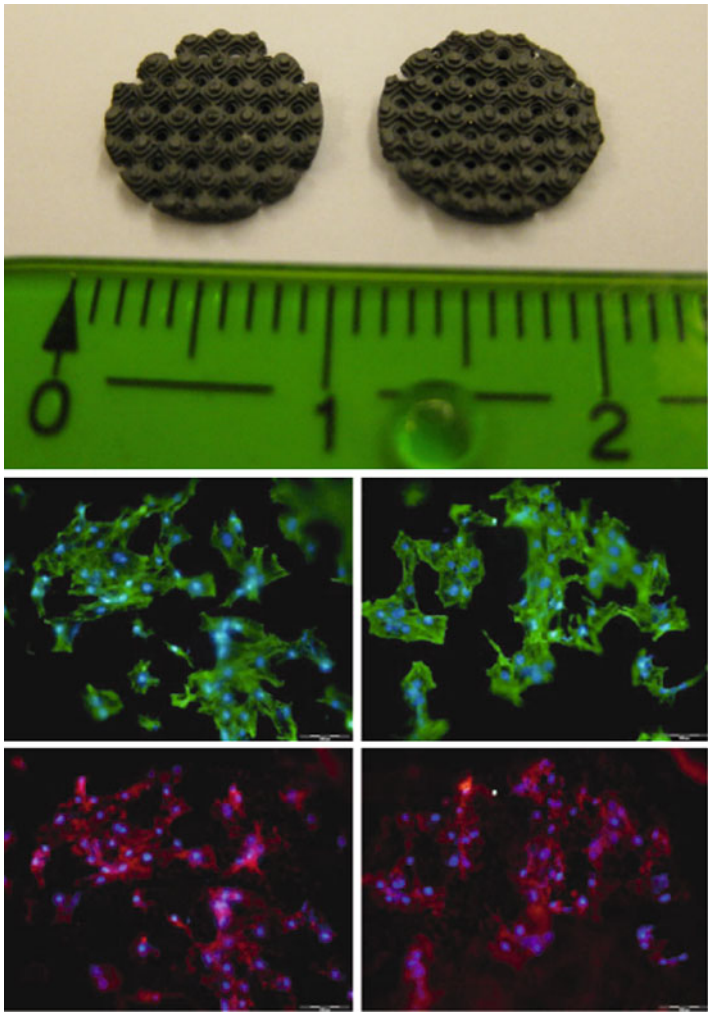

Fig. 15.11 Ex vivo trials using DLC-coated rapid prototyped scaffolds. Cell trials courtesy of J.P. García-Ruíz and V. Sánchez from the Department of Molecular Biology – Universidad Autónoma de Madrid

In some cases, normally within research projects and if the biodevice is not an implant but a device for gathering signals and monitoring patient′s behaviour from the outside, pilot studies with prototypes are performed by the researchers involved in the development (Lafont Morgado et al. 2008; Díaz Lantada 2009) (Fig. 15.12).

Fig. 15.12 In vivo trials of instrumented splint with piezoelectric sensors for monitoring of bruxist activity. Comparative study with results from "S-EMG" (surface electromyography). Accessories for trials. Researchers: Dr. Andrés Díaz Lantada and Dr. Alexánder Martínez Álvarez

15.5 Main Conclusions and Future Research

Design validation is a complex process in all kinds of industries but especially in the biomedical field, due to the potential risks of using devices for interacting with organs and biological structures. The rapid manufacture of prototypes is an enormous help for carrying out validation trials; however, reaching preproduction stage in the case of biodevices is still complicated, as the normative environment is also multifaceted and several steps have to be followed.

As already explained, systematic validations throughout the whole development process, by using simulations and computer-aided engineering resources for in silico testing, rapid prototypes with increasing level of detail for in vitro trials and (only when working principles and safety have been verified) in vivo trials with animal models, are essential for reaching the preproduction stage.

In this chapter, we have introduced the different kinds of procedures used for testing biodevices, providing examples of in silico, in vitro and in vivo testing and trying to detail some novel resources for more adequate validations, from workbenches and automated test systems to physical biomimetic models and virtual reality (VR) haptic devices.

Some commercial systems from relevant enterprises in their respective sectors have been described, as a help for researchers seeking novel, improved and secure ways of probing their biodevices and medical appliances, without directly resorting to the use of animal models.

Again it is important to highlight that before carrying out any in vivo trials, as working with animals is a privilege and should be taken very seriously, exhaustive in silico and in vitro testing is necessary and, if adequately performed, leads to fewer in vivo trials needed. In addition, biocompatibility of the biodevice has to be adequately assessed, not only with the in vivo trials in animal models in perspective, but as it will provide also necessary information required for the clinical trials and final production. Of course evaluating the biocompatibility of a device is aimed at protecting patient safety.

Important advices can also be obtained by consulting the most relevant related standards, which have been also discussed. It is necessary to highlight again the importance of multidisciplinary teams in projects linked to the development of novel biodevices as, also for the different kinds of trials, abilities from physicians, surgeons, engineers and scientists are needed.

This chapter is directly linked to the proposal for structured development methodology treated in Chap. 17, which incorporates some of the knowledge acquired along the handbook, in order to modify the systematic development methodologies used in conventional product development, so as to adapt them to the special requirements linked to biodevices.

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15.5.1 "New Approach" Directives Related to the Medical Industry

Directive 93/42/EEC related to "Medical devices"
Directive 90/385/EEC related to "Active implantable medical devices"
Directive 98/79/EC related to "Medical devices for "in vitro" diagnosis"

15.5.2 Standards Related to the Development of Medical Devices

ISO 10993 standard on "Biological evaluation of medical devices"
ISO 13485 standard on "Sanitary products. Quality management and regulatory affairs"
ISO 13488 standard on "Quality systems. Medical devices, sanitary products and especial requirements for applying ISO 9002 standard"
ISO 14971 standard on "Application of risk management to medical devices and sanitary products"
ISO 15223 standard on "Symbols used for labelling and information provided together with medical devices"

15.5.3 Additional Documents of Interest

Council of Europe "Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine: Convention on Human Rights and Biomedicine" (1994)
UNESCO "Universal Declaration on the Human Genome and Human Rights" (1997) and "Guidelines for Implementation" (1999)
World Medical Association "Declaration of Helsinki. Ethical principles for medical research involving human subjects" (current revised edition 2008)

15.5.4 Some Interesting Related Websites

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Chapter 16
Methods to Promote Creativity and Technological Transfer

Andrés Díaz Lantada and Juan Manuel Munoz-Guijosa

Abstract The different technological advances commented in previous chapters provide a broad range of tools for promoting the development process of novel biodevices, and multidisciplinary teams are sometimes needed to master and integrate all of them, so as to maximize their benefits for the development process.

Such technologies also promote very innovative approaches, although for such promotion it is essential to strengthen collaboration among the whole research team, as each expert controls a few technologies, and integrating the advances of all of them may be complex. Therefore, from the conceptual stage of a development project, it is necessary to adequately involve all researchers. The establishment of programmed control and working meetings is, thus, highly advisable for final project success.

Several tools for promoting creativity, also in programmed collaborative meetings, are indeed very useful for increasing, for promoting the involvement of the whole team in a new project, and, especially, for finding possible product concepts different to those from the concurrence and with remarkable features for improved diagnosis or therapy. In this chapter, we introduce several of these most adequate creativity promotion tools and present a case study comparing some of them.

Such creative differentiation from other already available (or under development) devices surely proves to be strategic, as intellectual property rights normally arise and patenting the device can protect our interests. Final approach to market may comprise serial manufacture of the device, normally in the case of projects funded by enterprises, or licensing agreements after prototype validation, normally in the case of projects tackled by academia, although some mixed solutions as funding a "spin-off" are also commonplace. We briefly discuss these different possibilities at the end of the chapter.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_16,

16.1 General Aspects Linked to Highly Innovative Projects

In words from Isaac Asimov, "A person's greatest good is an inquiring mind," and perhaps the greatest good for a project, linked to the development of a novel product or appliance, is a team of researchers with inquiring minds.

Ideally a project development team, here focusing on the bioengineering field, should include some scientists with a generalist background and conscious of main current medical needs and industrial challenges, for leading the project, as well as researchers with a more specific curriculum for tackling with the concrete problems arising along the project. Typical backgrounds for leading the project include physicians in internal medicine, physicists, and mechanical engineers, while the more specific tasks usually require professionals such as chemical engineers, molecular biologists, surgeons, or telecommunication engineers.

Such a combination, especially if many inquiring minds are within the team, promotes multidisciplinarity, creativity, and innovative valuable solutions. During the project, continuously asking questions such as "Why?," "Why not?," or "What would happen if?" helps to verify every subsystem of final device and to find the most adequate working principle and solution for the functionalities of the biodevice under development. The mentioned question-based strategy also promotes the incorporation of additional diagnostic or therapeutic features and the search for novel approaches, in a continued search for achievements and new challenges in a highly competitive industrial field.

The promotion of creativity, of course connected to improving and enhancing products and processes, is also normally an essential part of the enterprise's long-term strategy, as innovative solutions can be usually patented, what places the enterprise in a very favorable situation for marketing and commercialization (in fact a patent is a 20-year monopoly), with respect to its main competitors.

In complex biodevice development projects and in enterprises with an important background and a broad product portfolio, continued evolution is coupled with a need for organized information management and several of the computer-based technologies previously described and integrated with the help of "PLM" or product lifecycle management resources are indeed of great help, as will be discussed further on in this chapter.

In many occasions, exchanging information or carrying out technological transfers between enterprises may be part of expansion strategies and "win-win" agreements among competitors trying to reinforce their positions with respect to other companies. Also common is the creation of a "spin-off" company for bringing more adequately a novel discovery, typically realized in the academic world, to society. These aspects connected to technological transfer of innovative solutions are also briefly commented in this chapter.

Next section introduces the basic aspects of creative though and some of the most used techniques for promoting creativity, providing also a brief case study linked to the combined application of a couple of techniques for improving the performance of hip prostheses.

16.2 Promoting Creativity for Developing Innovative and Successful Biodevices

Successful development projects linked to novel products, here novel medical appliances and biodevices in general, involve dividing the overall main problem or system in several easier to handle subproblems or subsystems, assessing the best solution for each subproblem or subsystem, and, finally, integrating all of them for reaching the general solution for the global problem or system. The search for alternatives in every subsystem of the device under development is very relevant for promoting novel combinations and leading to more innovative devices and is completely aligned with the general advices for promoting creative thinking included below (De Bono 1970, 1972, 1992).

There are many exhaustive and well-referenced handbooks completely devoted to creative thinking, but here we would like to provide a brief introduction to main common features and discuss a couple of application examples associated to the development of innovative biodevices. In general terms, persons who continuously question the state-of-the-art and constantly look for new ideas, solutions, and working principles, and subsequently assess their feasibility, are considered creative people. In consequence, creativity involves two main stages or mental processes, "inspiration" and "elaboration," and creative people shift easily from one stage to another.

The "inspiration" stage is connected to asking questions ("Why?," "Why not?," or "What would happen if?") and finding alternatives for solving a problem or a subproblem, and the "elaboration" stage includes experimentation, systematic comparative studies, qualitative and quantitative analyses, and final establishment of associations for combining the best concepts into an improved solution.

Several techniques have been developed for promoting a systematic search of alternatives, thus empowering the "inspiration" stage. The most common ones are describe below:

- Brainstorming. Consists of finding alternatives for solving a specific problem by gathering a list of ideas spontaneously contributed in public by the participants.
- Brainwriting. It is similar to brainstorming, but the ideas are written down by the different participants and finally listed down in public, so as to avoid a couple of participants to lead the session and to promote the involvement of shy researchers.
- Brainwriting 6×3×5. Is a variation of brainwriting (and also linked to the Crawford slip writing method), in which 6 people are asked to write down 3 alternatives or ideas in 5 min, for further collaborative discussion. It seems important to establish a minimum quote (three alternatives), so as to promote hard work and avoid "parasite" researchers taking a rest.
- Philips 6–6. Is a dynamic collaboration technique consisting of dividing a group in subgroups of 6 people for finding alternatives during 6 min and subsequently putting them down in common with the whole group.

- Lotus blossom. Is an evolution of brainwriting, in which a central idea is written down, discussed for finding eight possible solutions, which are then written in eight surrounding circles for further brainwriting based on each of the possible solutions. The process is iterative and the number and quality of solutions is remarkably improved.
- SCAMPER. Is a technique using direct questions for promoting lateral thinking (forcing to answer indirect questions), including Substitute?, Combine?, Adapt?, Modify?, Put to other purposes?, Eliminate?, and Reverse?
- KJ technique. It is normally used to structure information after a brainstorming, with keywords written on stickers and grouped together by subject.
- TRIZ contradiction analysis. Consists of finding alternatives by looking at solutions already described in patents, as will be further detailed in Sect. 16.3., entirely devoted to TRIZ due to its importance in several engineering fields.

We have just included above some of the most used procedures for alternative generation, although there are more than 50 techniques commonly described in the literature for such purpose, because many of them are just slight variations from these main ones (López de Ávila 2011).

In many cases, the power of serendipity (or discovering by accident) has also proven to be essential for finding radical approaches to several problems, although always linked to highly prepared scientists capable of linking together apparently innocuous facts in order to come to a valuable conclusion. Again the search for alternatives needs additional association efforts for reaching final solution. Many examples can be cited of discoveries realized "by accident," including penicillin by Alexander Fleming, insulin by Frederick G. Banting, or (as the legend says) even Newton's gravitation theory.

Another way of searching highly innovative solutions for technological problems (with potential for patent granting and usually remarkable socioeconomical impact), especially in the field of Biomedical Engineering, is "bioinspiration." The concept of "bioinspiration" involves the study and distillation of principles and functions found in biological systems that have been developed through evolution and application of this knowledge to produce novel and exciting basic technologies and new approaches to solving scientific problems.

The potential success of bioinspired solutions has led to relevant research interest and even to the birth of interesting scientific journals, such as "Bioinspiration & Biomimetics" from IOP Science. In words from Walt Disney, "Nature is the best author" (and teacher).

Regarding the "elaboration" stage, there are also some advisable procedures for adequate assessment and further association of potentially valid concepts, as we try to explain below:

- Originality and value. An initial evaluation of the proposed solutions and ideas may be in form of two-variable analysis, comparing each solution by its "originality," linked to the degree of novelty, and its "value," linked to its actual viability.

- Radar chart. In a second more exhaustive analysis, a radar chart can be constructed for providing a multivariable assessment of the proposed ideas and solutions. Among typical factors of interest are design, ergonomics, manufacturability, scalability, cost, effectiveness, and innovation, although each development project may have its specific factors.
- Analytic hierarchy process (AHP). Is a structured technique for helping with complex decisions, in which the evaluation is converted into numerical values for easier comparison and systematization. The different aforementioned factors can be weighted, for establishing priorities (i.e., a factor of 0.1 for ergonomics and a factor of 0.4 for cost would lead to an assessment in which cost is four times more important than ergonomics), and each solution can be more precisely assessed. Results are typically represented in form of matrix, with the solutions for the different subsystems in lines and the different factors for assessment in columns. Final column shows the numerical result for helping with final decision.

Finally, once the alternatives are obtained and the best ones selected for each subproblem or subsystem, association leads to final global solution. Such association step, as part of the elaboration stage, can also be helped by using some of the following techniques:

- Morphological box. A technique consisting of listing in form of matrix the different viable solutions (i.e. in lines) for each product subsystem (i.e., in columns), thus helping to generate multiple "paths" or combinations for the global solution, before an additional final validation stage.
- Mind maps. Are graphical representations usually employed to represent relationships between concepts, for instance, the subsystems of a biodevice and its most adequate subsolutions, in order to organize information and decision making.
- PERT (program evaluation review technique) chart. Once the different subsystems of a new biodevice, with its particular solutions and its mutual relationships, are represented in graphical form, a derived graphic can be also implemented (PERT chart) for helping with project management and preliminary cost–time evaluations. The PERT diagram consists of a number of nodes (events or tasks) connected by lines for depicting interdependence relationships.

Other association techniques, including matrix-based processes, the random word method, and the use of metaphors, help to find interesting relationships with any kind of concept, system, or problem but are normally used to promote the first "inspiration" stage.

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The following example shows the combined application of brainwriting and a subsequent lotus blossom for finding several alternatives for the problem "optimizing the weight of a hip prosthesis," which can lead to the encouragement of

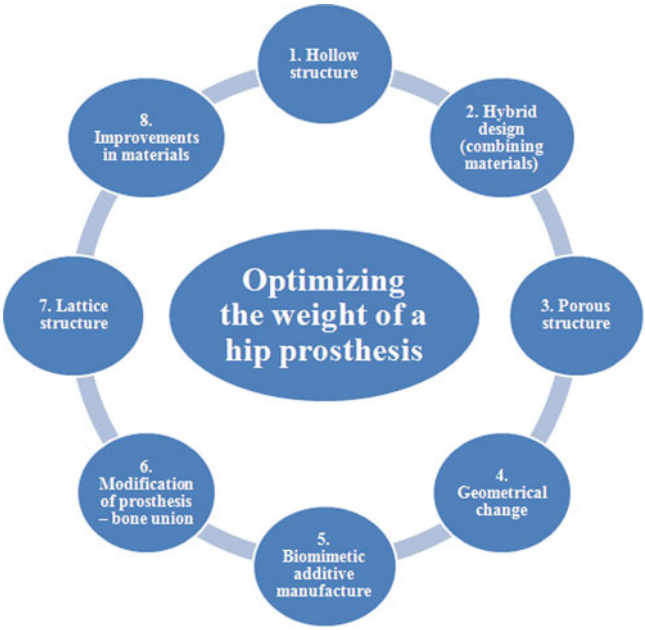

Fig. 16.1 Result of brainwriting (or brainstorming) for finding possible solutions for optimizing the weight of a hip prosthesis

numerous novel design approaches in the prosthetic industry. An additional evaluation helps to find the most promising strategies for further development.

Figure 16.1 shows the results of a brainwriting carried out a creativity session at the "bioengineering" subject of the Master's Program in Mechanical Engineering at Universidad Politécnica de Madrid (subject explained further on in Chap. 18 together with our analysis about project-based learning – "PBL" – for promoting the development process of biodevices). Such brainwriting involved the opinions of 12 students, who were asked to write down at least three solutions for the proposed problem in 5 min time. Many of them presented similar solutions and finally eight relevant ones were summarized.

After obtaining the proposals for solution, these were assessed by their "value" and "originality," as a preliminary approach for detecting those with more future potential. Result from assessment is included in Fig. 16.2 for further analysis. It is important to note that the best valued proposals include "change geometry," "use porous structure," and "use lattice structure." More pragmatic solutions include "improvements in materials" or "combining materials."

Regarding the use of lattice and porous structures for improving prosthesis' mechanical features and their overall properties, Chap. 7 already provided many examples of current research trends, linked to the design and manufacture of such structures and typical software for helping with design tasks (together with conventional CAD software, also some specific tolls such as MeshLab and within).

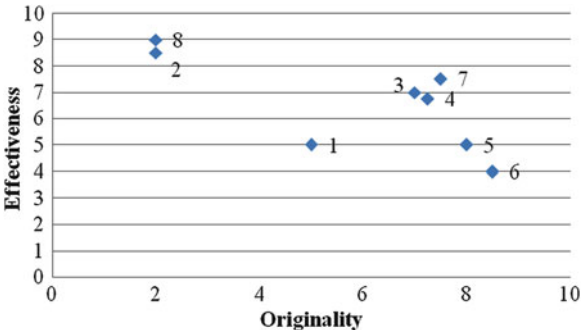

Fig. 16.2 Assessment and comparison of the proposed solutions analyzed by their potential effectiveness and originality. Numbers are according to the aforementioned brainstorming results

Not only design of such lattice and porous geometries is relevant, but also its manufacture has to be considered, as has also previously been made. Chapter 10 included examples of additive manufacture lattice structures, in that moment aimed at promoting tissue engineering approaches, but anyway showing real manufacturing possibilities also for implantable lattice structured prostheses. Chapter 12 gave an overview of technologies for producing porous structures (including gas-assisted foaming, solvent casting, phase separation, additive manufacture, among others), many of them with direct application also for tissue engineering scaffolds and implantable prostheses.

In any case a simple brainwriting process, realized by students, combined with subsequent assessment, has put forward solutions that are actually being seriously considered, and funded, by relevant companies from the biomedical field.

Figure 16.3 shows the result from a lotus blossom based on the results from the previous brainwriting. Each initial solution is taken as a new problem for carrying out additional brainwriting processes, and the process is, thus, iterative, helping to find more specific solutions.

Focusing, for example, in the previously well-assessed pragmatic/conservative solution based on "improvements in materials," an additional brainwriting puts forward interesting solution such as the use of superalloys, metal–polymeric–ceramic foams, biopolymers, bioceramics, and functional graded materials.

Even for solutions of the first brainwriting such as "hollow structure", initially not very well assessed, a second brainwriting can lead to promising directions, such as the use of CAD-based topological optimizations or FEM-based material elimination. In fact such modules are progressively being implemented in CAD packages for helping with geometrical optimizations in all kinds of products and industrial sectors.

Next section solves the same problem by applying an alternative methodology, the "TRIZ" problem-solving process. An introduction to such process is included and the case study is solved and compared with the example already provided here. Several interesting results are obtained and discussed, especially due to the fact that some relevant coincidences appear, but also because both procedures can complement each other, when trying to find innovative solutions in the conceptual stage (see Chaps. 1 and 17) of the development projects of novel biodevices.

8.8. Funtional gradient materials	8.1. Superalloys	8.2. Metal foams	1.8. Boolean operations	1.1. Longitudinal hole	1.2. Transversal holes	2.8. Biocomposite	2.1. Metalic nucleus and ceramic coating	2.2. Metalic nucleus and polymeric coating
8.7. Polymers with biological origin	8. Improvements in materials	8.3. Polymeric foams	1.7. CAD topological optimization	1. Hollow structure	1.3. Holes in perpendicular directions	2.7. Metal - metal composite	2. Hybrid design (combining materials)	2.3. Polymeric nucleus and ceramic coating
8.6. Ceramics with biological origin	8.5. Sol-gel based improvements	8.4. Ceramic foams	1.6. FEM based material elimination	1.5. Inner grooves	1.4. Lateral grooves	2.6. Natural fibre reinforced polymeric matrix	2.5. Synthetic fibre reinforced polymeric matrix	2.4. Polymeric nucleus and ceramic coating
7.8. Apply ad hoc CAD (Nettfab)	7.1. Square section thrusses (homogeneous)	7.2. Circular section thrusses (homogeneous)	8. Improvements in materials	1. Hollow structure	2. Hybrid design (combining materials)	3.8. Cubic holes gradient distribution	3.1. Spheric holes	3.2. Cubic holes
7.7. Apply ad hoc CAD (Within)	7. Lattice structure	7.3. Square section thrusses (heterogeneous)	7. Lattice structure	Optimizing the weight of hip prosthesis	3. Porous structure	3.7. Spheric holes gradient distribution	3. Porous structure	3.3. Tetrahedric holes
7.6. Irregular lattices	7.5. Regular lattices	7.4. Circular section thrusses (heterogeneous)	6. Modification of prosthesis - bone union	5. Biomimetic additive manufacture	4. Geometrical change	3.6. Mixed spheric and cubic holes	3.5. Cubic holes two sizes	3.4. Spheric holes two sizes
6.8. Change external structure by inner fixation	6.1. Alternative external fixation	6.2. Alternative internal fixation	5.8. Apply ad hoc CAD (Mimics)	5.1. Photo-polymerization	5.2. Selective laser sintering	4.8. Apply hollow structure	4.1. Shorten prosthesis	4.2. Change material stiffness and reduce section
6.7. Change inner structure by external fixation	6. Modification of prosthesis - bone union	6.3. Reduce section by changing fixation	5.7. Apply biomimetic Euclidean	5. Biomimetic additive manufacture	5.3. Selective laser melting	4.7. Apply lattice structure	4. Geometrical change	4.3. Divide into several parts
6.6. Separate fixed parts	6.5. Join separate parts	6.4. Shorten prosthesis by changing fixation	5.6. Apply biomimetic fractal geometry	5.5. Radiolaria process	5.4. Fused deposition modelling	4.6. Apply porous structure	4.5. Change section	4.4. Aggregate different parts

Fig. 16.3 Lotus blossom obtained by further discussion on the original brainstorming (or brainwriting)

In fact, some relevant solutions, undetected, were directly found with the help of the TRIZ-based methodology, such as the "use of composite materials," as explained further on.

16.3 Case Study: TRIZ-Based Prostheses

TRIZ ("*teoriya resheniya izobreatatelskikh zadatch"* or theory of solving inventive problems) was developed by Genrikh Saulovich Altshuller (1926–1998) and his team (after studying a huge number of patents 40,000–400,000 according to estimations) during the 1960s and 1970s in the USSR and is currently experiencing a worldwide expansion due to its potential, as explained below.

Such theory presents a systematic approach for analyzing the kind of challenging problems where inventiveness and creativity are needed and provides a range of strategies and tools for finding innovative solutions. One of the earliest findings of the research on which the TRIZ methodology is based is that the vast majority of problems that require innovative solutions typically reflect a need to find a compromise between two contradictory product or system features. In other words, novel products and systems are not usually based on radical inventions, but on slight improvements on a determinate feature, trying not to worsen other important ones (Altshuller 1984, 1994, 1999).

Altshuller and his colleagues noticed that similar solutions could be found for similar contradictory features and that most solutions for engineering problems could be grouped into 40 relevant inventive principles (see Fig. 16.5.). Keeping this idea in mind, they set down to develop a methodology including a conversion from a specific problem to a more generic problem, for which a generic solution could be found and further worked out to obtain a specific solution (as Fig. 16.4 shows).

Following this approach, the "generic solution" shown in the diagram can be found by defining the contradiction which needs to be resolved and systematically considering which of the 40 principles (see Fig. 16.5) may be applied to provide a specific solution which will overcome the "contradiction" in for the actual problem, enabling a solution that is closer to the "ideal result."

One of the tools which evolved, as an extension of the 40 principles, was a contradiction matrix (the so-called TRIZ matrix) in which the contradictory elements of a problem were categorized according to a list of 39 factors which could impact on each other. The combination of each pairing of these 39 elements is set out in the matrix (for instance, the weight of a moving object, the manufacturability of a product, the energetic resources needed).

Each of the 39 elements is represented down the rows (as the factor to improve with an innovative solution) and across the columns (as the negatively affected element) and based upon the research and analysis of patents. The cells in the matrix typically contain a set of three or four inventive principles that have been applied most frequently in inventive solutions that resolve the contradiction between the two elements. The main objective of the contradiction matrix (available with open

Fig. 16.4 Schematic description of the TRIZ process

1. Segmentation
2. Extraction
3. Local quality
4. Asymmetry
5. Combination
6. Universality
7. Nesting
8. Counterweight
9. Prior counteraction
10. Prior action
11. Cushion in advance
12. Equipotentiality
13. Inversion
14. Spheroidality
15. Dynamicity
16. Partial, overdone or excessive action
17. Moving to a new dimension
18. Mechanical vibration
19. Periodic action
20. Continuity of useful action
21. Rushing through
22. Convert harm into benefit
23. Feedback
24. Mediator
25. Self-service
26. Copying
27. Inexpensive short life
28. Replacement of a mechanical system
29. Use pneumatic or hydraulic systems
30. Flexible film or thin membranes
31. Use of porous materials
32. Changing the colour
33. Homogeneity
34. Rejecting and regenerating parts
35. Changing physical or chemical states
36. Phase transition
37. Thermal expansion
38. Use strong oxidizers
39. Inert environment
40. Composite materials

Fig. 16.5 TRIZ's 40 inventive principles

access in several websites about product development) is to simplify the process of selecting the most appropriate inventive principle to resolve a specific contradiction.

A number of TRIZ-based computer programs, under the umbrella of recent computer-aided innovation (CAI) tools, have been developed for providing assistance to engineers, scientists, physicians, and inventors in finding innovative solutions for technological problems. Some of these programs are also designed to apply other TRIZ methodologies (ARIZ, TRIZICS, BioTRIZ, etc.).

However, in most cases, the by-hand process explained in the following pages is more than enough for finding highly innovative solutions and proves to be a good complement for any conceptual design stage linked to new products or processes (Cameron 2010). Before introducing the case study, we provide also some references to the successful use of TRIZ in Biomedical Engineering projects.

In the Biomedical Engineering field, TRIZ has successfully been applied for improving the design and long-lasting behavior of prostheses, for designing light prostheses for elite athletes and for adapting the geometry of prostheses to the stiffness of human organism, hence avoiding phenomena such as stress shielding, as the references cited in the following paragraph explain in detail.

Novel total knee prostheses, with help of TRIZ, have been designed to avoid accumulation of debris particles (Hsu et al. 2006). The conceptual design of prosthetic hands has also been revised and benefited from the innovative inclusion of different gripping configurations (Chan et al. 2008). High-flexion total knee prostheses have also been proposed and their design has benefited from using contradictory factors for searching appropriate inventive principles (Benabid et al. 2011).

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The case study included here is the same previously tackled, by combination of brainwriting, assessment, and lotus blossom, linked to "optimizing the weight of a hip prosthesis." It is clear that the "factor to improve" is "the weight of a moving object," referenced with number "1" in the TRIZ contradiction matrix.

The "factors not to worsen" depend on many aspects including enterprise's strategy, industrial field, type of product, current technological trends, and available patents (establishing boundaries), among others. Typically, improving (reducing) the weight of an object has a relevant (negative) influence on its mechanical strength, on fatigue behavior and durability, on overall reliability, and, if such improvement is based on geometrical changes, probably also on manufacturability or also productivity and final device cost.

In this analysis cost optimization, manufacturability and productivity (typical "factors not to worsen") have not been taken into account, as medical devices are usually quality oriented and personalization is also normally pursued. Therefore, aspects as device final cost or productivity lose importance, when compared to products from more conventional industries.

Regarding manufacturability, the capabilities provided by novel additive manufacturing technologies, even for the production of final implantable parts, also help to reduce the importance of such factor, as very complex geometries can be easily achieved (see Chap. 10).

In accordance with previous comments, we focus in this example on a weight improvement, trying not to affect in a negative weight the following factors: "strength," "durability of moving object," and "reliability," referenced, respectively, with numbers "14," "15," and "27" in the TRIZ contradiction matrix. The different inventive principles found in cells (1, 14), (1, 15), and (1, 27) in the contradiction matrix are included in Table 16.1 as a summary of the process.

Such Table 16.1 includes, highlighted in green, those inventive principles that are assessed as more promising for further finding adequate solutions.

Normally, the TRIZ methodology, after analyzing several pairs of "factor to improve" with "factors not to worsen," provides normally around 10 possible inventive principles for solving the contradictions.

Commonly 3–4 principles will be considered valid ones for further study, while 6–7 will not be linked to the specific problem at all, as happens in present example. In any case, the methodology helps to orient greatly the conceptual design stage, and as some of the principles provided are normally highly interesting, innovation is promoted and its application in every research project can be strategic for an enterprise with a broad product portfolio.

Table 16.1 Summary of factors of interest and their related inventive principles as obtained from applying the TRIZ methodology. Highlighted in green those with direct application and most valued potential benefit

Factor to improve → factor not to worsen	Inventive principles: reference	Inventive principles: description
1(weight of moving object) → 14 strength	28	Replacement of a mechanical system
	27	Inexpensive short-lived object for expensive durable one
	18	Mechanical vibration
	40	**Composite materials**
1(weight of moving object) → 15 durability of moving object	5	Combining (elements, materials, etc.)
	34	Rejecting and regenerating parts
	31	**Use of porous materials**
	35	**Transformation of physical/chemical state, i.e., change of density distribution**
1(weight o f moving object) → 27 reliability	3	**Local quality**
	11	Cushion in advance
	1	**Segmentation**
	27	Inexpensive short-lived object for expensive durable one

In general, when assessing several contradictions using TRIZ, an inventive principle can appear several times, what provides an additional clue for "starting point" possible solutions, as happens in a brainwriting process when an idea is cited by different researchers.

In our case study, valid principles detected include "use of porous materials," "change of density distribution," and "change of local quality," all of them also somehow detected with the previous "brainstorming–assessment–lotus blossom" more conventional procedure.

However, the use of "composite materials" is directly advised by TRIZ, while with our previous approach, we did not take it into account.

It is our personal opinion that relying only on TRIZ, as a way of promoting creativity in novel developments, may be very limited, and the use of previously described methods for promoting the search of alternatives, together with assessment and final association and integration for end solution, is almost a must.

Even though not being sufficient, it is also true that TRIZ-based techniques are a very remarkable complement for finding interesting directions for approaching the solutions of technological problems. Several examples can be found in the literature, which may serve of inspiration for future developments.

In addition, Table 16.1 and 16.2 includes also a brief comparison between the possible solutions found by using the brainwriting-based approach and the TRIZ-based approach, and a very interesting similarity can be found, although some differences already commented help to highlight the importance of using combined alternative search methodologies.

Table 16.2 Comparison of best valued proposals for improvement obtained from the brainwriting session and similar results obtained using TRIZ

Most valued solutions	Brainwriting proposals	TRIZ proposals
1st	Lattice structure	Change of density distribution, use of porous materials
2nd	Porous structure	Use of porous materials
3rd	Geometric change	Segmentation, change of density distribution
4th	Improving materials	Composite materials, local quality (functional gradient materials)
5th	Hybrid design (combining materials)	Composite materials, local quality (coatings)

Again it is important to remark that, although several computer-aided innovation resources are continuously appearing, in most cases the conventional use of handwritten analysis, with help of the TRIZ matrixes, matrixes for assessment of relevant proposals, common discussion with diagrams and conceptual maps drawn on a blackboard, and perhaps basic software tools such as Excel, is enough for reaching interesting design improvements.

Online resources can be also helpful and the references provided at the end of this chapter provide additional basic examples for further studying innovation-driven design approaches.

16.4 The Connections Between Intellectual Property and Technological Transfer

Research efforts involve also important economical investments and it seems clear that enterprises, universities, and scientists devoted to promoting research should be granted with some kind of special rights, derived from their intellectual property. Normally benefits from patents (and those derived from their licensing) are precisely aimed at granting researchers for their efforts and at the further promotion of research-driven, or at least innovation-driven, strategies.

Such intellectual property, and related product, system, or technology, is in many cases transferred to other entities or partners (from universities to enterprises, from enterprises to other companies, etc.) for several reasons, including a need for a more rapid industrial expansion, for a more direct impact on society, or for finding funds for additional projects. Some common solutions are described below:

Typical solutions linked to intellectual property and to technological transfer in industry include:

- Unfair competition activities. It is common that big and very big enterprises employ several intellectual property consultants for studying the innovations of their competitors, as well as their possible research directions, for subsequently patenting solutions linked to such possible directions, in order to block the progression of main competitors. These strategies are normally resolved in courts

of justice or by reaching economic agreements, and the related details are more linked to advocacy than to engineering.
- "Win-win" strategies for the establishment of duopoly. In many occasions the combination of a couple of technologies can lead to completely novel systems with enhanced features, and sometimes enterprises carry out fusions or exclusive mutual licensing or collaboration agreements, in what is typically described as "win-win" strategies, for increasing their control of related control and almost eliminating any kind of competitors, creating a duopoly or in the "best" cases an oligopoly.

Interesting models can help to understand these effects on market (Cournot and Bertrand models, Nash equilibriums, etc.), but the truth is that small and medium companies, especially in the complex field of medical devices, encounter great problems when facing the strategies of multinationals, and only by continued research and innovation can they survive in the long term.

- Invention licensing agreements. In some cases, an enterprise develops a remarkable innovation with application in several fields, even out of their own sector. Final decision of expansion to other areas or the establishment of invention licensing agreements, for letting companies of other sectors use the developed technology, is a complex one, especially if the enterprise is acquiring a good market position and prestige.

Typical solutions linked to intellectual property and to technological transfer in Academia include the following:

- Collaborative projects between enterprises and research groups. Industrial innovation clearly benefits from research and development tasks accomplished by research groups in the departments and laboratories of all kinds of universities. In a similar way, state-of-the-art industrial limitations and problems are a continuous source of motivation and ideas for research activities, as well as for collaborative projects, carried out at universities with the participation of enterprises. Hence, university–industry collaborations have proved to be helpful for continuously enhancing the quality of commercial products and the efficiency of industrial processes and for improving the functionalities of novel devices.

Inventions derived from such projects are typically patented by inventors of both entities and there are several possible agreements regarding patent ownership and industrial exploitation of results. Normally a patent co-propriety agreement is sought and typically the university licenses its part to the enterprise, normally under an "exclusivity" clause, while the enterprises usually pays back around 10 % of the outcome linked to the product or process developed.

- Invention licensing agreements. In a similar way, inventions derived from research projects carried out at universities typically find their way into market and reach society, through licensing agreements with enterprises wishing to exploit the mentioned advances. Normally the patent ownership remains at the university, but several types of licensing agreements can be used, with a percentage of payback (from enterprise to university) linked to the degree of exclusivity desired and to the size of market derived.

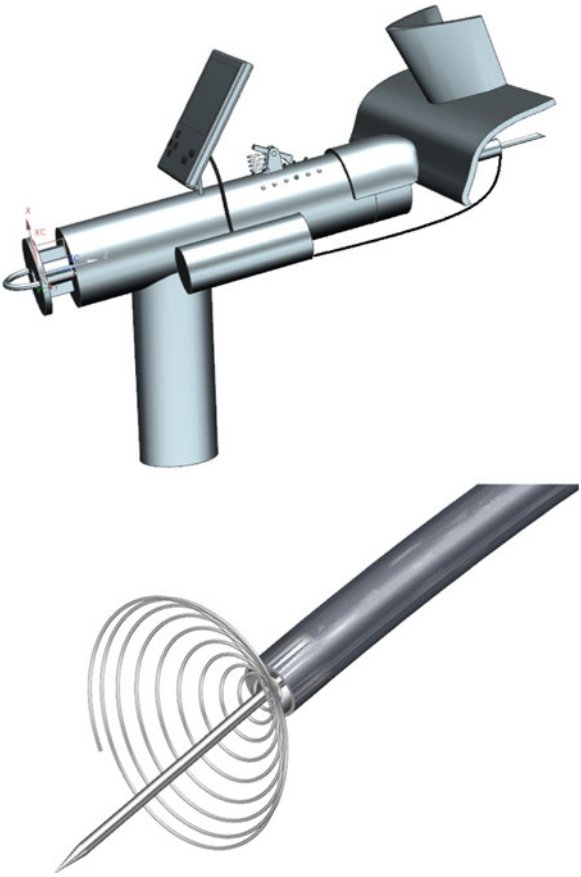

Fig. 16.6 Computer-aided design as a help for clear patent documents. Tracheotomy device based on medical imaging and aided by expandable spring that helps with long-term establishment of airway, once the trachea is punctured

- Creating a "spin-off" company. In many cases, researchers themselves want to bring their new product or system to the market and society, what is normally achieve by establishing a "spin-off" company. Usually the team of researchers participates in the "spin-off" constitution and main dedication is provided by young researchers, after finishing their doctorates or postdoctoral stays, who want to experience industrial world. The university normally licenses the original invention under exclusive agreement with the novel "spin-off."

After having discussed some brief details about intellectual property and described main strategies for reaching market and final technological transfer to society, it is important to remember the importance of some design resources (mainly CAD-CAE) for better describing inventions and elaborating more complete (and easier to be granted) patent documents. Just providing a main view of the device and its components (Fig. 16.6 provides an example of a novel biodevice) helps evaluators to assess the invention and other researchers to use such information for further studies.

16.5 Main Conclusions and Future Research

This chapter has presented the strategic importance of creativity, innovation, and technological transfer in a continuously changing (or evolving) industrial environment like the Biomedical Engineering field. Several tools for promoting innovative solutions, capable of leading to improved diagnostic or therapeutic solutions and of placing our products and systems in a relevant market position, have been presented and compared by means of a case study linked to "optimizing the weight of hip prostheses."

A more systematic employment of these innovation-driven design approaches and of related tools (i.e., alternative generation–assessment–association, TRIZ, and similar methodologies) can promote many advances in all kinds of biodevices and medical solutions with relevant novel features.

We propose future research linked to the development of a handbook including case studies of innovation-driven redesigns of all common implants and prostheses, with comparative studies showing the application of complementary methodologies for solving similar problems, as the case study described here.

In addition, completing such a handbook with design proposals based on the application of more recent methodologies, such as BioTRIZ (see Vincent et al. 2006), serendipity-driven innovation, or further application of biomimetic principles, would be interesting indeed and surely provide relevant advances for the bioengineering community.

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Chapter 17
A Proposal for Structured Development Methodology for Biodevices

Andrés Díaz Lantada

Abstract This chapter contains a detailed description of a proposal for a structured methodology for developing medical devices. The intention is to simplify and promote the industrial expansion of biodevices, taking advantage of recent developments, whose special features can be applied for the enhanced development of biodevices with remarkable diagnostic or therapeutic capabilities. For this purpose, the use of systematic processes can be highly beneficial, as highlighted in several previous chapters.

This proposal is not only a result of the examination made at the beginning of the handbook, of the use of systematic methodologies for conventional product development and of the current state of technology related to the use of advanced design and manufacturing technologies, together with novel materials in medical devices, but also a result of the knowledge acquired during the specific developments covered in previous chapters.

Solutions are put forward for the different problems encountered that affect the development of any medical device together with an analysis of how the use of these novel technologies and materials has influenced the different stages of the systematic design methodologies already set out.

The promotion of teaching–learning activities linked to the development of medical devices and all kinds of biodevices, within programmes of Mechanical and Manufacturing Engineering, Bioengineering and even Medicine, is especially noteworthy for further scaling the effectiveness, capabilities and industrial impact of such devices. Collaboration between researchers of different fields is also necessary for continued improvements.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_17,

17.1 Introduction

This chapter contains a detailed description of a proposal for a structured methodology for developing medical devices. The intention is to simplify and promote the industrial expansion of biodevices, taking advantage of recent developments, whose special features can be applied for the enhanced development of biodevices with remarkable diagnostic or therapeutic capabilities. For this purpose, the use of systematic processes can be highly beneficial, as highlighted in several previous chapters.

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Solutions are put forward for the different problems encountered that affect the development of any medical device together with an analysis of how the use of these novel technologies and materials has influenced the different stages of the systematic design methodologies already set out. Therefore, each step of the conventional methodologies for systematic product development (including "arranging a team", "finding a need", "defining specifications", "conceptual design", "basic engineering", "detailed engineering" and "pre-production considerations") is modified to incorporate the special characteristics of biomedical products.

The promotion of teaching–learning activities linked to the development of medical devices and all kinds of biodevices, within programmes of Mechanical and Manufacturing Engineering, Bioengineering and even Medicine, is especially noteworthy for further scaling the effectiveness, capabilities and industrial impact of such devices, as is covered in depth in Chap. 18, including case studies linked to project-based learning. Collaboration between researchers of different fields is also necessary for continued improvements.

17.2 The Relevance of Multidisciplinary Teams

17.2.1 Multidisciplinary Teams: Advantages and Limitations

A typical medical device development team is usually made up of doctors, pharmacologists, engineers, computer experts, physicists, chemists and biologists, as well as economists and law graduates, to provide financial and legal advice, respectively. Some of the main benefits of having multidisciplinary teams are as follows:

- Creativity is encouraged (see Chap. 16).
- More varied responses to problems arise.

- The division of labour makes finding the right solutions easier.
- It is easier to assign responsibilities.
- It is more difficult to take key design aspects for granted.
- The end solution is checked from different points of view.

The development process undoubtedly benefits from such a wealth of approaches; however, having experts in specific areas can also give rise to problems of communication (misunderstandings, imprecisions, lacks of information, false assumptions) and of organisation that can lead to specific work schedules and budgets not being adhered to, and even to personal conflicts that affect the project. Explained below are diverse instruments that may serve to avoid these kinds of problems.

A lack of understanding, frequently arising from a wrong use of language, has resulted in economic, political, social, religious and many other types of conflict throughout history. This has caused many scholars to undertake a systematic, in-depth examination of the roots of these conflicts, as a way of seeking solutions in order to avoid future problems.

Analytical philosophers, starting in particular with Bertrand Russell and Ludwig Wittgenstein, focused attention throughout the twentieth century on the importance of language and how it is used and placed these topics at the core of Philosophy. Both coincide in stating that the duty of Philosophy is to clarify language, by which many of the traditional problems of this discipline of knowledge can be eradicated, since most problems are due to a wrong use of language.

As occurs in other fields, communication problems (often the result of not using a common terminology or language) also give rise to problems in product development projects in any industry. Medical device development-related work teams, in particular, are usually made up of experts in many different fields that can generally be classified as "specialists in technological sciences" and "specialists in medical sciences" among whom communication is not always effective.

On the other hand, the small number of training programmes existing in Europe on Bioengineering topics (in its widest sense) is making it difficult to find people who can liaise between medical science specialists and technological science specialists as part of medical device development teams. This means that establishing a fluid dialogue between these teams is no easy matter.

17.2.2 Proposals for Improvements

17.2.2.1 The Use of a Common Language

Preparing an initial document to suitably define the medical condition under study has been proved to be very useful for the developments put forward in previous chapters as a tool for facilitating communication from the very start of the development process.

This document should deal with the various aspects related to the condition in question as a way of facilitating the search for new diagnostic or therapeutic solutions that can benefit from the new possibilities to be had from using active materials, by comparing the advantages and disadvantages of the different families. We propose a common framework for these initial documents which, based on the proposal of the "6P Document" by Dr. Jesús Latorre and including the advices of Dr. Andrés José Díaz Fernández, should take into account the following issues:

- General aspects of the condition:
  - Definition and physiopathology
  - Main types or manifestations
  - Aetiology
  - Diagnosis (also differential diagnosis when appropriate)
  - Prognosis
  - Treatment
- Available diagnostic or therapeutic products:
  - Passive commercial devices
  - Active commercial devices
  - Non-commercial devices and designs
  - Other devices under development (competitor analysis)
  - Devices used in other related conditions
- Main national and international researchers:
  - Hospitals
  - Research centres
  - Universities
- Main related publications:
  - Books
  - Scientific papers
  - Papers presented at congresses
  - Related web pages
  - Specialisation forums
- Patents:
  - National patents
  - International patents
  - Patents pending
- Diagnostic proposals or alternative therapies:
  - Diagnostic proposals
  - Therapeutic proposals
  - List of requirements
  - Biomaterials typically employed in such devices

  - Possible use of active or "intelligent" materials, as sensors or actuators
  - Benefits associated with the use of different biomaterials
  - Benefits associated with the use of different sensors or actuators
- Annexes, proposal for the terminology to be used:
  - Dictionary of basic terms
  - Abbreviated notations
  - Basic units to be used (promoting International Unit System)

Preparing these documents is a considerable learning process in itself and provides an overall vision of the conditions for which diagnostic or therapeutic solutions are being sought. Once prepared and throughout the entire development process, this document acts as a point of reference for the whole team taking part and helps provide a common terminology between the experts in technology and the experts in health.

Figures 17.1 and 17.2 provide examples of an analysis of available solutions and products for a couple of pathologies (bruxism and mitral valve insufficiency), resulting from the development of the aforementioned document.

17.2.2.2 Teaching Requirements

As commented in the second chapter, the medical device industry in Europe employs around 350,000 people, which is some proof of the social importance of this sector. However, this high demand is not completely satisfied from an educational point of view, particularly in countries like Spain, where the journey along the path to teaching in matters of Bioengineering is only just beginning.

Of course there are some exceptions, including a few remarkable and well-established, and funded, Bioengineering programmes in Germany, France, Denmark, England or Sweden, with more than two decades of tradition, but still not comparable, for instance, with the vast number of bio-programs offered by the universities in the United States or with the research efforts currently addressed by China.

If this industry is to evolve properly, a major issue is to have a choice of graduates available from training programmes that provide their students with the knowledge, skills and aptitudes required to effectively carry out (among other things) the supervision, communication and information management tasks associated with medical device development projects.

Since we are dealing with experts in technological sciences and health sciences, it is exactly this type of Bioengineering programme graduate that can most help to minimise the problems from an imprecise use of language by taking on the role of "communication facilitator" on the multidisciplinary teams working in this sector.

It is important for these training courses to be officially recognised (with clearly identified job competencies), with a degree and postgraduate degree structure like other branches of engineering, which may encourage students to choose this option.

Fig. 17.1 Several devices for the diagnosis or treatment of bruxism: personalised discharge splints. Discharge splints (serial manufacture) ("Teleflex Medical", "DenTek Night Guard", "Sleep Right"). Incisive splints "NTI-tss". "S-EMG" detectors ("Grindalert", "BiteStrip"). Devices for detection and treatment (biofeedback) ("BruxStop" with electrical alert and "Cycura" with acoustic alert)

To only depend on postgraduate programmes intended to supplement graduate training in different branches of engineering, often in too specific aspects, can result in a mistaken strategy, since it limits the job spectrum open to students, as is currently the case with various postgraduate courses in Bioengineering.

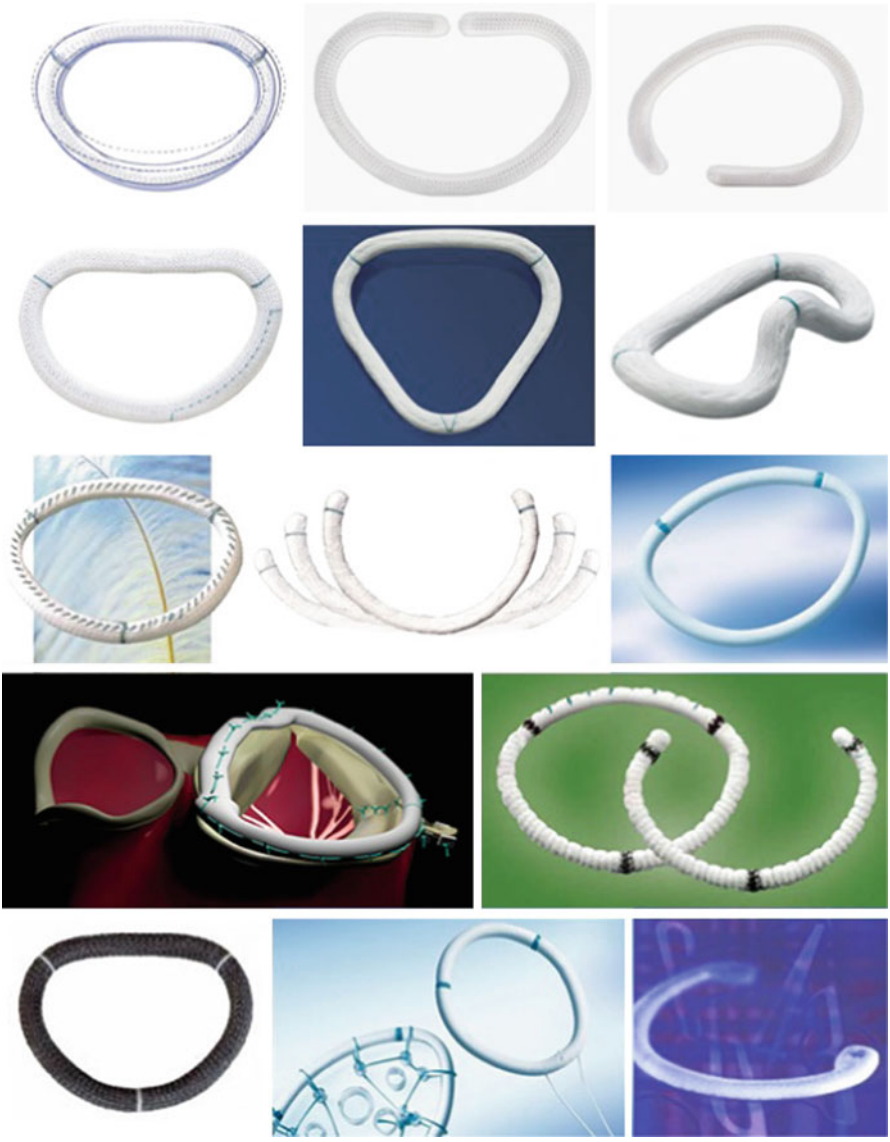

Fig. 17.2 Several models of annuloplasty rings (from *left* to *right* and from *up* to *down*): "Carpentier–Edwards Physio", "Carpentier–Edwards Classic" (mitral and tricuspid), "Carpentier–McCarthy–Adams", "Myxo ETlogix", "GeoForm", "Duran", "Cosgrove–Edwards", "Jostra–La Pitié", "CG Future", "SJM Taylor", "Sorin Sovering", "Jostra–Maazouzi" and "Colvin–Galloway"

Cooperation among technology branch and health branch teachers in the preparation and teaching of these courses is also important. It is in this respect that the participation of departments from different universities is very positive, as they can

make their laboratories and research centres available to students. In addition, having the support of sector companies and hospitals to offer internships linked to final degree or end-of-course projects is also very positive for achieving the teaching aims of this type of course.

Additional aspects on how to promote collaboration between academia and industry can be found at the forthcoming special issue of the International Journal of Engineering Education on "Impact of Collaboration Between Academia and Industry on Engineering Education", which I am currently editing with the help of contributions from several universities worldwide, covering teaching methodologies, case studies linked to blended learning, systematic student grants for industrial training, impact of spin-offs/start-ups on students' learning, project-based learning, student competitions, win-win strategies and future directions for improvement.

17.3 Preliminary Studies: The Need for Addressing and Medical Problem

As mentioned when analysing systematic development methodologies and the special considerations for medical devices, it is essential to have a medical need requiring a solution as the main objective. This factor needs bearing in mind from the very beginning of the "defining objectives and planning" stage as well as in the "preliminary studies". If there is no such need, it is not logical to start developing a new product to provide a solution to a non-existent problem or one that is being adequately solved by other methods.

The appearance of new technologies or other materials, which is happening now, normally arouses tremendous expectation, as to the different fields in which these technologies or materials can be applied. A use obviously needs to be found for this scientific–technical progresses, but on occasions a desire, normally from teams of engineers, to find an immediate application of a technological advance can lead to awkward situations or to the offering of solutions to problems, for which there is no demand either by medical specialists or by society.

When using novel design and manufacturing technologies, together with novel materials as a basis for the development of medical devices with enhanced capabilities, one should act prudently. *A real goal arising from a real medical need should be pursued* and the novel technologies and materials used for this end should be properly mastered, characterised and tested due to their novel properties and possibilities they offer. If this is borne in mind and selection is made according to specific criteria in the "conceptual design" stage, the rest of the development process will be a straighter road, with fewer obstacles, what will lead to a more successful solution.

To ensure that new technological supply meets the existing social and medical demand, we must once again focus our attention on the importance of encouraging these issues to be taught on courses at different programmes, even from high school to centres for professional training and universities.

The creation of new Bioengineering syllabuses with the cooperation of doctors (physicians) and engineers and the active participation of universities and medical centres would be of tremendous help for this purpose, since it is precisely in hospitals and health centres where diagnostic and therapeutic needs are continuously detected. Then, once the technical schools have been informed of these needs, they can set about finding technological solutions through research and development projects into new biodevices.

Especially in the United States there are noteworthy examples of hospitals that have major engineering departments that actively collaborate not only in health science-related teaching work but also in purely technological aspects. Some examples are the "John Hopkins Hospital", the "Mayo Clinic", "Massachusetts General Hospital" and the "Cleveland Clinic".

Similar moves in this direction, to take advantage of the period of change which European universities are going through, linked to the implantation of the European Area of Higher Education, could be highly beneficial for promoting major advances in this issue.

17.4 Conceptual Design and the Protection of Intellectual Property

Complementary to the work described in the chapter on systematic product development methodologies (Roozenburg and Eeckels 1995; Pahl and Beitz 1996; Ulrich and Eppinger 2007 this subchapter analyses in finer detail the importance of making a correct initial choice of biomaterials and "intelligent materials" that have the right diagnostic and therapeutic characteristics for the medical devices and active medical devices under development. When choosing any novel biomaterial or any multipurpose material and comparing the different candidates, the following characteristics must be looked at in detail, as they can mark the difference between which materials are suitable for the device to be developed and which are not (Díaz Lantada 2012):

General properties:

- Mechanical strength
- Thermal resistance
- Chemical resistance
- Density
- Effects on the receiver organism
- Evolution of properties over time
- Availability (time period and despatch facilities)
- Cost (repercussion on the price of the end device)
- Additional difficulties
- Data on its interaction with tissue and sterilisation possibilities

For activation purposes and related therapeutic improvements:

- Attainable deformations
- The stresses that must be faced
- Response speed
- Power required
- Feed voltage
- Feed current
- Reversibility

For detection purposes and related diagnostic improvements:

- Useful measurement range
- Sensitivity
- Signal/noise ratio
- Frequency response
- Time resolution
- Amplification requirements
- Packaging requirements

It is then very useful to construct a decision matrix based on these characteristics where the candidate materials are ordered in columns and the relevant properties in rows. In this way, each material can be scored according to different criteria, and after due consideration of the relative importance of the different properties, the ideal material or group of materials can be chosen objectively for a specific medical use.

In conventional medical product processes, this initial choice of materials is based on the information of similar devices and similar materials to those of existing products are usually chosen. However, if a medical device with novel characteristics or based on novel materials is to be developed, this prior information is generally not available, which means this stage has to deal with more difficulties.

On the other hand, several biomaterials have been only recently developed and are not fully characterised and the manufacturers' information is not always complete. So, when choosing possible candidates, it is important right from the conceptual design stage to ensure that there is an availability of suppliers of these materials and that delivery schedules and prices are reasonable. Furthermore, it should be checked that suppliers are willing to supply basic information about the properties of these materials, as well as processing and design instructions, which may be useful in the following stages of development. If information on certain essential material properties required for the work is lacking, an appropriate solution is to obtain a sample of the material and carry out a study or pre-characterisation using the raw material to evaluate the crucial properties.

Once a list of possible candidate materials has been made, it is advisable to contact the main suppliers and ask them if they would be willing to collaborate in the development process. In this way the suppliers that are most willing to help their customers can be selected and more formal collaboration agreements reached,

which in turn can lead to better results on completion of the research and a more effective end device.

The competitive edge of a new product often lies in its reaching the production stage and then being marketed before any of its competitors' products. This is particularly the case when conventional products conceptually similar to others already on the market are developed but which have some slight differences in design, shape, ergonomics, colour and appearance that could boost sales due to subjective factors.

It is not unusual for the success of a conventional product to depend on such peculiarities as appearance, brand image, the stamp of exclusivity, the feeling of belonging to a group, the advertising used and other emotional criteria that are difficult to predict.

In these cases protecting intellectual property is not especially relevant since there is not sufficient novelty or inventive genius for the product to be patented. Occasionally the new form of a product can be registered as "industrial design", which gives the title holder the exclusive right to make, manufacture, produce, sell, utilise and exploit the object registered, including the possibility of preventing the importation of any products copying the protected design. The "brand" and "brand names" registered can eventually take on a significant commercial value for new products, as well as for future developments, in the event of the manufacturer having sufficiently outstanding growth.

However, products that are the result of notable technological progress (and the new fields opened up by that progress) usually have more objective competitive edges based on conceptual or functional originality that involves a radical change of focus in the sectors where they will be used. These notable original ideas of outstanding inventive genius usually linked to new products or procedures (e.g., manufacturing procedures) can benefit from being patented. A patent gives the holder the exclusive right to prevent others from making a commercial use of the patented invention, thereby reducing the uncertainty, risk and competition from imitators by providing a means of protection for the intellectual property but with major additional benefits, which are listed below:

- For companies that invest large amounts of time and money in research and development work, protecting any inventions with a patent usually means costs are recovered and greater returns are on the investment.
- Additional income can be obtained by granting a licence on the patent or its surrender, usually to other more powerful sector companies that wish to counter any threat to their privileged position.
- Certain companies that are interested in technologies that are the property of others can use the patents of which they are holders to negotiate agreements to transfer crossed licences.
- Transferring patents to others under licence can open up access to new markets that would be otherwise inaccessible. If this is done, the invention must also be protected in the corresponding foreign markets.

- Being in possession of a patent considerably increases the chances of obtaining financing at a reasonable rate of interest. This, in turn, increases the chances of placing the patented product on the market.
- Being in possession of a patent considerably increases the chances of taking successful legal action against those who copy or imitate the protected invention.
- Being in possession of patents gives a positive corporate image. Some companies mention or enumerate their patents in their advertising as a way of projecting an innovative image to the public.
- In academic circles it is an additional tool for assessing the quality of research of universities and research groups, often with positive financial repercussions on these institutions.

It should be underlined that the scope of this handbook, which is focused on the use of novel technologies in the development of medical devices, is open to major intellectual property-related activities. Since many active material formulations are the fruit of recent research in search of applications and given the intrinsic difficulties of any medical device development process, any medical devices that integrate active materials such as sensors or actuators usually have features that are subject to protection by patent. These developments can therefore benefit from the advantages set out above.

It is precisely at the end of the conceptual design stage, after completion of the preliminary studies (which include existing product and patent analysis, as already stated) and after choosing the working principle most suited to the diagnostic and therapeutic tasks, when it is the right moment to apply for a patent. At least this is what we have learned from our experience in developing some of the products presented in earlier chapters.

If the patent is not applied for until later stages of development (like basic engineering, detailed engineering or in vitro or in vivo tests), it is very likely that other research teams working on a similar topic will patent an analogous invention that will strip our development of its novelty and may block any future projections after having invested large sums of time and money.

Neither is it advisable to make any type of public announcement, giving any information about the active medical device under development, until a patent has been applied for, as once the fundamentals of a device have been made public, it cannot be patented.

For this reason, it is important to prepare and apply for the patent in the early stages of development, since after doing so the work can be made known, the preliminary results published, congresses and conferences attended to seek possible collaborators and other types of actions taken to remark and make the originality of the device being developed known. All this also facilitates the search for financing to complete and develop the product launch onto the market under more beneficial circumstances.

Throughout the design process, significant new issues can emerge that may also require various forms of intellectual property protection. Having completed the development of the device and made an objective analysis of its benefits and

limitations, different future actions or modifications can be considered, which, if sufficiently original and utilitarian from an industrial and medical point of view, may also require a patent.

It is also necessary to underline the scientific importance of patenting any inventions arising from research and development. To exemplify this importance, we will mention the following issues that demonstrate the positive outcomes for the scientific community of using patents, which go well beyond the purely financial and strategic purposes of having a patent from an entrepreneurial point of view:

- Patents are an excellent source of updated technological information since different data bases (easily accessible in the Internet and free) place over 60 million documents at the disposal of researchers, both patents granted as well as those applied for. In principle, the information in a patent document must be sufficiently complete and exact for the invention to be reproduced, which from a scientific and teaching point of view is highly valuable.
- Furthermore, searching these data bases by field of application lets researchers find products and procedures that are quite often aimed at solving technical problems similar to their own. It also helps find the most recent emerging technologies and locate strategic sectors by analysing the applications for a patent submitted for a particular subject.
- Applying for a patent is one of the most effective ways of making public an idea for the benefit of society, as it is presented as a document with an international standard framework. It includes an abstract, a description of the invention and some explanatory diagrams, at least one way of making the invention and the inventor's claims concerning what they consider to be their own creation. As no prototypes or tests are required, as is the case with other documents, such as scientific papers or congress communications, but simply to explain an idea on paper, publishing the information is also quicker, which is yet another advantage.
- On many occasions, the information that can be extracted from patents is unique, often the fruit of unfinished research or proposals made to continue along specific lines of research. As an example, we can cite a study from the United States Patent Office which found that around 70 % of the technology described in patent documents in the United States between 1967 and 1972 had not been described in any other media. However, whatever the case, drawing up patent documents is a valuable way of generating knowledge as a foundation for future developments.

We have so far explained the benefits of utilising patents in the development processes of medical devices based on the new possibilities opened up by active materials, particularly at the end of the conceptual design stage. In the next section, we shall now go on to examine further aspects to ensure that the basic engineering stage is successfully embarked upon.

17.5 Basic Engineering: From a Concept to a Product

This section covers different issues that are specifically linked to the basic engineering stage in medical device/biodevice development projects and which can promote the use of this kind of solution. The issues analysed here complement those already listed in the chapter on an introduction to systematic product development methodologies.

17.5.1 Integrating Patent Information

The new medical image capture technologies combined with the progress made in design and manufacturing tools allow new approaches for developing customised medical devices (see Chap. 5). Producing a customised device is in itself an entire development project, and if novel biomaterials or active material are included, it may be beneficial to use the methodology detailed here. For producing a unique customised device, even more than when developing a device for mass production, it is important to correctly manage any patient-associated information throughout the whole development process.

When dealing with a customised device, this information has a direct implication on the design because the patient's individual circumstances are a determining factor for the choice of therapeutic approach and may lead to different devices being used, according to the severity of their condition. For example, for the treatment of mitral insufficiency, one of the solutions chosen may be to utilise annuloplasty rings or to use a full-valve prosthesis. Both devices can be made to measure, but the choice depends directly on the patient's individual circumstances (Díaz Lantada 2009).

If dealing with a device for mass production, possessing information on a large number of patients, which can be used for demographic studies on a particular condition, can help reveal the most appropriate diagnostic and therapeutic approaches and provide information on the devices that can be most beneficial, hence helping with design and material selection tasks.

In fact, the generalised use of computer tools and data bases has been promoted by the national health systems of the most advanced nations. Diagnosing and treating patients thus becomes much easier as does communication between primary care (in health centres) and specialist care (in hospitals), which enhances the overall efficiency of health systems (Saiz Morón et al. 2008). This progress has been given an enormous boost through doctors, engineers and computer scientists collaborating to develop the tools to manage this information, particularly over the last decade. Some of the most recent major advances can be consulted in the 2008, 2009, 2011, 2011 and 2012 "Biostec–Healthinf" conference reports.

17.5.2 Characterisation of Novel Biomaterials and "Intelligent" Materials

As already explained, several biomaterials and active or "intelligent" materials are very recent, often resulting from synthesis processes carried out in university laboratories or research centres, and have not always reached the commercial stage. For this reason it is important, right from the conceptual design, to ensure that there are suppliers of the active materials intended to be used and that adequate information is available. However, sometimes very appropriate biomaterials or active materials may be marketed by suppliers that do not provide all the information required for the design, either because they have not examined the properties of the material in depth or because they do not want to disclose certain information about their materials.

This often means that additional characterisation tests need to be done at the beginning of the basic design stage to reveal important information on particular properties required to design the associated device correctly. Characterisation tests can be performed systematically following the procedures set out in ISO standards, some of which have already been described in different chapters of the handbook, especially in Chap. 15.

When characterisation tests lead to little satisfactory information on some property that is crucial to the correct functioning of the device, this material must be replaced by another of the possible candidates selected in the previous stage.

17.5.3 The Use of Modelling and Simulation Technologies

These tools are especially useful once the product concept and its main functions have been decided, just when we begin to examine in more detail the characteristics required by each of the subsystems and the relations among the different subsystems and the environment, so that the diagnostic or therapeutic mission will be properly carried out.

These technologies allow constructing simulators that can rapidly and accurately analyse the influence of different factors on the device's end performance and optimise the desired response. Thanks to the use of tools like "Matlab–Simulink" (and others like "Maple" and "Mathematica"), the said simulator construction can be done progressively by encouraging a division of work as a basic problem-solving tool. In this way, simple simulators can be had to model a very specific phenomenon. These simple simulators can then be combined with one another in a series of subsystems to obtain a simulator that will let a much more complex system be modelled where the responses can be analysed in accordance with multiple input variables.

In every case, it is very important to compare the simulation outcomes with the preliminary estimates calculated "by hand" and check these results in more detail

by carrying out actual tests, using several stages of prototypes and related in vitro, ex vivo and in vivo trials. These real tests allow the theoretical models to be adjusted so that their use in later device optimisation operations will be more accurate and effective.

17.5.4 The Use of "CAD-CAE-CAM" Technologies

A proper use of the different computer-aided design, engineering and manufacturing technologies ("CAD-CAE-CAM" technologies) throughout the basic engineering stage is a great asset at the design stage and for making a right choice of materials, components, geometries and manufacturing processes so that everything will fit the initial specifications of the device being developed.

Recent advances have made it possible to exchange information between the design, calculation and manufacturing programmes, from different software companies, which makes exchanging information with suppliers, customers or other researchers easier.

Furthermore, the results of simulation programs like "Matlab–Simulink", as well as data from calculation sheets like "Excel", can be used as loads or boundary conditions for subsequent FEM-based calculations made with the help of "CAE" programs. So, the various parts of the design can be studied with the aid of different software support tools, each with its own remarkable advantages and specific fields of application.

Once again, we must highlight the great importance of checking the simulation results given by these software tools, by comparing them with the results obtained from actual tests, to help validate the hypotheses made and acquire a greater confidence in the use of these simulation tools for similar calculations in the future.

17.5.5 The Use of "Rapid Prototyping and Manufacturing" Technologies

In the last 20 years, these new technologies have become powerful support tools for product development processes as they help minimise design iterations thereby reducing delivery schedules and costs, as explained earlier and which can also be seen in other research papers (Freitag and Wohlers 2003; Kuklick 2006; Lafont Morgado et al. 2000; Díaz Lantada et al. 2007).

In medical device-associated developments, it is especially important to make full use of the customised manufacturing that can be achieved with these technologies. By taking the information from high-quality medical image capture technologies and using CAD tools like MIMICS, geometric models can be obtained of the different parts of live organisms from which physical models can then be made.

This customisation not only lets customised implant prototypes be obtained but also helps in planning surgical tasks with the manufacture of physical models of the patient's internal organs.

The many examples given help show how these technologies can be used as a support for the different development stages of medical devices and, in general, any product development-associated research. The prototypes obtained in this way are of major importance for validating the outcomes of different simulations as well as design decisions by means of actual tests. We also propose their being used throughout the entire development process and their being used even earlier than described for conventional product-associated methodologies. In this way, even in the conceptual design stage, physical models can be available for testing and comparing the properties of the different materials or components chosen by integrating them into very simple prototypes.

17.5.6 In Vitro Tests: Characterisation of Novel Materials, Geometries and Devices

Before setting about any in vivo test, it must be checked that the basic design decisions made for an active medical device are the right ones and that the design works correctly in general terms. To achieve this, in vitro tests using prototypes of the device under development are essential.

The results will enable the design to be validated or provide guidelines as to what changes are required to optimise its functionality.

These in vitro tests do not involve risks to any living being as they are performed with synthetic tissue or perhaps from ex vivo samples. Their combined use with the results from simulation tools has become an essential instrument in the development process of these devices, since many in vivo tests are made unnecessary, leading to reductions in costs, delivery schedules and the suffering caused to the animals subjected to such in vivo tests.

However, carrying out these in vitro tests involves additional design problems to be taken into account that will demand further preparation and work from the research team members. If the results of these tests are to be meaningful, the device must be tested under conditions that try to recreate the actual circumstances under which it will need to function. It is therefore a good idea to build test benches to reproduce the environment of the device under real working conditions to evaluate its response and propose design improvements. Highly useful are automated devices to perform these tests in a semi-automatic manner in order to optimise the time schedules associated with these tests as well as for enhancing their repeatability.

In vitro tests are also associated with a first approach evaluation of the biocompatibility of the biodevices being designed and of the influence of the materials used, as has been detailed in Chap. 15 and is summarised in the following section.

17.5.7 Deliberations on Standards, Final Safety and Quality

In the chapters on product and medical device development, reference was made to the importance of keeping in mind *safety* and *quality* requirements throughout the development process, above all in the basic engineering stage where the fundamental aspects of the device are decided. The mandatory directives have been explained (according to the type of medical device), as well as the main regulations, and carefully adhering to them, throughout the design process, will facilitate obtaining devices that fulfil the requirements of the directives that apply.

We have also analysed many different tools and ways to proceed to assure the quality and safety of the products under development and their implications throughout the design process. It is vital that the entire team should collaborate to optimise these two aspects, with specific responsibilities being assigned according to each member's work area.

Further information on the application of different basic safe design principles to specific cases, such as "the safe life principle", "the safe failure principle" or "the redundancy principle", may be found in other references (Pahl and Beitz 1996).

Their adaptation to medical device design is immediate and was taken into account for certain aspects of the designs and prototypes detailed.

A conclusive factor is the experience acquired beforehand, from other development projects, as well as all the information gathered from previous research and development work.

When choosing materials for conventional medical devices, it is highly recommended to use the materials that have already provided compatible biodevices and have successfully been biologically tested in previous developments.

However, if novel materials are to be used, this information is often unavailable since we are dealing with recently synthesised materials intended to be placed on the market through research projects. In these cases, extra tests need to be made for in vitro as well as in vivo evaluations of the device's biocompatibility and safety of usage, as summarised in the following section.

However, it is always important to bear in mind that the resulting devices must fit the quality management requirements that are part of the national health systems global framework. Again we must emphasise the need for engineers and doctors to collaborate during the different development stages (which also include marketing, distribution and application to patients) and consult the conclusions of other relevant researchers (Ruiz and Simón 1994, 2004; Simón and Ruiz 1995; Simón et al. 2001; Jiménez et al. 2000).

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Taking the above procedures as a basis, more close attention should be paid to several aspects for further defining and improving the product, hence connecting the basic engineering and the detailed engineering stages.

Thus, the design stage can be approached as a whole with a precise level of detail being progressively obtained. When developing medical devices, certain issues prior to production start-up, and traditionally included in the detailed engineering stage, need to be again highlighted, and the following section provides an interesting summary.

17.6 Detailed Engineering and Reaching Market

The proposed methodology is particularly oriented toward obtaining medical device prototypes based on the use of novel design and manufacturing technologies, usually as part of research projects that are reaching the in vivo test or pre-production stage.

In whichever case, this section includes certain considerations regarding "preclinical research" that must be borne in mind and stages that must be completed before placing medical devices into production, as a summary of those detailed in Chap. 15.

Some of these stages may require entire research projects, particularly if newly synthesised biomaterials or active ("intelligent") materials are to be integrated that are not fully characterised.

17.6.1 Ex Vivo/In Vivo Tests

Medical devices need to be tested in some living organism (in vivo tests) before being subjected to clinical trials, in order to obtain demographic data on their diagnostic capabilities, therapeutic effects or the effect of the device on human beings (Kuklick 2006).

Once the device has been subjected to preliminary tests in vitro, in order to evaluate its functionalities, it is advisable to analyse how the device performs ex vivo. This often means acquiring tissue from living beings or corpse samples to test the device and identify the changes required as a prior step to conducting the in vitro tests in order to avoid using animal tissue. As an example of the advances in this respect, the developments of "Edwards Lifesciences LLC" may be quoted for obtaining synthetic pericardial patch tissue, as a support for research work and surgical operations.

After conducting the in vitro/ex vivo tests and making the necessary design change, it is essential to make a right choice of the place where the in vivo tests will be conducted. This decision is crucial to the success of the tests and the project, since choosing a laboratory with inexperienced staff may lead to unacceptable deviations in costs and schedules. Again we must emphasise the need for multidisciplinary teams for medical device development and the benefits to be had by occasionally seeking advice and assistance outside the research team for any issues that are beyond their capabilities.

A generally good option is to pre-select the most renowned preclinical research centres in the field (province, autonomous region, participating team members' countries) basing choice on objective quality criteria, such as experience, staff and available resources.

The major universities in Medicine, Biology and Veterinary Science in the country are always among the candidates, as well as important research centres and laboratories, which quite often are associated with the universities. These centres usually

combine research work, training and external services whose founding is usually promoted by public investment to aid the purchase of facilities and equipment.

A good strategy for choosing the right centre is to visit the various pre-selected centres and speak to the people in charge, to deal not only with technical matters but also with schedules and costs to help make the final decision.

Another key issue for the success of in vivo tests is the right choice of animal model to be used. Working with live animals to support a medical device development project is a privilege not to be taken lightly, and exhaustive planning should aim at reducing the required number of animals needed. To help choose the most suitable animal model, the following procedure may be followed:

- Study the animals used in similar developments.
- Analyse the species whose anatomy is most similar to humans (for the organ associated with the device in question).
- Exchange opinions with other researchers in the same area.
- Consult the main scientific publications.
- List the equipment needed (which will also help choose the centre for the tests).
- Calculate the number of animals required.
- Decide if the operations will be terminal or not.
- List all the parameters wished to be studied.

Only after an exhaustive planning stage and assigning the right responsibilities to all the participating personnel (particularly regarding the centre where the in vivo tests will be conducted, as they are not usually part of the initial development team), the in vivo work can be begun. The ethical guidelines contained in the "Helsinki Declaration" may assist and guide the participants in this kind of project in their decision-making.

17.6.2 Verifying Biocompatibility

As already explained, the term biocompatibility refers to the interaction between a medical device and the tissues of the patient treated with that device. A biocompatibility evaluation is part of the overall quality assurance and safety process for medical devices. It must be taken into account throughout the development process from the initial selection of materials even though it must be evaluated by using the end device, since the body's response depends on many factors.

Some of the factors that usually influence the biocompatibility of a device are as follows:

- The physical–chemical nature of the device materials
- The type of tissue exposed to the device
- The length of contact
- Device geometry
- Sterilisation method
- The patient themselves

The best starting point to understand the biocompatibility requirements of a medical device and decide the process to evaluate it is probably ISO standard 10993 on the "Biological Evaluation of Medical Devices". A set of guided steps are described for carrying out this evaluation on the biocompatibility of new medical devices, which in itself makes it a proposal for the methodology of this specific stage.

As certain biocompatibility-related data are always required for devices that are in contact with tissue, it is important to refer to the flow chart included in ISO standard 10993–1, to examine which type of in vitro and in vivo biocompatibility tests need to be conducted. In general, the number of tests needed to fulfil the requirements can be reduced if some of the following types of data are available:

- Data from previous evaluations. If data is available from previous satisfactory tests on similar devices, certain verification tests will need to be made to check if any significant changes have occurred in the materials used, the manufacturing processes, the nature of the contact or the sterilisation methods.
- Data from the components or materials suppliers. If data is available from evaluations made by the suppliers, it is always important to obtain copies of these original studies and it is also advisable to carry out some verification tests.
- Analytical data. Usually provided by manufacturers from the chemical characterisation tests conducted to verify the low hazard associated with using certain materials and devices in contact with body tissue.
- Clinical data. Having clinical data from tests carried out with devices containing similar components or materials may help satisfy certain biological effect-related requirements to be found in the categories included in ISO standard 10993–1.

In whichever case, a good strategy for choosing the biological tests to be passed, by the device in question, is to develop the ISO biocompatibility matrix for the objective device. This matrix classifies medical devices according to type and duration of contact. It also provides a list of potential biological effects.

For each device category certain biological effects have to be looked at in detail and satisfactorily addressed by taking previous data or conducting new tests to obtain a positive evaluation that will allow production start-up.

Again, it is highly recommended to enlist the aid of organisations that are experts in these kinds of studies and procedures to provide external advice to the development team. Most sector multinationals have departments exclusively devoted to the biological evaluation work need to fulfil requirements and undertake their own biocompatibility studies.

In fact, many medical device development projects carried out in universities or research centres end up producing a prototype of the device, usually for in vitro but sometimes in vivo tests. When they have been proved to work properly, it is very often attempted to licence this technology to a sector company, which will then take charge of the biocompatibility tests and the official approval procedures, as well as its subsequent production start-up and marketing. Proceeding in this way is the quickest and most effective way of facilitating the transfer of research results to society.

It is also possible to set up technology-based businesses that commit themselves to exploiting the outcomes of medical device development-related research. To this end, many universities are promoting specific actions (like "ActúaUPM" initiative from Universidad Politécnica de Madrid, which provides training and financial support for its researchers so they can set up businesses of this kind).

In addition, right from the start of the development project, consideration can be given to contracting the collaboration of a sector company to help the research team with the many issues related to the market launch.

Another recommended step, regarding the biological evaluation of the devices being developed, consists in discussing in detail the biocompatibility tests proposed directly with the evaluators of the competent bodies who can always provide guidelines on the safest and most direct way to act.

After a medical device has passed all the different tests required of it in accordance with its classification and the applicable directive (as explained in the second chapter, when detailing some special considerations about regulations and standards), the manufacturer or its authorised representative in the European Union may place the "CE mark" on its product and subsequently begin with production and marketing.

In whichever case, it is important to point out that the biological requirements for medical devices, as well as the relevant standards, are constantly changing and correctly updated information must be used. This information can be found on the website of the "International Organization for Standardization": www.iso.org.

Other markets are subject to an alternative regulatory framework, which means that the information from other entities should be consulted (particularly the "Food and Drug Administration": www.fda.gov, for the US market).

17.7 Comparison with Conventional Methodologies

The suggested methodology is in essence an adaptation of structured methodologies for systematic product development but includes important considerations aimed at making the medical device development process easier (Saaksvuori and Immonen 2008; Stark 2004).

Throughout the chapter we have itemised the main issues to be borne in mind, when developing medical devices based on the use of novel design and manufacturing technologies and modern biomaterials, which is what differentiates this proposal from other structured methodologies used for systematic product development.

Of all these issues, the following are worth mentioning once again:

- The importance of multidisciplinary teams
- The importance of using tools to facilitate communication
- The importance of managing information properly, particularly patient-related information

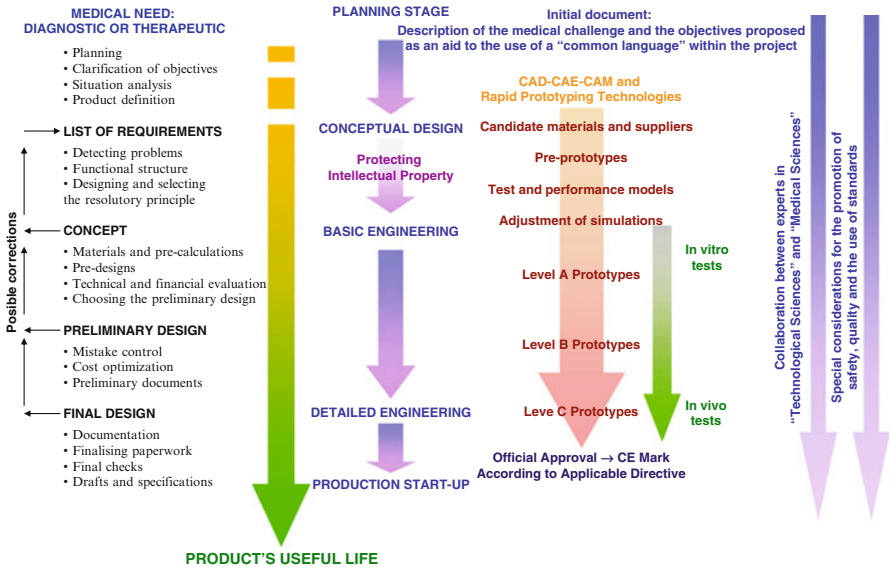

Fig. 17.3 Outline of the proposed development methodology

- The benefits of taking measures to protect intellectual property
- The special relevance of making a careful choice of material suppliers
- The need to conduct property characterisation tests as a design basis
- The benefits of using simulation technologies as a design basis
- The benefits of using "CAD-CAE-CAM" tools in combination with rapid prototyping technologies throughout the basic engineering stage
- The need to validate simulation results with actual tests
- The need to carry out in vitro tests to validate materials and applications
- The need to carry out in vivo tests to validate the diagnostic or therapeutic benefits
- The importance of keeping in mind safety issues and standards throughout the development

The following Fig. 17.3 includes a general outline for this proposal that can be compared to the diagram usually used for more conventional products, as shown in the first chapter when dealing with systematic product development methodology.

The changes made are as a result of the research that gave rise to this handbook and the enquiries made into the cutting-edge developments of other research centres, universities, technology-based companies and university hospitals.

Applying this proposed methodology to future research and development projects will enable it to be improved and its range of applications extended.

17.8 The Importance of Collaboration, Information Exchange and Teaching–Learning Activities

To promote the industrial expansion of advanced design and manufacturing technologies, as well as of novel biomaterials, and facilitate their use for the development of new medical devices, it is very important for universities, research centres and major sector companies to collaborate and exchange information in respect of the scientific–technological progress in these fields and their applications.

It is an inherent mission of teachers and researchers to focus attention on these new fields of study and on the importance of examining them together in a coordinated manner and to look on other researchers as potential valuable companions and never as rivals.

Other areas of knowledge have given examples of how joint action leads to rapid scientific progress with no less important socio-economic impacts. Worth quoting again, as an example is the call for collaboration in matters of micro- and nanomanufacturing made by the scientist Richard Feynman in his talk, "There's plenty of room at the bottom" in 1959 at the California Institute for Technology, "Caltech". A little more than two decades after this talk, IBM scientists succeeded in positioning atoms for writing (and reading) words, far exceeding the initial challenges of that call.

For instance, in the issue of active materials, remarkable efforts of international collaboration have begun to emerge in recent decades. Outstanding events related to the use of electroactive materials may be cited, such as the call to seek answers to the current limitations of these materials made by Yoseph Bar-Cohen from NASA's "Jet Propulsion Laboratory".

Relevant forums have also been created to exchange information on the advances in materials science, such as "Scientific.net" and "Biomat.net", that help spread results, exchange opinions and promote meetings and events on this subject.

Regarding the promotion of novel technologies and materials for innovative medical device development, it is interesting to consider ways to exchange information and enhance teaching, like those listed below:

- It is highly beneficial to set up a specific forum on medical needs and novel medical applications, where researchers, universities and companies can get in contact to match technological offers and market requirements, of major importance to the Medical Industry.
- Congresses and scientific meetings are very useful instruments for bringing together the main researchers in an area of knowledge, particularly when this is done according to a fixed schedule to discuss specific topics. A continuous update of the topics covered here can be achieved by attending congresses on the field, such as the annual "BIOSTEC International Joint Conference on Biomedical Engineering Systems and Technologies", which usually includes the Biodevices, Biosignals, Bioinformatics and Healthinf Conferences.
- The development of properties data bases for different materials (e.g., "Campus Plastics" or "Polymers: A Properties Database") has proved highly useful when selecting commercial formulations for conventional products made of polymeric

materials. Many novel biomaterial and active material formulations are the result of developments carried out in small companies and research centres and are not commercially available. On the other hand, these companies and research centres are not usually included in the commercial materials' data bases mentioned. It would be a great help if information concerning any new biomaterial or active material development, including the results of different characterisation tests and data on synthesis and processing, would be progressively added to the most used data bases.
- To encourage the use of novel design and manufacturing technologies, it is important to make known the advantages expected from their use and teach people to make designs that are based on their special features and benefit from their possibilities. Therein lays one of the basic benefits of carrying out research work in the university, since the discoveries made encourage changing and gradually updating the syllabuses of the various subjects. This helps to promote and maintain students' interest and to increase the transfer of knowledge arising from research to society as a whole.
- To promote the information exchange of available biodevices, providing an historical perspective of their evolutions can help researchers to find very remarkable inspirations, based on actually successful devices. Such a task could be carried out by implementing an exchange website, blog or users forum, in which researchers could exchange opinions and share developments.

As an additional source of information to aid the future development of novel biodevices, several websites linked to design and manufacturing technologies and several websites of very relevant medical device manufacturers have been included in the annexes, together with those references that have been of special help for the development of this handbook.

Standards Summary

Main Organisations

- International Organization for Standardization "ISO" (www.iso.org)
- The World Medical Association (www.wma.net)

17.8.1 "New Approach" Directives Related to the Medical Industry

- Directive 93/42/EEC related to "medical devices"
- Directive 90/385/EEC related to "active implantable medical devices"
- Directive 98/79/EC related to "medical devices for 'in vitro' diagnosis"

17.8.2 Standards Related to the Development of Medical Devices

- ISO 10993 standard on "biological evaluation of medical devices"
- ISO 13485 standard on "sanitary products, quality management and regulatory affairs"
- ISO 13488 standard on "quality systems, medical devices, sanitary products and especial requirements for applying ISO 9002 standard"
- ISO 14971 standard on "application of risk management to medical devices and sanitary products"
- ISO 15223 standard on "symbols used for labelling and information provided together with medical devices"

17.8.3 Standards and Associations Related to Medical Imaging

- DICOM standard – Digital Imaging and Communications in Medicine: Strategic Document (http://medical.nema.org)
- Medical Imaging and Technology Alliance (www.medicalimaging.org)
- NEMA – The Association of Electrical and Medical Imaging Equipment Manufacturers (www.nema.org)

17.8.4 Additional Documents of Interest

- Council of Europe "Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine: Convention on Human Rights and Biomedicine" (1994)
- UNESCO "Universal Declaration on the Human Genome and Human Rights" (1997) and "Guidelines for Implementation" (1999)
- World Medical Association "Declaration of Helsinki. Ethical principles for medical research involving human subjects" (current revised edition 2008)

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Chapter 18
Project-Based Learning (PBL) in Bioengineering

Andrés Díaz Lantada

Abstract A frequent problem of project-based learning (PBL) experiences linked to product design is the difficulty in reaching the detailed design stage, particularly if the experience is linked to a single subject that is timetabled for a single 4-month period. Quite often, the application tasks are focused on the most general stage of conceptual design but hardly ever reach the detailed design stage, when it is this stage that is the most interesting for applying the specific concepts of the subject being studied.

In this situation the information contained in patent documents can prove to be an endless source of conceptual designs that can be used to build PBL experiences in every field of engineering. In this way, the detailed stage can be reached more easily and lead to "patent-based project-based learning" or "P^2B^2L". In this kind of experience students can also acquire some notions regarding the standard structure of patent documents and learn to understand the importance of patents as a design tool and as documents that are essential for promoting innovation.

This chapter describes an experience of this kind carried out in the subject of "Bioengineering" on the Master's in Engineering at Universidad Politécnica de Madrid during the 2010–2011 course. It describes the teaching methodology used and the main achievements and makes proposals for future improvements. The use of similar experiences in subjects linked to Biomedical Engineering and to the development of medical devices can be an effective tool for promoting the industrial impact of the technologies described in this handbook.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_18,

18.1 Introduction to Project-Based Learning

Problem- or project-based learning experiences (usually referred to as "PBL") have enormous benefits but also certain limitations and difficulties that will be analysed further on. Problem- or project-based learning clearly tends to motivate students to participate and become involved in their own learning process and is an excellent way of analysing whether students have acquired the basic concepts taught in the theory classes and are capable of applying them in real situations.

These PBL experiences have proven to be effective in primary, secondary and university education and in scientific–technological, bio-sanitary, humanistic and artistic contexts. In fact, most technical universities, before awarding the engineering degree, almost always include the standard final project as part of the final studies, which, basically, is a PBL learning experience. The doctoral programmes are also oriented toward being completed by a doctoral thesis where the PhD students are confronted with solving a problem or have to complete a more complex project.

Therefore, PBL experiences are an excellent teaching–learning tool for guiding students, particularly in engineering, regarding their future working life in industry which will involve solving not only technical or financial problems on a daily basis but also human problems. Regarding the human element of PBL experiences, work is done differently depending on the students for whom the experience is intended. In the case of final projects or doctoral theses, the relationship between the tutor and student encourages critical discussion of the results by strengthening their ability for analysis and the synthesis between both. In respect of PBL experiences within the context of specific subjects, teamwork is usually the preference, so that students may learn to collaborate with their fellow students when finding solutions to complex problems.

In the field of Mechanical Engineering and the experiences linked to the development of new products, experiences of this kind have proven to be of enormous benefit for encouraging students to use all kinds of advanced innovation, design, simulation and computer-aided manufacturing technologies (usually referred to as CAI, CAD, CAE, CAM and in general CA-x), helping students not only to look closely at the conceptual aspects but to really get to grips with handling the tools that are more and more required by industry (see Fig. 18.1).

Also described are certain PBL experiences regarding the development of products that culminate in the production of prototypes, thanks to the use of "rapid manufacturing" technologies as an aid to verifying the designs produced and as a way of boosting student's motivation. These kinds of teaching activities are also directly linked to many others that can be grouped together under the title of "play-based experiences" (Díaz Lantada 2011). One such experience is competitions for students where the goal is to implement a new product or device, a series of laboratory experiments aimed at solving real problems, problem-solving based on the use of simulators and subjects in which students are assessed according to their involvement in entertaining activities.

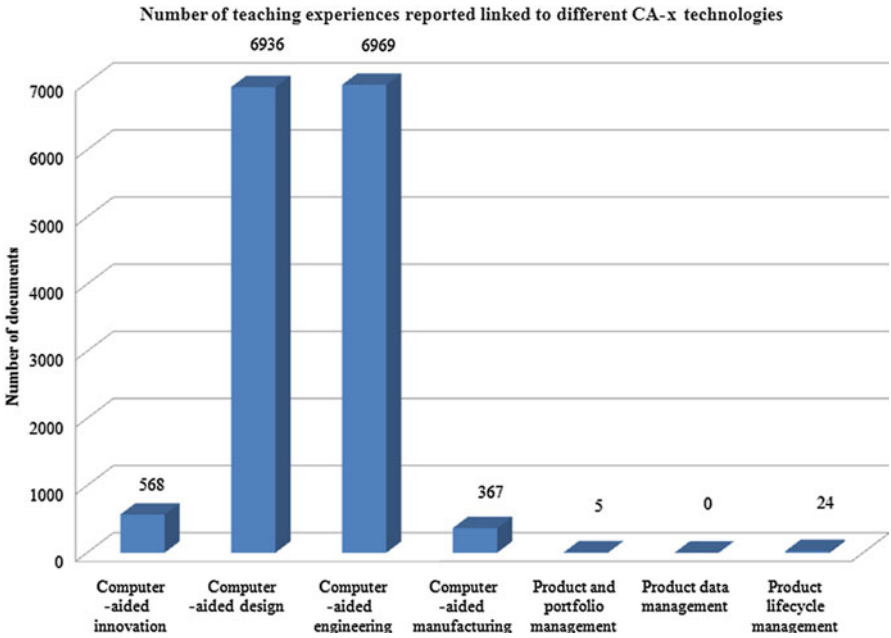

Fig. 18.1 Number of documents included in "ISI Web of Knowledge" describing teaching experiences linked to different CA-x technologies

Apart from stepping up student motivation and their perception that what they learn at university "is actually of some use", all these activities also help teachers become more involved in their relationship with students and to be continually up to date with new developments and renew or update subject content year after year in line with the specific topic chosen for the PBL experience, although all this requires considerable time and a desire to interact with students. The benefits are evident, although these activities are usually more enriching in the final years of the course when students have learnt sufficient concepts regarding basic science, materials science, applied mechanics, energy technology, mechanics, chemistry and electricity and the foundations of automation and electronics. These are just some of the many disciplines students can fall back on to tackle problem-solving or complex projects.

18.2 Application to "Bioengineering"

However, PBL experiences are not without certain difficulties. These must be borne in mind and efforts made to limit their effects, otherwise they can lead to educational gaps and imbalances when assessing students. The following paragraphs describe some of the most important experiences and put forward some solutions

that have proved their worth in prior research or in teaching experiences like the one described in this document.

When the projects or problems to be solved are tackled in a group, certain students usually take on the role of leaders, while others tend to "let themselves be led" or even cease to participate, particularly if the final mark is the same for all members of the group.

Our understanding is that the alternatives for putting an end to this situation are to assign individual projects, although somewhat easier tasks than would be assigned to a group of students, supplement student assessment with co-assessment (among students of the same team) either including some individual component that is usually a result of their class participation, or a supplementary exam. In whichever case, the presence of "parasite" students that benefit from others' efforts may also turn out to be good experience for the most assiduous students to prepare themselves for the reality of the world of work.

On other occasions, PBL experiences give students some freedom when proposing the problem or project to be solved. This can boost creativity and be highly enriching if common goals are sought. However, this can sometimes lead to considerable discrepancies in the projects' degree of difficulty or the amount of time required to complete them, which, in turn, will make it more difficult for teachers to carry out the assessment. To limit these difficulties, teachers can resort to verifying (or modifying) the projects put forward by students by offering the freedom to choose from a wide list of possible projects or a selection of monographic studies with certain variations (toy design, the synthesis of certain mechanisms, the development of products for a single sector, etc.).

On the other hand, when PBL experiences are conducted in a subject over several consecutive courses, there is a repetition of some similar developments, which makes it much easier to copy works from other years. Therefore, it is not advisable to use the same field or area of application for the projects being developed for more than three or four courses. It is also highly advisable in product development-related courses to allocate each course a different single topic in order to avoid a gradual loss of creativity and the inevitable "ageing" of the topic dealt with. This is also applicable to other experiences such as student competitions and other play-based activities.

A more difficult problem to solve, especially when PBL experiences are linked to product development (including defining specifications, conceptual design, selecting alternatives, basic design, detailed design and, on occasions, prototype production), *is the difficulty in reaching the detailed design stage,* above all, if the experience is linked to a single subject that is only timetabled for a 4-month period or semester.

Obviously, defining the specifications for a new product and proposing and evaluating alternatives for a thoroughly explored conceptual design stage are complex but enriching tasks. However, they are also slow to carry out, which is why some subjects devote whole PBL experiences to the "detection of a relevant need" and "conceptual design" phases.

However, the basic design and detailed design stages are also very relevant, particularly within the context of subjects in highly specialised programmes, like a master's or a doctorate, because it is in these stages that the student must apply all the specific concepts of the subject, that is, all the calculations and considerations that often make engineering specialists, normally also highly demanded professionals. Quite often in this type of subject, where PBL experiences are linked to product design, due to the amount of effort demanded by the conceptual stage, students do not have time to go beyond a conceptual design or the beginnings of a solution for the product being developed.

Usually, when a student reaches a master or doctoral subject, they will have been exposed to some previous PBL experience, or at least, to numerous case studies linked to finding the beginnings of a solution to a specific problem. For this reason, the conceptual design stage and the methodology required are usually familiar. For these students to be able to apply the concepts taught in highly specialised subjects and put them to good use, carrying out PBL experiences could prove to be highly effective. In order to promote the level of detail acquired, students should begin by taking a conceptual design of a specific product and then work on it to attain what will be very close to a "pre-commercial detailed design".

For such purpose, the information to be found in patent documents can prove to be an endless source of conceptual designs for PBL experiences in all kinds of engineering fields, giving rise to "patent-based problem-based learning" initiatives or "P^2B^2L". This kind of experience also lets students acquire some notions about the structure and typical content of patent documents. They begin to understand the importance of patents as a design tool and appreciate them as essential documents when it comes to encouraging innovations in any development to be undertaken. They can even have their first experiences related to the protection of intellectual property.

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This document describes an experience of this kind carried out in the subject of "Bioengineering" on the Master's in Engineering at Universidad Politécnica de Madrid (Technical University of Madrid) during the 2010–2011 course.

18.3 Application to "Bioengineering": Teaching Methodology Employed

In the subject of "Bioengineering", on the Master's in Mechanical Engineering course at Universidad Politécnica de Madrid, students undertake development tasks (projects) which are an important source of learning and for which they are assessed. Different patents (Fig. 18.2) for real medical devices are taken as a starting point for their projects, and by using these, students must reach a detailed design that precisely defines the geometries, materials and auxiliary devices, with everything carefully calculated to achieve a satisfactory interaction with the patient.

(19) OFICINA ESPAÑOLA DE PATENTES Y MARCAS
ESPAÑA

(11) Número de publicación: **2 277 794**
(21) Número de solicitud: 200603149
(51) Int. Cl.:
A61F 2/24 (2006.01)

(12) SOLICITUD DE PATENTE A1

(22) Fecha de presentación: 13.12.2006

(43) Fecha de publicación de la solicitud: 16.07.2007

(43) Fecha de publicación del folleto de la solicitud: 16.07.2007

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(74) Agente: No consta

(54) Título: **Sistema de anuloplastia activo para el tratamiento progresivo de insuficiencias valvulares y otras patologías cardiovasculares.**

(57) Resumen:
Sistema de anuloplastia activo para el tratamiento progresivo de insuficiencias valvulares y otras patologías cardiovasculares.
Sistema de anuloplastia activo y teleoperado con capacidad para el tratamiento controlado, progresivo, reversible y postoperatorio de la insuficiencia mitral y otras patologías cardiovasculares, corregibles mediante el empleo de anillos de anuloplastia. Se basa en el empleo de un anillo actuador con memoria de forma, que puede calentarse con ayuda de dispositivos externos para activar el "efecto memoria de forma", que produce el cambio geométrico destinado a disminuir la insuficiencia mitral. La prótesis dispone de electrónica de control, que recibe las órdenes externas y actúa a tal efecto. La posibilidad de actuación "paso a paso", progresiva y reversible, por los medios propuestos en esta invención, lleva a un método, que resulta más controlado y produce menor desequilibrio hemodinámico, para el tratamiento de diversas valvulopatías.

(19) OFICINA ESPAÑOLA DE PATENTES Y MARCAS
ESPAÑA

(11) Número de publicación: **2 316 307**
(21) Número de solicitud: 200800905
(51) Int. Cl.:
B60L 3/02 (2006.01)
B60K 28/06 (2006.01)

(12) SOLICITUD DE PATENTE A1

(22) Fecha de presentación: 02.04.2008

(43) Fecha de publicación de la solicitud: 01.04.2009

(43) Fecha de publicación del folleto de la solicitud: 01.04.2009

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(74) Agente: No consta

(54) Título: **Dispositivo seguro para conducción frente a situaciones de hombre muerto o dormido.**

(57) Resumen:
Dispositivo seguro para conducción frente a situaciones de hombre muerto o dormido.
La presente invención detalla un dispositivo seguro para conducción frente a situaciones de hombre muerto o dormido que comprende mandos para control manual de vehículos o máquinas sobre los que se distribuye una red de sensores piezoeléctricos y pieoeléctricos. La información de dichos sensores es gestionada por la electrónica de control con ayuda de un modelo de comportamiento para evaluación de situaciones de riesgo. Dicha electrónica permite envío de señales de mando a elementos que actúan sobre el usuario para alertarlo o bien sobre el vehículo o máquina para retomar a una situación de seguridad. Resulta especialmente útil para evitar intentos de desactivación intencionados por parte del usuario, que han sido causantes de muchos accidentes de ferrocarril.

Fig. 18.2 Different patents provided as information for the projects

The following paragraphs deal with the aims and objectives of the subject in detail, together with the methodology adopted and the results of the first experience during the 2010–2011 academic course, accompanied by some reflections on the benefits of the approach taken.

Face-to-face classes (2 h sessions for 15 weeks), together with the additional seminars and organised laboratory visits, attempt to show students the different basic concepts of bioengineering, biomechanics, biomaterials and medical devices, for which reason each session usually starts by explaining the basic concepts and usually finishes with some examples of specific applications and case studies. Some sessions also include laboratory visits, especially to the university's Product Development Laboratory and our group's Microsystems Laboratory to supplement the sessions on computer-aided design and manufacturing.

Since we are dealing with a master's subject and many students are already working in an industrial context, there is a special interest on the part of teachers and students to orient the subject to the knowledge and tools that can be directly applied to the tasks of industry. We believe that a "problem-based learning" or PBL approach is particularly well-suited to motivating students to apply what they have learned to a complex task.

By proposing an application project, we are encouraging students to apply the concepts acquired in the theory sessions and trying to encourage them to use all types of advanced innovative, design, simulation and computer-aided manufacturing technologies (usually referred to by their abbreviations as CAI, CAD, CAE, CAM and in general CA-x), which are the tools that are being more and more demanded by industry, as explained in the preceding paragraph.

In order to better prepare students for their everyday tasks in industry, the work is oriented to the application of these tools (NX, Catia, Solid Edge, Solid Works, Abaqus, Ansys), although each student is free to choose what they prefer. In any case, the different options most used in Spanish industry are at their disposal in the computer room at the university's Machine Engineering Division.

At the start of the subject, students are given a question linked to the application task to be performed. This consists in reaching the detailed design stage of a specific medical device by using the conceptual information contained in the device's patent document which they are given together with the question. Every student is given a different proposal of similar difficulty thereby reducing the likelihood of them copying the work of other students. The application task involves another 35–50 h of individual work on the part of the student. However, it is necessary to allow some study hours and time to do the assessment tests to be handed in so as to be able to complete the 3 ECTS credits for the subject, as this is a fundamental part of the assessment.

A typical question format given to students is shown below:

> Referring to the medical device described conceptually by means of text and figures in the attached patent document, the student must tackle the following issues as an essential part of their evaluation by applying the concepts of biomechanics, biomaterials and design and manufacturing technologies:

1. Study the attached patent document in detail, and find and study in detail 3 other device patents that fulfil the same purpose and prepare a brief comparative study of the devices analysed.

2. Using standard CAD tools (computer-aided design tools), produce an initial basic design of the components of the medical device following the instructions in the attached patent document or even incorporating potential improvements.
3. Using standard CAD tools, make an initial assembly of the device as an aid to verifying the designed dimensions and geometries and with a view to simulating movement, if necessary.
4. Make an initial choice of materials and methods for joining the different parts of the device so they can then be validated using calculations and simulations.
5. Using standard CAE tools (computer-aided engineering tools), analyse the critical parts of the device and check that the stresses, deformations and temperatures that appear during operation are acceptable. Redesign until satisfactory results are achieved.
6. Make a final list showing all the parts of the medical device, including related materials, with reference to the chosen commercial components.
7. Analyse and list any possible design alternatives, important future improvements and any, as yet, unresolved uncertainties. As an additional activity, any suggested improvements can be implemented to achieve an optimised design.

Some of the products given to students for their application task (with an adequate conceptual description in the patents) during the 2010–2011 course include the following: gastric rings, rings for mitral insufficiency, pumps for drug delivery, surgical collars, tracheotomy devices, arterial blood filters, self-disposable syringes, extracorporeal pumps, elbow orthoses, shoulder orthoses, knee prostheses and mitral valve prostheses. In certain special cases when the student is beginning to think about their doctoral thesis and wants to focus it on a specific topic, there is no problem in assigning a device as an application task that is more closely linked to the student's interests, as this may also serve them as a final project on the master's and prepare them for their doctoral thesis. Some conceptual designs for these devices, taken from the patents given to students as an aid to the questions, are included in Fig. 18.3.

The purpose of the initial part of the task is for the student to reach an understanding of how the device works and to be able to compare the problem-solving principles with the alternative solutions detailed in other patents (or scientific papers), as this strengthens their ability to access databases and understand how important they are for introducing innovations in any field. It also helps students to become accustomed to a multilingual working environment as they will need to consult various technical documents, which are usually in English, German or French. We believe this is a positive step for their future career in industry, very probably in multinationals where the mastery of several languages is highly valued. Among the patent databases usually used by students in their subject, the following are to be particularly recommended:

– www.espacenet.com (open access platform for patent documents)
– www.freepatentsonline.com (open access platform for patent documents)
– www.wipo.int (for international patents)
– www.oepm.es (for Spanish patents and trademarks)
– www.google.com/patents (with access to over seven million documents)

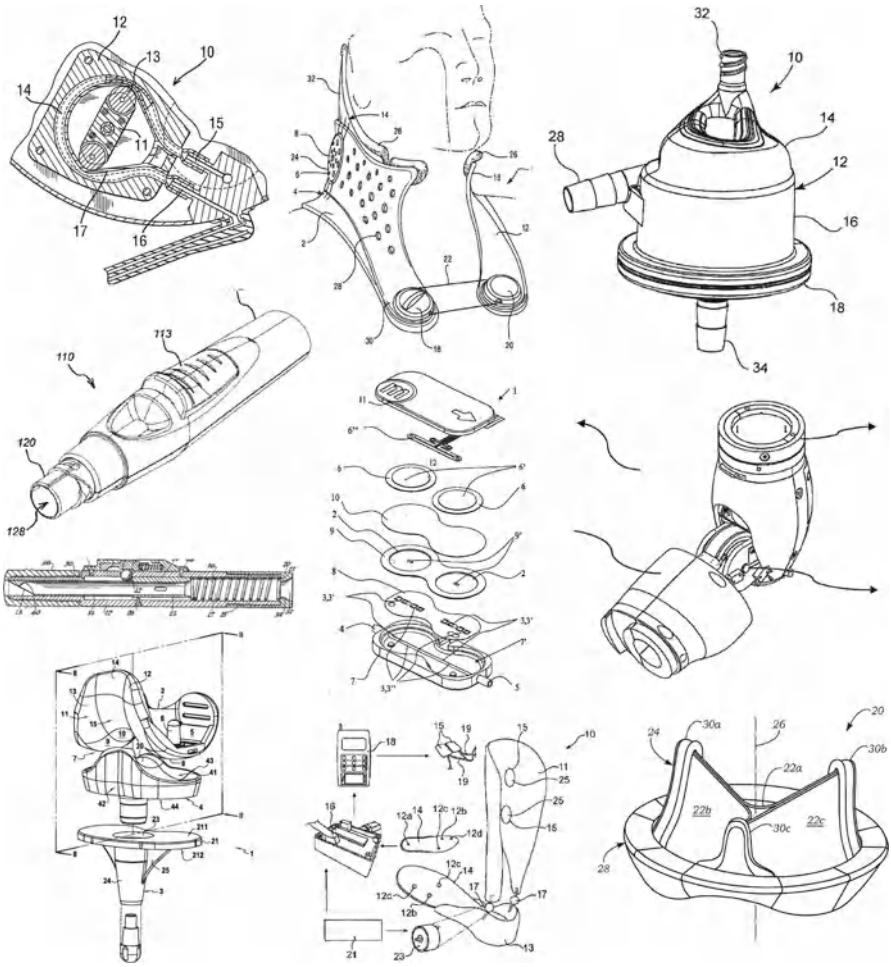

Fig. 18.3 Examples of conceptual designs as taken from patent documents of different medical devices. Students receive them as starting point for their application projects linked to our subject on "Bioengineering"

Also, in the "Thomson Reuters^{SM} (ISI) Web of Knowledge", students have an institutional access from the computers of Madrid Technical University to the "Derwent Innovation Index" database, which has been collecting information on patents since 1980. It also enables information searches to be conducted by topic as well as a subsequent analysis so that studies can be carried out according to certain criteria, such as the following: how patents concerning a topic have evolved over time, the main countries that issue patents for a specific technology or product, the number of mentions of a patent or family of patents, the languages generally used in the patent documents and other relevant data. This database includes information on

over 14 million patents and has links to over 40 national institutions for the protection of intellectual property.

Encouraging students to use the different databases and do patent document searches for devices similar to those given as the application task is aimed at fostering their creativity through a methodical study of design alternatives. This is precisely what Leonardo da Vinci did when laying the foundations for systematic product design. It is also sought to help students understand the different ways that can be used to interact with the human body to solve the same problem. It is also hoped that after completing the detailed design stage, students will be able to follow the problem-solving principles described in the different patents they are given as questions and also be able to propose possible design improvements and even implement them. On the other hand, as has been the case for the previously described PBL experiences of our group (Díaz Lantada et al. 2007a, b; Díaz Lantada et al. 2010), for the most successful developments and the students showing the most interest in continuing their research so as to be able to go on to a final project or doctoral thesis, rapid manufacturing technologies are available in our Product Development Laboratory at the university, particularly "laser stereolithography" and "vacuum casting in silicone moulds".

The purpose of rapid prototyping or rapid manufacturing technologies is to obtain a rapid and accurate three-dimensional replica of the designs that have been generated by "CAD" or computer-aided design applications. These physical models may be merely aesthetic and only useful to study shapes as a way to assess their potential acceptance by the market for which they are intended (in the industrial context these are known as level "A" prototypes or "A-samples").

They may also meet some or most of the mechanical requirements that the final part would have and provide the chance to perform working trials and know if they would receive official approval before making the preliminary moulds (in the industrial context these are known as level "B" prototypes or "B-samples"). The benefits of systematically using these technologies as part of a new product's global launch process affect every department that is directly or indirectly involved in the product.

As previously mentioned in this handbook, some of the marked benefits are the improvement in customer/supplier communications (by reducing the number of misunderstandings) and the ability to perform working trials, assembly tests and check interferences. As an aid to application tasks in teaching, a combination of first stage (directly obtaining the part) and second stage (obtaining the prototype through various interim stages) rapid manufacturing technologies is made available to students.

However, sometimes a development task may show some marked improvements on the initial patent. If this is so and there is a commitment on the part of the student or department to continue working on these improvements, our university's Research Results Transfer Office will take the necessary steps to help teachers, researchers and students, generally students working on a master's or doctorate, to patent these improvements, or at least register them as an industrial design. This is explained in the brief seminar on intellectual property that is also part of the subject.

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During the last 10 years our university has also clearly been in favour of teachers, researchers and students becoming involved in setting up companies based on technological developments or spin-offs from the results produced in the framework of the university. To this end, the university has implemented its Company Creation "Actúa-UPM" flagship programme (actuaupm.blogspot.com).

This holds an annual competition with over 30,000 euros in prize money, where some 250 business ideas are presented, that usually ends up with 10–15 technology-based companies being set up. Students with outstanding achievements taking our subject are encouraged to take part in these initiatives, possibly in parallel with their final master's project or at the start of their doctoral thesis. In this way, students also learn to make a more direct link between the concepts of "knowledge generation"–"intellectual property"–"competitive edge", which they will then always be able to apply in their industrial practice.

18.4 Results From Our Experience

During the 2010–2011 course, 12 students from different degrees and with a varied range of professional experience took part in the subject. There were students from various engineering degrees and students from further degrees and several years' experience. Because of the need to adapt to the level of the students and prepare additional exercises, teachers might see a multidisciplinary background as a problem. However, we are not of that opinion. Instead it should be seen as an opportunity to enrich the course with a larger number of opinions as a way of contributing to the continuous improvement of teaching quality and as a stimulus to update and optimise course content.

A major benefit that helps minimise the impact of the different student backgrounds is the situation of the subject in the second 4-month period and the fact that in the first 4-month period students take "Computer-Aided Mechanical Engineering". In this subject all the students have learned the basics about different design modules, simulation and computer-aided manufacturing (CAD–CAE–CAM technologies), using the NX-7.5 package (Siemens PLM Solutions), although there are other very similar packages. So when students begin "Bioengineering", they have the necessary skills (they are at least able to use the software) to confront the set application task.

In addition, the fact that they are using the tools learned in the previous subject of "Computer-Aided Mechanical Engineering" for the "Bioengineering" development task also reminds them of the previously learned concepts and helps consolidate them. It is worth pointing out that 5 students of a total of 12 said they wanted to continue by doing the final project of their master's course on product or biodevice development so they could combine what was learned in both subjects.

Illustrated below, in Fig. 18.4, are some examples of the application tasks set in the first teaching experience in the subject, which help students to understand the benefits of starting off from the conceptual designs described in the different patents.

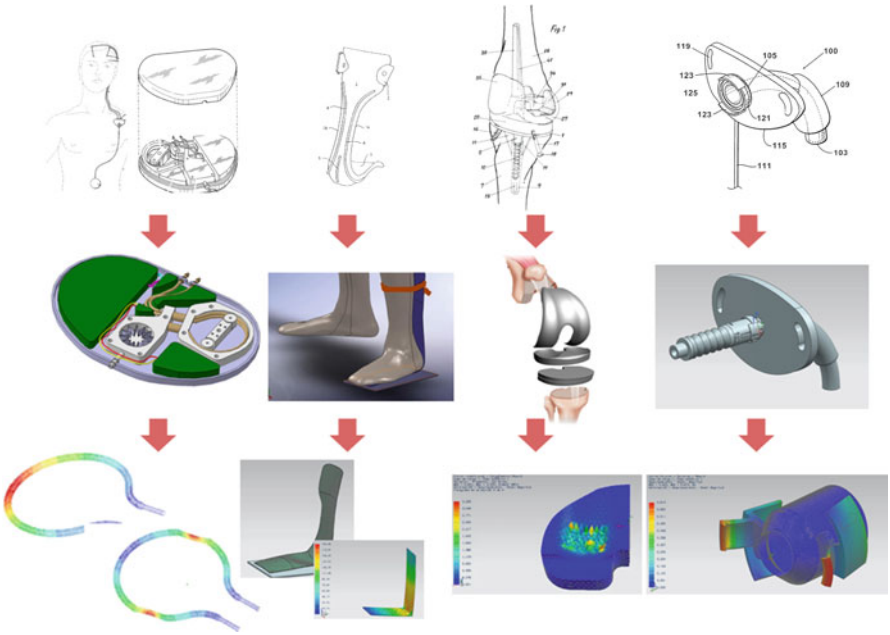

Fig. 18.4 Some examples from students' development tasks: conceptual design (as included in the patent documents), basic CAD design and results from CAE FEM simulations for design validation of different medical devices. Implantable pump, ankle protector, knee prosthesis, device for aided tracheotomy

With the aid of these designs, students can reach the detailed design stage faster, where they can then apply the more specific concepts of the subject and check the devices function properly by making more exact calculations or even conduct studies on prototypes.

Using patents and then handling CAD–CAE tools help students get to know the device under study in detail. They also perform a very thorough analysis, which boosts their creativity and their proposals for innovative improvements when they have to incorporate innovations into synthesis problems.

Regarding other subjects on the same master's degree, the dropout rate was reaching almost 30 % in some cases during the final years, and student motivation, particularly in lectures, was quite low. This new subject focused toward "patent-based PBL" has motivated students and encouraged them to become involved, the result being a success rate of up to 100 %.

Other subjects in our group that also applied the previously described PBL experiences (Díaz Lantada et al. 2007a, b, 2010, 2011; Lorenzo Yustos et al. 2009) used an approach where the students themselves chose their application task in line with their interests and with a view to developing their future doctoral thesis. However, in these cases, the disparity in the results of the different tasks, the different levels of difficulty of the problems set and the applications

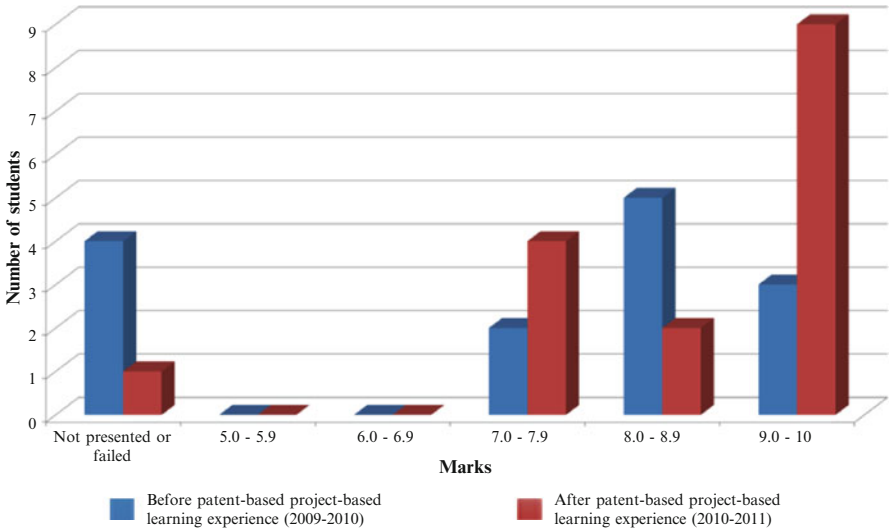

Fig. 18.5 Students' marks evolution

based on "non-closed" questions made assessment difficult and had very different implications for the students.

We believe that the patent-based project-based approach helps to tackle the developments in a carefully guided "step-by-step" manner and students are encouraged to become involved in their own learning process, because they could see the problems were feasible, and this has helped to balance the quality of the results. In fact the students' marks evolution is also noteworthy, as can be appreciated in Fig. 18.5, included below. On the other hand, taking patent documents as a starting point is an endless source of new exercises. The focus can be completely changed for each course with a monographic study being included, if so wished, on the different patents connected with the same problem (hip prostheses, valve prostheses, cell growth devices, etc.), and moreover, it is an excellent way of preventing students from taking ideas or copying work from other years, all of which motivates them to become personally involved in the subject.

Regarding the workload for teaching staff, this is similar to the workload for the PBL experiences devoted to the design of the products already analysed. However, if a standard difficulty is to be achieved for the application tasks, the patents to be initially used must be chosen with great care. It can take about 15 h to select 20 possible patents. Project monitoring also requires commitment on the part of the teacher, but it is also rewarding, particularly if it encourages students to further pursuing final degree project and, subsequently, a doctoral thesis.

18.5 Main Conclusions and Future Research

The summary of the learning–teaching experience presented describes the first active teaching experience in the subject of "Bioengineering" on the Master's Degree in Engineering at Universidad Politécnica de Madrid. It has been designed following the guidelines of the European Higher Education Area in an attempt to encourage students to work individually while seeking a balance between the time devoted to face-to-face classes and the time for individual work. The experience is marked by its use of examples of medical devices taken from patents as questions for application tasks, which students develop in parallel to the subject and for which they are awarded marks.

The proposal is especially suited to master's degree subjects where there are students from very different backgrounds, since the application examples explained and set in the face-to-face sessions gradually prepare students to tackle the final application task that is linked to a complete study of a biodevice, biomechanism or specific medical device. Collaborative approaches for designing more complex products are also worth of future research.

We believe that similar experiences can be valid for any type of subject where it is wished to implement project-based teaching experiences, particularly on master's programmes. They can also promote joint collaboration between different subjects where students can gradually gain a deeper understanding of the same device, starting with the basic problems and then going on to the more complex problems of synthesis. Several concepts and technologies explained in this handbook can be also applied by students in such patent-based problem/project-based learning experiences.

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Annexes of the Handbook

Andrés Díaz Lantada

A.I Summary of Especially Relevant References Linked to the Contents Covered in the Present Handbook

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A.II Summary of Especially Relevant Websites

On Computer-Aided Design and Engineering Resources

More linked to design tasks:
- http://usa.autodesk.com
- http://usa.autodesk.com/3ds-max
- http://usa.autodesk.com/autodesk-inventor
- http://usa.autodesk.com/product-design-suite
- http://www.3ds.com/es/products/catia
- http://www.plm.automation.siemens.com/en_us/products/nx/nx8
- http://www.plm.automation.siemens.com/en_us/products/velocity/solidedge
- http://www.rhino3d.com
- http://www.solidworks.com

More linked to calculation tasks:
- http://www.3ds.com/products/simulia/portfolio/abaqus/overview
- http://www.ansys.com
- http://www.comsol.com
- http://www.mscsoftware.com/products/cae-tools/msc-nastran.aspx
- http://www.mscsoftware.com/products/cae-tools/patran.aspx
- http://www.mathworks.com

On Medical Imaging and Design Based on Medical Images
- http://biomedical.materialise.com/mimics
- http://biomedical.materialise.com/mis
- http://www.amira.com
- http://www.mathworks.com (Users community for open access software)
- http://www.skyscan.be

On Additive Manufacturing (Rapid Prototyping) Resources
- http://reprap.org/wiki/RepRap
- http://www.3dsystems.com
- http://www.additive3d.com
- http://www.bitsfrombytes.com
- http://www.digilabglobal.com
- http://www.digilabglobal.com/celljet
- http://www.dimensionprinting.com
- http://www.envisiontec.de
- http://www.fabathome.org
- http://www.makerbot.com
- http://www.nanoscribe.de
- http://www.stratasys.com
- http://www.zcorp.com/en/home.aspx

On Micro- and Nano-manufacturing

- http://e.drexler.com
- http://www.ceramed.pt
- http://www.efds.org
- http://www.intelligentmp.com
- http://www.nanoscribe.de
- http://www.oxfordlasers.com
- http://www.svc.org

On Systems for Characterization Trials and Biological Models

- http://biomedical.materialise.com/anatomical-models
- http://biomedical.materialise.com/heartprint
- http://biomedical.materialise.com/other-anatomical-models
- http://simbionix.com
- http://worldwide.bose.com
- http://worldwide.bose.com/electroforce/en/web/home/page.html
- http://www.3bscientific.es
- http://www.cae.com/en/healthcare/home.asp
- http://www.simulab.com

A.III Summary of Main Standards and Associations

Main Organizations
- International Organization for Standarization "ISO" (www.iso.org)
- The World Medical Association (www.wma.net)

"New Approach" Directives Related to the Medical Industry
- Directive 93/42/EEC related to "Medical devices"
- Directive 90/385/EEC related to "Active implantable medical devices"
- Directive 98/79/EC related to "Medical devices for "in vitro" diagnosis"

Standards Related to the Development of Medical Devices
- ISO 10993 standard on "Biological evaluation of medical devices"
- ISO 13485 standard on "Sanitary products. Quality management and regulatory affairs"
- ISO 13488 standard on "Quality systems. Medical devices, sanitary products and especial requirements for applying ISO 9002 standard"
- ISO 14971 standard on "Application of risk management to medical devices and sanitary products"
- ISO 15223 standard on "Symbols used for labelling and information provided together with medical devices"

Standards and Associations Related to Medical Imaging
- DICOM standard – Digital Imaging and Communications in Medicine: Strategic Document (http://medical.nema.org)
- Medical Imaging and Technology Alliance (www.medicalimaging.org)
- NEMA – The Association of Electrical and Medical Imaging Equipment Manufacturers (www.nema.org)

Additional Documents of Interest
- Council of Europe "Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine" (1994)
- UNESCO "Universal Declaration on the Human Genome and Human Rights" (1997) and "Guidelines for Implementation" (1999)
- World Medical Association "Declaration of Helsinki. Ethical principles for medical research involving human subjects" (current revised edition 2008)

A.IV Relevant Scientific Journals Linked to Medical Devices and Related Topics of Interest

Listed below there are several high-quality scientific journals, linked to the different topics covered within the handbook, where researchers can find additional information on biodevices and medical devices, as well as on recent advances on Materials Science and Technology for further promoting such advances:

- "Acta Biomaterialia", Elsevier
- "Annals of Biomedical Engineering", Springer
- "Annual Review of Biomedical Engineering", Annual Reviews
- "Annual Review of Materials Research", Annual Reviews
- "Biochip Journal", Springer
- "Biofabrication", IOP Publishing
- "Bioinspiration & Biomimetics", IOP Publishing
- "Biomaterials", Elsevier.
- "Biomechanics and Modeling in Mechanobiology", Springer
- "Biomedical Engineering", Springer
- "Biomedical Engineering Letters", Springer
- "Biomedical Engineering Systems and Technologies", Springer
- "Biomedical Microdevices", Springer
- "Cardiovascular Engineering and Technology", Springer
- "Cellular and Molecular Bioengineering", Springer
- "Computer Methods in Biomechanics and Biomedical Engineering", Taylor & Francis
- "IEEE Transactions on Biomedical Engineering", IEEE
- "International Journal of Biomedical Engineering and Technology", Inderscience
- "International Journal of Mechanics and Materials in Design", Springer
- "Journal of Applied Physics", American Institute of Physics
- "Journal of Biomedical Engineering", Elsevier
- "Journal of Biomimetics, Biomaterials and Tissue Engineering", Scientific.net
- "Journal of Materials Science: Materials in Medicine", Springer
- "Journal of Microelectromechanical Systems", IEEE ASME
- "Journal of Nano Research", Scientific.net
- "Journal of Physics D: Applied Physics", IOP Science
- "Journal of Tissue Engineering and Regenerative Medicine", Wiley & Sons
- "Materials & Design", Elsevier
- "Nature Materials", Nature Publishing Group
- "Nature Nanotechnology", Nature Publishing Group
- "Plasma Processes and Polymers", Wiley & Sons
- "Rapid Prototyping Journal", Emerald
- "Science Translational Medicine", Science AAAS

- “Science Signalling”, Science AAAS
- “Sensors”, MDPI Publishing
- “Sensors and Actuators A: Physical”, Elsevier
- “Sensors and Actuators B: Chemical”, Elsevier
- “Smart Materials and Structures”, IOP Publishing
- “The Open Biomedical Engineering Journal”, Bentham Open
- “Tissue Engineering: Parts A, B & C”, Mary Ann Liebert Inc.

A.V Relevant Enterprises Linked to Medical Devices

Listed below there are several websites of multinationals and highly relevant companies linked to the development of medical devices, as a help for researchers needing information on conventional commercially available biodevices for their own development projects:

- http://biomet3i.es
- http://global.smith-nephew.com/master/6600.htm
- http://integralife.com
- http://www.3dbiotek.com/web
- http://www.admedes.com
- http://www.bbraun.de
- http://www.biotronik.de
- http://www.bostonscientific.com/home.bsci
- http://www.clevemed.com
- http://www.edwards.com
- http://www.gehealthcare.com
- http://www.gpc-medical.com
- http://www.healthcare.philips.com
- http://www.hitec-implants.com
- http://www.insphero.com
- http://www.jnj.com/connect
- http://www.medical.siemens.com
- http://www.medtronic.com
- http://www.sfm.de
- http://www.sjm.com
- http://www.smiths-medical.com
- http://www.sorin.com
- http://www.spacelabshealthcare.com
- http://www.stryker.com
- http://www.valtronic.ch
- http://www.zimmer.com
- http://www.zyvex.com

A.VI Some Matlab Programs for Helping Designers

Program for Designing Fractional Brownian Fractal Surfaces

```
%Fractal surface (based on fractional Brownian fractal
model)
  clear all
  close all
  for ibis = 1:0.1:31
  for jbis = 1:0.1:31
  i=ibis*10;
  j=jbis*10;
  X(i)=ibis;
  Y(j)=jbis;
  sum = 0;
  lambda = 1.5;
  alfa = 0.8;
  % Fractal dimension is given by 3-alfa
  for n = 1:1:100
  sum = sum + (random('norm',0,1))*(lambda^(-
  alfa*n))*sin((lambda^n)*(i*cos(2*pi*rand(1))+
  + j*sin(2*pi*rand(1))+2*pi*rand(1)))/100;
  end
  Z(i,j)=sum;
  end
  end
  surface = surf(X,Y,Z)
```

Program for Fractal Surfaces Based on the Mandelbrot-Weierstrass Model

```
% Mandelbrot-Weierstrass fractal surface
  clear all,
  close all,
  clc;
  x=[0:0.1:10];
  y=[0:0.1:10];
  A=5;
  B=5;
  D=[0:0.5:2];
  gamma=[1:1:4];
```

```
  z=zeros(length(x),length(y),length(gamma),length(D));
  for jj=1:length(D)
        for ii=1:length(gamma)
              for i=1:length(x)
                      for j=1:length(y)
                              for n=1:50
  z(i,j,ii,jj)=z(i,j,ii,jj)+A^(D(jj)-
1)*cos(2*pi*gamma(ii)^n*x(i))/(gamma(ii)^((2-
  D(jj))*n))+B^(D(jj)-
  1)*sin(2*pi*gamma(ii)^n*y(j))/(gamma(ii)^((2-
  D(jj))*n));
                                  end
                      end
              end
        end
  end
  figure;
  a=1;
  for i=1:length(D)
       for j=1:length(gamma)
  subplot(length(D),length(gamma),a)
  mesh(x,y,z(:,:,j,i));title(['D =',
  num2str(D(i),'%10.1f'),' Gamma =',
  num2str(gamma(j),'%10.1f')]);            xlabel('x');
ylabel('y'); zlabel('surface');
            a=a+1;
       end
  end
```

Program for Designing Fractal Spheres

```
%Fractal spheres
  clear all
  close all
  i = 0;
  j = 0;
  [X,Y,Z]=sphere(50);
  Xbis = X;
  Ybis = Y;
  Zbis = Z;
  l1=0;
  l2=0;
  for numespx=0:1:2
  for numespy=0:1:2
  for i = 1:1:51
  for j=1:1:51
```

```
  radius = 1;
  lambda = 1.5;
  alfa = 0.1;
  sum = 0;
  for n = 1:1:5
  sum = sum + (random('norm',0,1))*(lambda^(-
  alfa*n))*sin((lambda^n)+2*pi*rand(1))/5;
  end
  r=radius+sum;
  Xbis(i,j) = Xbis(i,j)*sqrt((r^2)/(Xbis(i,j)^2+
  Ybis(i,j)^2+ Zbis(i,j)^2));
  Ybis(i,j) = Ybis(i,j)*sqrt((r^2)/(Xbis(i,j)^2+
  Ybis(i,j)^2+ Zbis(i,j)^2));
  Zbis(i,j) = Zbis(i,j)*sqrt((r^2)/(Xbis(i,j)^2+
  Ybis(i,j)^2+ Zbis(i,j)^2));
  Xbis2(i,j) = Xbis(i,j)*40+l1*110;
  Ybis2(i,j) = Ybis(i,j)*40+l2*110;
  Zbis2(i,j) = Zbis(i,j)*40;
  end
  end
  surf(Xbis2, Ybis2, Zbis2)
  hold on
  l2=l2+1;
  end
  l2=0;
  l1=l1+1;
  end
  % surf(Xbis,Ybis,Zbis)
  surf(Xbis2, Ybis2, Zbis2)
  hold on
```

Program for Designing Fractal Circumferences (and Cylinders and Cones)

```
%Fractal circumference
  clear all
  close all
  i = 0;
  j = 0;
  k = 1;
  FI = 0;
  RO = 10;
  Z = 0;
  k = k+1;
  for fi = 0:3.1415/320:2*3.1415
  j=j+1;
  radius = 10;
```

```
  lambda = 1.5;
  alfa = 0.2;
  sum = 0;
  for n = 1:1:20
  sum = sum + (random('norm',0,1))*(lambda^(-
  alfa*n))*sin((lambda^n)+2*pi*rand(1))/10;
  end
  r = radius + sum;
  FI = [FI; fi];
  RO = [RO;r];
  [Xint,Yint] = pol2cart(FI,RO);
  end
  plot(Xint,Yint)
```

Program for Designing Fractal Biomimetic Surfaces (Lotus Flower)

```
%Fractal biomimetic surface
  clc
  clear all
  close all
  i=0;
  j=0;
  for ibis = 1:0.1:30
  i=i+1;
  j=0;
  for jbis = 1:0.1:30
  j=j+1;
  X(i)=ibis;
  Y(j)=jbis;
  sum = 0;
  lambda = 1.5;
  alfa = 0.4;
  for n = 1:1:4
  sum = sum + (random('norm',0,1))*(lambda^(-
  alfa*n))*sin((lambda^n)*(i*cos(2*pi*rand(1))
  +j*sin(2*pi*rand(1))+2*pi*rand(1)))/10;
  end
  Z(i,j)=sum+10*abs(sin(pi*ibis/10)*sin(pi*jbis/10));
  end
  end
  surface = surf(X,Y,Z)
```

Program for Designing Microsystems with Fractal Channels

```
%Fractal channels
  clc
  clear all
  close all
  %Working in microns
  %Square 1 mm x 1 mm
  i=0;
  j=0;
  for ibis = 1:25:151
  i=i+1;
  j=0;
  for jbis = 1:25:4001;
  j=j+1;
  X(i)=ibis;
  Y(j)=jbis;
  sum = 0;
  lambda = 1.5;
  alfa = 0.9;
  for n = 1:1:3
  sum = sum + (random('norm',0,1))*50*(lambda^(-
  alfa*n))*sin((lambda^n)*(i*cos(2*pi*rand(1)) +
  j*sin(2*pi*rand(1))+2*pi*rand(1)));
  end
  Z(i,j)=sum;
  end
  end
  for ibis = 152:25:302
  i=i+1;
  j=0;
  for jbis = 1:25:4001;
  j=j+1;
  X(i)=ibis;
  Y(j)=jbis;
  Z(i,j)=100;
  end
  end
  for ibis = 303:25:453
  i=i+1;
  j=0;
  for jbis = 1:25:4001;
  j=j+1;
  X(i)=ibis;
  Y(j)=jbis;
  sum = 0;
```

```
lambda = 1.5;
alfa = 0.5;
for n = 1:1:3
sum = sum + (random('norm',0,1))*50*(lambda^(-
alfa*n))*sin((lambda^n)*(i*cos(2*pi*rand(1)) +
j*sin(2*pi*rand(1))+2*pi*rand(1)));
end
Z(i,j)=sum;
end
end
for ibis = 454:25:604
i=i+1;
j=0;
for jbis = 1:25:4001;
j=j+1;
X(i)=ibis;
Y(j)=jbis;
Z(i,j)=100;
end
end
for ibis = 605:25:755
i=i+1;
j=0;
for jbis = 1:25:4001;
j=j+1;
X(i)=ibis;
Y(j)=jbis;
sum = 0;
lambda = 1.5;
alfa = 0.1;
for n = 1:1:3
sum = sum + (random('norm',0,1))*50*(lambda^(-
alfa*n))*sin((lambda^n)*(i*cos(2*pi*rand(1)) +
j*sin(2*pi*rand(1))+2*pi*rand(1)));
end
Z(i,j)=sum;
end
end
for ibis = 756:25:906
i=i+1;
j=0;
for jbis = 1:25:4001;
j=j+1;
X(i)=ibis;
Y(j)=jbis;
```

```
  Z(i,j)=100;
  end
  end
  for ibis = 907:25:1057
  i=i+1;
  j=0;
  for jbis = 1:25:4001;
  j=j+1;
  X(i)=ibis;
  Y(j)=jbis;
  Z(i,j)=0;
  end
  end
surface = surf(Y,X,Z)
```

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2,