Computational Methods in the Modeling of Scaffolds for Tissue Engineering

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Abstract Tissue engineering uses porous biomaterial scaffolds to support the complex tissue healing process to fulfill two main functions: (1) to support mechanical loading and (2) to allow mass transport. Computational methods have been extensively applied to characterize scaffold morphology and to simulate different biological processes of tissue engineering. In addition, phenomena such a cell seeding, cell migration, cell proliferation, cell differentiation, vascularisation, oxygen consumption, mass transport or scaffold degradation can be simulated using computational methods. A review of the different methods used to model scaffolds in tissue engineering is described in this chapter.

1 Introduction

Tissue engineering is considered as "an interdisciplinary field that combines the knowledge and technology of cells, engineering materials, and suitable bio-chemical factors to create artificial organs and tissues or to regenerate damaged tissues" [1]. More recently, Williams defined tissue engineering as "the creation (or formation) of new tissue for the therapeutic reconstruction of the human body,

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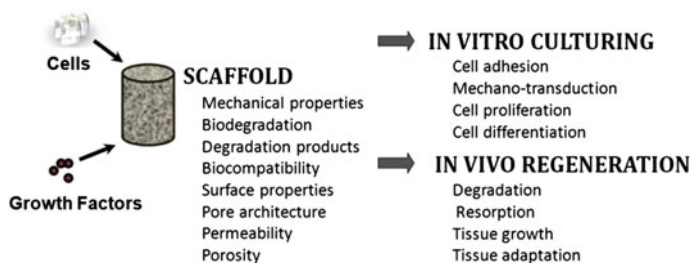
Fig. 1 Tissue engineering process using biomaterial scaffold (modified from Liu et al. [6])

by the deliberate and controlled stimulation of selected target cells through a systematic combination of molecular and mechanical signals" [2]. The process of creation of biological tissue needs an artificial substrate to guide the tissue and control the cell response to the supply of specific molecular and mechanical signals. "Scaffold" is the denomination for the temporal artificial support. Generally studies of biomaterial substrates are done in two-dimensions in order to evaluate the cell-biomaterial interactions. However, it is desired that the scaffold substitutes the defect or mimic the organs or tissues structures in a three-dimensional manner so that it ensures the functions of the damaged tissues.

In the last decade the advances made in tissue engineering and scaffold research have increased substantially [3]. These substantial changes in this scientific field should generate a higher quality of life of people. However, the main barrier found so far is related to the difficulties of translating scientific results into clinical applications. Another problem is related with the high complexity of the biological processes that are taking place and that are not well controlled or understood. The complexities and the use of the human cells as a cell source make tissue engineering an expensive process with usually a low reproducibility of the results at an industrial scale.

The requirements of a scaffold are multiple and different for each application. Nonetheless some common characteristics can be found such as: a good network of interconnecting pores, open channels capable to provide the oxygen and nutrients to the cells inside the scaffold, an easy removal of the waste product and a biocompatible material able to provide the appropriate mechanical strength and biodegradable properties. Some of the characteristics and phenomenon involved in tissue engineering are summarized in Fig. 1. The intrinsic biomaterial properties in relation to the scaffold architecture influence the affinity and response of the cells within the scaffold. During the cell culture it is desirable (a) to know the forces supported by the cells attached on the scaffold, (b) to study the distribution of cells after seeding, (c) to study how occur cell migration, proliferation, and differentiation, and (d) to study the influence of the mechanical stimuli on the cell response. This complexity is further increased under in vivo conditions where the biomaterial degradation and tissue formation, and the adaptation of a new tissue with the new blood vessel formation (angiogenesis) are combined.

Computational methods have been introduced in tissue engineering as tools to comprehend and predict the phenomenon occurring inside scaffolds. Initially, the

cells are seeded on a porous scaffold that acts as a template to facilitate the formation of functional new tissue and organ. Some variables such as pore size, material type and fabrication process are known to influence the cell response [4]. A computational analysis of scaffold properties should consider the overall problem as a continuous two phase's problem: a solid bulk scaffold and a fluid medium inside the pores. The diversity of the methods used so far shows that different assumptions have been made to simplify the complex experimental or physiological conditions. Nevertheless the common aim of these studies is to predict, understand or determine the optimal culture conditions or scaffold morphology [5]. Mechanobiological concepts are also being used more commonly to explain how the cells sense the signals from the environment and how their response to them can affect the cell phenotype related processes. In this chapter, we will discuss some of the results obtained with the computational methods used to characterize the scaffold as an artificial structure to be used in tissue engineering applications.

2 Computational Structural Characterization of Scaffolds

Generally, the conventional scaffold fabrication techniques (salt leaching, phase separation or gas foaming) present difficulties to obtain a precise and repeatable scaffold microstructure in which pore interconnectivity or pore size are guaranteed [7–10]. Each technique is usually most suited to a specific biomaterial or scaffold and for a specific tissue engineering application. Porous scaffolds need to be characterized due to the irregular microstructures that give a different microenvironment to the cells attached onto the scaffold surface.

Novel techniques allow an initial computational control of fabrication using computer-aided design (CAD). The common name used for these techniques is rapid prototyping (RP). These techniques lead to better pore reproducibility of regular shape and better interconnection than the conventional methods. Regular scaffolds offer an easier understanding and optimization of diverse biological phenomena. However, once fabrication using RP techniques is made, it is necessary to characterize the regular pores because the accuracy of the fabrication method depends on the biomaterial properties, the RP techniques used and the conditions applied during the process [11, 12].

In both cases (conventional and RP techniques) it is useful to characterize the sample in a non destructive manner. Computationally it is possible to apply imaging techniques (micro-Computed Tomography and Nuclear Magnetic Resonance) and using reconstruction algorithms. Through scaffold reconstruction it is possible to know the pore interconnectivity, the overall porosity, the pore size distribution and the specific surface area. Some examples of scaffold structures reconstructed and characterized using computational techniques are shown in Fig. 2. The irregular distribution of pores of calcium phosphate (CaP) cement microstructure is shown in a cross section in Fig. 2a [9]. The reconstruction was
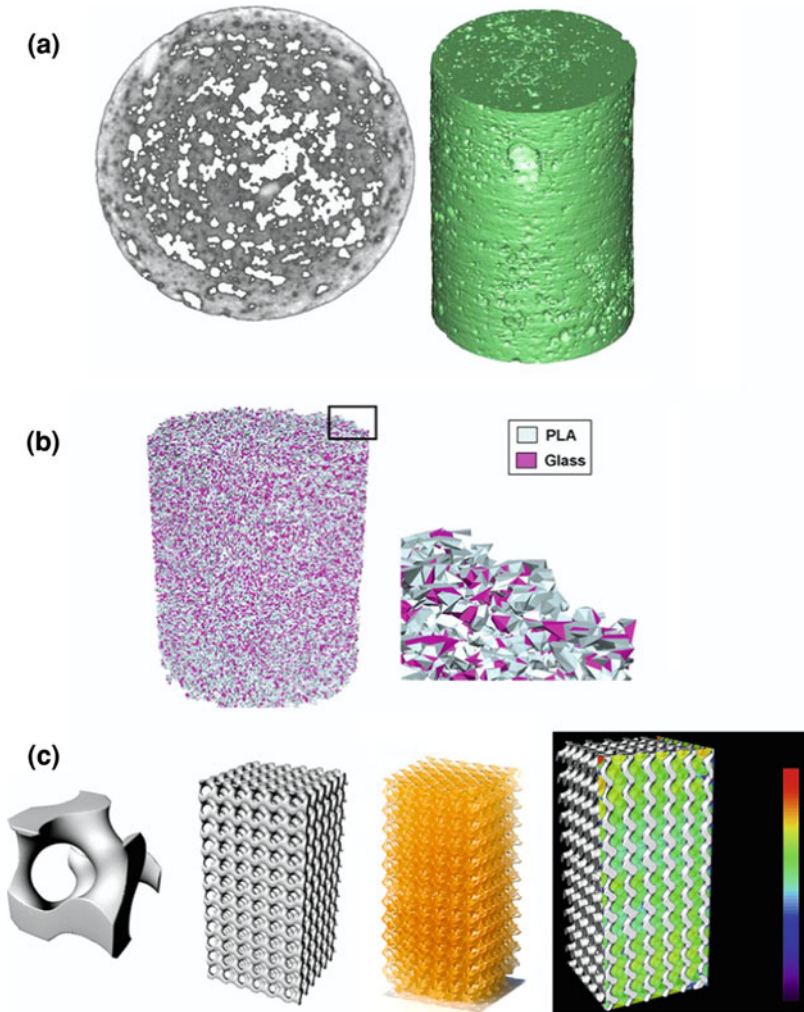
Fig. 2 Computational approaches for characterize of the scaffold. **a** (*left*) 2D cross section of micro-CT images of a non injected CaP cement and (*right*) 3D reconstruction in MIMIC (Materialize)of the CaP cement (from Lacroix et al. [9]). **b** Reconstructions of PLA-G5 (polylactide acid and glass) scaffold and representation of component in the finite element model (from Milan et al. [13]). **c** CAD-designs of the repeating gyroid unit cells assemble of $6 \times 6 \times 12$ unit cells, photo of build structures and μCT-scanning of the built structures (modified from Melchels et al. [14])

obtained by superimposing consecutive cross sections to form a three-dimensional reconstruction of the final sample (Fig 2a, right).

Usually, after this characterization based on the distributions, shape and size of the pores, the scaffold solid and internal volume of pores are computationally reconstructed to simulate different physical and cellular processes. For these

reasons the reconstruction step is vital to obtain the correct characterization and numerical analysis. The second example (Fig. 2b) selected shows a volume of one cylindrical sample of a PLA (poly-lactide acid) polymer with glass composite biomaterial [13]. PLA and glass particles were identified using the gray values for each material allowing separation of the material properties for the computational analysis.

Until now it has been possible to obtain a complete structural characterization of irregular structure scaffolds. However, the heterogeneity of the geometry in non-regular scaffold minimizes the use of scaffold models since each sample is unique. Therefore it is difficult to know whether the modeled scaffold is representative of the real scaffolds used. For RP scaffolds the steps to follow are easier (Fig 2c). Initially the desired design (CAD) of pores is drawn, through a representative volume element (for example of a gyroid shape in Fig. 2c) and the complete scaffold (cylindrical volume) are designed [14]. After the scaffold fabrication using RP techniques (stereolithography in this example) is characterized by means of micro-CT method allowing comparison of the initial design with the final product.

3 Computational Evaluation of Mechanical Properties of Scaffold

3.1 Mechanical Properties Depending on the Scaffold Microstructure

The desired mechanical properties of porous scaffolds vary depending on the clinical applications. It is therefore desirable to be able to control and tune such properties on a specific case basis. The digital scaffold reconstruction methodology showed above offers the possibility to develop the scaffold structure maintaining the specific micro pores. The Finite Element Method (FEM) can be used to predict the mechanical properties of a scaffold. FEM is a numerical technique that gives approximate solutions through partial differential equations. Defining the problem from the geometry, the domain is divided in finite sub-domains called elements. Through an adequate mesh of elements, the bulk material properties and the loading conditions that correspond to the scaffold are applied. In tissue engineering, the FEM is used principally to determine the effective mechanical properties of the porous scaffold. For example, the method allows to calculate the effective Young's modulus E_f under compression (Eq. 1) dependent on the reaction force R computed at the nodes, the total cross section area of the scaffold A, and the axial strain applied $\varepsilon = \frac{\Delta l}{l}$ [6, 9].

$$E_f = \frac{R}{A\varepsilon} \tag{1}$$
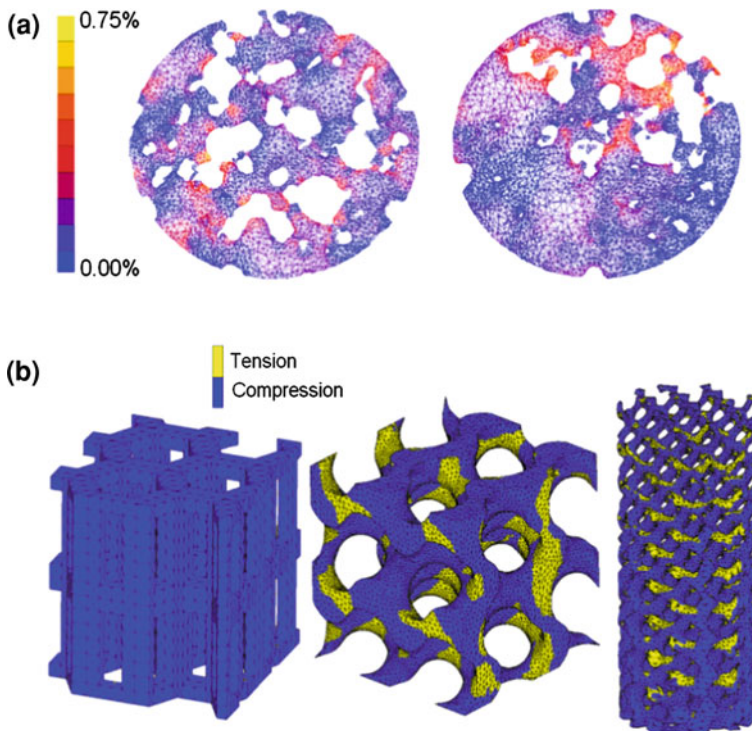
Fig. 3 **a** Examples of distribution of octahedral shear strain in two samples for CaP cement (*left*) and glass (*right*) scaffold morphologies (modified from Lacroix et al. [9]). **b** Major strain distribution in RP pores; the zones under tension or compression strain are delimited; prism hexagonal shape with 70% of porosity (*left*), gyroid pore structure with 70% of porosity (*middle*), and gyroid pore shape distributed gradually through the height of scaffold (global porosity equals 70%) (*right*) (data from Olivares et al. [5])

The mechanical parameters computed in the scaffold surface are considered as the stimuli or signals felt by the cells attached. Dependent on the stimuli magnitude (strain for example), the stimuli will alter cell proliferation or phenotype differentiation. Generally, for bone tissue engineering applications a compressive load is applied to determine the strength and the strain distribution in the scaffold wall surface (see Fig. 3). The effect of mechanical stimuli was studied through micro-FE models for macroporous CaP cement and for a porous glass ceramic scaffold. The octahedral shear strain distribution on a two dimensional section of both samples is shown in Fig. 3a; higher strains are found in areas close to the pores with magnitudes up to 0.75% for the application of a compressive strain of 0.5% [9]. The strain distribution throughout the section is quite inhomogeneous due to the inhomogeneous pore distribution.

Under a compressive load equivalent to a uniaxial strain of 0.5%, the structures shown in the Fig. 3b presented a higher proportion of material experiencing

compressive strain than tensile strains. Hexagonal structures lead to lesser variability of major strain distributions (compressive strain from 0.25 to 0.75%) on the walls than the gyroid structures (from tensile value of 0.25% until compressive values of 1%) [5]. Thus, the stimuli not only is dependent on the uniform distribution of pores, but also depend on pore shape [6, 14].
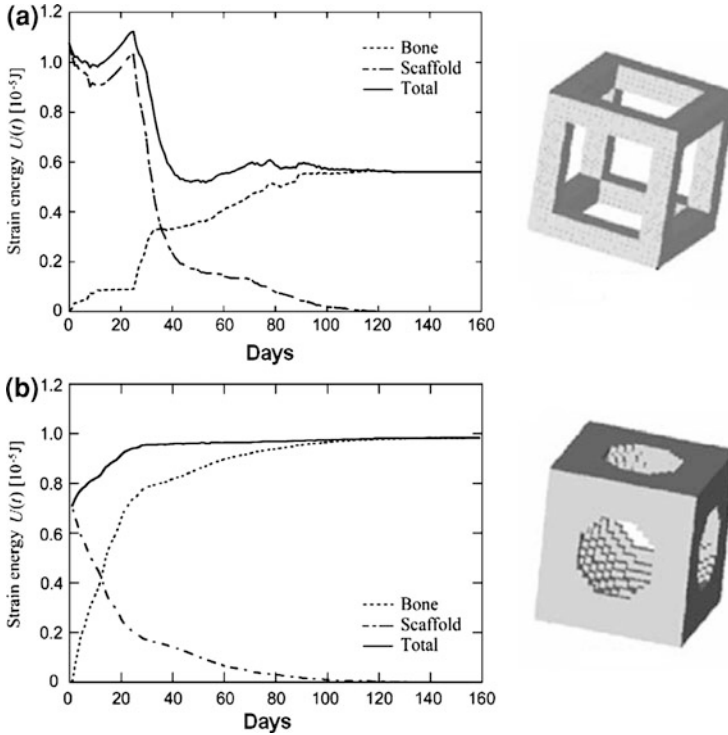
3.2 Scaffold Degradation and Tissue Regeneration

Optimum scaffold degradation is related directly with the temporal mechanical properties needed to substitute the tissue damage. Few computational studies try to explore the scaffold implantation and in vivo response. One example is to correlate the relationship between the scaffold geometry with the resorption of the scaffold, but independently of its composition [15]. Another study based on multiscale simulation [16] shows that the degradation kinetic of polymer (PLGA, poly (lactic-co-glycolic acid) is fast and has a negative effect in the balance of tissue regeneration within scaffolds.

Another example selected here to explain the scaffold degradation was developed by Adachi et al. [17]. They proposed a framework to simulate bone regeneration, which includes the degradation rate. They evaluated the mechanical function in the bone regeneration process by changing the strain energy at the bone–scaffold system. Scaffolds with lattice-like and spherical pore structures were assessed (Fig. 4). The scaffold degradation was assumed to be due to hydrolysis, decreasingthe polymer molecular weight W, and therefore inducing a decrease in the scaffold Young's modulus E_S (Eq. 2). E_{S0} is the initial scaffold Young's modulus and W_0 is the initial molecular weight. The rate of degradation is affected by the morphology of the scaffold microstructure, and large surface areas accelerate the diffusion of water molecules into the bulk of the polymers.

$$E_s = E_{s0} \frac{w(t)}{w_0} \qquad (2)$$

Bone formation and bone resorption are accomplished by osteoblastic and osteoclastic cellular activities respectively. New bone formation was modeled using the rate equation for trabecular surface remodeling (Eq. 3) based on the uniform stress hypothesis [18, 19]. Here, σ_c is the representative stress at point x_c on the bone or scaffold surface on which the osteoblasts form new bone matrix, and σ_d is the representative stress in the neighboring area around point x_c. S denotes the surface; σ_r is the stress at neighboring point x_r within the sensing distance $l_L(l = |x_r - x_c|)$ and $w(l)[w(l) \geq 0\,(0 \leq l \leq l_L)]$ is the decaying weighting function.

$$\sigma_d = \frac{\int_S w(t)\sigma_r \mathrm{dS}}{\int_S w(t)\mathrm{dS}} \qquad (3)$$

Fig. 4 Computational simulation of bone tissue regeneration that consists of scaffold degradation and new bone formation using the voxel finite element method. **a** Lattice-like structure with l = 1.6 mm and **b** spherical pore structure with $d = 2.6$ mm (modified from Adachi et al. [17])

The changes in the total strain energy of the bone–scaffold system, $U(t)$, in the regeneration process are plotted in Fig. 4 for the lattice-like and spherical pore structures. A transition of the mechanical function between two structural components can be seen. For the lattice-like structure the crossing point occurs at 40 days, while for the spherical pore it occurs at 20 days. The scaffold pore structure design presents the highest influence in the bone regeneration process. Through the case presented, it was demonstrated that the optimal design variables of the scaffold can be determined by computational simulation of bone regeneration. However, the rate equations for new bone formation and scaffold degradation were derived on the basis of various simplifications and assumptions.

3.3 Homogenization Method for Scaffold Design

Studies of different mathematical cell units designed for RP methods were made to create a library of structures based on CAD design [20–22]. Porous scaffold design is a compromise between high mechanical function and high mass transport needs.
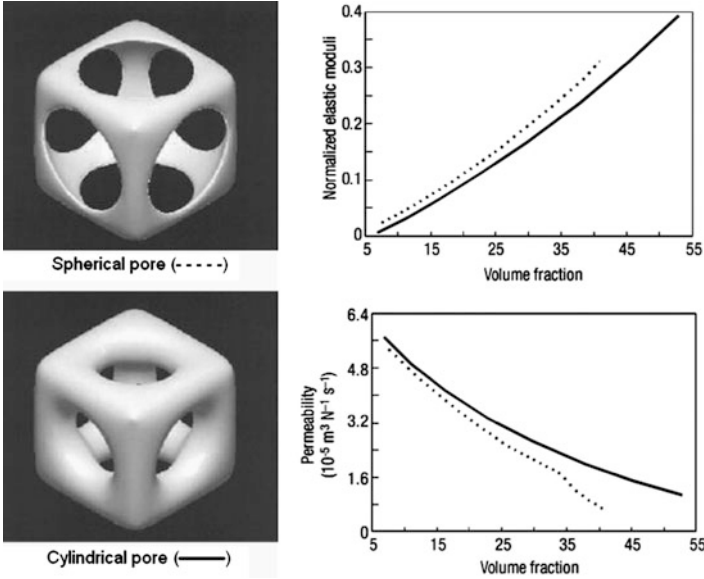
Fig. 5 Elastic modulus and permeability versus porosity on two pore cell units; spherical pore (*top, in plot with dashed line*) and cylindrical pore (*bottom, in plot with solid line*), modified from Hollister [23]

The homogenization theory is used to generate the multiscale equilibrium equations to compute effective properties of these unit cell designs [21, 22]. The study presented by Hollister [23] has been selected to illustrate to the reader the homogeneity method. The mechanical properties such as the macroscopic effective stiffness E^{macro} (Eq. 4) can be computed from the stiffness at a microscopic E^{micro} level depending of the strain tensor M and the volume of unit cell V. The mass transport (fluid inside the pores) is also homogenized focusing in the macroscopic permeability K (Eq. 5) computed through the average Stokes flow velocity v and pressure gradients [23].

$$E^{macro} = \frac{1}{|V_{unit\,cell}|} \int_V E^{micro} \, M \mathrm{d}V_{unit\,cell} \qquad (4)$$

$$K^{macro} = \frac{1}{|V_{unit\,cell}|} \int_V v \mathrm{d}V_{unit\,cell} \qquad (5)$$

Hollister [23] have found that an increment of the amount and disposition of material in a pore induces an increment of elastic properties, but with a reduction of the permeability (Fig. 5). Results demonstrate that the modulus increases as expected with volume fraction, and that the spherical pore leads to a stiffer scaffold. The permeability decreases as expected with volume fraction and cylindrical pore design allows fabricating a more permeable scaffold. Others

studies illustrate how for different scaffold microstructure designs, different effective stiffnesses and permeabilities are computed [6, 14]. However, the importance of this method lies in the ability to maximize the permeability for cell migration and mass transport, always taking care to maintain the effective elastic properties similar to that of the natural tissue [24].

Homogenization is a powerful mathematical technique and can be applied in tissue engineering to optimize the process inside the scaffold. The study proposed by Shipley et al. [25] used this theory to optimize the oxygen, glucose and lactate transport through the maximum value of diffusion, consumption and production with optimal choice of cell density. So select the most favorable scaffold structure and the preference of perfuse direction.

## 4 Simulating Fluid Flow Within Porous Scaffolds

4.1 Computing Fluid Stimuli on the Scaffold Pores

In tissue engineering bioreactors are usually used as systems to provide the dynamic environment to the cells. The stimuli can be obtained from the scaffold surface deformations or from the fluid flow inside the pores. Mass transport within the pores is related with the cell seeding and with the possible response of the cells to the stimuli. Perfusion bioreactors are systems extensively used in tissue engineering, due to the capacity to lead to a uniform distribution of fluid over the scaffold [26–28]. Micro pore shapes in the scaffold have a higher influence in flow profile. Generally, the flow is simulated using computational fluid dynamic (CFD) method. In the specific case of direct perfuse flow, a laminar and Newtonian flow are simulated, computed by the Navier–Stokes equation (Eq. 6) and the continuity equation (Eq. 7), where u and ∇p are the fluid velocity and pressure gradient respectively.

$$\rho \vec{u} \cdot \nabla \vec{u} = -\nabla p + \eta \nabla^2 \vec{u} \qquad (6)$$

$$\nabla \cdot \vec{u} = 0 \qquad (7)$$

In Fig. 6 results of CFD for irregular pores morphologies [13] and regular morphologies [5] are presented. Irregular morphology models were developed from the micro-CT images and the fluid volume inside the pore was modeled (Fig. 6a). The scaffold material property in itself was not accounted for in these studies, only the pore morphological characteristics influenced the results. Milan et al. [13] obtained a non homogeneous distribution of fluid flow due to the irregular interconnection between the pores. For an inlet velocity of 100 μm/s, the highest velocities (150–780 μm/s) were found in the center of the scaffold pores whereas the lowest velocities (0–50 μm/s) were found close to the pore walls (Fig. 6a).
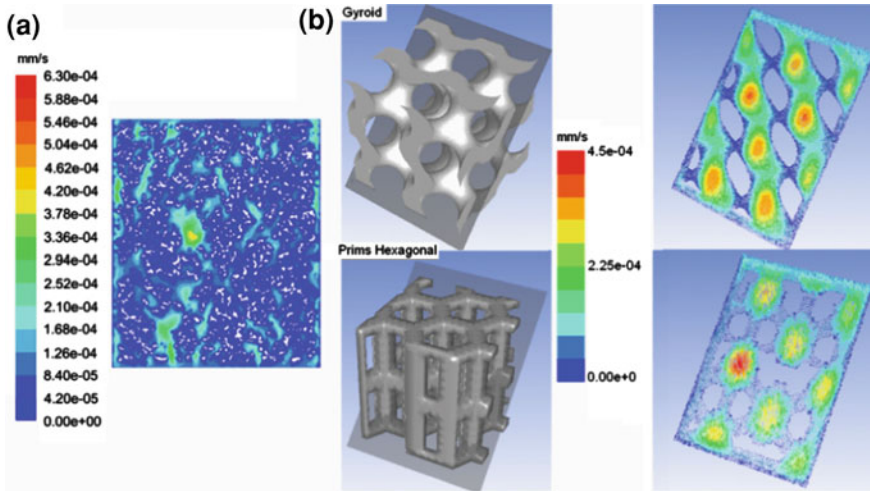
Fig. 6 Velocity profiles represented in a cross section under fluid flow perfusion (v = 100 μm/s). **a** Irregular scaffold morphology fabricated with PLA-G5 (poly-lactide acid and glass), model obtained from micro-CT (modified from Milan et al. [13]). **b** Representative volume element obtained from CAD of rapid prototyping scaffold. Gyroid shape with 70% of porosity (*top*), hexagonal prism with 70% of porosity (*down*) (modified from Olivares et al. [5])

RP can be an excellent fabrication technique to control the fluid stimuli within scaffolds. From the study developed by Olivares et al. [5], two different scaffold morphologies were selected (Fig. 6b). A gyroid structure was compared with a hexagonal straight prism. Pore interconnections of the hexagonal prism limited the accessibility of the fluid to some areas inside the scaffold. With an inlet velocity of 100 μm/s, the fluid flow distribution for the gyroid structure was in the range of 220–450 μm/s while for the hexagonal prism structure it was in the range of 220–300 μm/s.

4.2 Cell Seeding Simulation Using CFD Models

Cell seeding is a critical step in tissue engineering since it precedes the further steps for the in vitro and in vivo culture. In tissue engineering, the optimization of cell seeding and the comparison between different studies are problematic because cell seeding depends highly on the structure of the scaffolds, such as porosity, tortuosity, pore size and pore shape, the number of cells in suspension, etc. Recently, a system to control cell seeding through perfusion was proposed by combining a CFD study of a rapid prototyping porous scaffold with the perfusion fluid flow experimentation [12]. Gyroid pore design was used for the scaffold stereolithographic fabrication. The values of pore size distribution in an isotropic
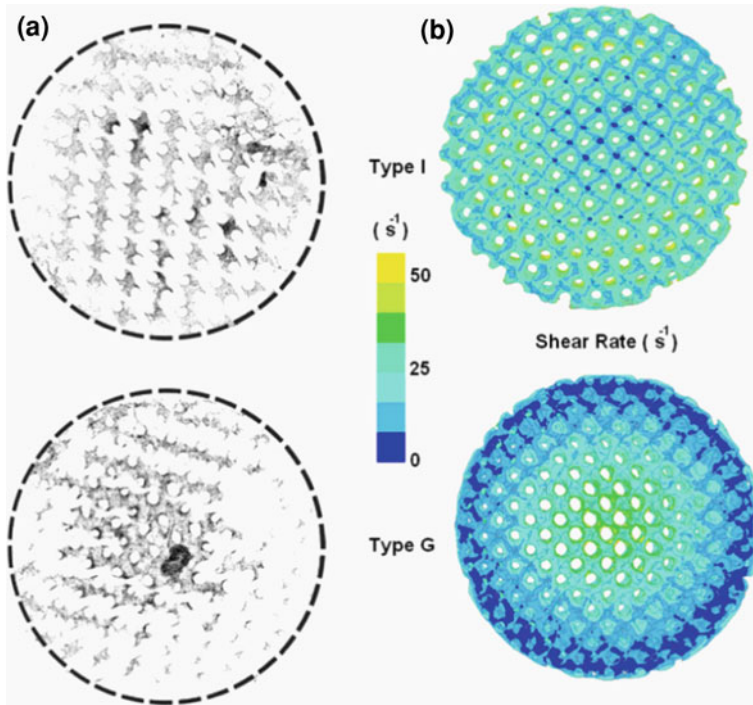
Fig. 7 Representative threshold z-stacks of confocal microscopy images (500 μm thickness) showing adhering cells after perfusion seeding. The fluid shear rates were measured in the scaffold surface through the CFD methods. **a** Type I. **b** Type G (from Melchels et al. [12])

scaffold (type I) were of 412 ± 13 μm with porosity of $62 \pm 1\%$ (Fig. 7a). In order to study the influence of pore size variation, a gradual variation of pore size (type G) was introduced where the scaffold pore size was ≈ 500 μm at the center and ≈ 250 μm at the periphery with a total porosity of $56 \pm 3\%$ [12]. Fluid volume was reconstructed from micro-CT images and represented the actual design of the perfusion chamber. These models assumed steady state conditions for maximum fluid flow while an alternant flow was applied in vitro when the cells are suspended in the medium. However, even with this restriction, the computational model demonstrated a close relation between distribution of maximum stimuli and final cell seeding distribution (Fig. 7).

When the distribution of pore size was uniform (Type I), the distribution of cells densities observed through confocal images after seeding was also homogeneous, in a similar behavior obtained numerically (Fig. 7a). In the gradient pore size (Type G), a gradient of shear stress was obtained in the cylindrical scaffold, which compared well with the gradual distribution of cells obtained after 16 h of seeding (Fig. 7b).
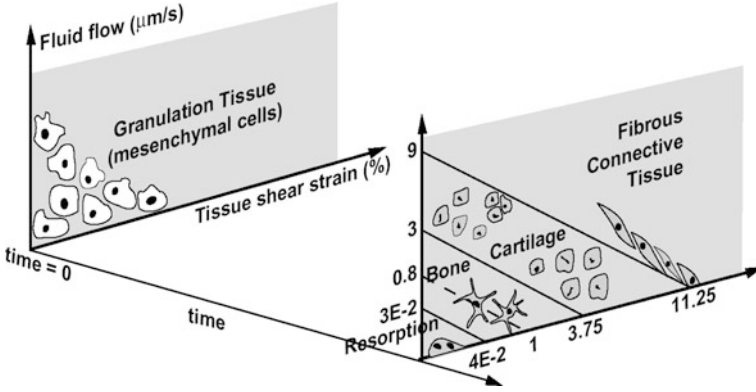
Fig. 8 Mechano-regulation model. The tissue phenotype is determined for each element dependent on its position in the mechano-regulation diagram (not drawn to scale) from Lacroix et al. [37])

## 5 Simulation of Mechano-Biological Concepts

5.1 Cell Differentiation Studied Through Separated Phases

A mechanobiological concept was proposed by Prendergast et al. [29] to explain the relation between mechanical stimuli with cell differentiation and tissue formation. This concept was applied on various applications such as implant–bone interface [30], fracture healing [31], osteochondral defect [32], bone chambers [30, 31, 33], and bone distraction [34, 35]. The first numerical application to tissue engineering of this concept was performed by Kelly and Prendergast [32] in which a mechanoregulation algorithm for tissue differentiation was used to determine the influence of scaffold material properties on chondrogenesis in a finite element model of an osteochondral defect.

The basis of the concept is that the stimulus S defined as a combination between the octahedral shear strain SS and the fluid velocity FF can produce some distortion of the cell and therefore affects the cell differentiative activity. In the stimuli equation (Eq. 8), a and b are empirical constants; $a = 0.0375$ and $b = 3~\mu\mathrm{ms}^{-1}$. If $S > 3$, then fibrous tissue differentiation occurs; if $3 > S > 1$, then cartilage differentiation occurs; if $1 > S > 0.267$, then immature bone differentiation occurs; and if $0.267 > S > 0.01$, then resorption occurs (Fig. 8).

$$S = \frac{\mathrm{SS}}{a} + \frac{\mathrm{FF}}{b} \tag{8}$$

One example to illustrate the use of the mechano-regulation model on scaffold analysis is the study performed by Sandino and Lacroix [36] on irregular CaP scaffold morphology where tissue differentiation was simulated for mechanical stimuli transmitted under compressive load and perfusion fluid. The properties of
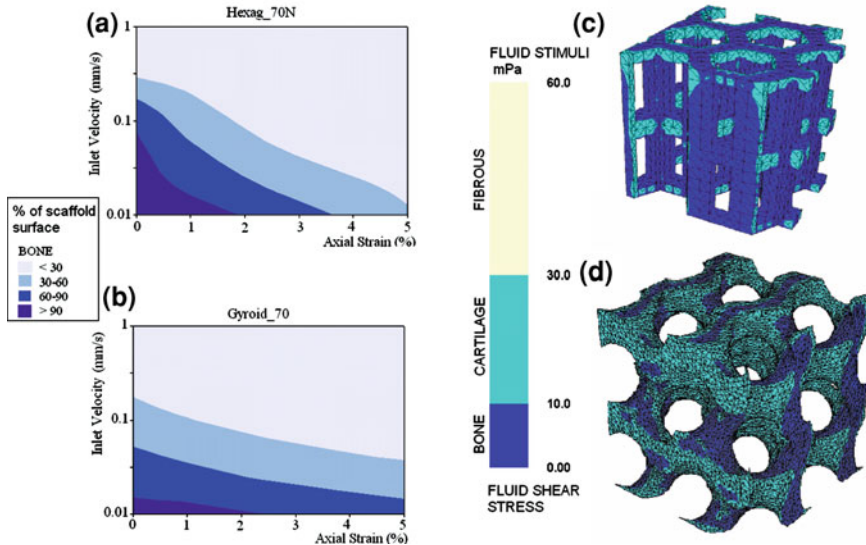
Fig. 9 Influence of scaffold morphology [**a, c** Hexagonal Prism, porosity 70%; **b, d** Gyroid, porosity 70%] in stimuli for tissue differentiation. **a, b** Optimization for conditions represented through the percentage of stimuli that correspond with bone tissue differentiation. **c, d** phenotypes representations in models distributed for fluid stimuli induced by 0.1 mm/s (modified from Olivares et al. [5])

the finite element (tissue) were changed depending on the stimuli. The fluid phase was the only phase to change (through a change of viscosity) to simulate the growth of tissues within the pores. The discretization of the fluid phase and the solid phase captured the discontinuity of mechanical stimuli affecting cells seeded within a scaffold over time. Using regular scaffolds with ideal morphology, Olivares et al. [5] concluded that the mechanoregulation diagram on these scaffolds was more sensitive to fluid flow changes than to solid strain changes. They studied the influence of the experimental conditions for eight different scaffold designs to create a bone formation optimization plot (Fig. 9a, b). In the same study, the authors related the scaffold design with the phenotype (Fig. 9c, d) using the mechano-regulation theory explained previously. For the same inlet fluid stimuli and porosity a scaffold with a hexagonal prism leads to increased bone formation areas compared with a gyroid structure.

5.2 Lattice Point Approach

The lattice formulation was introduced in a mechano-biological model by Perez and Prendergast [38] in order to include individual behavior of cell. A lattice is created within each finite element and is assumed with granulation tissue
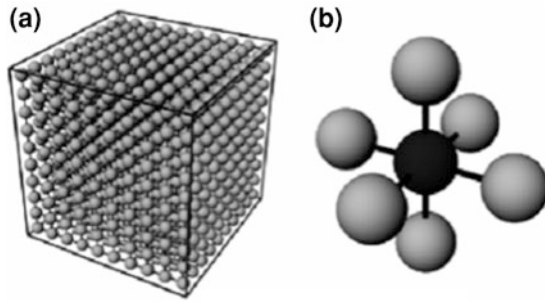
properties (typical initial tissue that fill wounds). Each lattice is considered a region of space for both the cell and extracellular matrix (Fig. 10).

The lattice model has been used as an alternative to simulate cell proliferation and migration. The proliferation of a cell is initially assumed (in 3D) to be surrounded by six possible locations. First a new position is randomly selected from the surrounding locations (including its original position). In turn one of the remaining neighboring positions is then chosen for the daughter cell to occupy. In the event that the chosen location is already occupied, another position is chosen again at random. This process continues until either the simulation ends or all lattice positions are occupied. Recognizing that migration is a more rapid process, a new location for a migrating cell is chosen per iteration of the proliferation process. A lattice point can be occupied by a mesenchymal cell (MSC), a fibroblast, a chondrocyte, an osteoblast or an endothelial cell. The sequence of endothelial cells and the vessel growth direction, growth length and branching are defined through the lattice formulation as probabilistic functions.

The lattice concept was applied in tissue engineering by Byrne et al. [39] (Fig. 11). They studied the effect of important design properties such as scaffold porosity, degradation rate and scaffold mechanical properties, on the tissue formation process inside a regular structured bone scaffold. Initially the scaffold was assumed to be filled with granulation tissue and 1% of lattice points, chosen at random, were "seeded" with mesenchymal stem cells. Over time, the scaffold dissolved at a rate of 0.5% per iteration of the simulation, leaving space for the developing tissue. In this study, they were able to identify optimal scaffold properties that would lead to the highest amount of bone formation.

Studies of angiogenesis during tissue differentiation were performed by Checa and Prendergast [40] using the lattice model. The angiogenesis model was applied to a simplified scaffold for bone tissue engineering and the number of cells initially seeded into the scaffold was related to the rate of vascularization and the penetration of the vascular network. They showed that the initial cell seeding conditions had a significant effect on the vascularization of the scaffold.

In order to simulate also the angiogenesis phenomenon in CaP cement, Sandino et al. [41] applied the lattice approach in a scaffold with irregular morphology (Fig. 12). For the magnitudes of mechanical strain studied (0.5 and 1% of total
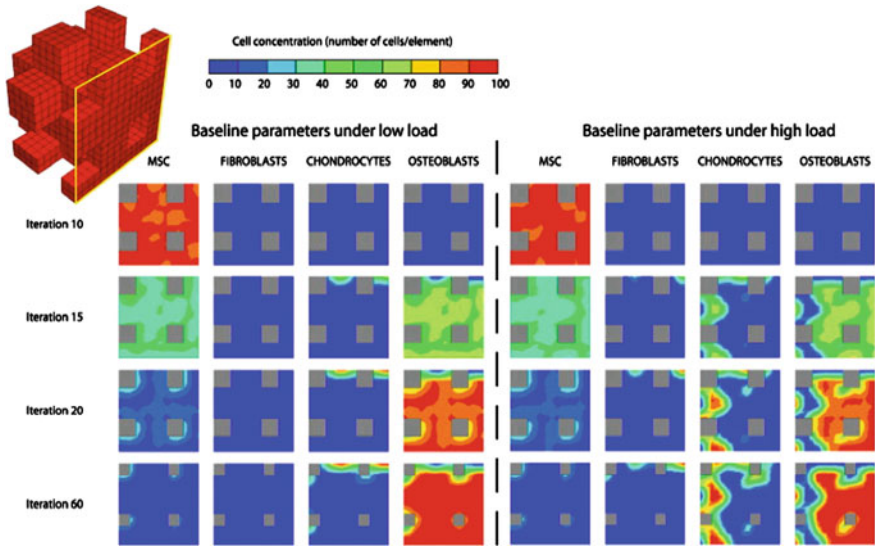
Fig. 11 Cells distribution in a simplified scaffold using lattice method. (from Byrne et al. [39])
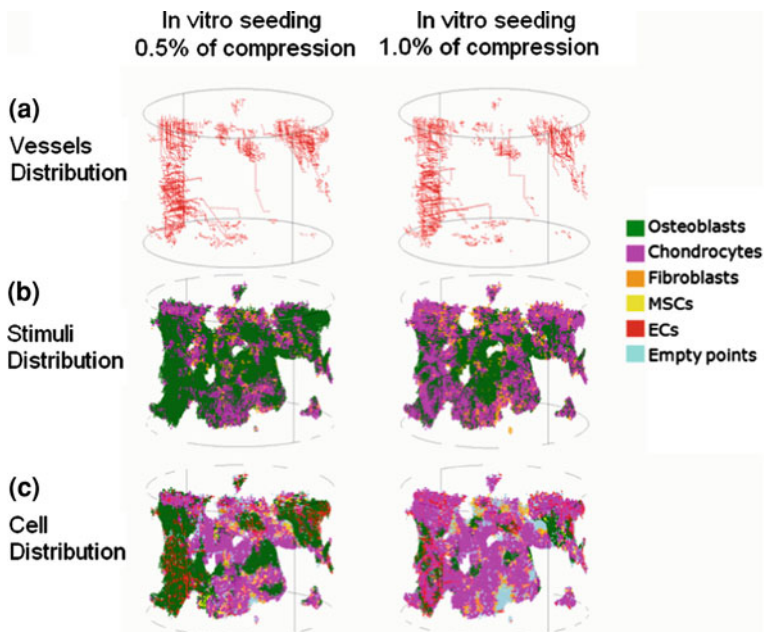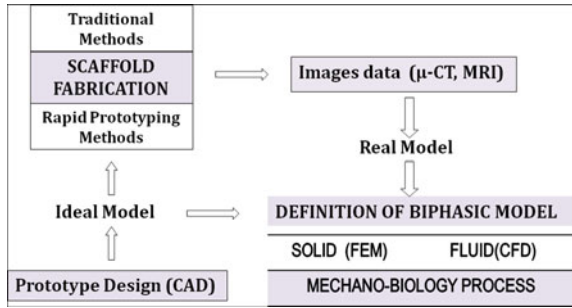

Fig. 12 Angiogenesis and mechano-regulatory stimuli to cell differentiation in simulation (0.5 and 1% of total strain and in vitro MSCs seeding) after 100 iterations are showed. **a** Vascular network. **b** Stimuli distribution. **c** Cell distribution (modified from Sandino et al. [41])

Fig. 13 Scheme representing the main methods applied for in tissue engineering scaffold

deformation), there was not a noticeable effect on angiogenesis. Similar vessel networks were observed in both cases of strain (Fig. 12). The angiogenic process was mostly driven by the actual porosity and permeability of the scaffold rather than by the load magnitude.

6 Conclusions and Future Trends

In this chapter, computational methods used in the modeling of scaffolds for tissue engineering were illustrated through some examples selected from the literature. Figure 13 shows a summary of the different schemes used to model scaffolds. Initially the characterization of the scaffold is based on image acquisition and treatment in order to obtain the morphological parameters. These parameters (porosity, pore shape, pore size) can be designed previously (CAD) when a rapid prototyping method is used in the fabrication process; but the real structure can be assessed using micro-CT scanning. In order to control the mechanical properties of the scaffold; displacement or load are applied to simulate the experiment condition and the effective stiffness can be computed. Generally, the FEM is applied in the characterization of the mechanical integrity of scaffold, including the possible simulation of scaffold degradation. The irregular scaffold morphology leads to heterogeneous distributions of stimuli induced from the solid phase. The best control of the mechanical stimuli can be obtained using RP scaffolds. Studies with RP scaffolds allow to develop methods such as homogenization were the optimization of the macro-scaffold properties are related with the micro pore properties.

For the evaluation of mass flow inside the scaffold, computational fluid dynamic (CFD) simulations can be used. Generally, the fluid shear stress is defined as the stimulus acting on the scaffold wall to characterize the fluid flow. In the literature different ranges of stimuli are found and a consensus must be found, but in principle using this methodology it is possible to control precisely the design of the size and shape of the scaffold pores. The mechano-biological phenomenon can also be simulated from the perspective that the porous scaffolds have two phases

(fluid and solid), and that both phases will have an influence in the processes of seeding, migration, proliferation, differentiation, and cell death. In the future, a more direct comparison between computational and experimental results is needed, including differences between biomaterials in term of reaction with the cells and the possibility to discretise the cells (similar to the lattice approach) with cellular properties. Multiscale factors and chemical reaction can also be included in order to simulate oxygen and nutrient transport and consumption. More integration is also needed between the interrelations of biology, materials science and biomechanics. The effect of angiogenesis is crucial for the processes of tissue engineering and should be simulated in computational models.

Several studies [42, 43] have looked at the bone–implant interface when prosthesis is implanted. The formation of fibrous tissue, cartilage or bone depends mostly on the local loading conditions at that interface. Due to the intrinsic patient variability in terms of bone morphology, loading conditions and biological response, the patient specific modeling of such interface remains a challenge. In tissue engineering the same issues remain to be elucidated. However, the advances in in vitro techniques have enabled to control better the loading conditions and biological response, and to define precisely the morphological properties of the scaffold used. It is therefore believed that most of the work performed previously on the interaction of the implant with the host tissue can be transposed directly to the tissue engineering application. The use of multiscale modeling that span (1) from the molecular interaction of the scaffold coating with the molecules present to the surrounding medium, to (2) the cellular interaction with the scaffold surface, and to (3) the formation of extracellular matrix tissue will enable to unravel new knowledge of the interactions between material scaffolds and biological entities. As a conclusion the development of computational methods within tissue engineering opens many perspectives with the possibility to simulate the cellular processes that take place inside the scaffold and to optimize and maximize the formation of functional tissues.

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