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ORIGINAL ARTICLE

Computational mechano-chemo-biology: a tool for the design of tissue scaffolds

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Abstract Computational modeling is usually employed for simulation, design and manufacturing of tissue scaffolds, specially focused on macroscopic and microscopic properties, relying on anatomy and geometrical constraints. However, these models typically require to take into account the effects of cell-matrix interaction due to its crucial influence on a range of cellular processes including cell adhesion, differentiation and tissue formation among others. Computational mechano-chemo-biology is a numerical approach that aims to consider this interaction by means of a multiphysics and/or a multiscale computer framework. This article reviews some of the recent progress made in modeling bone regeneration induced by scaffolds, taking into account cell-matrix interactions. The issues covered in this work include different kind of numerical models at different length scales that go from cell-matrix interaction to tissue mechanics. The review concludes summarizing the main challenges that researchers face to consolidate modeling as a final design tool for tissue engineering.

Keywords Computer-aided tissue engineering · Computational mechano-biology · Cell-material interaction · Scaffold manufacturing

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Introduction

Currently, computational modeling is one of the tools that is being recognized as an important partner of experimental work in biology [51] and biomedical engineering sciences in different applications like cancer [19], cardiovascular [89], bone [21] and wound healing [86].

One of the computing technologies that is widely used in biomedical applications is CAD (Computer Aided Design), ranging from construction of patient-specific models to customized implant design [58]. 3D anatomy based on computed tomography (CT) or magnetic resonance imaging (MRI) data provides the required technology to create specific models in cardiovascular [31, 39, 83], bone [44] or other applications [61]. For example, Bah et al. [3] recently developed a framework to model the geometric variability of the anatomic structures within a large population of femurs. Vahdati et al. [66] combined gait analysis and a subject-specific musculoskeletal model with subject-specific bone geometry in a computational bone remodeling methodology to predict bone density distribution. González-Carbonell et al. [26] used the patient-specific geometry and material properties to study tibial torsion. Dao and Pouletaut [18] created integrated contact models for the simulation of knee replacement implants. Also, Carey et al. [12] created subject-specific FE models of the tibiofemoral joint using dynamic stereoradiography data and kinematic analysis. Therefore, it is clear that CAD is a tool especially adequate for the personalized modeling of anatomies and subject-specific geometries. This circumstance has been possible largely thanks to the developments made in imaging technologies and analysis.

Computer-aided technologies are also especially useful for advanced modeling and simulation in regenerative medicine, where subject-specific characteristics of the

injury have to be taken into account. Indeed, one particular strategy in regenerative medicine is tissue engineering, where biomaterials are used in combination with cells and other stimuli to promote self-repair of injured tissues. Hence, the design of these biomaterials, normally known as scaffolds, is fundamental to induce an adequate healing. These scaffolds, present an specific 3D architecture that aims to mimic the complex behaviour of extracellular matrix in healthy tissues [81]. Their design is defined by the properties of the biomaterial itself and the architecture characteristics. Recently, tissue engineering (TE) has benefited from the development of additive manufacturing (AM) techniques in combination with computer-aided technologies in a novel field known as Computer-Aided Tissue Engineering (CATE), which have led to the design and fabrication of porous scaffolds with custom-tailored architectures [25, 46, 79]. CATE combines different technologies [81], like computer-aided design (CAD), medical image processing, computer-aided manufacturing (CAM), and solid freeform fabrication (SFF) for three major applications in tissue engineering:

1. computer-aided tissue modeling, including 3D anatomic visualization, 3D reconstruction, CAD-based tissue modeling, and bio-physical modeling for surgical planning and simulation;
2 tissue scaffold modeling and biomimetic design, including computer-aided scaffold design and application for virtual scaffold characterization, biomimetic design under multi-constraints, and multi-scale modeling of biological systems incorporating interaction with scaffolds;
3. bio-manufacturing for tissue and organ regeneration, including computer-aided manufacturing of tissue scaffolds, bio-manufacturing of tissue constructs, bio-blueprint modeling for 3D cell and organ printing.

One of the applications where CATE is being successfully applied is Bone Tissue Engineering [32, 80]. These computer-based works mainly focus on the control and design of the overall shape of the scaffold to match patient-specific anatomical constraints and the internal architecture of the scaffold (pore size, porosity, permeability). Therefore, a heterogeneous scaffold can be designed according to the specifications of each patient and of their injuries. However, these computational works are mainly based on the most adequate scaffold design and preoperative plans, but do not analyze the impact of one specific design on the biological response of cells at the cellular level. As the structural and functional unit of life, cells actively sense the surrounding mechano-chemical microenvironment and respond accordingly to regulate tissue formation and healing [9, 15, 54, 85]. Actually, the cell-scaffold interplay exerts an essential role during bone regeneration as cells adhere to the scaffold surface, differentiate and secrete new tissue (see Fig. 1). Therefore, it is fundamental to advance in the understanding of how scaffold properties (biomaterial and architecture) may regulate cell response at scaffold level and how it can affect to the macroscopic properties of bone tissue, is fundamental. In fact, to understand how different mechano-chemical conditions may also regulate this cell response is a topic of relevant interest. Both aspects are normally studied by the field of Computational Mechano-Chemo-Biology, being its main purpose to predict the long term response of cells for a specific scaffold design and for specific local mechano-chemical microenvironment. This aspect has not been thoroughly studied by CATE, although it is clearly in the spirit of this technology.

Therefore, this article aims to review some of the recent progress made in modeling cell-scaffold interactions at multiple length scales and involving multiple fields of physics. Although many different and diverse methodologies have been used for computational modelling in Tissue Engineering, our review focuses on the multiphysics and multiscale analysis. Hence, the first section presents the multiphysics modeling approach. Next, we show a review of multiscale approaches in tissue engineering. And finally, a more detailed description of models that aim to simulate cell-scaffold interactions is presented. The review concludes with a look at future opportunities and challenges to be faced in computational modeling of tissue regeneration.

Multiphysics modeling in tissue engineering

Due to the wide variety of physic fields involved (solid mechanics, fluid flow, mass transfer or biochemistry among others), many different works based on computational

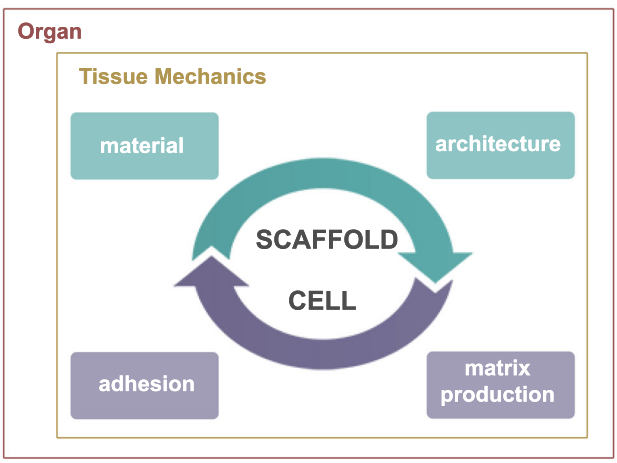

Fig. 1 Interplay between cells and scaffold. When the scaffold is implanted, cells adhere to it to produce matrix. Matrix production is determined by the scaffold properties (material and architecture) which subsequently evolve due to cellular activity

modeling of tissue engineering phenomena can be found in literature [23]. One possible classification is to divide them into three main categories (see Fig. 2) according to the biophysical stimuli that regulates tissue differentiation and formation: solid mechanics, fluid mechanics and mass transport. Certainly, these stimuli are not used in an isolated way, but as a combination of stimuli that establish regulatory theories in function of these stimuli.

Mechanistic-based models normally establish hypotheses of tissue differentiation and/or tissue formation depending on the *solid mechanics* variables that describe the macroscopic or microscopic deformation of the scaffolds. Several authors evaluate the strain energy density to quantify bone tissue formation [1, 53] like in common bone remodeling theories [17]. For example, Adachi et al. [1] simulated bone tissue regeneration and scaffold degradation within a scaffold unit cell based on a voxel finite element approach, optimizing the scaffold microstructure that provides the desired mechanical function during and after the bone regeneration process. They used the change in total strain energy as fundamental mechanical variable to regulate bone formation. Meanwhile scaffold degradation was due to hydrolysis, which was simply assumed to depend on the water content diffused from the surface to the bulk material, also taking into account the decrease of the mechanical properties of the scaffold. Sanz-Herrera et al. [68, 71] also proposed mechanical stimuli to regulate bone formation inside a specific type of scaffold, although they also included cell invasion within the scaffold, which was modeled as a diffusion process based on Fick's law. Bone formation was predicted within idealized or theoretical scaffold geometries and submitted to external mechanical loading. Then, the effects of scaffold material properties such as porosity, stiffness, permeability or degradation rate were analyzed.

However, there exist other biophysics-based theories that hypothesize that fluid shear stress can be the key variable determining cell differentiation in bone [48]. All biological tissues are porous media [36], which means that they contain pores filled with a fluid. These characteristic

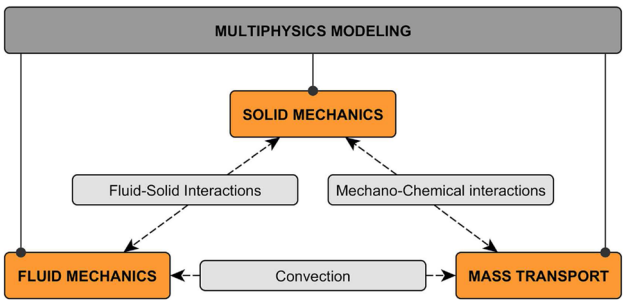

Fig. 2 Classification of multiphysics models according to the involved fields

materials produce exceptional mechanical properties to our biological tissues, like impact absorption, lubrication at joints, adequate transport (diffusion and convection) of ions, nutrients and waste products by means of fluid flow, and finally, promoting mechano-sensing mechanims at cell level. Actually, *fluid mechanics* mainly based on Navier–Stokes equations, has also been widely used in tissue engineering to estimate wall shear stress magnitudes (WSS) [62], only considering the influence of the scaffold architecture. For instance, several works determined that the distribution of WSS is strongly dependent on scaffold architecture [38, 59].

All these models assume that there exists no interaction between the mechanics of the scaffold and the movement of the fluid within the scaffold pores. However, the mechanical deformation of the scaffold may induce the movement of the fluid inside the scaffold, or equivalently, the fluid flow can generate strains on the scaffold. Therefore, a coupled formulation is required where fluid-solid interaction is considered. Two main numerical approaches have been used to model this phenomenon. The first one is based on the use of fluid-structure interaction (FSI) models, where fluid is simulated by means of Navier–Stokes equations combined with the corresponding equations of solid mechanics and the solid-fluid interface. The second one is known as Darcy's law which describes the flow of a fluid through a porous deformable medium. Actually, the Darcy's law has been derived from the Navier–Stokes equations via homogenization [90].

Fluid-structure interaction (FSI) approaches have been applied to understand the role of scaffold stiffness and architecture on the wall shear stress distribution. In fact, McCoy et al. [50] determined that he applied flow rate dominated the mechanical stimulation when compared to the pore size in collagen-GAG scaffolds. More recently, Zhao et al. [93] also applied this method to investigate the role of scaffold geometry (architecture, pore size and porosity) on pore wall shear stress (WSS) under a range of different loading scenarios (namely: fluid perfusion, mechanical compression and a combination of perfusion and compression), finding that scaffold geometry (spherical and cubical pores), and in particular the pore size, has a significant influence on the stimulation within the scaffolds. In addition, they concluded that the combination of loading conditions would allow amplifying these wall shear stresses.

In addition, fluid-structure interaction has also been used to simulate how the fluid movement deforms the cell body, modeling the cell as a solid in many different applications of tissue engineering. Vaughan et al. [87] developed a fluid-structure interaction model to characterise the deformation of integrin and primary cilia-based mechanosensors in bone cells under fluid flow stimulation. Actually, fluid flow through a channel region of a pressure-driven parallel-

plate flow chamber was interacting with a single bone cell which was adhered to the bottom wall of the channel region and simulated as a solid. There are many models [47] that investigate the role played by fluid flow on the primary cilia deflection and how this deflection is involved in the mechanotransduction process whereby fluid flow indirectly induces strains on the internal cell components.

Other authors have, on the other hand, focused on understanding how fluid flow can deform cells when they are moving inside the bioreactor, helping to determine the fluid flow conditions in the inside. With this purpose in mind, Ruberg and García-Aznar [64] presented an immersed finite element method that allowed the simulation of solid-fluid interactions specially focused on highly deformable elastic bodies in a Stokes flow environment. The method was based on a global balance equation which combined the solid and fluid momentum balances, the fluid mass balance and, in weak form, the interface conditions. The method resulted in a full coupling of the solid-fluid system which is solved by an exact Newton method. This kind of models are very useful because they allow estimating the stresses and strains that cells are bearing inside the scaffold in different conditions both during cell culture and when this scaffold is implanted.

Nevertheless, different approaches are possible, for instance, considering that our tissues and scaffolds are porous media. In fact, Prendergast and Huiskes et al. [35] presented a biphasic approach based on the Darcy's equation to define a mechanoregulatory phenomenological law, which proposes a combination of solid and fluid mechanics stimulus to define tissue differentiation and formation. They assumed that the relative velocity between fluid and solid and shear strain are the main mechano-fluid stimuli. Indeed, this law has been widely used to simulate bone fracture healing conditions in Finite Element-based models [27, 30] and also to simulate bone tissue formation and cell differentiation [11, 40, 53]. For instance, Kelly and Prendergast [40] determined the influence of scaffold material properties on chondrogenesis in a finite element model of an osteochondral defect, predicting that increasing the stiffness of the scaffold increases the amount of cartilage formation and reduces the amount of fibrous tissue formation in the defect. Byrne et al. [11] developed a fully three-dimensional model for the computer simulation of tissue differentiation and bone regeneration in a regular scaffold as a function of porosity, Young's modulus, and dissolution rate, all of this done under both low and high loading conditions. Milan et al. [53], predicted homogeneous mature bone tissue formation under strain levels of 0.5–1 % at strain rates of 0.0025–0.005 s^{-1}, finding that, under higher levels of strain and strain rates, the scaffold shows heterogeneous mechanical behavior which leads to the formation of a heterogeneous tissue with a mixture of mature bone and fibrous tissue.

More recently, Guyot et al. [29] proposed a combination of numerical methods to solve the fluid-solid interaction problem in a scaffold where bone is growing. They proposed to divide the whole domain of the scaffold in three parts: biomaterial, neotissue and void. Hence, the fluid flow profile is treated differently in each domain using respectively the Brinkman's law, Darcy's law and Stokes, aiming to determine an accurate estimation of the shear stress profile.

The third main category of multiphysics models are based on mass transport by diffusion phenomenon. Actually, there are many macroscopic models that use the diffusion of growth factors as regulatory elements for mediating cellular processes in regenerative process in bone healing [4] and bone regeneration [24]. However, most of these models are not based on pure diffusion transport approaches, but involve convection too, also regulating the transport of these growth factors by means of fluid flow. The production of these growth factors is normally associated to the cells but mediated by the mechanical stimuli that cells are bearing. Therefore, mechano-chemical relations have to be defined. In a recent work, Nava et al. [57] proposed that bone growth was regulated by shear stress and oxygen concentration, but also including the volume occupied by the cell and the tissue growth by using a moving boundary formulation. Therefore, this approach allows not only estimating the fluid shear stress for the initial scaffold geometry, but also predicting the dynamical evolution of the tissue growth within the scaffold, guided by the combination of a fluid-based stimulus and oxygen concentration.

Finally, we should show the application of mechano-chemical models to perform simulations in tissue engineering. Despite the wide use of mechano-chemical models for the simulation of bone healing or wound healing [4, 24, 37, 85], there are not many computational works assessing the use of growth factor delivery devices in tissue engineering. Ribeiro et al. [65] recently developed a mechanochemical regulatory model to study the effect of bone morphogenetic protein-2 (BMP-2) on bone regeneration. In particular, they did a comparative study of the impact of different strategies to induce healing to a bone large defect, comparing: natural healing, an empty hydrogel implanted in the defect, and a hydrogel soaked with BMP-2 implanted in the defect. The proposed mechano-chemical model successfully predicted the positive effect of BMP-2 on the evolution of healing in large bone defects.

Multiscale modeling in tissue engineering

Multiscale modeling is a technology inherent to all the biological systems, and Tissue Engineering is not an exception. The overall purpose of this methodology is to

understand material behaviors from a fundamental perspective taking into account all relevant length and time scales, ranging from the atomic scale to the macroscopic continuum viewpoint. Multiscale modeling has to take into account the fine scale requirements, such as allowing particle flow, and at the same time guarantee the large scale functionality and support. There are many computational multiscale models in the literature that describe different mathematical approaches to recreate biological processes that occur in tissue engineering or tissue regeneration [13, 33, 78, 82, 88].

Despite the variety of different methods, in this work we focus on those approaches in which there exists a separation of the length scales, based on the asymptotic homogenization theory (AHT) [34, 72, 84]. Normally, at scaffold or microscopic level, a representative volume element (RVE) is chosen to recreate the geometry of the scaffold and involve most of the cellular processes, however, at macroscopic level, the whole organ is simulated. See Fig. 3 showing one example of how both scales can be linked [69]. The fundamental idea is to decompose each fundamental variable into a macroscopic $\overline{\mathbf{V}}(\mathbf{x})$ and microscopic variable $\mathbf{V}'(\mathbf{y})$:

$$\mathbf{V_T}(\mathbf{x},\mathbf{y}) = \overline{\mathbf{V}}(\mathbf{x}) + \mathbf{V}'(\mathbf{y}) \quad (1)$$

where $\mathbf{y}$ represents the space description at tissue level and $\mathbf{x}$ at macroscopic level. Actually, $\mathbf{V}'(\mathbf{y})$ describes the evolution of the variable at the fine scale considering that their average on the RVE is zero.

In order to connect both scales, homogenization and localization numerical techniques have been widely developed based on different multi-scale approaches [34, 63, 84] for multiple applications. In particular, in the case of bone tissue engineering, in the work of Sanz-Herrera et al. [69], a solid mechanics problem and a transport problem are solved to simulate bone regeneration. Therefore, they use this technique in order to homogenize stiffness and diffusion tensor, and they use localization in order to determine locally the cell concentration and strain field. This numerical approach represents a promising strategy for the design and optimization of scaffolds, because it allows to developing a multiphysics approach taking into account solid mechanics, fluid mechanics and transport phenomena. Fundamental scaffold design parameters are considered in the model including porosity, pore size, interconnectivity and mechanical properties. Actually, it is worth noting that there exist multiple evidences linking the bone formation process with the scaffold design parameters: pore size [92], pore shape [43], pore interconnectivity [42] and local curvature [29].

Traditionally, many different models in tissue engineering have been working only at the Scaffold level, in order to understand how different mechano-chemical conditions modify the cell response updating the local architecture of the scaffold [1, 14, 75]. However, these models do not link the evolution of the neotissue bone formation within the local scaffold properties with the macroscopic/organ scale properties.

Computational multiscale modeling has made possible the design and manufacturing of multiple scaffolds in the last years [77]. In fact, multiscale scaffolds have been successfully incorporated into different biological tissues such as heart valves[16], tympanic membrane [56], or cartilage [45].

Modeling cell-material interactions for tissue engineering applications

To achieve a controlled and reproducible tissue regeneration under multiple different conditions, it is fundamental to understand cell-material interactions [22, 74]. It is

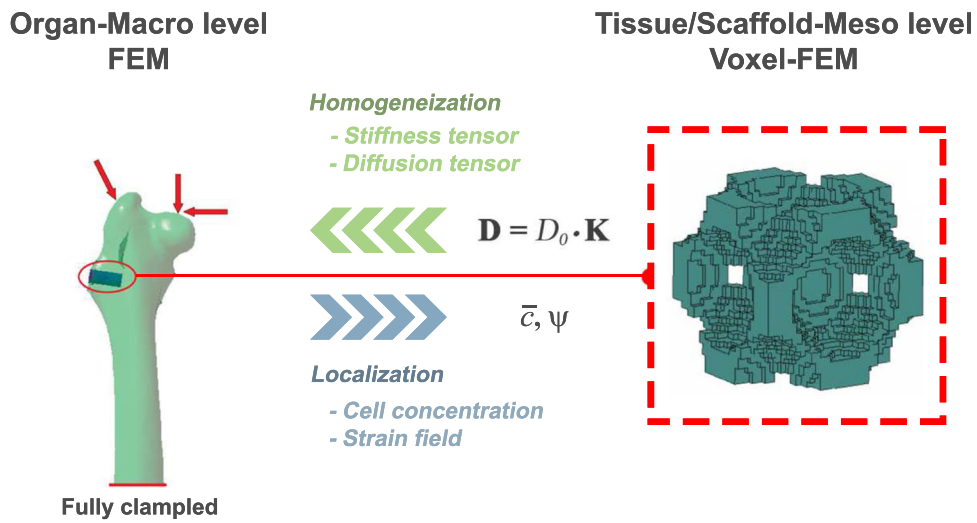

Fig. 3 Multiscale model of a scaffold (tissue level) implanted into the organ level

currently accepted that many different kind of biophysical and chemical factors stimulate cells regulating their response. Actually, it is recognized that cells actively sense the mechanical properties of the material in which they are adhered, such as, rigidity, geometry or deformation [15, 54, 73].

There are many mathematical and computational models in the literature that have focused on modeling the active mechanosensing behaviour in cell-matrix interactions (see [15] for a review). In fact, most of these works have focused on modeling directional cell migration regulated by mechanical properties, such as, durotaxis and tensotaxis [7, 10, 54].

With respect to tissue engineering applications, computational models have been focused on mechanical variables representing the different components of the cell body. For instance, by using a simple model, García-Aznar et al. [22] showed that cell forces increase with stiffness of the material until saturation, orienting the actin stress fibers in this direction. Furthermore, this work also predicts that external mechanical loads may affect cell forces and orientation. The proposed model [8, 54] consists on two parallel springs representing the stiffness of the passive mechanical components of the cell and the actin filaments in series with the myosin contractile system (see Fig. 4) . This approach was purely mechanical and static, so that the contractile system exerted a specific force depending on the cell strain, and thus depending on the material stiffness. Additionally, a discrete approach including actin filaments, actin cross-linking proteins (ACPs) and molecular motors, was proposed by Borau et al. [9] to study the mechanosensing phenomenon at the microscopic level. This model evaluated the network contraction and reorganization using different ranges of ECM stiffnesses and actin, ACP and molecular motor concentrations, finding that actin-myosin contractility is one plausible stand-alone mechanism capable of contributing directly to cell mechanosensing.

Topographical cues mimicking the extracellular matrix (ECM), such as curvature, have demonstrated to play a relevant role over a diverse range of cellular behaviours including: initial adhesion, migration, cell growth, differentiation and death [6, 60, 91]. This fact has motivated a high interest in understanding the role of curvature on cell mechanics, thus, several numerical models have been developed to evaluate the stress distribution on the cell body. For example, [22, 73] obtained that substrate curvature determines the stress distribution over the cell, concluding that cell forces are higher in the direction of minimal curvature. Moreover, it showed that stresses become larger at peripheral locations of the cell, since curvature decreases as you move away from the cell centre. This dependence of cell stresses on the scaffold local curvature also helps to understand the phenomenon by which cells tend to align with the direction of minimum principal curvature [76].

Different numerical and theoretical models have postulated the dependence of tissue growth on geometrical features due to the local mechanical forces based on continuum growth theories [5, 20, 67]. More recently, in-vitro experiments showed that local scaffold topography (curvature) [2, 28, 29, 49, 52] enhances cell growth and neotissue formation. As a consequence, most of these recent numerical models [28, 29] propose phenomenological local growth laws of this neotissue formation, depending on the local mean curvature. From our point of view, this is an indirect way to consider the mechanosensing mechanism that cells use to sense their local mechanical microenvironment.

Future challenges

There are many challenges that computational mechano-chemo-biology needs to face for the optimal design of scaffolds, as recently reviewed in [25]. But, in our opinion,

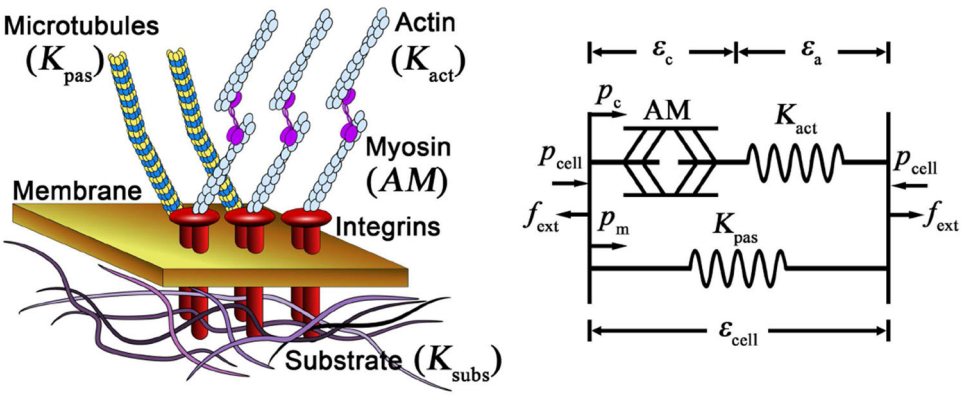

Fig. 4 Cell-material interaction model of a scaffold (tissue level) implanted into the organ level

the consideration of the multiple specificities that characterize the tissue that has to be replaced by the scaffold is probably the most crucial aspect. Tissue-specific microenvironment is relevant, but macroscopic patient-specific characteristics, such as geometry, material properties or loads are significant too. In addition, the full integration of the scaffold into the replaced tissue is fundamental, being critical to reduce the relative movement between tissue and scaffold to enhance regeneration at the damaged tissue [55].

To achieve this, it would be desirable to integrate multiple fields (involving mechanical, chemical and biological factors) at different length and time scales that allow linking phenomena that occur at organ, tissue and cell scales.

The coordinated mechanical cell-material interaction (with adequate biochemical conditions) may help to define a local favorable mechano-chemical microenvironment for tissue regeneration, allowing to control the preferential movement of cells, their regulated proliferation and differentiation and the corresponding matrix formation. Therefore, one of the most relevant challenges in tissue engineering is the mechanical design of tissue replacements (scaffolds) with sufficient mechanical integrity to bear loads during tissue regeneration that, at the same time, allows the creation of a local favorable mechanical environment to regulate cell behavior. Moreover, we have to keep in mind that to overcome these challenges, the design of scaffolds presents some relevant constrains that need to be taken into account. Firstly, the porous architecture of the scaffold should allow an adequate mass transport and vascularization in order to facilitate the movement of nutrients and the removal of wastes. Scaffold degradation properties must be precisely adjusted to avoid excessive mechanical forces if the material is removed quickly, or to avoid porosity decrease and reduction of mass transport if the material disappears very slowly [70]. Finally, it is necessary to create scaffolds with non-homogeneous properties and combining different kind of materials, which were called by Giannitelli [25] as *hybrid scaffolds*. These scaffolds would help to achieve adequate local microstructural properties to activate mechano-sensing cell response, but as well, to keep the macroscopic mechanical role that our organs are playing. Additionally, more steps should be given to achieve the clinical translation of this tissue engineering technology. For this aim, it is essential to improve the robustness of this technology, increasing the repeatability in the results of its clinical application. With this idea in mind, Kerckhofs et al. [41] developed recently an innovative approach for robust screening of scaffolds by means of the combination of microCT characterization with empirical modeling. It is, therefore apparent that, computational models have to be designed in order to facilitate the clinical translation of these scaffolds.

Conclusions

In this article we have presented some recent modeling works in Tissue Engineering, aiming to show the possibilities that computational modeling offers to scaffold design. It is clear that tissue regeneration by means of Tissue Engineering techniques is a complex process that occurs at different length scales regulated through different mechanical, chemical and biological factors.

As we have shown, computational design of scaffolds is not a novel technique, and has been widely used in CATE [25, 80]. However, as many authors postulate it is still in an early stage [80]. In the future, CATE should provide the use of multiscale and multiphysics modeling techniques to achieve the integration of the macroscopic design of tissue scaffolds with sufficient mechanical integrity to bear loads during tissue regeneration. At the same time, it should allow the simulation of the local mechano-chemical microenvironment that favors the cell activity to produce new matrix. Therefore, the computational design of scaffolds requires both the optimization of macroscopic properties (to support the tissue- and patient-specific conditions) and microarchitecture (to precisely regulate cell behavior).

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