Chapter 6
Addressing the Complexity of Biomaterials by Means of Biomimetic Computer Aided Design

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Abstract The degree of optimization achieved by biological materials and their very special properties, their hierarchical designs and their multi-scale structures, continue to be great sources of inspiration for engineers and materials scientists world-wide. Fortunately, the development, in the last decades, of advanced computer-aided design, engineering and manufacturing technologies and the groundbreaking manufacturing paradigm consequence of the advent of additive manufacturing technologies, which enable solid free-form fabrication, have provided extremely relevant resources for the development of new knowledge-based multifunctional materials following biomimetic approaches for enhanced performance. This chapter covers some of the new design and manufacturing strategies that promote biomimicry and their advantages will be also put forward by means of several cases of study included in the following chapters, linked to the complete development process of tissue engineering scaffolds, organs-on-chips and other microfluidic biomedical devices benefiting from bioinspired designs. Section 6.1 introduces the term biomaterial and compares it to the concept of biological material, also detailing main differences between synthetic and biological materials, which constitute challenges as well as sources of inspiration for materials scientists and engineers. Sections 6.2 and 6.3 cover different strategies for obtaining biomimetic designs using the information from imaging techniques as principal input, while Sects. 6.4 and 6.5 detail procedures based on direct modeling by means of advanced computer-aided design, recursive and Boolean operations and models based on precise mathematical descriptions of living organisms, tissues and biological structures.

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6.1 Biomaterials and Conventional Man-made Materials

The term "biomaterial" generally designates materials 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:

- Bioinert materials. Characterized by their low reactivity in the body, which means they can co-exist 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 zirconium oxide.
- 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 metabolized by the body. Some materials of this family are porous hydroxyapatite, the salts of calcium phosphate and some polymers, such as poly-(lactic acid) and poly-(vinyl alcohol).
- 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 tricalcium phosphate.

Some authors identify the term "biomaterial" with that of "biological material", although we will use the aforementioned definition of biomaterial, which is more versatile, as it includes all types of materials used for the successful development of biodevices, including those natural and synthetic, as well as those coming from living organisms (biological materials) and those obtained from inert sources.

In any case, for the progressive improvement of synthetic biomaterials, towards more effective performances in the field of biomedical microdevices, it is very important to take into account the main differences between biological materials and man-made materials.

Biological materials typically include special features, such as: (a) functional gradients of density and mechanical properties consequence of their anisotropic lattice and porous structures; (b) self-healing properties thanks to the presence of cells able to re-configure the extra cellular matrix and tl correct problems related to ageing or damages; (c) optimal performance considering the energy employed to develop the biomaterial, the energy consumed during its life-cycle and the strains and stresses required to adequately interact with the environment.

Many biological materials also incorporate self-sensing abilities and the biological materials and structures can be considered smart systems with sensing and actuating capabilities. Regarding even more specific features and properties of some biological materials, it is interesting to highlight aspects such as the control of contact phenomena achieved by means of incorporating multi-scale geometries and surfaces with micro-/nano-topographies, which has a very relevant impact in the development of advanced functionalities including self-cleaning properties (as happens with the lotus flower leaves to cite just an example), improved self-healing abilities and enhanced endurance to external dangers.

On the other hand, traditional man-made or synthetic materials have normally mainly focused on a progressive improvement of yield stresses, Young's moduli, hardness and toughness, in some cases taking also into account materials density and trying to optimize the mechanical endurance/density ratio. The development of composite materials and foams, the application of thermal processes such as tempering or the application of surface hardening coatings, among other already common materials and industrial processes, has enabled additional degrees of freedom for designers and led to the concept of "knowledge-based materials" and "knowledge-based multifunctional materials".

According to the European Virtual Institute of Knowledge Based Multifunctional Materials, KMM-VIN AISBL, these "knowledge-based (multifunctional) materials" are designed for enhanced performance in very demanding loading and environmental conditions like thermo-mechanical and impact loading, high strain rates and temperature regimes, aggressive chemical environment, and possible combinations thereof. Such regimes are typical of applications in health, aerospace and automotive transport, energy, turbo-machinery industry, tribology, chemical industry, electronic devices and microsensors. These materials (abbreviated as KMM) include inter alia advanced ceramics, metal-ceramic composites, other composites, functionally graded materials, intermetallics, shape memory alloys, coatings, high temperature steels, biomaterials and other types of smart materials, capable of responding in a desired way to external stimuli (http://kmmvin.eu/).

However, the degree of optimization achieved by biological materials and their very special properties, continue to be great sources of inspiration for engineers and materials scientists world-wide. Fortunately, the development, in the last three decades, of advanced computer-aided design, engineering and manufacturing technologies and the new manufacturing paradigm consequence of the advent of additive manufacturing technologies, which enable solid free-form fabrication, have provided extremely relevant resources for the development of new "KMM" materials following biomimetic approaches for enhanced performance.

This chapter covers some of the new design and manufacturing strategies that promote biomimicry and their advantages will be also put forward by means of several cases of study included in the following chapters, linked to the complete development process of tissue engineering scaffolds, organs-on-chips and other microfluidic biomedical devices benefiting from bioinspired designs.

But before entering into details, it is important to consider the main differences between of Euclidean geometry, used by most computer-aided design software for product development, and non-Euclidean geometry, which is better suited for describing natural objects. The fact is that Euclidean geometry is limited for describing and modeling the complexity of our Universe. Some of Euclid's axioms were in fact revised during XIX and XX 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 distorsions (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 1982). 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 1982; Falconer 2003) and the details are out of the scope of present 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 1982; Falconer 2003).

6.2 Medical Images as Source for Inspiration

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 machines as well in the reliability of the diagnoses made based on this information and the therapeutic decisions taken as a result. 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 non-ionizing radiation, while computed tomography or positron emission tomography use 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. PET is typically 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 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 centres and researchers. This is thanks to the "DICOM" (Digital Imaging and Communication in Medicine) standard and its generalised usage as a working format for different three-dimensional image reconstruction software, particularly with the introduction of version DICOM 3.0 in 1993.

Software resources 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 more universal formats usable by "CAD-CAM" design, engineering and manufacturing programs. As already explained, these CAD-CAM programs (Solid Edge, Catia, NX-8.5, 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 personalised prostheses and bimiemetic biomedical devices can be performed in a question of hours while also making easier comparisons between alternative designs (Hieu 2002; Harryson 2007). In addition, 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, that enable schedules and costs to be reduced by manufacturing parts directly from geometric information stored in CAD-CAM program files, are presenting new opportunities for a personalised response to the development of implants, prostheses and biodevices in general, 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 resulting benefitial for the promotion of bioinspired or biomimetic approaches in all kinds of products and industries, and very especially in the biomedical field. The more remarkable software resources, 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 & Surgiguide (Materialise NV), 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, c, d).
- Reverse engineering (Flisch 1999; Vasilash 2009).

- Object reconstruction (Effenberger et al. 2008; Vasilash 2009).
- Prototyping and trials (Flisch 1999; Effenberger et al. 2008).
- Inspection of manufacturing defects (Losano et al. 1999; Effenberger et al. 2008).
- Inspection of crack propagation (Losano et al. 1999; Effenberger et al. 2008).
- Non-destructive 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 non-destructive.

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 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. In addition, the final manufacture towards a final porous structure could lead to enhanced osseointegration, allow the incorporation of antibiotics for improved recovery and lead to mechanical properties mimicking those of bone, hence promoting a biomimetic and biomechanical performance.

Regarding the design and manufacturing strategy, the usual procedure to carry out a customized examination, with a view to using a biomimetic 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 for selecting parts of the patient's bone geometry and storing them 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".

Figure 6.1 provides an example of the damaged geometry of a hip joint, as seen using nuclear magnetic resonance and as three-dimensionally reconstructed by means of CAD resources.

After having selected the relevant part of the biological component, in this case of study the internal cavity of the patient's femur, to which the metal part of a customized prosthesis must be adapted, this 3D 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. Final Boolean operations with previously designed lattice or porous structures lead to a final porous biomimetic and biomechanical implant (Fig. 6.2).

A similar process is used in other cases of study along the Handbook (see Chaps. 16 and 19 for the design of tissue engineering scaffolds for tibial and vertebral repair respectively).

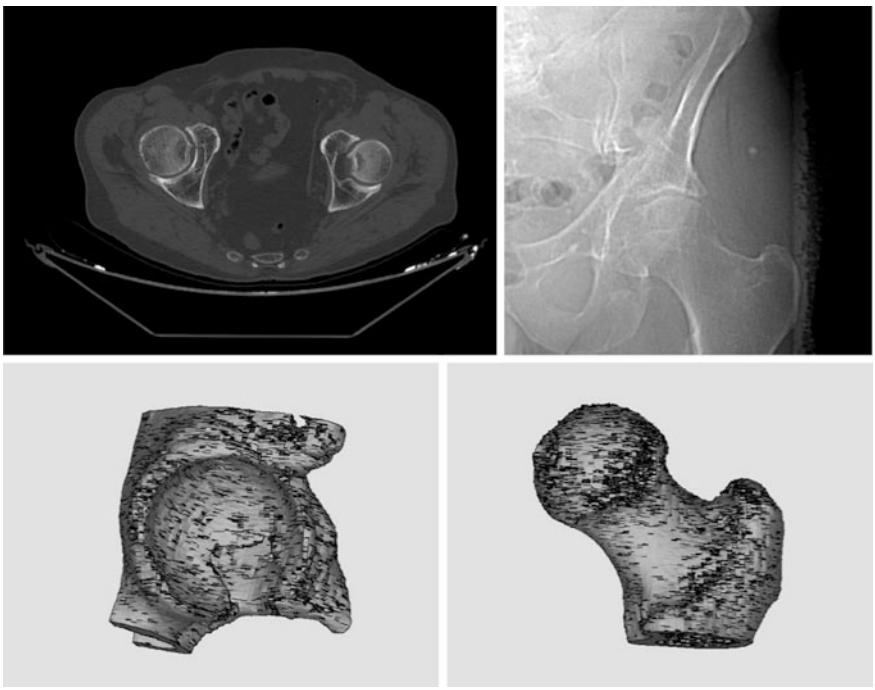

Fig. 6.1 The damaged geometry of a hip joint, as seen using nuclear magnetic resonance and as three-dimensionally reconstructed by means of CAD resources

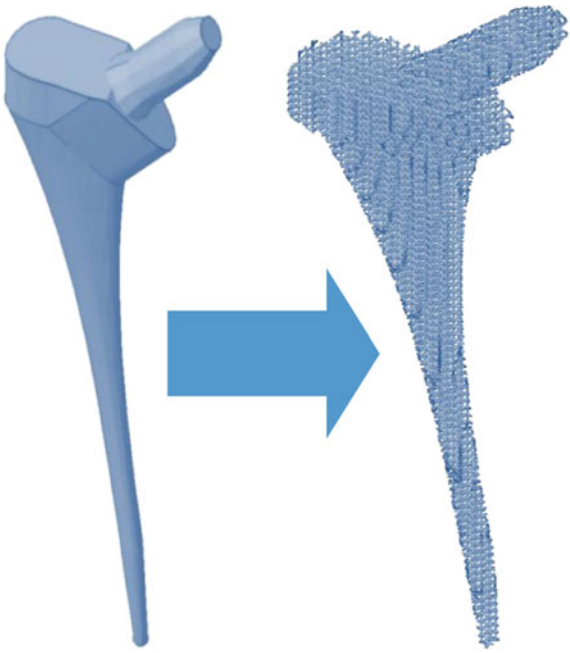

Fig. 6.2 Personalized design of the femoral component of a hip prosthesis and porous prosthesis obtained, by means of Boolean operations, for the promotion of osseo-integration and biomechanical performance, thanks to elasticity matching

6.3 Digitalizing Biological Materials for Design Purposes

Digitalizing biological materials, either resorting to imaging technologies based on optical scanners, laser systems or penetrating radiation, or by developing and employing mathematical models capable of describing the degree of complexity of biostructures and biosurfaces, has relevant implications in the final development of biomimetic biomedical microdevices.

The use of mathematical models to generate biomimetic surfaces (see Sect. 6.5), 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. However, said biological surfaces, generated from mathematical models, present sometimes excessive homogeneity or self-similarity. In consequence, the slight imprecisions of living organisms, which are responsible for certain interesting properties, cannot be adequately represented and their further connection with final applications in the field of biomedical devices is sometimes complex.

Therefore, processes using imaging techniques for the digitalization of biological materials may be preferred in many cases, although some technologies may be extremely expensive for small and medium design enterprises. Depending on the

desired level of precision, low-cost imaging resources (desktop scanners, photo-based reconstructions) may also provide rewarding results.

In this section we provide an example of a fast, low-cost and efficient method to yield biomimetic 3D CAD files of the microtopography of biological materials, files that can subsequently be used as an aid for simulating various interactions (mechanical, thermal, fluid, etc.) between the environment and the biomaterial, as well as for the micromanufacturing of small specimens, whose texture resembles that of the model. The process is applied to reconstructing a small skin patch and a superhydrophobic patch of cloth.

The process relies on a high-resolution photo-camera to obtain images of the area being analyzed and on converting the resulting images into height matrixes, which are then used to construct the CAD files that imitate the tiny details of the original three-dimensional geometries. Using a similar process several microtopographies and micro-textures of living organisms can be mimicked and further used for designing biomedical microdevices with improved features for interacting at a cellular level.

Just as a brief revision, 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 heels. 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, avoigint the incorporation 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 videogame 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. 2010a, b, c, d), 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 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, modeling and simulation and with surgery planning (Sun and Lal 2002). This, in conjunction with new advances in biomanufacturing (see also Chap. 23) and associated biomaterials-based additive manufacturing tools (bioplotters), points to the manufacture of small body structures in the not-to-distant future. In any case, in order to benefit from the advantages of high-precision aided manufacturing systems aimed at producing artificial biostructures, we have to take into account all 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. 2010a, b, c, d, Biocoat), though imitating the desired topography is not always simple (Sect. 6.5).

In this section, as already metioned, we resort to a low-cost process based on high-resolution photography. 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. 8), as well as for analyzing any kind of cutaneous pathology. The area photographed corresponds to a section of the fingerprint of the author. 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 that converts the gray scale to an altitude scale, similar to some open-access programs used for 3D printing of photographs. The program also converts the files into the .stl format for use in computer-aided design.

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-8.5 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 photo. 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. In our case we use a maximum difference of 160 μm for the fingerprints. Values between these maximum and minimum values are linearly interpolated. 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 height 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 non-zero 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. Figure 6.3 shows the high-precision picture of the skin patch and CAD model showing the three-dimensional reconstruction. The model has been obtained by converting the colours of the two-dimensional image, into the values of

Fig. 6.3 High-precision picture of a skin patch and CAD model showing the three-dimensional reconstruction. The model has been obtained by converting the colours of the two-dimensional image, into the values of height over a grid planar

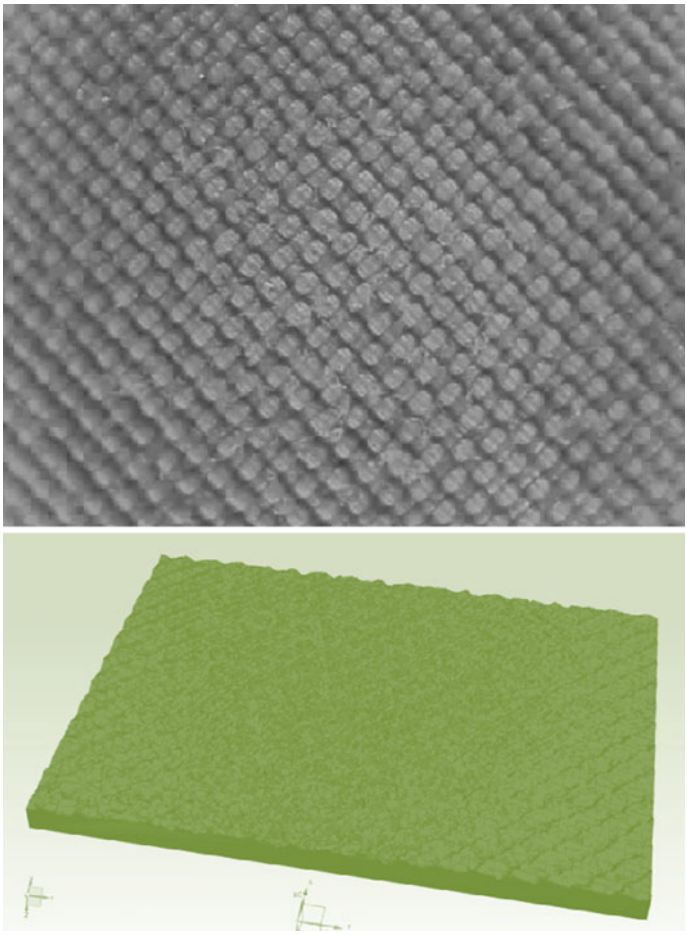

Fig. 6.4 High-precision picture of a super-hydrophobic cloth patch and CAD model showing the three-dimensional reconstruction

height over a grid planar. Figure 6.4 provides and additional example, obtained using a similar procedure, related to the three-dimensional reconstruction of a super-hydrophobic cloth patch.

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 the surfaces of biological and biomimetic object for further bioinspired design tasks. 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 behaviour with the aid of FEM-CFD software, as has already been done with certain biomimetic surfaces. It should prove interesting to employ this type of files 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 manufacture of biological and bioinspired surfaces, the proposed design method, with the help of high-precision additive manufacturing, may well be an important complement to current biofabrication and bioreplication tools, such as biotemplating, sol-gel, atomic layer deposition, physical-/chemical-vapour deposition or imprint lithography and casting, for several industrial applications (Pulsifer et al. 2010; Lakhtakia et al. 2009). For large series of parts and devices soft-lithographic approaches and micro-replication techniques, such as micro hot-embossing and micro injection molding, may also be good choices, as detailed in Chap. 10.

After having detailed in Sects. 6.2 and 6.3 different strategies for obtaining biomimetic designs using the information from imaging techniques as principal input, Sects. 6.4 and 6.5 detail procedures based on direct modeling by means of advanced computer-aided design, recursive and Boolean operations and models based on mathematical descriptions of living organisms and tissues.

6.4 Computer-Aided Design for Controlling the Structure and Density Distribution of Materials

The structure and density distribution of biomedical devices for interacting with human tissues, from prostheses and tissue engineering scaffolds, to micromembranes for microfluidic devices and organs-on-chips, can be in fact easily controlled with the use of common computer-aided desing resources.

The process, for biomimetic lattice structures, normally includes combination of solid operations (cylinders, piles…) for obtaining a unit cell. Subsequently, a pattern operation or a periodic replication of such solids and unit cells leads to a 3D portion of the space being filled with the desired lattice structure. Intersecting the obtained lattice with a solid device leads to the final biodevice with controlled inner structure. In the case of porous structures, the process instead of additive is subtractive. It normally begins with a cube, sphere or cylinder, 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.

Using different sizes of lattices and pores, just by employing 2D patterns in the XY plane, and by changing the dimensions of each 2D pattern along the z axis, leads to functional gradients of density and mechanical properties. With this approach, another typical property of biological materials, which usually include functional gradients of properties, can be obtained. Pore size and lattice thickness

can be also controlled from the inside to the outside, with applications in the development of artificial bone models.

Hierarchical and multi-scale approaches can be also used, working recursively for the development of fractal-like structures, with pores at different scale levels, as also happens in biological materials. Modeling human vasculature, which has a typical hierarchical fractal-like geometry and developing advanced types of tissue engineering scaffolds, in which the generation of vasculature is promoted, are just some examples of potential applications.

Even though all conventional CAD programs already commented (Solid Edge, NX-8.5, Catia v.5, Solid Works, Autodesk-Inventor…) 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 meta-materials to product development.

Among ad hoc CAD software resources 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), "Inspire" (www.solidthinking.com), and "Netfabb" (www.netfabb.com), as the most advance ones, and with direct application in Biomedical Engineering and in the development of biomedical microdevices for interacting at a cellular and even molecular level.

Recent advances in topological optimization, a mathematical approach that optimizes 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).

Several cases of study linked to the use of porous geometries, lattice structures, multi-scale and hierarchical designs for the development of advanced biodevices, including: tissue engineering scaffolds for bone, muscle, cartilage and ligament repair; microfluidic devices with microporous membranes, for static and dynamic cell culture procedures; and organs-on-chips, for modeling relevant physiological interactions benefiting from the use of hierarchical and multi-scale microtextures, micromembranes and micropillars, are included in Chaps. 15–23.

Figure 6.5 introduces some three-dimensional CAD structures, with controlled distributions of density and mechanical properties, which can be physically obtained by means of additive manufacturing technologies in a wide set of materials, from (bio)polymers and (bio)ceramics, to metals, alloys and composites. Some of them will be further employed and detailed as complete development cases of study in the aforementioned chapters. In many cases these geometries are also referred to as cellular structures.

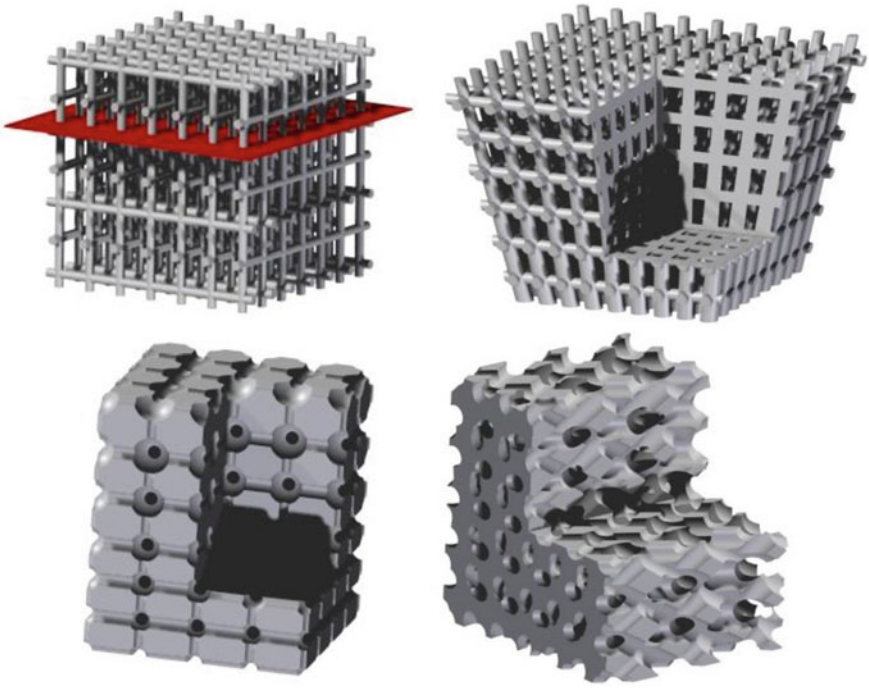

Fig. 6.5 Examples of three-dimensional structures, with controlled distributions of density and mechanical properties and with direct applications in the field of biomecial microdevices for interacting at a cellular level (Téllez, M., Díaz Lantada (advisor), 2015, see Chap. 15 for additional details)

6.5 Computer-Aided Design for Controlling the Textures and Topographies of Materials

Several studies have focused on the importance of surface topography and microtexture for promoting positive effects in all kinds of biomedical devices, from implantable prosthesis to extra cellular 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 modeling, design and simulation tasks in several areas of Biomedical Engineering, some of them also linked to the development of novel biomedical microdevices for interacting at a cellular and even molecular level. The most remarkable ones include:

- Modeling 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).
- Modeling complex organisms and their systems. Regarding complex organisms (including human anatomy) fractals have been applied to modeling systems of pulmonary and blood vessels and vascular networks, as well as for carrying out subsequent fluid mechanics simulations (Lin et al. 2004).
- Modeling 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 et al. 2010a, b, c, d, 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 (Díaz Lantada et al. 2013).

We explain in this section the use of mathematical fractal models for designing the complex and highly irregular surfaces of biomimetic objects. In this way, some parameters including roughness, waviness, skewness… can be controlled from the design stage and adapted in a more efficient way to the requirements of the final applications. The final bioinspired or biomimetic multi-scale surfaces z(x,y) can be considered as the sum of two different types of surfaces (z_m (x,y) for the micro-textures and z_n (x,y) for the nanotextures), each providing a relevant components at a different scale level. Fractal models can be applied to controlling both micro- and nano-textures or just for providing a micro or nano-texture upon already available geometries. Therefore the process offers the possibility of tailoring the surfaces micro-/nano-textures (in combination with high-precision manufacturing technologies) for inducing contact phenomena determinant for the success of biomedical microdevices, including superhydrophobicity, superhydrophilicity, self-cleaning properties, enhanced osseointegration, improved lubrication, among other features.

The surfaces and substrates, as a basis for the deisgn of prostheses, implants, tissue engineering scaffolds, cell culture platforms and biomedical microdevices can be based either on static or on dynamic fractal models. Among static models, it is

important to note the use of fractional Brownian fractal surface models and of 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 can be found in the relevant references of the field of fractal geometry (Weierstrass 1886; Mandelbrot and Ness 1968; Mandelbrot 1982; Berry and Lewis 1980; Kardar et al. 1986; Falconer 2003; Coffey et al. 2004). The use of fractional Browninan fractal surfaces is also additionally detailed in Chaps. 8, 10, 12 and 13, when describing the complete development process of micro-textured microdevices for the assessment of cell adhesion, motility and overall behavior.

In short, a fractal model is evaluated above a grid according to the degree of precision of the final manufacturing process. The multi-scale surface is obtained as sum of the micro- and nano-textures defined accordingly and, in our case, stored in form of Matlab surface or surfaces. Once the Matlab surfaces have been obtained, using some of the fractal 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 recognized and imported with a CAD program, for additional design operations (i.e. providing the surface with a thickness different to zero, copying the surface atop a previously designed geometry…).

Figure 6.6 shows the multi-scale design of a surface mimicking the micro- and nano-topography of self-cleaning biological surfaces similar to those of the lotus leaves. The Matlab code used can be found in the Annexes of the Handbook and is based on the incorporation of a fractal "noise" on top of trigonometric functions in the form:

$$Z(x, y) = A \cdot \sin(x) \cdot \sin(y) + B \cdot \sin(x/10) \cdot \sin(y/10) + \text{Brownian motion}.$$

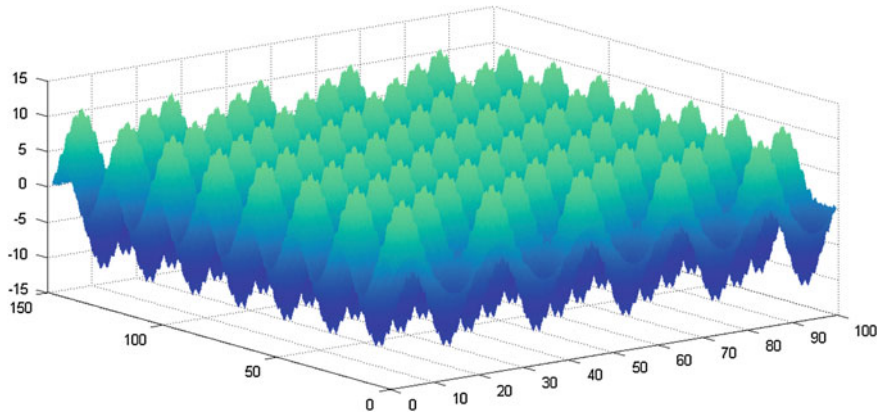

Fig. 6.6 Multi-scale design of a surface mimicking the micro- and nano-topography of self-cleaning biological surfaces similar to those of the lotus leaves

The three terms allow for the surface control at different scale levels, with a couple of "wavy" terms of different frequency and a final more random noise for the incorporation of irregularities typical from biological materials.

Figure 6.7 shows the scheme for the fractal-based computer-aided design of surfaces for biofabrication and biomimetic purposes, according to a patented process by our team (Spanish Patent and Trademark Office P201030956).

Some additional biodevices based on this process for fractal-based biomimetic design, including scaffolds for cell growth and Tissue Engineering related procedures, as well as microsystems for studying cell motility, can be found in Chaps. 10–13, when focusing on the manufacture of biodevices with micro and even nano features.

Previous paragraphs have 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 introduce here the use of "fractal spheres" or "fractal seeds", whose spatial distribution for filling the 3D space and subsequent Boolean combination with the solid objects of prostheses, organs or biostructures, 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. 6.8 and is based on combining "fractal spheres", which can be defined by the equations detailed below. A fractal sphere, by adapting the definition

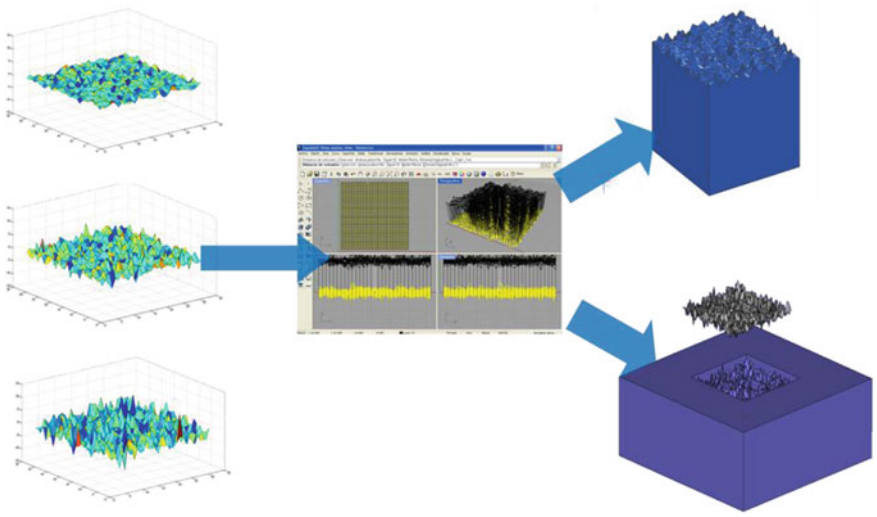

Fig. 6.7 Scheme for fractal-based design of surfaces for biofabrication. Patented process: Spanish Patent and Trademark Office P201030956

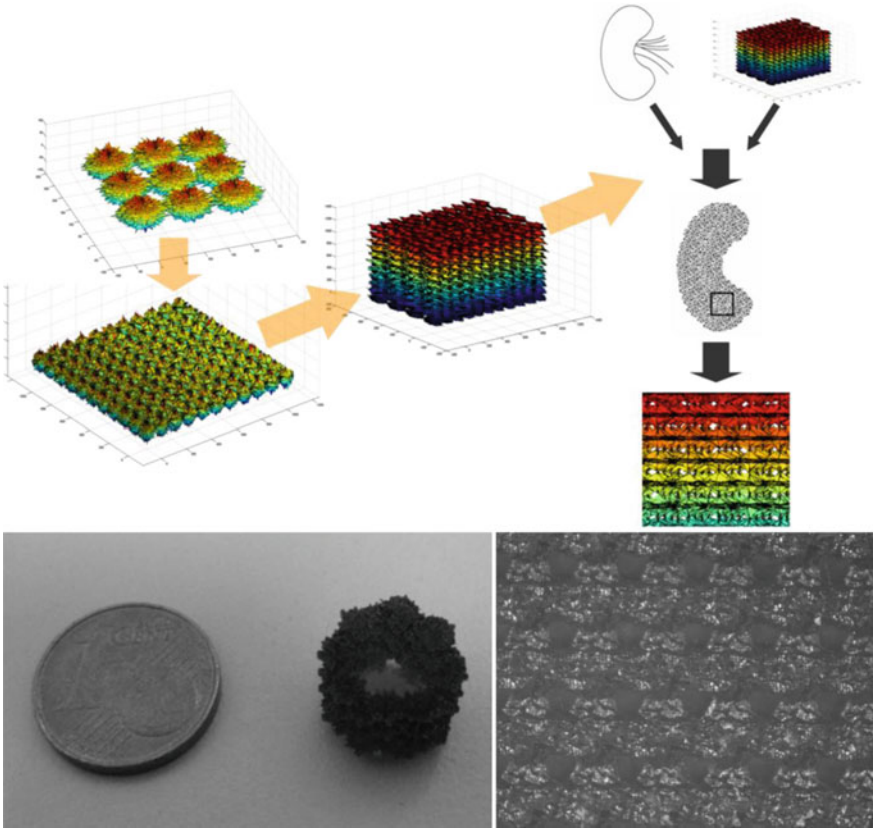

Fig. 6.8 Scheme for fractal-based design of structures for biofabrication. Patented process: Spanish Patent and Trademark Office P201030957. Rapid prototypes of three-dimenstional structures of microtextured scaffolds for tissue engineering and cell culture platforms based on fractal seeds

of fractional Brownian fractal surface, can be defined by an almost-randomly changing radius in the form:

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

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 programs included in the Annexes of the Handbook.

Similar and novel ways of extending the texturization process, based on fractal biomimetic models, to the external features of several prostheses and to the features of tissue engineering scaffolds, may promote very interesting biological and contact phenomena. The progressive incorporation as an additional command (i.e. "apply roughness" or "apply fractality") to conventional CAD programs is also matter of research and can be already achieved in modeling programs present in the cinematographic industry.

Of course these complex geometries can be even impossible to manufacture with conventional subtractive procedures, due to their inner porosity, irregular features and fractality. However, the use of additive manufacturing technologies, as thoroughly done along the Handbook, constitutes a right approach.

Similar procedures are applied along the Handbook for the design of several cases of study linked to biodevices aimed at interacting at a cellular level and at the assessment of the impacts of surface topographies on cell behavior and fate (see Chaps. 8, 10, 12 and 13).

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, for the promotion of primary stability and subsequent osseointegration, also promoted by textures and edges to which osteoblasts typically attach properly.

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 (prototypes for electrophoresis, prototypes with controllable capillarity, among others). They are also commonly applied to modeling cell motility and their usual random walks on top of planar surfaces. as further discussed in Chap. 12, when focusing on micro-manufacturing technologies and related photo-lithographic approaches.

In the near future biofabrication 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. Certainly biomimetic approaches will further benefit from the input of several disciplines, as mathematical modeling, computer-aided design process and reverse engineering technologies (including the combined utilization of medical imaging and CAD), for providing more versatile solutions.

6.6 Main Conclusions and Future Research

The degree of optimization achieved by biological materials and their very special properties, their hierarchical designs and their multi-scale structures, continue to be great sources of inspiration for engineers and materials scientists world-wide. Fortunately, the development, in the last decades, of advanced computer-aided design, engineering and manufacturing technologies and the groundbreaking manufacturing paradigm consequence of the advent of additive manufacturing technologies, which enable solid free-form fabrication, have provided extremely relevant resources for the development of new knowledge-based multifunctional materials following biomimetic approaches for enhanced performance.

This chapter has covered some of the new design and manufacturing strategies that promote biomimicry and their advantages will be also put forward by means of several cases of study included in the following chapters, linked to the complete development process of tissue engineering scaffolds, organs-on-chips and other microfluidic biomedical devices benefiting from bioinspired designs.

Main detailed strategies for the promotion of biomimicry and of biomimetic designs can be grouped in two main categories: those based on the use of imaging resources for the digitalization of biological structures and those based on the use of mathematical and software resources for the construction of geometries with properties similar to those found in biological materials. Both categories have been covered and different cases of study have been introduced and will be additionally detailed in following chapters of the Handbook.

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Some Interesting Related Websites

On fractals with demonstrations:

http://mathworld.wolfram.com/Fractal.html
http://mathworld.wolfram.com/FractalDimension.html
http://mathworld.wolfram.com/HausdorffDimension.html
http://demonstrations.wolfram.com/fractals

On Euclidean and non-Euclidean geometries:

http://mathworld.wolfram.com/EuclideanGeometry.html
http://mathworld.wolfram.com/Non-EuclideanGeometry.html

Note: For using some Matlab (The Mathworks Inc.) programs for constructing fractal surfaces and fractal spheres, please have a look at the Annexes of the Handbook.