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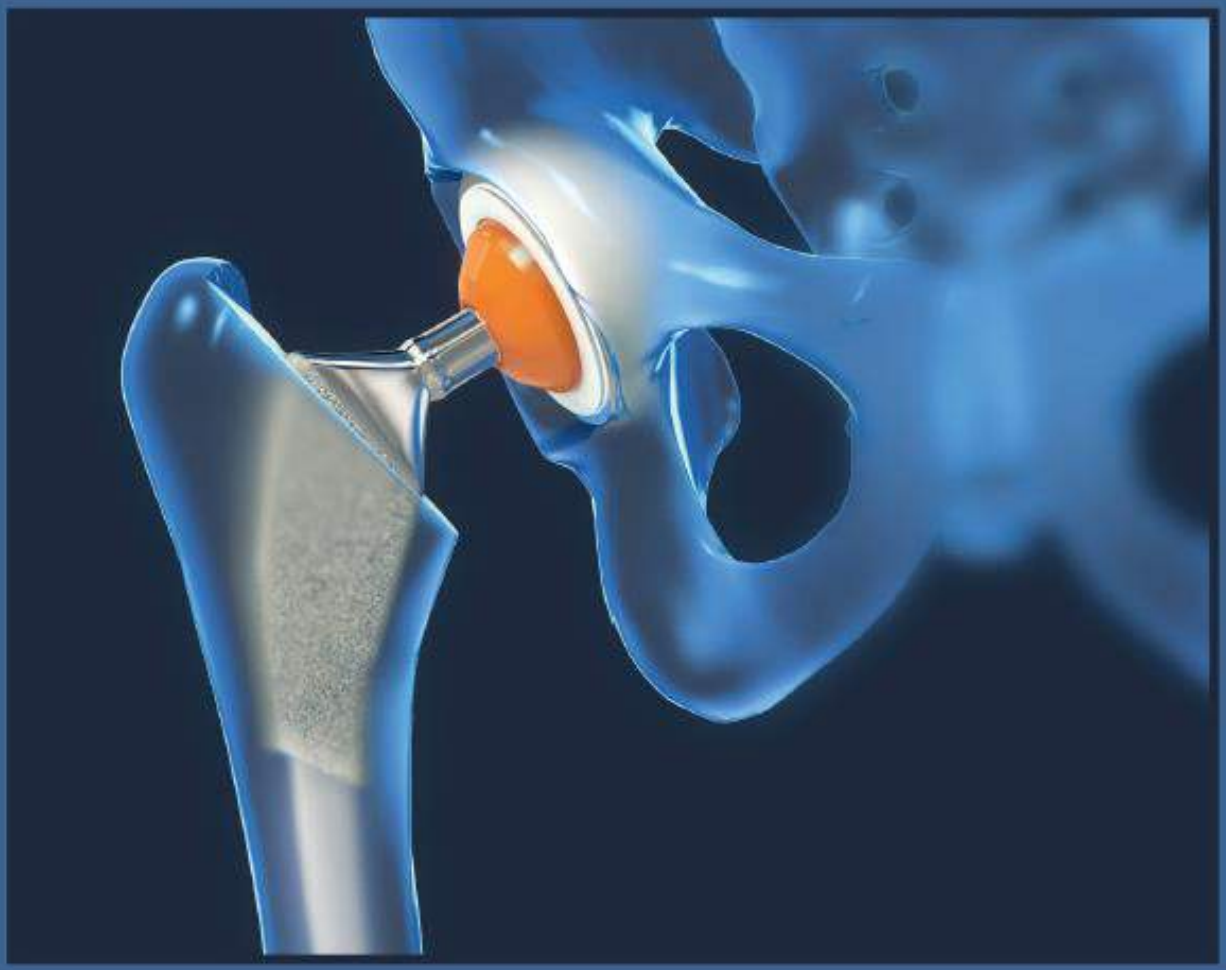

COMPUTATIONAL MODELLING OF BIOMECHANICS AND BIOTRIBOLOGY IN THE MUSCULOSKELETAL SYSTEM

BIOMATERIALS AND TISSUES

SECOND EDITION

Edited by
ZHONGMIN JIN
JUNYAN LI
ZHENXIAN CHEN

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Computational Modelling of Biomechanics and Biotribology in the Musculoskeletal System

Biomaterials and Tissues

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Geometry optimization of scaffolds for bone tissue engineering

12

Óscar L. Rodríguez-Montaño[a,b], Carlos Julio Cortés-Rodríguez[b], Antonio E. Uva[a], Michele Fiorentino[a], Alessandro Evangelista[a], Michele Gattullo[a], Vito M. Manghisi[a], and Antonio Boccaccio[a]

[a]Department of Mechanics, Mathematics, and Management, Polytechnic University of Bari, Bari, Italy, [b]Department of Mechanical Engineering and Mechatronics, National University of Colombia, Bogotá, Colombia

12.1 Introduction

The availability of bone substitutes to respond to the growing demand of bony tissue for replacing bones affected by trauma or disease is still a concern in the clinical context (Wang and Yeung, 2017). Despite the advances in bone tissue engineering (BTE) in the last decades, the challenge to replace bone grafts with artificial bone substitutes remains actual and of crucial importance. Bone regeneration and repair is the result of complex biophysical and biochemical phenomena, bone-tissue engineers focused their research on many key factors that can favor it, such as cell and genic therapies, biochemical signaling and matrix structure and composition (Murphy et al., 2013). The last factor aims to the generation of three-dimensional porous templates imitating the matrix in which the regeneration process takes place. These templates are known as scaffolds and serve to provide a support favoring the bone regeneration process. Scaffolds must guarantee: (i) an adequate environment to cells and tissues, (ii) the mechanical stability in surrounding tissues and structures, (iii) the transport of nutrient and oxygen. Furthermore, the device should favor cellular processes such as adhesion, motility, growth, differentiation, and extracellular matrix secretion, which can be summarized into the properties of osteoinductivity and osteoconductivity (Poh et al., 2019). In general, these properties are strictly related not only to the specific features of the healing process itself but also to the properties of the materials the scaffold is made from, that may be natural or synthetic polymers, metals, ceramics, and composites.

Bone fracture healing is a very complex process that depends on multiple cues of physical, chemical, and biological nature. Many varieties of bones with specific functions are present in vertebrate species, which means that the fracture healing process occurs differently depending on the specific anatomic site (Morgan et al., 2013). These cues occur at various length and time scales, which makes the bone

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regeneration process inside the scaffold a very complex phenomenon requiring, yet, a clear explanation (Akbarzadeh et al., 2015).

A number of studies have recently demonstrated that the geometry of scaffolds for bone tissue engineering significantly affects the tissue differentiation process and the rate of bone tissue regeneration (Zadpoor, 2015). For instance, larger amounts of bone were demonstrated to create on concave surfaces as compared to flat or convex ones (Bidan et al., 2012, 2013). These findings and the possibility of fabricating any kind of sophisticated geometries by additive manufacturing techniques led many researchers throughout the world to devote their study on the designing of scaffolds and the optimization of their geometry. Computational models are currently being developed to explore how the scaffold geometry influences the cellular response. Different studies have been carried out also on complex microarchitectures that can be utilized as the repeating unit cell geometry of regular scaffolds for bone tissue engineering. Relationships were also determined between the shape of the repeating unit cell and the equivalent mechanical properties of the entire porous biomaterial (Zadpoor and Hedayati, 2016).

These studies respond to the requirements of the medical model recently developed and denoted as Precision Medicine. While the traditional medicine is based on statistics and on the definition of "average" patient, Precision Medicine or even personalized medicine proposes the personalization of health, with therapies, practices, and/or "tailor-made" medical devices for the specific patient. So far, the bone tissue scaffolds have been produced and made available on the market without any specific prescription regarding: (i) which is the most suitable geometry to support the loads acting in a given anatomical region; (ii) the possible load values to which they can be subjected to guarantee sufficient bone formation. With these studies, researchers aim to "customize" scaffolds, i.e., to design ad hoc scaffolds that adapt to specific boundary and loading conditions and which are therefore particularly suitable for filling the bone deficiency in a specific anatomical region of a specific patient. By adopting these innovative design methodologies it is possible to improve the quality of newly formed bone, to reduce the healing times and, ultimately, to increase the success rate of the scaffold implantation procedure.

As the scaffold is a therapeutic device, an expected ideal goal is that when the recovery is successfully completed, the scaffold should not be present anymore in the body. This condition is achieved by the degradation capability of the scaffold, which is also generally used for the controlled delivery of biochemical factors to promote the healing processes (De Witte et al., 2018; Porter et al., 2009). The degradation process makes the scaffold material properties depending on the variable time. As the degradation takes place, the pore architecture, the porosity, the stiffness, the permeability, and the other properties of interest change dynamically. This aspect makes the design process of scaffolds extremely complex and tremendously expensive in terms of the computational cost. However, there are specific situations in which the scaffold remains intentionally in the body, that is, degradation is not present and the device acts as a permanent implant (De Witte et al., 2018; Li et al., 2016; Pobloth et al., 2018).

In this chapter, after revising the numerical optimization algorithms recently implemented to determine the best scaffold geometry we will investigate, in

particular, those that are mechanobiology-driven. The basic principles of computational mechanobiology as well as its main applications in the field of the regenerative medicine will be briefly outlined. The optimization algorithms based on mechanobiological criteria and implemented to optimize the scaffold geometry will be, then, briefly described. These algorithms perturb the scaffold microarchitecture until the optimal scaffold geometry, i.e., the geometry that allows maximizing the amounts of bone forming within the scaffold pores, is computed. Different applications of these algorithms to different unit cell geometries will be shown. Finally, the implementation of these algorithms for the optimization of irregular load-adapted scaffolds will be briefly outlined.

In a clinical context dominated by customized medical solutions, this study supports the orthopedic/maxillofacial surgeon in the task of choosing the best scaffold for a given patient, as well as describes possible design strategies to maximize the formation of bone and definitively to shorten the healing and the hospitalization time.

12.2 Optimization and design of bone scaffolds

Currently, many efforts are done in the scientific community to find the ideal scaffold for bone fracture healing (Zeng et al., 2018). The ideal scaffold should not only provide an adequate physical microenvironment and support the load acting on it but should also include exogenous substances such as growth factors, genes, and even cells to stimulate the osteogenesis (Poh et al., 2019).

Despite the extensive studies on the design of the ideal scaffold, this remains a complex research objective, without yet a clear and exhaustive solution. The huge number of key factors, the fact that these factors were separately studied in previous studies but their reciprocal interactions were never deeply investigated, makes the design of the ideal scaffold a very complex challenge. Often these key factors can have opposite effects, and this necessarily implies the inclusion of tradeoffs to balance the design constraints (Egan, 2019). A typical example that can be done to this purpose is the case of the porosity and the stiffness that are physically opposed properties but that are both necessary for the success of the scaffold implantation. In fact, the porosity guarantees the adequate mass transport, fluid flow, vascularization and biological supplies, the stiffness, instead, serves to guarantee the mechanical stability of the structure until the newly formed tissue is capable to withstand the load acting on the scaffold (Chen et al., 2011b).

12.2.1 Computational models to design scaffolds

As stated earlier, optimizing the scaffold performance, definitively leads to shorter healing times and higher success rates of the scaffold implantation process. However, the experimental approaches required for the scaffold optimization are very expensive in terms of time and costs and this has led, also thanks to the increase of the computational power, to the development of computational models capable of predicting with a given degree of approximation how the tissue differentiation evolves in time

for scaffolds subjected to specific boundary and loading conditions (Ballini et al., 2017; Boccaccio et al., 2011; Cantore et al., 2018; Sanz-Herrera et al., 2009). In these models, the newly formed tissue is often treated as biphasic material; the key factors related to the solid phase and frequently studied in the literature are stiffness, mechanical resistance, and porosity, whereas the most important factors related to fluidic influence are permeability and wall shear stress (WSS) (Zhang et al., 2019). However, other characteristics such as the microporosity of the walls, the hydrophobicity, and the surface roughness have been demonstrated to have influence in the evolution of the tissue within the scaffold and were accordingly studied (Zhang et al., 2018). The computational models hypothesize that the neo-formed tissue is subjected to a biophysical stimulus (that is a function of quantities related to the solid and to the fluid phase) that triggers, based on the values that it assumes, the differentiation toward different phenotypes (Byrne et al., 2007).

Nowadays, different computational frameworks were integrated in a new research field known as computer-aided tissue engineering (CATE) to assist in the design, evaluation, and manufacture of tissue scaffolds, providing the possibility to define virtually the physical and geometrical characteristics of any structure through the computer-aided design (CAD), reverse engineering (RE) tools, and simulation environments (Giannitelli et al., 2014). The most common numerical tools utilized to investigate, analyze, assess, and characterize the scaffold design and its related key factors from a physical point of view are the finite element method (FEM) and the computer fluid dynamics (CFD). These tools are frequently coupled with optimization approaches based on gradients (Roberge, 2016), iterative methods (Boccaccio et al., 2016a), heuristics and artificial intelligence techniques such as evolutionary algorithms (Asadi-Eydivand et al., 2016) and fuzzy logics (Wang and Yang, 2018). The finite element method is suited not only to analyze the design key factors but also to solve the partial differential equations (PDE) that well represent and describe the biochemical processes occurring inside a scaffold. Also, combinations of FEM with experimental procedures such as microcomputed tomography (μCT) have been used to optimize the scaffold performance (Lohfeld et al., 2015).

12.2.2 Optimization algorithms

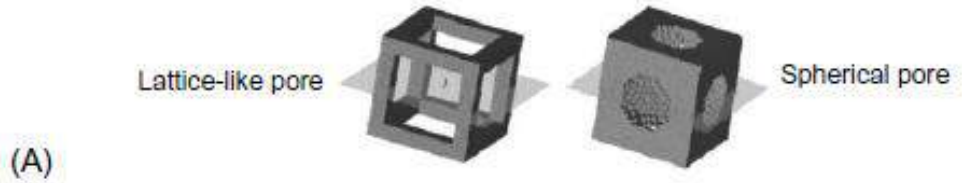
In silico models, based on optimization algorithms, present an important limitation. There are as many optimization models in the literature as there are optimized variables. The resulting solution is, therefore, optimal with respect to the variable taken into account but is not optimal in general. Mechanical and biological properties measured in terms of physical characteristics such as the surface area, the permeability, the stiffness, and the porosity are some commonly used variables for optimization. However, all these quantities are, in general, not reciprocally independent. For instance, the stiffness is the most common design variable optimized (Dias et al., 2014). One of the typical issues deriving from the implantation of the scaffold is the difference between the mechanical properties of scaffold and those of the tissues surrounding it. In general, using a scaffold with material properties close to those of the adjacent tissue allows avoiding inconvenient effects such as stress shielding that leads to bone

resorption and finally to failure of the bone repair (Wu et al., 2017). One of the first studies where the scaffold stiffness was optimized was the study by Hollister et al. (2002) and Hollister and Murphy (2011) where the optimization aimed at minimizing the difference between the equivalent stiffness of the scaffold and that of the regenerated tissue. Later, Adachi et al. proposed a computational framework to design the optimal scaffold microarchitecture considering the degradation process of the scaffold as well as the growth of the tissue inside the scaffold pores (Adachi et al., 2006). Single unit cells with square and circular topologies were simulated as case studies and optimization analyses were carried out using as evaluation function a function based on the difference between the strain energy of the tissue-scaffold system and the strain energy of healthy bone, which are measures of the stiffness of the structural systems (Adachi et al., 2006).

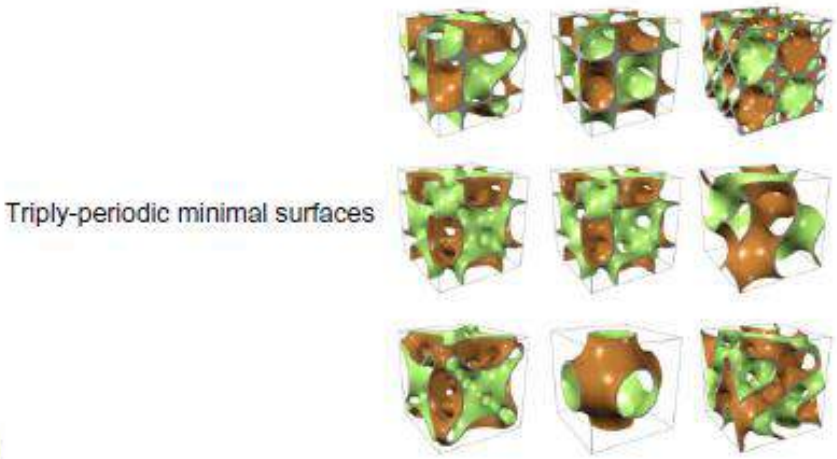
12.2.3 Design optimization of regular and irregular scaffolds

One of the most important constraints to the possible scaffold geometries is represented by the fabrication method. The manufacturing techniques currently available allow obtaining regular and irregular architectures (Ahmadi et al., 2015; Chantarapanich et al., 2012; Giannitelli et al., 2014). The latter ones are those commonly used in the experimental studies and, unfortunately, allow controlling a small number of parameters in the design such as the average pore size, the average porosity and stiffness but not in a precise form (Serra et al., 2011). Irregular architectures, in other words, are controlled in some extent according to the capabilities to control the process parameters such as particulate leaching, solvent casting, gas foaming, phase separation, freeze drying, fiber bonding, etc. (Huang et al., 2017; Tan et al., 2011; Zhang et al., 2017). One of the main disadvantages of the techniques for the fabrication of irregular scaffolds is that they often lead to manufacture structures without fully interconnected pores. The first ones are sophisticated architectures and can be fabricated with additive manufacturing techniques: a given unit cell geometry is replicated many times in the scaffold volume. Scaffolds based on regular repeated unit cells have gained importance in the last years because of their capabilities to allow a precise control on geometry, which leads to produce uniform and repeatable physical environments ease to analyze and evaluate. The most important drawback of regular scaffolds is the limited number of possible materials that have biocompatibility with cells and tissues and that are suited to be treated with additive manufacturing techniques (Roseti et al., 2017).

Scaffolds based on regular geometries have been proposed in a number of studies: lattice-like such as cubic (Adachi et al., 2006), face cubic centered (FCC) (Sanz-Herrera et al., 2008), beam-based scaffolds (Ahmadi et al., 2015; Egan et al., 2017b; Rodríguez-Montaño et al., 2018), hexahedron with elliptic and rectangular pores (Boccaccio et al., 2016a), minimal surface scaffolds (Ambu and Morabito, 2019, 2018; Kapfer et al., 2011) (Fig. 12.1). Optimization analyses were carried out on these scaffolds using as design variables, both quantities related to the mechanical behavior (Dondl et al., 2019) and quantities related to the cellular mechanobiological response (Chen et al., 2011b). Another scaffold with regular geometry recently



(A)



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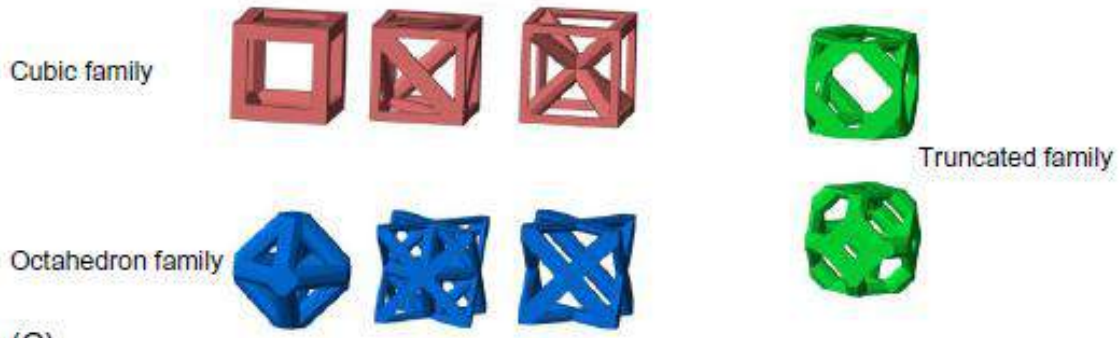

(C)

Fig. 12.1 Investigated unit cells for regular scaffolds: (A) lattice-like and spherical pore, (B) triply-periodic minimal surfaces, and (C) cubic and octahedron families. (A) Reprinted from Adachi, T., Osako, Y., Tanaka, M., Hojo, M., Hollister, S.J., 2006. Framework for optimal design of porous scaffold microstructure by computational simulation of bone regeneration. Biomaterials 27, 3964–3972. https://doi.org/10.1016/j.biomaterials.2006.02.039 with permission from Elsevier, (B) reprinted from Kapfer, S.C., Hyde, S.T., Mecke, K., Arns, C.H., Schröder-Turk, G.E., 2011. Minimal surface scaffold designs for tissue engineering. Biomaterials 32, 6875–6882. https://doi.org/10.1016/j.biomaterials.2011.06.012 with permission from Elsevier, (C) reprinted from Egan, P.F., Gonella, V.C., Engensperger, M., Ferguson, S.J., Shea, K., 2017b. Computationally designed lattices with tuned properties for tissue engineering using 3D printing. PLoS One 12. https://doi.org/10.1371/journal.pone.0182902.

investigated is the one produced with 3D printing technique known as the fused deposition modelling. Cylindrical filaments, all oriented and spaced at the same way, are deposited in layers. Adjacent layers have, in general, different orientations. The effect of the layer orientation was extensively investigated in recent studies (Gleadall et al., 2018). Numerical and experimental studies were carried out to determine the optimal process parameters such as the spacing between the filaments, the printing speed, etc. (Roberge, 2016). Optimization analyses were also carried out to improve the scaffold performance using as a design variable the diameter of the filaments and the pore size among others (Uth et al., 2017). An important advantage of designing regular scaffolds based on specific unit cell geometries is the possibility of describing the global properties of the entire scaffold volume from the properties of single unit cell. Analytical solutions were recently developed that put in relationship the material properties of the entire scaffold with those of the specific unit cell geometry (Ahmadi et al., 2014; Campoli et al., 2013; Hedayati et al., 2016a,b; Zadpoor and Hedayati, 2016). Another approach utilized to describe the global properties of the entire volume from the calculated properties of the topology of a unit cell consists in implementing the homogenization theory (Makowski and Kuś, 2016). The localization theory, that allows doing the contrary, i.e., to compute the microstructure properties from the global ones, was also implemented in the design of scaffolds (Chen et al., 2011a). Scaffolds located in proximity of interfaces may require possessing material properties gradually changing from those of the first material with which they are in contact to those of the second material they are in contact with. This condition, that can be realized with both regular and irregular scaffolds, could be achieved with functionally graded scaffolds (Loh and Choong, 2013), multilevel material assignments (Paz and Monzón, 2019), hierarchical three-dimensional scaffolds (Egan et al., 2017a).

It is worth noting that often a single objective function is not sufficient to analyze a key factor or a set of key factors. In such cases, in order to address the different tradeoffs involved in the scaffold design, the optimization procedures should be multiobjective. Obviously, a multiobjective optimization procedure will produce a set of optimized solutions instead of a unique solution (Barán and Pinto-Roa, 2015).

In addition to scaffolds with regular and irregular geometry, scaffolds with microarchitecture obtained by means of topological optimization procedures were also proposed (Almeida and Bártolo, 2013; Velasco Peña, 2016). The optimization technique was utilized, for instance, for the generation of the optimal scaffold for a large defect model in a human mandible (Hu et al., 2019). The mandible included a solid cortical layer filled by a porous structure. The topological optimization technique seems an interesting choice to design customized scaffolds based on specific mechanical environments. However, this technique presents some limitations as reported by Almeida and Bartolo, who found that if different optimized scaffolds are generated for several mechanical environments, some of these include interconnected cells and are, hence, valid, others include not interconnected cells and are therefore invalid (Almeida and Bártolo, 2013). Furthermore, the topological optimization approach could lead to float material issues, which implies difficulties in manufacturing the microstructure using the available techniques.

12.2.4 Mechanobiology-based optimization algorithms

In general, it is possible to design and fabricate scaffolds with the same properties such as the porosity, the volume fraction, the surface area, the stiffness, but with a completely different microarchitecture. Mechanobiology-based optimization algorithms can be implemented to choose the best microarchitecture capable of guaranteeing the optimal mechanobiological performance. These algorithms typically compute the biophysical stimulus acting on the tissue occupying the scaffold and allow determining the microarchitecture for which this stimulus is oriented toward the formation of mature bone. These algorithms adopt systems of equation commonly utilized to describe physical phenomena such as the diffusion of heat through a media, to reproduce the cellular processes occurring in scaffold. Cell activities such as differentiation, growth, motion, dispersion have been described in discrete (Byrne et al., 2007) or continuum forms (Bidan et al., 2013; Gorriz et al., 2015; Sanz-Herrera et al., 2008). For instance, Gorriz et al. (2015) by using diffusion equations, modelled the tissue differentiation and the polymer degradation processes occurring in scaffolds for bone regeneration. The angiogenesis was also simulated by Sandino et al. (2010) in a CaP scaffold subjected to compressive strains. The mentioned mechanobiological approaches are based on partial derivative equations (PDE) that must be solved iteratively using numerical techniques or by means of empirical models. Another computational strategy utilized in mechanobiological algorithms is the use of the fuzzy logic. For instance, by means of fuzzy logic and finite element method, Shefelbine et al. (2005) simulated the healing process in trabecular bone.

12.3 Basic principles of computational mechanobiology

It is well known from the mechanobiological theory that the mechanical stimulus has a paramount influence in the fracture bone-healing process. Different mathematical formulations have been proposed in the literature for describing the mechanical stimulus. It was hypothesized to be a function of different mechanical quantities such as the hydrostatic pressure, the axial and shear stress and strains, the residual stress, the wall shear stress, etc. All these quantities have influence on the bone cells and specifically in the early phases of the healing process when the fracture is filled by soft tissues rich in pluripotential cells such as mesenchymal stem cells (MSCs), that will differentiate in more specialized cells like fibroblasts, chondrocytes, preosteoblasts, and osteoblasts that secrete extracellular matrix depending on the different stimuli that they sense. Furthermore, it is possible to have a biophysical stimulus not beneficial for osteogenesis that will lead to bone resorption or apoptosis of cells.

Different mechanobiological theories were proposed by different researchers throughout the world. For instance, Carter et al. related the hydrostatic stress history and the principal tensile strain history to the formation of the different tissues creating during the healing process such as fibrous tissue, fibrocartilage, cartilage, and bone (Carter et al., 1998). Claes and Heigele hypothesized that the biophysical stimulus that regulates the tissue formation is a function of the hydrostatic pressure

and the strain (Claes and Heigele, 1999). Furthermore, they established specific intervals of these quantities where endochondral or intramembranous ossification takes place. Prendergast et al. (1997) modelled the bone callus as a biphasic poroelastic material and proposed a mechanoregulatory pathway based on the octahedral shear strain and fluid relative velocity between the fluid and the solid phase of the regenerating tissue. In detail, if γ is the octahedral shear strain and v the relative fluid velocity, the biophysical stimulus S that triggers the differentiation process is given by:

$$S = \frac{\gamma}{a} + \frac{v}{b}, \tag{12.1}$$

where a and b are empirical constants previously determined (Huiskes et al., 1997). Based on the values that S assumes, the model of Prendergast and Huiskes hypothesizes that the mesenchymal stem cells MSCs differentiate into different phenotypes:

$$\begin{aligned}
&\text{if } S > 3 \rightarrow \text{MSC differentiate into Fibroblasts}\\
&\text{if } 1 < S < 3 \rightarrow \text{MSC differentiate into Chondrocytes}\\
&\text{if } 0.53 < S < 1 \rightarrow \text{MSC differentiate into Osteoblast (Immature Bone)}\\
&\text{if } 0.01 < S < 0.53 \rightarrow \text{MSC differentiate into Osteoblast (Mature Bone)}\\
&\text{if } 0 < S < 0.01 \rightarrow \text{Bone resorption}
\end{aligned} \tag{12.2}$$

Other computational mechanobiological models have been proposed, including growth factors (Bailón-Plaza and Van Der Meulen, 2001), angiogenesis (Checa and Prendergast, 2009), etc. Comparisons between the different mechanoregulation models and experimental data from fracture healing were performed by Isaksson et al. that concluded that the model of Prendergast and Huiskes predicted spatial and temporal distributions of the differentiating tissues closer to those observed experimentally (Isaksson et al., 2006).

Several scaffold architectures have been modeled and optimized, by the present authors, using an optimization algorithm based on the mechanobiological model by Prendergast and Huiskes (based on Eqs. 12.1, 12.2). The main assumption in these studies was that the volume inside the scaffold pores is already filled by granulation tissue, a fact that corresponds to the reality in the early phase of the fracture-healing process. Furthermore, we hypothesized that the granulation tissue is uniformly filled by MSCs that may differentiate in the phenotypes described here. The microgeometrical features that define the pore size were modified iteratively in order to find those with the best performance from a mechanobiological viewpoint, i.e., those that maximize the volume of the scaffold occupied by mature bone. The optimization algorithm includes the computational mechanobiological model by Prendergast and Huiskes (see Eqs. 12.1, 12.2) and parametric finite element models of the different scaffolds investigated. The algorithm computes in each iteration cycle the total volume of the elements where the formation of mature bone is predicted. Therefore, the algorithm perturbs the scaffold microgeometry so many times until the volume of the elements occupying the scaffold pores and that are predicted to differentiate into mature bone, is maximized. The design variable that is a specific geometric parameter

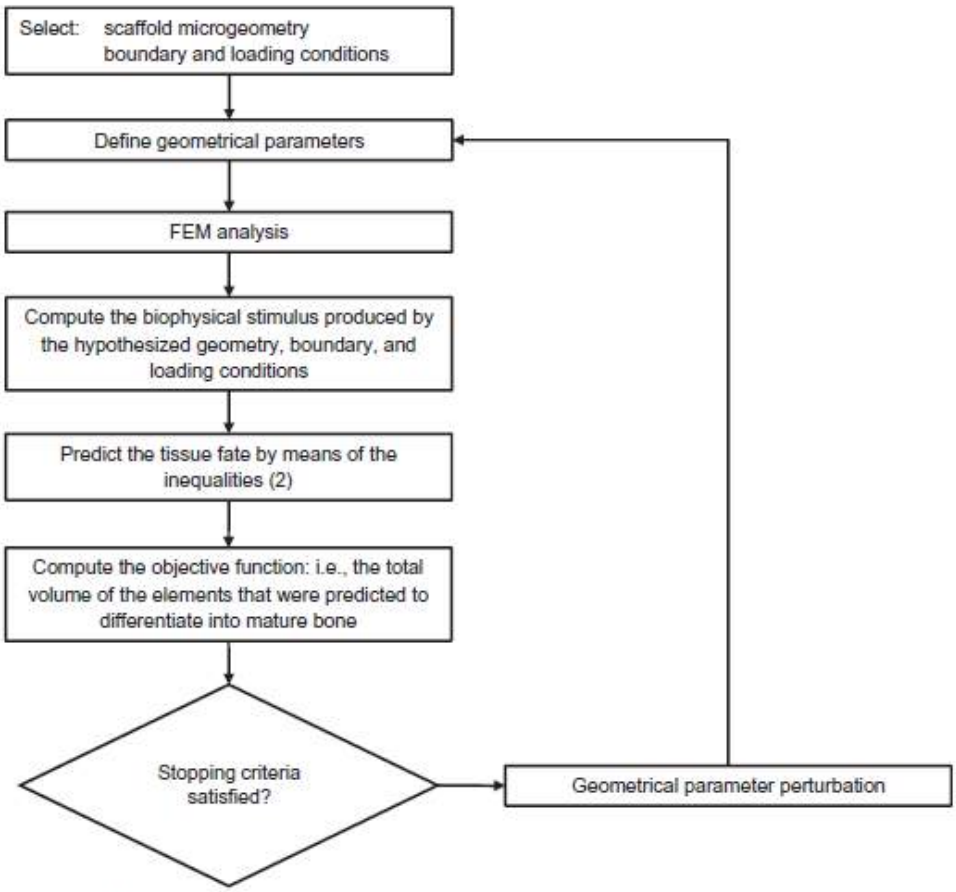

Fig. 12.2 Schematic of the algorithm based on mechanobiological criteria implemented to optimize the microgeometry of regular and irregular scaffolds.

of the scaffold geometry was perturbed by means of the *fmincon* function available in the MATLAB (MathWorks, Natick, USA) optimization toolbox. In detail this function uses iteratively the SQP method to evaluate the objective function until the stopping criteria are satisfied, i.e., when the algorithm finds the optimal value of the geometric parameter in correspondence of which the objective function reaches its maximum value (Fig. 12.2).

12.4 Optimization of regular and irregular scaffolds based on mechanobiological criteria

The first unit cell investigated and optimized with the described optimization algorithm is the hexahedron with both elliptic and rectangular pores (Fig. 12.3) (Boccaccio et al., 2016a). The parametric model of the single unit cell was first generated with the CAD tools available in ABAQUS (Dassault Systèmes,

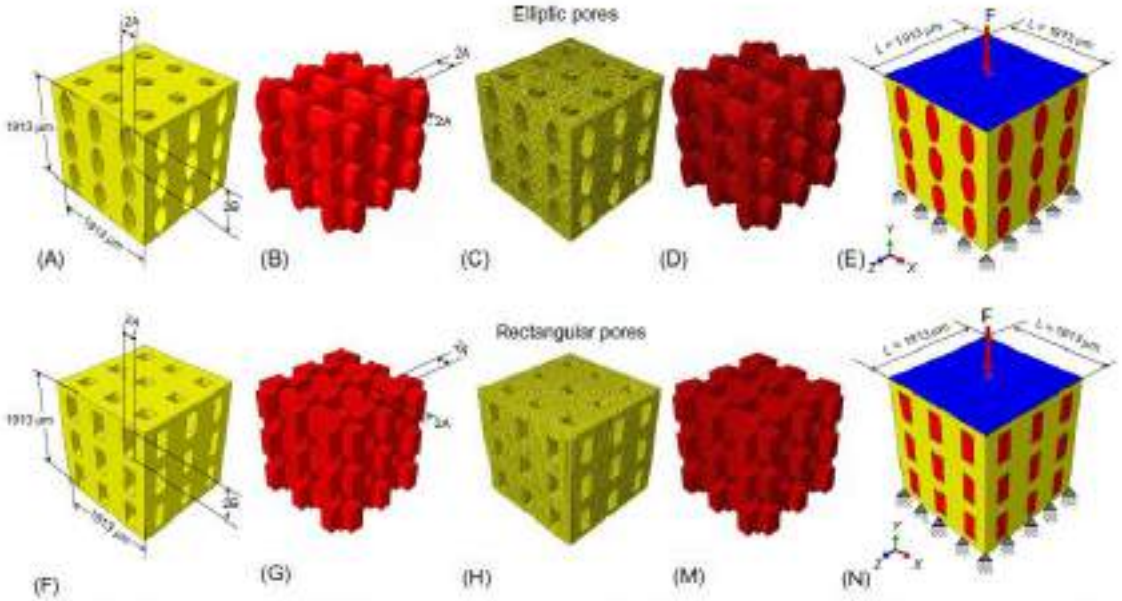

Fig. 12.3 CAD model, based on hexahedron unit cell (with elliptic (A–E) and rectangular (F–N) pores), of the scaffold (A,F) and of the tissue occupying the pores (B,G). These models have been meshed (C,D (elliptic pores), H,M (rectangular pores)) and subjected to compression loading (E, N). The geometrical parameters that have been optimized were the dimensions *A* and *B*.

Adapted from Boccaccio, A., Uva, A.E., Fiorentino, M., Lamberti, L., Monno, G., 2016a. A mechanobiology-based algorithm to optimize the microstructure geometry of bone tissue scaffolds. Int. J. Biol. Sci. 12, 1–17. https://doi.org/10.7150/ijbs.13158.

Vélizy-Villacoublay, France). Then, by mirroring this cell with respect to proper planes, the cell was replicated in the space creating the entire scaffold. At this point, the geometry of the tissue occupying the scaffold pores was generated via Boolean operations of subtraction. The scaffold models with both elliptic and rectangular pores were subjected to compression loading via a rigid plate properly constrained with the scaffold top surface. The design variables that were perturbed by *fmincon* to determine the optimal scaffold geometry were the dimensions of the major and the minor axes (A and B, Fig. 12.3) of the elliptic pores or the dimensions of the longer and the shorter side of the rectangular pores (A and B, Fig. 12.3). By implementing the optimization algorithm, it was found that the elliptic pores tend to orient with the major axis aligned with the loading direction (Fig. 12.4). The same trend can be observed for the rectangular pores. Furthermore, it was found that such a scaffold unit cell can bear significant values of load. In general, it was found that scaffolds with rectangular pores perform better than those with elliptic pores. In fact, the amounts of bone that are predicted to create in this case are larger than those predicted in the case of elliptic pores (Boccaccio et al., 2016a). Interestingly, the predictions of the proposed algorithm are consistent with what is observed in experimental studies. In particular, the patterns of the elements that are predicted to become mature bone appear similar to those found by Rumpler et al. (2008). The described optimization algorithm was properly changed and adapted to determine the optimal load that should act on scaffolds with hexahedron unit cell (Boccaccio et al., 2018b).

These scaffolds possess a homogeneous porosity. In other words, the dimension of the pores is constant and does not change in the space. Another interesting scaffold geometry that was investigated is the one including hexahedron unit cells with functionally graded porosity (Fig. 12.5) (Boccaccio et al., 2016b). In this case, the pores, that were hypothesized to be circular (which is a particular case of the elliptic shape), change along the vertical direction y according to specific laws. The objective of the study was to determine the best distribution law of the porosity that allows maximizing the amounts of bone predicted to create within the scaffold pores. For this scaffold type, two principal loading conditions were hypothesized, the compression and the shear load. Interestingly, it was found that in the case of compression loading, the pore dimensions remain almost constant versus the coordinate location y (Fig. 12.6). A very different trend was instead observed in the case of shear loading where the pore dimensions were predicted to significantly change along y. This result leads us to

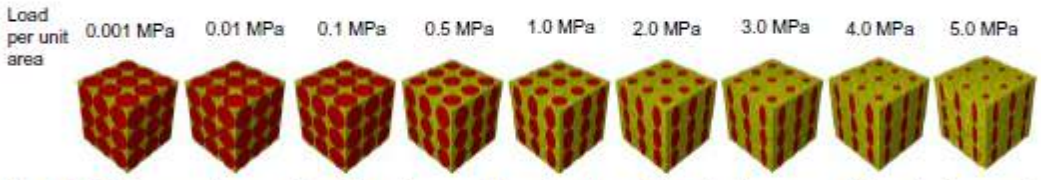

Fig. 12.4 Geometries predicted by the optimization algorithm in the case of hexahedron unit cell with elliptic pores, for different levels of load.
Adapted from Boccaccio, A., Uva, A.E., Fiorentino, M., Lamberti, L., Monno, G., 2016a. A mechanobiology-based algorithm to optimize the microstructure geometry of bone tissue scaffolds. Int. J. Biol. Sci. 12, 1–17. https://doi.org/10.7150/ijbs.13158.

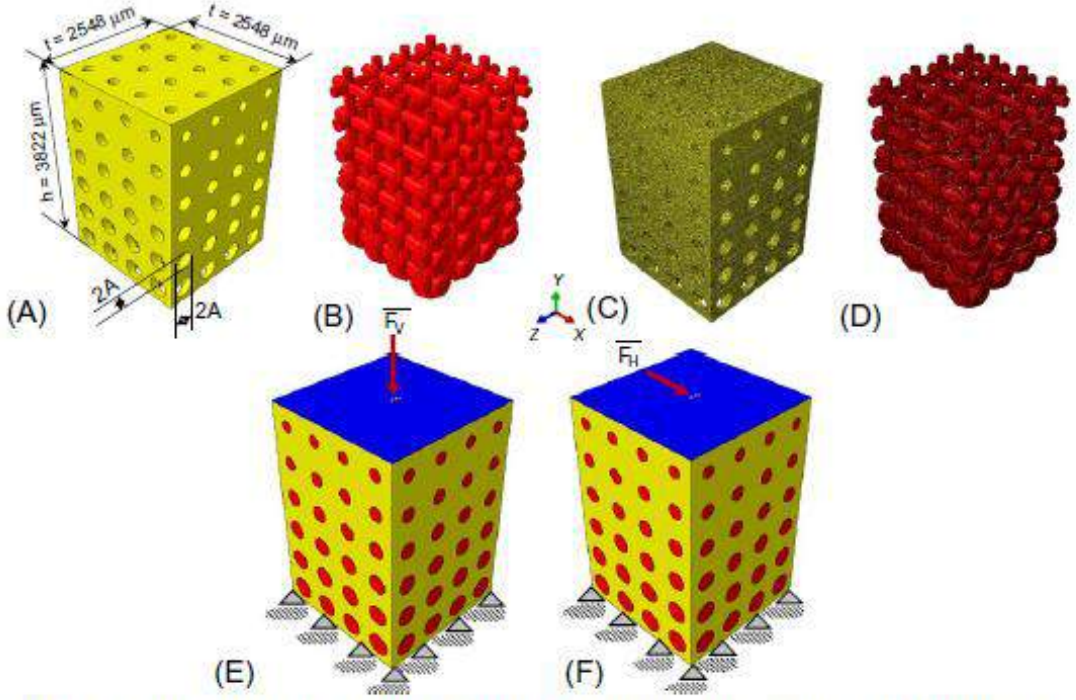

Fig. 12.5 CAD model of the scaffold (A) and of the tissue occupying the scaffold pores (B). These models were meshed (C,D) and subjected to two different boundary and loading conditions: (A) compression (E) and shear (F) loading. The optimization algorithm determined the optimal porosity distribution that allows maximizing the formation of bone, i.e., the optimal dimension *A* of the pores along the coordinate direction *y*.
Adapted from Boccaccio, A., Uva, A.E., Fiorentino, M., Mori, G., Monno, G., 2016b. Geometry design optimization of functionally graded scaffolds for bone tissue engineering: a mechanobiological approach. PLoS One 11. https://doi.org/10.1371/journal.pone.0146935.

conclude that scaffolds with functionally graded porosity are very useful only in the case they are subjected to shear loading. They are practically useless in the case they have to bear only compression loads (Fig. 12.6).

Another interesting scaffold geometry that was investigated in previous studies is the beam-based one. The generic unit cell includes beams that are properly oriented in the space, based on how they are oriented, different unit cells can be generated. In detail, the following unit cells were optimized via the optimization algorithm described: rhombicuboctahedron (Boccaccio et al., 2018a), truncated cube, truncated cuboctahedron, diamond and rhombic dodecahedron (Rodríguez-Montaño et al., 2018) (Fig. 12.7). The mechanical properties of these unit cells have been studied from a mechanical point of view (Ahmadi et al., 2015). Also in this case, the geometry of the single unit cell was first generated. Then, the entire scaffold was built by properly mirroring the unit cell with respect to planes. Again, the model of the tissue occupying the scaffold pores was generated via Boolean operations. The design variable that was perturbed by *fmincon* was the diameter *D* of the beams. In this case, differently from the case of the hexahedron unit cell, in order to correctly model such sophisticated geometries, it was mandatory to use a finer mesh, thus tremendously increasing the

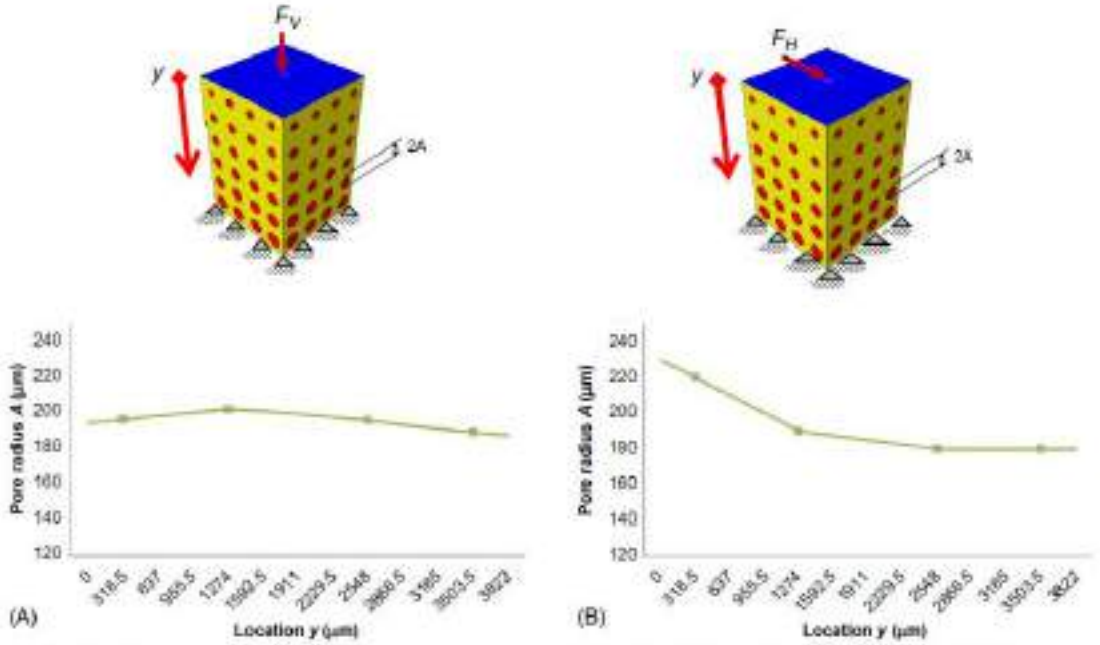

Fig. 12.6 Porosity distribution (i.e., dimensions of pores A) along the y-coordinate direction, predicted by the optimization algorithm in the case of compression (A) and shear (B) loading.

Adapted from Boccaccio, A., Uva, A.E., Fiorentino, M., Mori, G., Monno, G., 2016b. Geometry design optimization of functionally graded scaffolds for bone tissue engineering: a mechanobiological approach. PLoS One 11. https://doi.org/10.1371/journal.pone.0146935.

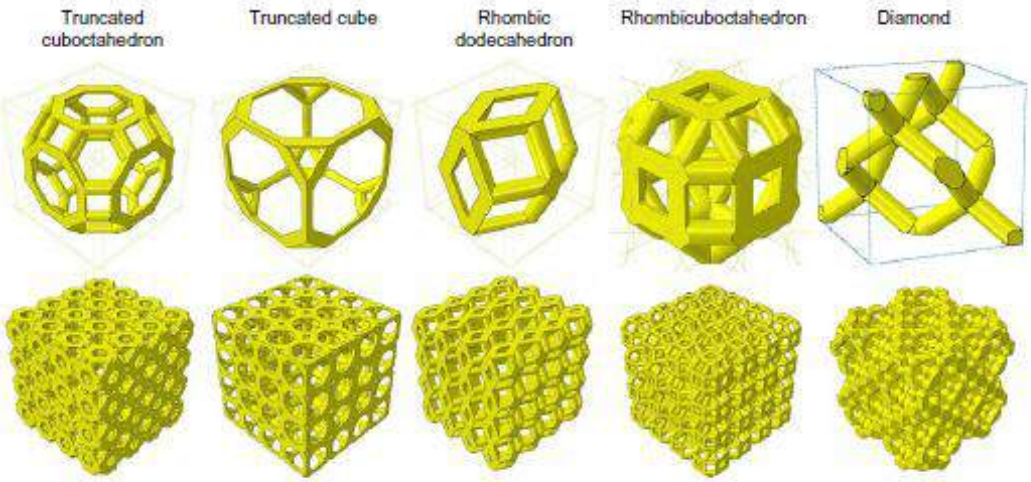

Fig. 12.7 Unit cell geometries (first row) and corresponding scaffold models (second row) investigated via the mechanobiology-based optimization algorithm described. Adapted from Boccaccio, A., Fiorentino, M., Uva, A.E., Laghetti, L.N., Monno, G., 2018a. Rhombicuboctahedron unit cell based scaffolds for bone regeneration: geometry optimization with a mechanobiology—driven algorithm. Mater. Sci. Eng. C 83, 51–66. https://doi.org/10.1016/j.msec.2017.09.004 (rhombicubocathedron unit cell) with permission from Elsevier and from Rodríguez-Montaño, Ó.L., Cortés-Rodríguez, C.J., Uva, A.E., Fiorentino, M., Gattullo, M., Monno, G., Boccaccio, A., 2018. Comparison of the mechanobiological performance of bone tissue scaffolds based on different unit cell geometries. J. Mech. Behav. Biomed. Mater. 83, 28–45. https://doi.org/10.1016/j.jmbbm.2018.04.008 (the other unit cells) with permission from Elsevier.

required computational times. To address this issue, the symmetry of the model was exploited and hence just one quarter of the entire model was considered. Proper symmetry constraints were utilized on the symmetry planes. Interestingly, it was found that for increasing levels of load, the diameter D tends to increase too (Fig. 12.8). This is consistent with the physics of the problem. In fact, as the load increases, for an increasing number of elements the formation of "softer" tissue as cartilage and fibrous tissue will be predicted. To counterbalance this, the algorithm tends to make the scaffold stiffer and hence to increase the diameter dimension.

Another geometry that was investigated is that of the load-oriented scaffolds (Rodríguez-Montaño et al., 2019). The rationale for which such scaffolds were proposed is that, in general, regular scaffolds cannot bear complex load distributions (Naddeo et al., 2017) but can properly bear only the loads oriented according to the orientation of the beams of the unit cell geometries. The skeleton of the load-oriented scaffolds was first designed utilizing the following strategy. A cloud of nodes/points randomly distributed in the space was created. Then, these nodes were connected reciprocally by means of beams. Different boundary and loading conditions were hypothesized to act on the beams and, for each of them, the elastic solution was computed via the finite element method. In detail, three boundary and loading conditions were hypothesized, a pure compression, a shear, and a lateral loading. An optimization cycle started that removed all the beams subjected to negligible stress values leaving only those actually working. The resulting optimized skeleton was "dressed"

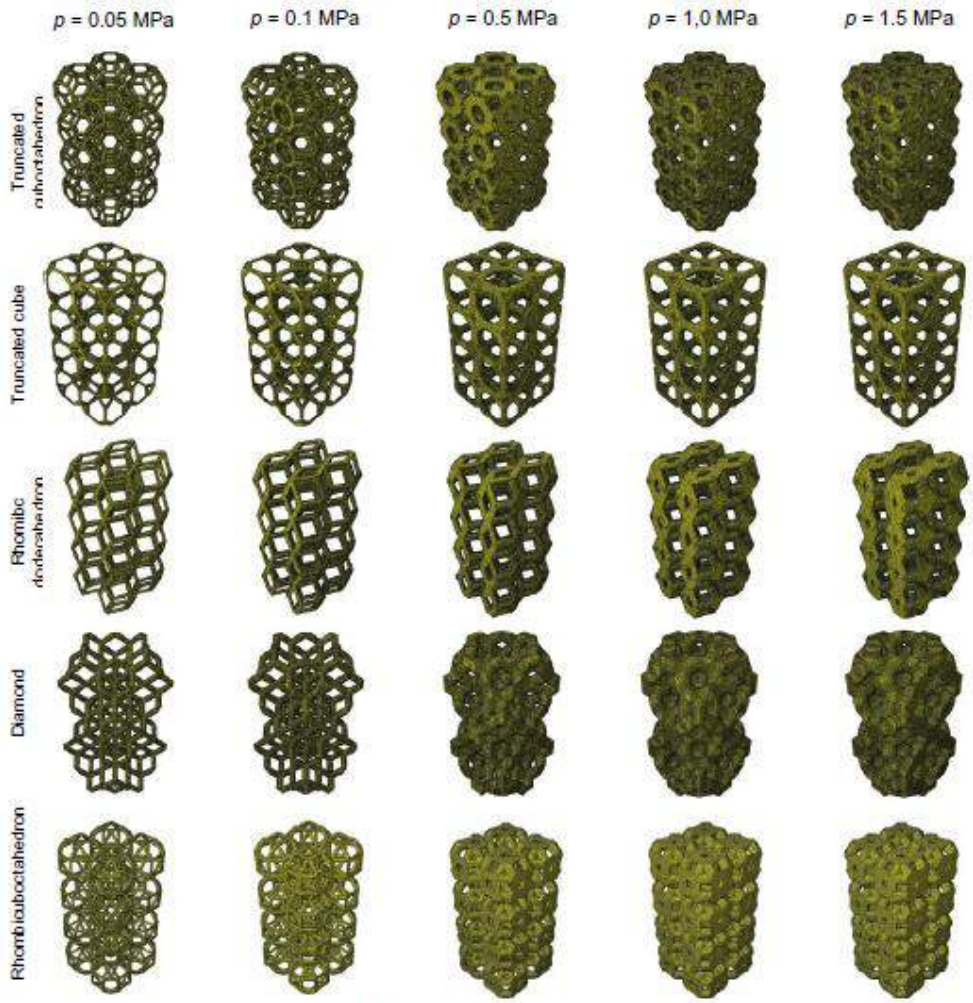

Fig. 12.8 Geometries predicted by the optimization algorithm for different levels of load. Adapted from Boccaccio, A., Fiorentino, M., Uva, A.E., Laghetti, L.N., Monno, G., 2018a. Rhombicuboctahedron unit cell based scaffolds for bone regeneration: geometry optimization with a mechanobiology—driven algorithm. Mater. Sci. Eng. C 83, 51–66. https://doi.org/10.1016/j.msec.2017.09.004 (rhombicubocathedron unit cell) with permission from Elsevier and from Rodríguez-Montaño, Ó.L., Cortés-Rodríguez, C.J., Uva, A.E., Fiorentino, M., Gattullo, M., Monno, G., Boccaccio, A., 2018. Comparison of the mechanobiological performance of bone tissue scaffolds based on different unit cell geometries. J. Mech. Behav. Biomed. Mater. 83, 28–45. https://doi.org/10.1016/j.jmbbm.2018.04.008 (the other unit cells) with permission from Elsevier.

with three-dimensional cylindrical elements the diameter D of which was optimized via the optimization algorithm described (Fig. 12.9). In other words, the optimization algorithm perturbed the diameter D of the beams so many times until the largest amounts of mature bone were predicted to create. The generation of the optimal scaffold skeleton was carried out in Ansys (ANSYS, Inc., Canonsburg, Pennsylvania), the conversion of the scaffold skeleton into the three-dimensional structure in Rhinoceros

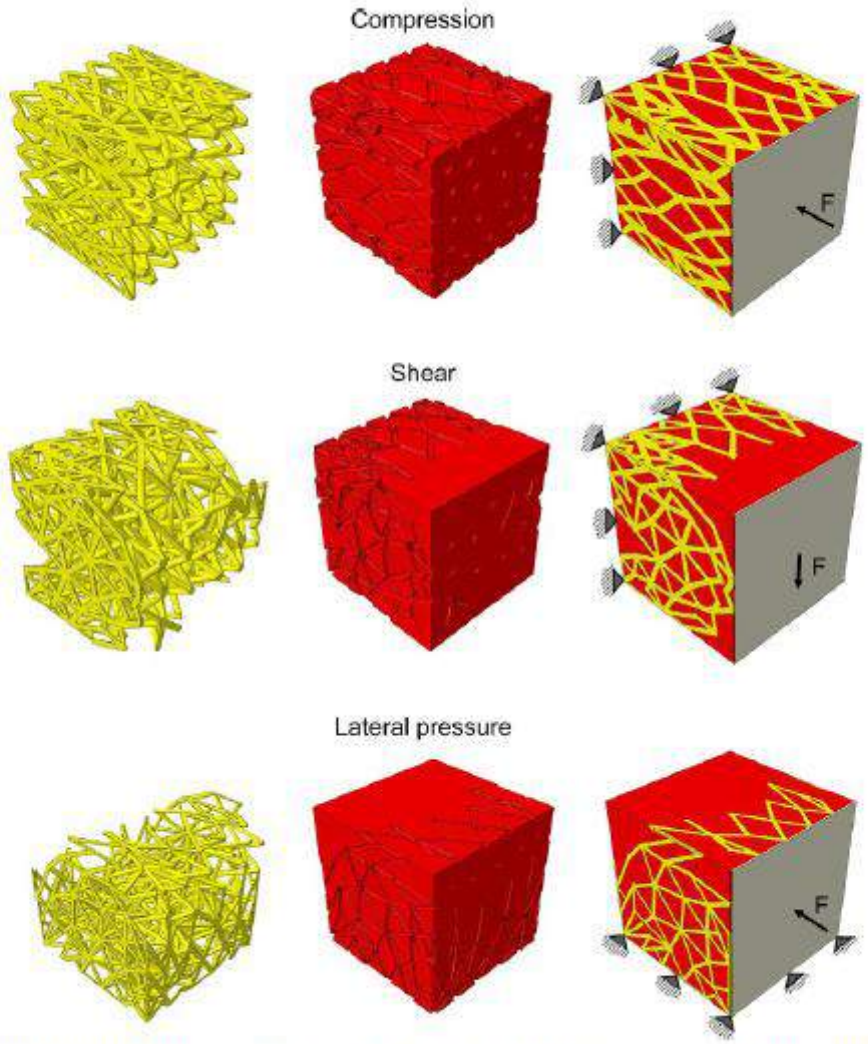

Fig. 12.9 Models of the scaffold (first column) and of the tissue occupying the scaffold pores (second column) optimized for the three hypothesized boundary and loading conditions: compression (first row), shear (second row), lateral pressure (third row).
Adapted with permission from Rodríguez-Montaño, Ó.L., Cortés-Rodríguez, C.J., Naddeo, F., Uva, A.E., Fiorentino, M., Naddeo, A., Cappetti, N., Gattullo, M., Monno, G., Boccaccio, A., 2019. Irregular load adapted scaffold optimization: a computational framework based on mechanobiological criteria. ACS Biomater. Sci. Eng. https://doi.org/10.1021/acsbiomaterials.9b01023. Copyright (2019) American Chemical Society.

(Robert McNeel & Associates, Seattle, Washington), the FEM analysis for the computation of the biophysical stimulus in Abaqus. All these applications were incorporated in the optimization algorithm that was written in Matlab.

Interestingly, comparing the percentage of the scaffold volume occupied by mature bone predicted for irregular load-adapted scaffolds and regular ones, we found that the highest amounts of bone are predicted to create in the irregular load-adapted scaffolds (Fig. 12.10). Furthermore, we found that the irregular load-adapted scaffolds perform

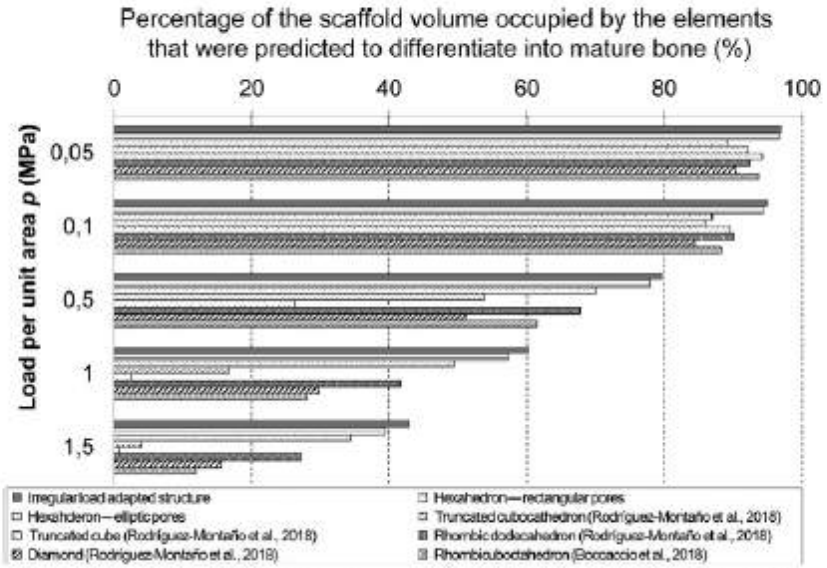

Fig. 12.10 Percentage of the scaffold volume occupied by mature bone for different levels of load.
Adapted with permission from Rodríguez-Montaño, Ó.L., Cortés-Rodríguez, C.J., Naddeo, F., Uva, A.E., Fiorentino, M., Naddeo, A., Cappetti, N., Gattullo, M., Monno, G., Boccaccio, A., 2019. Irregular load adapted scaffold optimization: a computational framework based on mechanobiological criteria. ACS Biomater. Sci. Eng. https://doi.org/10.1021/acsbiomaterials.9b01023. Copyright (2019) American Chemical Society.

better the regular ones also in the case they are subjected to "error" loads, i.e., to loads slightly different with respect to those for which they were optimized. The predictions on the scaffold performances are consistent with the experimental data of previous studies reported in the literature (Barba et al., 2018; Liu et al., 2013).

12.5 Concluding remarks and future perspectives

In the future, integrative approaches for scaffold design should be adopted, based on a full understanding of the different key factors involved in the scaffold design, such as the degradation of biodegradable scaffolds and the angiogenesis. Furthermore, the future studies on the optimal scaffold geometry should overcome the main limitations of those currently available in the literature. The main limitation of the proposed optimization studies is represented by the fact that a clear and direct relationship between the scaffold geometry and the consequent bone regeneration process is not yet known. The identification of the geometrical features that can affect the bone regeneration requires the study of different classes of pore shapes in a systematic way. However, no such studies are available, so far in the literature (Zadpoor, 2015).

Many studies are available in the literature on the geometry optimization of scaffolds for bone tissue engineering. However, all of them try to determine the optimal geometry based on specific criteria neglecting that the bone regeneration process occurring in scaffolds is the result of complex phenomena related to biological,

mechanical, and chemical aspects. To take into account all the mechanisms involved in scaffolds, it is necessary to implement multiobjective optimization algorithms where each objective function is related to a specific aspect. Order relations must hence be established to determine the importance of each objective function and to determine the weight of each of the valid optimized solutions in the identification of the final optimal solution.

Another limitation of the studies currently available in the literature on scaffold optimization is that they are far from being applied in the clinical context. The ideal procedure that should be carried out in the clinical context consists in determining, for the specific patient, the optimal scaffold to be implanted. To this purpose, after carefully investigating the anthropometric features of the patient, the specific geometry of the region where the scaffold should be implanted and the current state of the patient metabolism, computational procedures should be activated to determine the optimal scaffold to implant capable of favoring the formation of the largest amounts of bone in the shortest time. A very complex task is, at this point, to determine, given the specific anthropometric features, the actual boundary and loading conditions acting on the scaffold. In fact, anthropometric features regard the macroscale level while the scaffold dimensions are at the level of some microns. A possible strategy that can be adopted to pass from the macroscale to the microscale and vice versa consists in adopting multiscale approaches. In detail, the passage from the macro- to the microscale occurs with localization rules, the contrary, with homogenization rules. In other words, the macroscale model of the patient can be generated, albeit in an approximate way, with reverse engineering techniques or by using medical imaging techniques. Then, on the macroscale model the exact region where the scaffold must be implanted can be identified. Based on the type of bony lesion, the principal dimensions of the scaffold can be defined. The (microscale) model of the scaffold can be generated. Localization rules can be utilized to determine, starting from the macroscale model, the boundary, and loading conditions acting on the scaffold model. Homogenization rules can instead be utilized to determine the equivalent properties of the scaffold model that can be passed to the macroscale model. As it is clear, the most important requirement to conduct such computations is represented by an adequate computational power. This aspect becomes yet more relevant in view of the fact that for a clinical application of the optimization algorithms, computations have to be conducted quickly so as to allow surgeon to do his/her choice in the shortest time.

Acknowledgments

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