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Review Article

# Multiscale modeling of bone tissue mechanobiology

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ABSTRACT

Mechanical environment has a crucial role in our organism at the different levels, ranging from cells to tissues and our own organs. This regulatory role is especially relevant for bones, given their importance as load-transmitting elements that allow the movement of our body as well as the protection of vital organs from load impacts. Therefore bone, as living tissue, is continuously adapting its properties, shape and repairing itself, being the mechanical loads one of the main regulatory stimuli that modulate this adaptive behavior. Here we review some key results of bone mechanobiology from computational models, describing the effect that changes associated to the mechanical environment induce in bone response, implant design and scaffold-driven bone regeneration.

## 1. Introduction

Bone tissue develops different kind of functionalities ranging from a mechanical role to a biochemical regulatory capacity. Thus, bone is the most relevant mineral store site in the body [1] and bone marrow is the place where blood cells are produced [2]. If we focus on the mechanical bone capacity, bone tissue provides structural support to our body and protects our most relevant organs like brain, lungs and heart. At the same time, bones are the structural components that provide our movement capacity, transmitting forces from our muscles. In fact, muscles use bones as levers [3].

Hence, mechanical loads play a crucial role in the maintenance of bone tissue properties, but also in bone morphogenesis, healing and regeneration. We have to keep in mind that bone is an adaptive and evolutive material that is constantly adapting its internal properties, size and shape in function of the whole environment that is supporting [4]. Bone is an efficient 'servo' (feedback-controlled/steady-state) system [5] that continuously integrates environmental signals and responds accordingly to adapt its properties. One of the most determining factors is mechanical load, in addition to other biological or biochemical factors, such as, hormones, aging, nutrition [6]. In fact, bone tissue accommodates to usual daily activities: 1) low activity or lack of gravity induces bone loss, 2) daily activities such as walking have a modest effect keeping bone and 3) activities generating greater muscle force on bone, promote increased mineralization and external remodeling [7,8].

Thus, the detail analysis of how mechanical loads impact in bone biology is currently an emergent field known as mechanobiology, where engineers and biologists combine their knowledge in order to understand this complex interplay. Therefore, mechanobiology focuses on understanding how the mechanical forces regulate the response of cells within tissue. Many experimental works have focused on understanding how local mechanical stimuli regulate biological cellular processes at cell level: migration [9], differentiation [10], proliferation [11], apoptosis [12]. However, mechanical loads are normally applied at an organ level and they induce different types of stimuli in the tissue (such as, tissue strain or interstitial fluid flow) that are transmitted through the architecture of the tissue to the specific cells embedded in this tissue. In the case of bone, this architecture presents a clear hierarchical organization [13] that goes from the bone to the cells through the specialized architecture of cortical and trabecular bone. It would be desirable to quantify the effect of this spatial organization on the final bone cell responses to loading changes. The use of numerical simulations is a good strategy to unravel how macroscopic mechanical loads are transferred from the organ to the cells and viceversa (Fig. 1). In fact, computational models are developed to analyze bone mechanobiology from bone cells to the organ, integrating the information at different length scales [14–17].

To overcome the experimental challenges and advance the

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understanding of bone mechanobiology at different scales, computational modeling has been widely used [18–21]. In this work, we summarize the effects that changes in mechanical conditions at different levels, distinguishing between cells and Extracellular Matrix (ECM), have on bone mechanobiology as understood from computational models. Moreover, we aim to analyze the different numerical approaches focused on multiscale modeling, which have been proposed in the literature to improve understanding of bone mechanobiology at different scales.

There are many models in the literature that incorporate some feedback from mechanical stimuli on bone response [22–25]. Hence, the goal of this review is to focus only on key results regarding the influence of mechanical interactions on bone mechanobiology, which have been obtained by means of computer-based models. In particular, this review will be targeted for different adaptive and regenerative bone processes.

## 2. Physiological bone remodeling

The process of bone remodeling is responsible for the formation and maintenance of bone functionality [26,27]. Normally the term of bone remodeling involves two different concepts, what is known in the literature as external remodeling (or modeling) and internal remodeling. Bone modeling starts in fetal life and continues during all our life, shaping the form of our bones by removal of bone from different sites and adding bone at other sites [28–31]. Internal remodeling or simply bone remodeling is the process by which bone cells respond to mechanical stimuli by adjusting (modeling) its architecture and material accordingly [29,31,32]. Bone remodeling is crucial for repair of old damaged bone due to daily physical load and prevention of “stress fractures” or fractures due to mechanical fatigue [33]. This adaptive process consists in the balance of two main phases: bone formation and resorption. This balance is a tightly controlled and coordinated process regulated by mechanical loading and endocrine influences [34]. Impairment in the bone remodeling process often results in the progression to bone fracture. One of the most crucial diseases characteristics of this unbalance is osteoporosis, a major worldwide health concern.

The combination of mathematical models and computer simulation methods opened many possibilities to advance in the understanding of mechanobiological behavior of bone tissue. The most common numerical method that has been used to simulate bone is Finite Element (FE) Method, which has been used at the different scales: organ [35], tissue [36] and cell level [37,38]. Only in particular cases, other numerical methods have been used, such as, boundary element method [39] or meshless methods [40] among others. In the literature, there is a vast number of FE-based studies with the purpose of analyzing bone mechanobiology. One possible classification of these works could be defined according to the mechanical stimuli that regulate the bone response. From macroscopic strain computed at organ level, many phenomenological bone remodeling laws have been established [41–44], where many of them have been numerically evaluated [32,45,46]. The first notion of a relationship between form and function in bones, produced and maintained by mechanical forces, was proposed by the ‘Wolff’s Law’ [47]. All these macroscopic theories use the concept of dead zone (equilibrium range of strain) (Fig. 2), where bone is formed when the actual strain exceeds the equilibrium range, and resorbed when the actual strain is below this equilibrium range. This equilibrium zone is not constant and can change in function of the bone and the mechanical demands [48–50].

With the development of new high-resolution CT imaging techniques and micro-FE analysis, tissue level strains and microstructural changes have been measured and quantified, specifically in trabecular bone in humans [52] and mice [51,53]. All these works found that exist a relationship between bone formation/resorption and strain level: bone formation most likely occurs at sites of high local mechanical strain and resorption at sites of low local mechanical strain. In fact, they determined that ‘dead zone’ or ‘equilibrium zone’ does not exist at this tissue level. This fact confirms that this ‘dead zone’ is a consequence of the

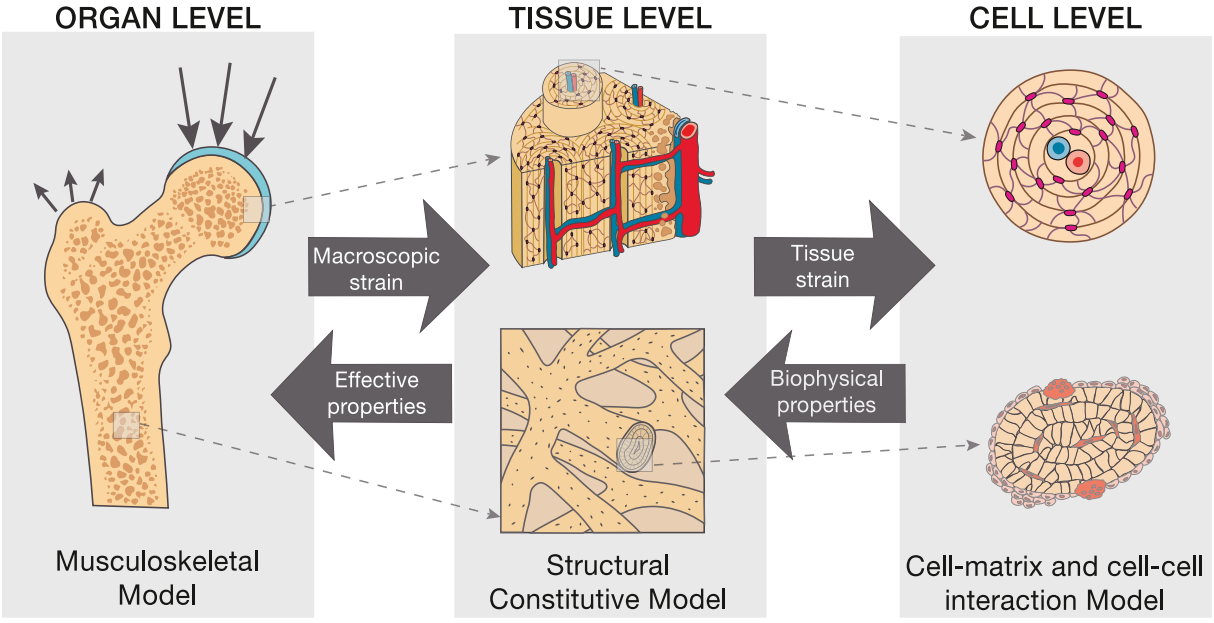


**Fig. 1.** Multiscale strategy for modeling bone tissue mechanobiology. At organ level, it is normal to create finite element (FE) models of whole bones (for example, femur, tibia or mandible) where loads provided by musculoskeletal models are used. At this level, it is common to distinguish between cortical and trabecular bone, because they present clearly different macroscopic, microscopic and ultrastructural properties. FE analysis allows to estimate macroscopic strain at organ level. The application of this macroscopic strain to a volume of bone tissue that includes their own microstructural characteristics can evaluate the strain at tissue level. Similarly, the consideration of a volume that incorporates the lacunocanalicular network (LCN) provides computational estimations of the interstitial fluid flow and how bone cells are strained. According to the signals perceived, cells can update the bone tissue properties by changing the LCN, altering the ultrastructural properties or with a new bone geometry. These changes modify the biophysical properties of the microstructural bone volume whose effects on bone macroscopic properties need to be evaluated, thus closing the multiscale loop.

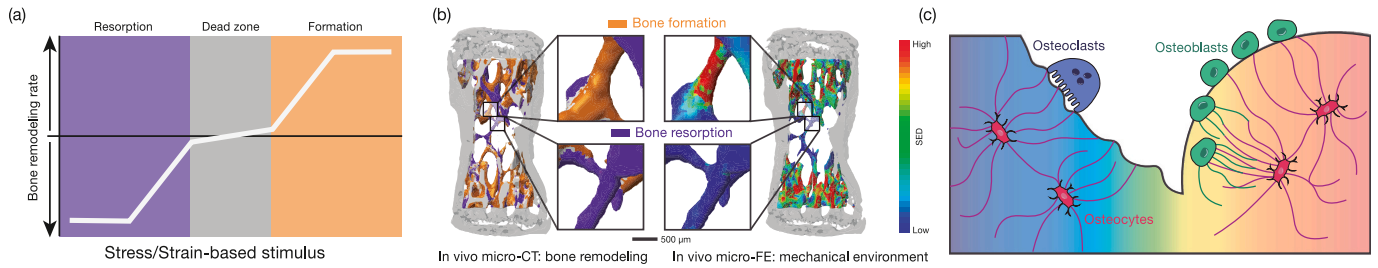


**Fig. 2.** Dead zone concept from a multiscale perspective. (a) Most of bone remodeling theories are based on an equilibrium stress or strain-based stimulus that defines the bone mass balance between bone formation and resorption. This stimulus is normally evaluated at organ level, although it is estimated at tissue level. (b) Recent works [51–53] at tissue level demonstrate that bone formation most likely occurs at sites of high local mechanical strain and resorption at sites of low local mechanical strain (image taken with permission from [51]). (c) Bone formation and resorption occur at bone surface due to osteoblasts and osteoclasts, respectively.

scale in which bone is analyzed. When bone is analyzed at organ level the reference volume of the analysis incorporates many sites where bone formation or resorption occurs, and therefore, when the amount of formed bone is similar the resorbed bone, the total bone formation is null (Fig. 2).

Given the porous characteristic of bone tissue [54,55], the second type of models have focused on modeling bone as a poroelastic material, considering as regulatory stimuli not only the macroscopic strain but also the interstitial fluid flow [22,56]. This assumption is based on experimental observations, in which bone cells such as osteoblasts respond to fluid flow more strongly than to the deformation of bone matrix [57,58]. It is widely hypothesized that mechanical adaptation is governed by the osteocytes, which respond to a loading-induced flow of interstitial fluid through the lacuno-canicular network [22,56,59,60]. Therefore, the prediction of bone remodeling based on interstitial fluid flow-induced cell response is a current tendency in most of computer models [61–63]. The simplest approach to estimate this interstitial fluid flow from organ level at cortical bone is the use of dual poroelastic models, which model both vascular porosity (PV) and lacuno-canicular porosity (PLC) in the same equations [61,62,64] coupled with solid deformation. However, other authors have established different multi-scale poroelastic FE models to try to evaluate this interstitial fluid flow at the bone cells: from an idealized lacunocanalicular network (LCN) [65–67] or from realistic canalicular networks of full cross sections of human osteons [38,59].

The third type of models aim to couple mechanical stimuli (macroscopic strain and/or interstitial fluid flow) with chemical transport and reactions [66,67]. These models go from continuum [68] to multiscale approaches [66,67,69]. If we focus on multiscale approaches, it is interesting to mention the work of Pastrama et al. [67], in which a multiscale bone cell population model of bone remodeling is coupled with a multiscale poromicromechanical model, where biochemical and mechanical factors regulate cell response. More recently, Kameo et al. [69] proposed a novel modeling platform to explore bone remodeling by linking the process of osteocytes producing biochemical signals with the macroscopic tissue/organ adaptations.

Finally, the fourth type of models, although they are less frequent, aim to include the electric stimulus, specially mediated by the piezoelectric properties of bone tissue. Certainly, several multiscale/multiphysics models have been developed to investigate the effect of mechanically generated electrical signals on bone modeling and remodeling (see [70] for a complete review). The macroscopic model proposed by Fernandez et al. [71] only considers the effect of bone matrix piezoelectricity, evaluating the electrical surfaces charges in bone surface under different mechanical forces. This model proposes that osteoblasts or osteoclasts could detect in the bone surfaces the different electrical charges promoting bone formation or resorption respectively. This theoretical hypothesis allows to simulate both bone modeling and remodeling. However, other works propose that piezoelectricity is mostly associated to streaming potentials due to the flow of fluid and ions driven by mechanical loading [72]. Thus, Lemaire et al. [73] presented a bone remodeling multiscale model combining piezoelectricity and electrokinetics to poromechanics.

Therefore, we could conclude that most of remodeling models can be classified according to the multiphysics phenomena that are simulated (Fig. 3). Mechanical forces applied to bone organ produces two main macroscopic stimuli: deformation of the extracellular matrix and extracellular fluid flow [57]. Both mechanical-based stimuli induce multiple localized signals on the bone cells due to the multiphysics characteristics of bone matrix and microarchitecture.

From a multiscale perspective, we have seen that most of the models are developed at organ level to connect with the bone tissue and in some particular cases with the osteocyte level (Fig. 1). But there are different models in the literature that have tried to evaluate the local osteocyte strain. For example, Verbruggen et al. [37] used confocal imaging of the lacunar–canalicular network to develop three-dimensional (3D) FE models of osteocytes, including their cell body, and the surrounding pericellular matrix and extracellular matrix. They quantified a strain amplification when modeling inhomogeneities in the microstructure around osteocytes, by incorporating Volkmann and Haversian canals into an osteon. These models are really useful to understand the local effects that osteocytes sense, but they lack the information provided by higher scale levels [74]. To avoid these problems, more recently Van Tol et al. [59] have combined a 3D FE model to evaluate macroscopic mouse tibia strains with load-induced fluid flow at the realistic LCN obtained by 3D confocal microscopy.

## 3. Bone fracture healing and distraction

When a bone fractures it can no longer provide mechanical support to the body, so there is a reaction in order to restore its initial mechanical properties. Multiple events at different spatial and temporal scales are orchestrated to regenerate the initial supporting capacity of the original bone. In fact, bone healing is an amazing process by which the bone regenerates and can even increase original mechanical properties without scarring.

Different stages overlap in time during bone healing [75]. Due to trauma, bone structure and vascularization are disrupted, the healing cascade starts right after the fracture with an inflammatory response, at this stage a fibrin clot is formed, the cells of the immune system are essential at this stage. Then, revascularization and migration of mesenchymal stem cells (MSCs) to the fracture site begins, the main sources of MSCs are periosteum and bone marrow, so the structural integrity of these bone structures play a key role to determine the evolution of healing. MSCs secrete ECM forming the granulation tissue, a low stiffness scaffold for the subsequent fracture events [75]. Following this stage, MSCs differentiate into chondrocytes or osteoblast depending on different factors, oxygen level and mechanical stimuli have been identified as the main drivers [76,77]. In general, hypoxia promotes chondrogenesis, whereas higher levels of oxygen are related to

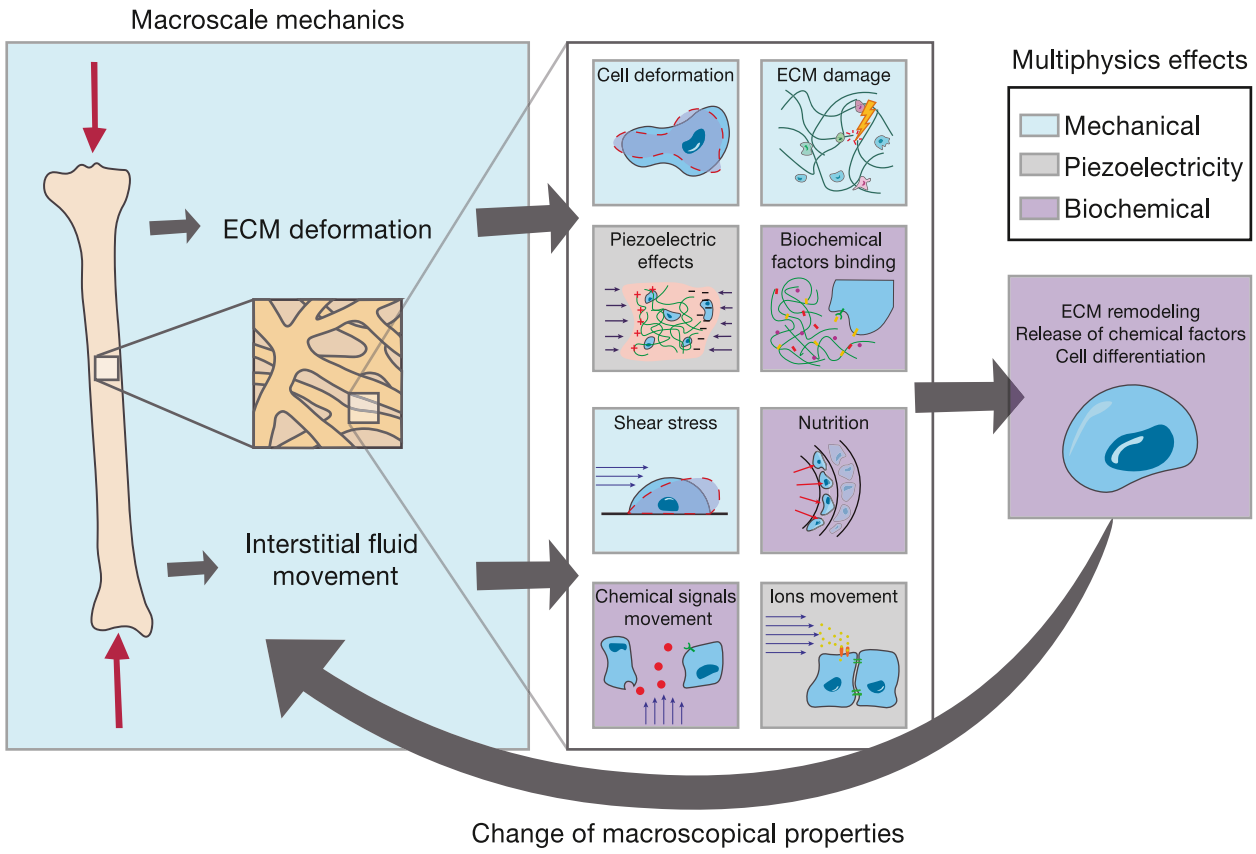


**Fig. 3.** Coupling between load forces at bone scale and multiphysics at tissue and cellular level. Under loading conditions, bone tissue is deformed causing the deformation of the extracellular matrix (ECM) and the flux of interstitial fluid. Matrix deformation can induce different multiphysics effects, such as, cell deformation, damage breaking the connections between cells, electric charges formation within the matrix and alteration of biochemical factors binding to the matrix. The movement of interstitial fluid also induces multiphysics effects like shear stresses on the cell, improving the nutrition, streaming potentials and movement of biochemical factors. All multiphysics stimuli have an impact at cell level with the corresponding biochemical cell response.

osteogenesis, low mechanical stimuli and distracted environments are also associated with osteogenesis while high mechanical and compressive environment are allied with chondrogenesis. In secondary healing, the soft callus predominates, which later will give rise to the hard callus through endochondral ossification. Finally, in the bone remodeling phase osteoblast and osteoclast coordinate to replace woven bone into an organized bone. It is worth mention distraction osteogenesis (DO) as a clinical application of bone healing to generate large quantities of bone. In DO a controlled osteotomy is performed and a continuous separation of the fracture fragments is applied [78]. Unlike bone healing, the main mechanical stimuli are tensile strains. In this case, both the fracture gap and the mechanical environment are controlled.

Different biochemical factors also influence the course of healing, for example, decrease healing capacity with aging is related to changes in macrophages and reduction of progenitors cells [75]. Whereas, mechanical factors play pivotal roles in fracture healing (for a review of experimental evidences see [79]): moderate compressive stimuli promote healing [80], tensional environments are associated to prevalent intramembranous ossification [81] whereas torsion and shear loads [82] are related to impaired healing, low amplitude high frequency mechanical stimuli accelerate healing and results in better quality fracture callus [83]. The size of the bone defect has also been identified as a critical factor of healing, in fact critical bone defect are still an important challenge in orthopaedics.

The influence of mechanical signals has been analyzed at different scales (molecular, cellular, tissue and organ), however how these mechanical stimuli are transferred among the different scales is still not well understood. In fact, the mechanical environment at the tissue and organ scale has been widely studied and also the influence of the mechanical signal in the cell and subcellular scale [84], however, as far as we know, there is no *in vivo* or *in vitro* model able to relate the stimuli at all these scales.

*In silico* fracture healing models have also demonstrated the importance of mechanical stimuli (for a complete review see [85]). These models analyze the fracture callus from a theoretical and computational perspective, successfully explaining events happening in the fracture callus focusing mainly on the mechanical stimuli the fracture site is subjected (Fig. 4), the models are calibrated against *in vivo* and *in vitro* experiments. The advantage of *in silico* models is that they allow to isolate the different mechanical factors, which are really difficult to isolate in a real case. These models are formulated at different scales (for a review see [14]).

Seminal *in silico* works on bone healing [86] relate the global mechanical stimulus at the organ level (one value of mechanical stimulus for the whole gap) to the healing outcome. The interfragmentary strain at the fracture gap is related with the tissue evolution at the fracture site. Following this idea, Alierta et al. [87] formulated a global theory, in which the fracture gap was simulated with cohesive elements; shear and axial stimuli determine the outcome of healing. This model does not consider local events occurring at the fracture site, it gives the global evolution of fracture through a measurement of the union degree. This type of models are quick and are useful to make clinical decisions when there is not much information as in human surgery, however they give no information about the interaction of the different agents involve in fracture healing.

The development of computers in the 1990s and the first decade of the 2000s saw the take-off of tissue-level bone healing models based on the existing experimental works. In fact, fracture healing is a very

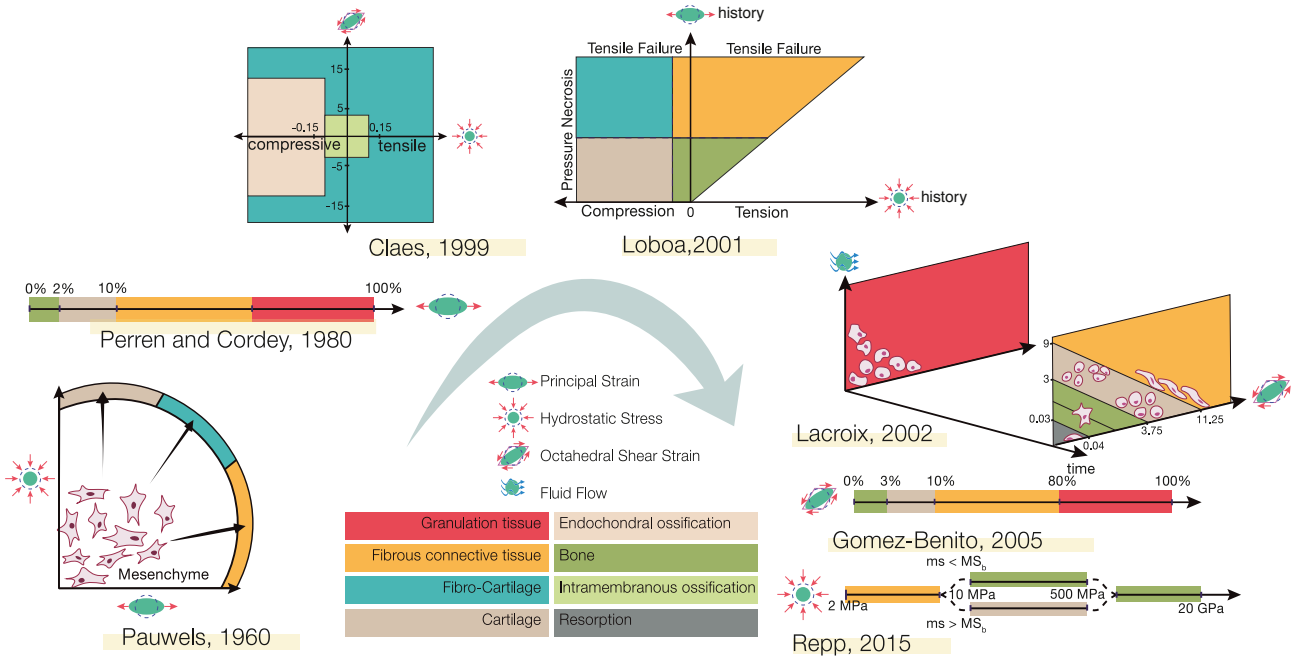


**Fig. 4.** Algorithms of tissue/cell differentiation at the tissue scale based on mechanical stimuli. All bone fracture healing algorithms based on mechanical stimulation assume tissue differentiation is driven by stress or strain invariants to which the different tissues of the fracture callus are subjected. Pauwels [88] formulated one of the first differentiation qualitative algorithms based on hydrostatic stress and shear strains, then Perren and Cordey [86] introduced a model driven by global interfragmentary strain of the fracture gap in which quantitative values determine tissue differentiation. Later, different authors introduce quantitative differentiation theories combining hydrostatic pressure and strain [76], history of principal tensile strains and hydrostatic stresses [89], tissue shear strain and fluid flow [35,90] or just one mechanical stimulus the second invariant of deviatoric strain tensor [91] or volumetric strain [92]. All these theories incorporate the differentiation of granulation tissue (red) into cartilage (light brown), bone (green) or fibrous tissue (blue), also cell/tissue necrosis and intramembranous ossification and resorption (grey) depending of the mechanical stimuli most of them incorporate in some way the effect of load history implicitly or explicitly. (Adapted from [35,76,86,88–92]). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

interesting process as it can be related to development and growth of new bones and it can control the mechanical environment through custom made external fixators able to apply just axial, shear or bending loads. These models implicitly simulate the bone and the fracture callus, adopting a continuum approach, where the external mechanical loads are used to determine the mechanical stimuli in the fracture callus.

First tissue level models analyzed fix time points of the healing processes relating the mechanical stimuli with the tissues which appear in the fracture callus [76,93]. In the 2000's tissue-level evolutive models proliferate, these models simulate various phases of the bone healing (hematoma, soft callus, hard callus and remodeling). These models are formulated as a sequential loop, simulating the time evolution of fracture healing in which the local mechanical properties of fracture callus and tissue and/or cell populations are continuously updating. These models are able to simulate most of the processes occurring at the tissue level: cell populations differentiation, death/apoptosis, migration and proliferation, ECM production and callus growth [90–92,94] just considering the mechanical stimulus as the principal regulator of the process. They simulate the evolution of the fracture site under different loading regimes [90,95], fracture gap sizes [91,96], stiffness of the fixation device [97] and distraction osteogenesis [94], among others scenarios. Nevertheless, when analyzing critical-bone defects, mechanobiological tissue models have not been able to capture the different healing outcomes in large bone defects when treated to enhance bone healing. This problem has been faced [98] incorporating growth factors to the mechanobiological models, following previous mechano-chemical models [99].

Multiscale models of bone healing introduce a combined continuum-discrete approach to simulate cell and tissue scales. The mechanical stimulus is computed at the tissue level [100] and different cellular events are simulated at a smaller scale such as angiogenesis or individual cell migration through a lattice model. They have been successful used to refine simulations of osteointegration of bone implant interfaces [100] and distraction osteogenesis [101]. These models go a step further to tissue models, however, they still do not incorporate the reorganization of the cell and extracellular to account the heterogeneous distribution of mechanical properties of the tissue. Thus, they are not able to determine the mechanical stimuli at this level, they also neglect cell-cell and cell-matrix interactions. As far as we know, the only bone healing model which incorporates the intracellular scale does not consider the mechanical stimulus [77] however they simulate blood vessels and oxygen from a multiscale perspective as critical factors of the healing outcome.

The beneficial effect of mechanical stimulation on fracture healing has long been recognized. In the 1980s Sarmiento et al. [102] reported the benefits on fracture outcome of walking on crutches. To accelerate and improve bone healing, different external stimuli have been successfully applied such as low amplitude and high frequency external mechanical stimulation [83] or ultrasound stimulation [103]. However, it is necessary to understand the cellular [104] and sub-cellular mechanisms associated with improved healing in these stimulating scenarios [105], to apply adequate therapy in clinical practice.

It is not difficult to determine the external mechanical stimuli transmitted to the fracture site at a global level by means of instrumented fixation devices [83]. In fact, bone healing models have been able to determine how these external mechanical stimuli are translated into tissue-level stimuli by means of continuous tissue models in which homogenized events at the tissue and cellular level are simulated. However, it is difficult to determine how the mechanical environment at the tissue level is translated to the cell level and the mechanical stimulus each cell sense and how these cells translate these mechanical stimuli into biochemical signals, therefore, it is necessary to apply multiscale techniques to communicate among scales.

## 4. Bone ingrowth and remodeling around implants

One of the main events that changes the bone mechanical environment is the incorporation of an implant. Clearly, implantation surgery may damage the osteocyte network, which is responsible to orchestrate load-driven bone formation and resorption. Additionally, the presence of the implant may alter the mechanobiology of peri-implant bone, causing a different response to mechanical loading. But also, the global mechano-responsiveness of bone is compromised when an implant is incorporated. In fact, it has been demonstrated that mechanical regulation of bone remodeling was transiently lost [106].

Implant loosening is the main failure cause in cementless systems (hip arthroplasty [107], dental implants [108] or knee systems [109]). In cemented systems, long-term failure due to bone resorption is caused by stress shielding or crack growth within the cement mantle. The fixation of an implant to bone tissue critically relies on the formation of new bone between the implant and the surface of the old peri-implant bone and depends on factors such as the surface microtopography, chemical composition and geometry of the implant, the properties of the surrounding bone and the mechanical loading process. Another important phenomenon is stress shielding, which reduces the support of the implant and therefore increases the risk of implant loosening. For example, in total hip arthroplasties, stress shielding in femur occurs when some of the loads are taken by prosthesis and shielded from going to the bone [110]. Normally, femur carries its external load from the femoral head through the femoral neck to the cortical bone of the proximal femur. When stiffer stem is introduced into the canal, it shares the load and the carrying capacity with bone. Now the load is carried by implant and bone. As a result, the bone is subjected to reduced stresses and hence the stress shielded occurs [111]. Based on Wolff's law, bone adapts its structure based on the stress or demands on them. Consequently, areas of bone experiencing high load or stress will respond by increasing bone mass and areas under lower load or stress will respond by decreasing bone mass. Decreasing in bone mass is known as bone resorption, may lead to the loosening of failure of the implant.

Therefore, bone ingrowth and bone remodeling are two different evolutionary processes which might occur simultaneously with the incorporation of an implant. Both processes depend on local mechanical stimuli and influence local mechanical stiffness, and thereby the mechanical environment. Bone remodeling is normally considered a macroscale phenomenon, whereas bone ingrowth is an interfacial phenomenon requiring separate microscale models and simulations. The majority of the existing computational works of this type on bone implants have focused on the biomechanical nature of the problem, trying to draw conclusions from the change of the mechanical state of bone after placement of implants, evaluating the influence of mechanical factors such as the geometry of the implant or the magnitude of loading and proposing phenomenological models for the study of bone ingrowth or remodeling [112–114]. This section discusses the role of mechanobiology in bone remodeling and bone ingrowth around an implant. As it was previously remarked, mathematical models and computational simulations are valuable tools to test load-driven changes in virtual bones at multiple scales. Normally, bone remodeling and bone ingrowth are independently simulated; but also, different mathematical approaches are considered: phenomenological or with a more mechanobiological point of view. Mechanobiological models in which specific biological processes coupled with mechanics are modeled together with their influence on the structure and mechanical properties of tissues constitute a richer source of information for the understanding of many problems for bone tissue.

Bone-implant interface has an important structural functionality, and it has a crucial mechanical behavior for its own performance, which can evolve with time depending on its mechanical state. On the one hand, certain works have used simple expressions to model the formation of new bone and the associated evolution of the interface mechanical properties (phenomenological models). An interface cohesive model simulated damage and bone ingrowth of living bony interfaces, where the bone-implant micromotion was the mechanical variable controlling osseointegration and failure [114]. There were models only considering two extreme conditions: complete bonding and complete debonding with friction [115]. On the other hand, mechanistic models explicitly modeled the most important biological phenomena involved in peri-implant bone healing [116,117].

Mechanoregulatory models describe the evolutionary bone ingrowth depending on the cellular activities, migration, proliferation, differentiation, apoptosis, extracellular matrix formation and tissue degradation, which are influenced by the mechanical stimulus [118]. Bone ingrowth have been modeled taking into account immediate events upon implantation as platelet activation which allowed to simulate the effect of different surface microtopography [116] (Fig. 5). In a second part of the work, the authors added other effects such as cell stimulation, the concentration in the host bone and the geometry of the implant [117]. They demonstrated that the speed of propagation of the osteogenic cells front, as well as the level of osteoblast concentration that can be achieved at the end of the osteoconduction phase. It was also observed that trabecular bone had a higher concentration of osteogenic cells or growth factors, which may accelerate the peri-implant bone healing if the host trabecular bone provides sufficient mechanical stability. It is known that moderate mechanical loading stimulates two crucial phenomena in peri-implant bone healing: osteogenic cell differentiation and growth factor secretion.

Therefore, mechanistic approaches allow studying and understanding how the mechanical factors influence and regulate the evolution of the biological processes taking place at living interfaces. This fact requires the development of more complex and sophisticated computational models including multiscale approaches.

Several computational studies based on the FE method combined with a mathematical model simulating bone adaptation have focused on the bone remodeling effects of incorporating femoral [112,122] and tibial prostheses [113,123] (Fig. 5). These biomechanical studies estimated the effect of prosthesis materials, the optimal stem length, the effect of the cement mantle thickness, or different interface conditions for the bone-cement and cement-prosthesis interfaces [123,124].

Most of previous computational works have been conducted using phenomenological approaches, based on the empirical relationships between mechanical stimulus and bone adaptation. Such approaches are limited in scale and do not allow direct incorporation of the biological processes potentially involved in pathological conditions such as osteoporosis. Moreover, implantation is often performed in aged and osteoporotic bones, which seem to have a reduce mechano responsiveness [125]. This fact remarks the importance of analyzing mechanical stimuli in the cellular mechanosensitivity within the bone remodeling processes. An interesting option could be the development of macroscopic models based on microscopic mechanisms, *i.e.*, osteocytic mechanosensing [120]. Colloca et al. [126] developed a multiscale analytical model providing an accurate and efficient tool for simulating patient-specific bone remodeling for the hip and spine, where a precise assessment of bone micro-architecture was not possible. All these mechano-chemo-biological models have not been yet applied to predict the effect of a prosthesis implantation and a deep understanding of these biological alterations when a prosthesis is implanted needs to be estimated.

Only few studies coupled both phenomena. Moreo et al. [116] incorporated bone remodeling in a simplified manner. In fact, implant loosening occurs within the first year and implant loss is significantly lower in subsequent years when bone remodeling is predominant. Mukherjee and Gupta [121] combined bone ingrowth and remodeling around an uncemented acetabular component using a multiscale mechanobiological approach. Peri-acetabular bone remodeling was based on a strain-energy density-based formulation. And bone ingrowth in the microscale was simulated using a mechanoregulatory algorithm. Authors demonstrated that bone ingrowth had hardly any effect on bone

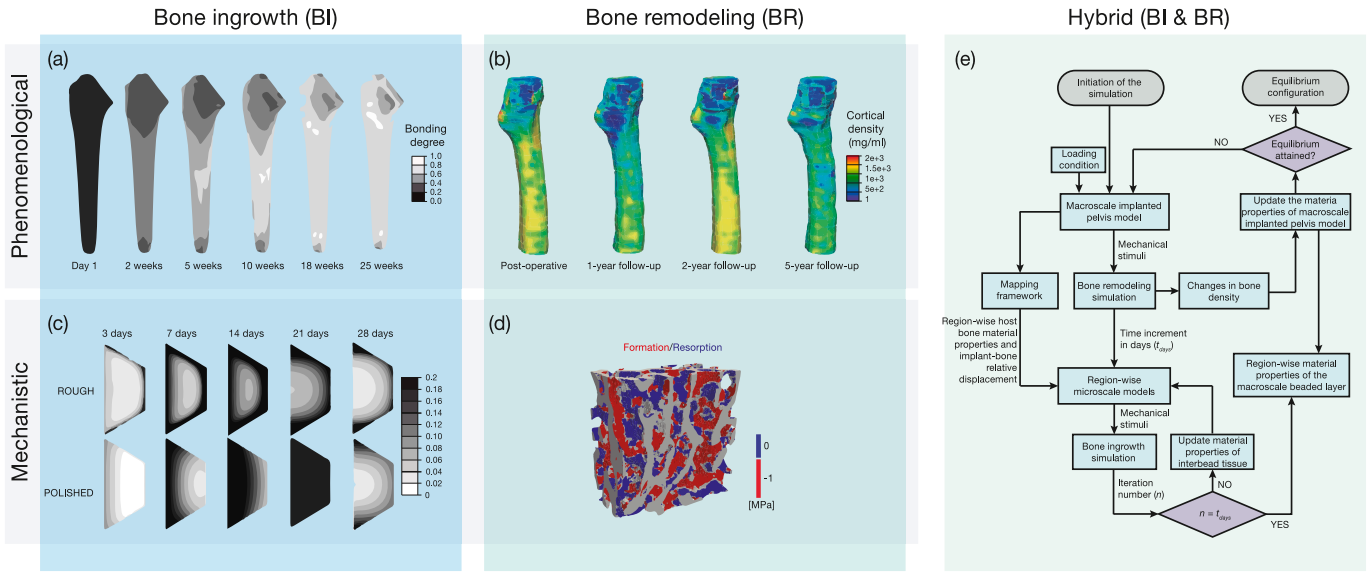


**Fig. 5.** Bone remodeling and ingrowth around implants. Bone ingrowth and bone remodeling are directly affected by the incorporation of an implant. Historically, they have been independently modeled using different mathematical approaches: phenomenological or mechanistic including biological processes. However, computational models should move towards multiscale approaches to improve the understanding of the mechano-response of bone after prosthesis implantation. Images taken with permission from (a) [114], (b) [116], (c) [119], (d) [120] and (e) [121].

remodeling; however, bone remodeling had considerable influence on bone ingrowth. This fact remarks the importance of multiscale modeling to understand the influences of bone ingrowth on bone remodeling and viceversa (Fig. 5).

## 5. Bone regeneration with scaffolds

The relationship between bone adaptation in the peri-implant region and implant mechanics laid the foundation for the control of scaffold mechanical properties in bone tissue engineering. Initially, bone scaffold mechanics was tuned only to fulfill the biomechanical requirements of the replaced tissue. Nowadays, bone tissue engineering is moving towards a thorough control of the scaffold mechanical design from macro- to nano-scale. Novel bone scaffolds are expected to regulate both the biomechanical integration, at the macro-scale, and cell mechanostimulation, at the micro and nano-scale [127].

In search of improving the mechanobiological response of bone scaffolds, recent advances in computational research and additive manufacturing (AM) provide an unprecedented control over the scaffold performance and the prediction of the regenerative outcome. On the one hand, computational models define an optimization framework that guides scaffold design and testing [15]. On the other hand, AM can produce open, interconnected and tunable scaffolds following the optimal guidelines of the computational analyses. This section presents the role of mechanobiology in scaffold-driven bone regeneration and how computational models are actively supporting the optimization of porous bone scaffolds.

Although bone scaffolds have been traditionally designed to match the mechanical requirements of the replaced bone tissue, there is recent compelling evidence that higher bone ingrowth occurs within the pores of softer scaffolds. Small changes in the strut diameter of a 3D printed porous scaffold can reduce the scaffold apparent stiffness and led to earlier bridging of critical bone defects in sheep [128]. Moreover, a FE analysis of the mechanical state in the defect site revealed that higher regenerative responses corresponded to higher maximum principal strains (Fig. 6) [128]. The scaffold apparent stiffness can be reduced by changing the printed material, while keeping the same architecture. Indeed, compliant polyamide scaffolds induced higher bone regeneration than their stiff titanium analogues in ewes, although not all recipients showed a strain-dependency of the regenerative response [134]. Therefore, mechanobiology can regulate scaffold-driven bone regeneration, but its significance can be drastically affected by the host sensitivity to mechanoregulation. The effect of the individual response on the scaffold performance is particularly relevant for 3D printed bone scaffolds and their application for patient-specific cases. Computational models present a unique solution to investigate the effects of both scaffold designs and host responses to the regenerative outcome.

The relationship between mechanical state and bone regeneration is translated into mathematical equations by mechanoregulatory theories, as discussed in the bone healing section. In general, mechanical variables and regenerative response can be correlated at multiple length scales. At the tissue level, where the newly formed bone tissue is considered as homogeneous continuum, the strain energy density (SED), octahedral shear strain and interstitial fluid flow are used to derive mechanical stimuli triggering bone formation (Fig. 6). The mathematical formulation associated to the SED is derived from the bone remodeling theory, thus bone regeneration is represented as newly mineralized tissue induced by a mechanical gradient [10,20]. The mathematical formulation associated to the octahedral shear strain and interstitial fluid flow leads to a biophysical stimulus driving the differentiation of mesenchymal stem cells into fibroblasts, chondrocytes and osteoblasts. The biological output of such mechanoregulatory theory is the amount of fibrous, cartilaginous and osseous tissue formed [130,135]. At the cellular level, the mechanical stimulation on individual cells seeded into a bone scaffold can be compared to the strains that bone cells experience *in vivo*, thus identifying the optimal perfusion and compression inducing osteogenic differentiation in a bone scaffold [136]. Besides implementing a mechanoregulatory theory, computational models of bone regeneration have a cellular component migrating within the scaffold pores and depositing new ECM [137]. For a more complete mechanobiological perspective, novel approaches include the effect of chemical factors on cell proliferation, apoptosis and differentiation, defining mechano-chemical models of scaffold-driven bone regeneration [15,98,138].

The validation of computational models, thus the correspondence between numerical predictions and *in vivo* outcomes, is an essential requirement for their use in an optimization workflow of the scaffold design. When applied to *in vivo* studies, computational results revealed

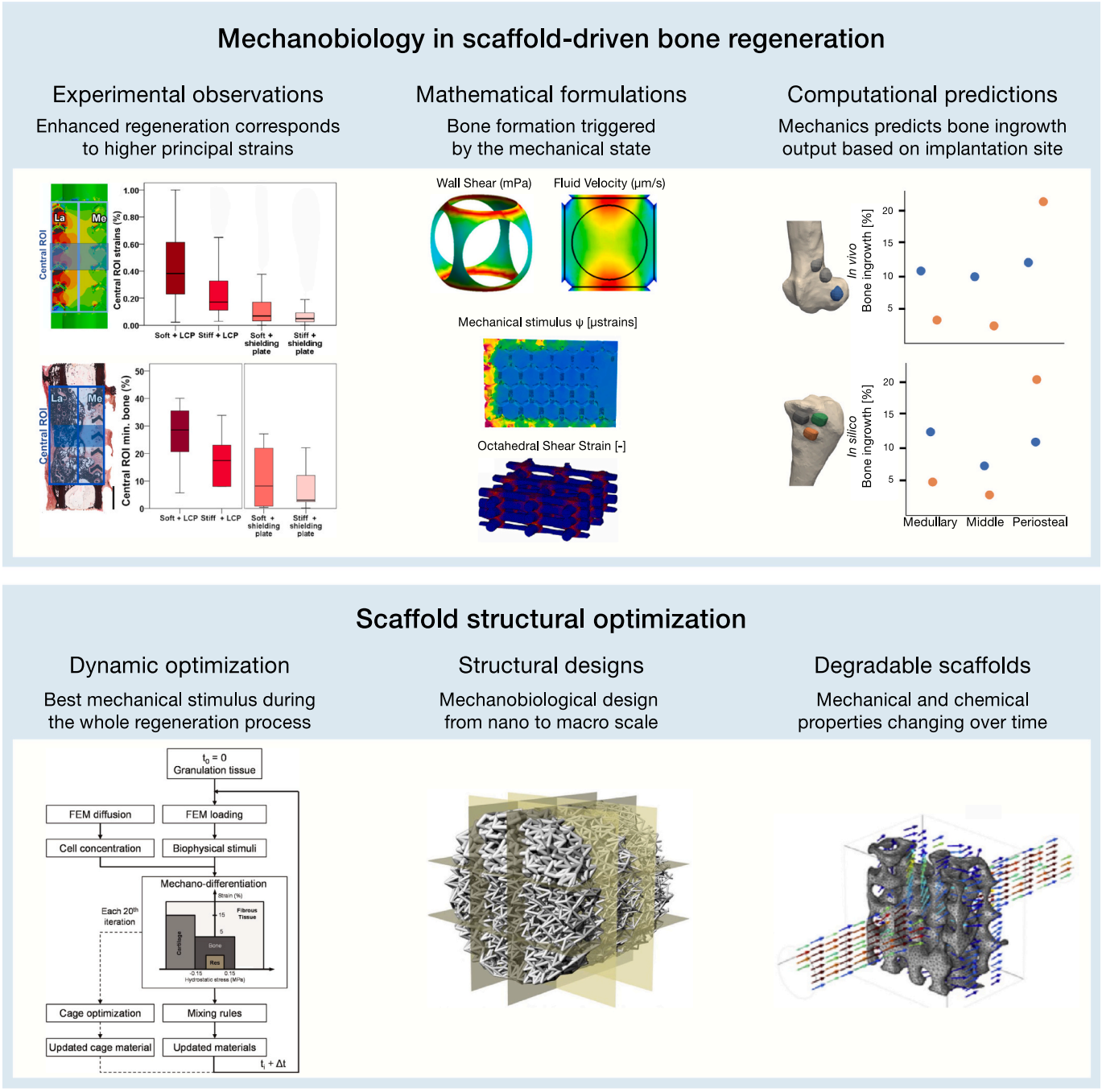


**Fig. 6.** Computer-based methods to evaluate the mechanobiological performance of bone scaffolds. Finite element methods support the experimental observations that reducing the apparent stiffness of a porous scaffold increases bone formation within the scaffold pores, identifying a correlation between maximum principal strains and regenerative response (image from [128]). Mechanoregulatory models of bone regeneration directly relate bone formation to mechanical variables, such as the wall shear stress (image from [129]), fluid velocity (image from [129]), strain energy density derived stimulus (image from [10]) or octahedral shear strain (image from [130]). When compared to *in vivo* data, a mechano-driven model of bone regeneration predicted variations in the bone ingrowth distribution based on the scaffold implantation site, confirming the relevance of the mechanobiological environment for the scaffold-guided bone regeneration (image from [10]). Computational models could therefore be implemented in optimization frameworks that find the scaffold designs maximizing bone formation (image from [131]). Results from optimization algorithms lead to structural designs that can be fabricated by a local control of additive manufacturing parameters (image from [132]). However, in order to maximize bone formation throughout the regenerative response, computational models should include the dynamic change of mechanobiological environment, which can be achieved with biodegradable scaffolds (image from [133]). Images taken with permission from publishers.

that scaffold mechanobiology can contribute to the regenerative outcome. A mechano-driven model of bone regeneration predicted variations in the bone ingrowth distribution when a cell-free titanium scaffold was inserted closer to the tibial diaphysis [10]. Moreover, the same model proposed that the limited bone ingrowth in the scaffold core, observed both *in vivo* and *in silico*, was associated to low mechanical stimulation (Fig. 6) [10]. Similarly, a mechanobiological model simulated the bone healing process supported by titanium scaffolds loaded with a bone graft. The computational analysis decoupled the individual effects on bone regeneration of the scaffold and the bone graft implanted. Results showed that the osteoconduction was the most determinant stimulatory effect of the bone graft, more than the

progenitor cells embedded [137]. The authors reported that the model predicted the bone formation dynamics and patterning for one of the two scaffold designs tested, suggesting that additional effects should be included to explain the *in vivo* differences [137]. Although the entire bone regeneration process cannot only depend on the scaffold properties, modeling the mechanobiological interaction between the scaffold and the host environment can identify the best design for each specific application.

Computational models evaluating the bone regenerative potential associated to bone scaffolds can be introduced in an optimization workflow where scaffold designs are finely tuned until optimal criteria are satisfied. In addition, FE analysis can test different loading conditions, thus identifying whether the same optimal design performs best in different applications. For example, optimizing the porosity distribution in functionally graded scaffold showed significant variations in bone formation only for a pure shear loading, while the regenerative outcome was almost unchanged under compression loading [139]. Given the dynamic interaction between scaffold, host environment and newly formed tissue, computational analyzes should consider the temporal variation of the mechanobiological environment when evaluating the scaffold performance. For this reason, optimization frameworks targeting the initial mechanical stimulus as optimal criteria might fail in the identification of the most effective scaffold during the whole regeneration process (Fig. 6) [131]. The description of topology optimization algorithms, as well as the objectives and constraints in the structural optimization of porous bone scaffolds, is beyond the scope of this review and it was recently described elsewhere [140].

Mechanobiological properties of bone scaffolds have been traditionally tuned by changing their mechanical properties. Recent advances in AM, biodegradable materials and computational tools enriched the control over scaffold mechanics and are becoming essential requirements of mechanobiologically optimized scaffolds.

As for laser AM, laser parameters can be changed to control the local mechanical properties in a bone scaffold. This fabrication approach has already been tested to manufacture titanium scaffolds matching the local mechanical properties of the replaced bone tissue (Fig. 6) [132]. A manufacturing strategy based on changing the laser parameters can be applied in a clinically relevant scenario and extended to a different design strategy that maximizes the bone ingrowth within the scaffold pores [132]. Therefore, AM parameters can be included in an optimization workflow using mechanobiological models of bone regeneration [141].

Despite its influence on bone regeneration, changing the scaffold fabrication parameters does not provide any temporal control over the mechanobiological environment. In search of actively influencing the mechanobiological response throughout the bone regeneration process, degradable materials have the unique advantage of gradually transfer mechanical loads, and thus stimuli, to the newly formed tissue. Numerical tools evaluate the mechanical state within scaffolds undergoing degradation, which might be related to experimental observation of weight loss and reduced mechanical properties (Fig. 6) [133]. As a result, computer-based methods can simultaneously model the degradation of bone scaffolds and their mechanobiological role in bone regeneration [142,143]. Scaffold optimizations based on combined degradative and regenerative models identify the initial designs and degradation kinetics that maximize bone formation during the entire regenerative response.

## 6. Conclusions and future perspectives

This review work focuses on computer-based adaptive mechanobiological models designed for the multiscale simulation of bone tissue, where mechanical stimuli act as a key regulator. As we have shown here, there are a vast number of models that aim to describe the effect of mechanical loads on bone tissue adaptation and regeneration. Specifically, we have presented models that revealed how changes in the macroscopic forces regulate the physiological bone remodeling. Additionally, we have reviewed computer-based models studying how mechanical conditions regulate bone fracture healing and how distraction forces determine bone formation. Not only did we analyzed these mechanobiological models, but we also showed their application for the computer design of prostheses and implants, culminating in the in-depth analysis of bone regeneration by means of 3D scaffolding.

The present review always kept the multiscale point of view in bone tissue modeling, taking into account the mechanobiological perspective. Macroscopic or organ scale mechanical forces propagate through the bone hierarchical architecture and transmit information at cell scale (see Fig. 1). Such force transmission mechanism is based on a strong interplay between physical and biological factors, with each one influencing the others, as is shown in Fig. 3. Bone cells can locally change the architecture and material characteristics, leading to an adaptation of the mechanical properties at the different higher scales. Therefore, novel simulations of tissue growth and remodeling have been coupled with computational systems biology approaches to better understand the fundamental mechanisms behind tissue adaptation [14,144].

As reflected in this review paper, most multiscale works are based on theoretical hypotheses or simplified ideal models. Although these simplified models are a powerful approach to simulate specific biological mechanisms, they are still a crude approximation to reality. The combination of multiscale simulation techniques with image analysis tools that provide more realistic information at different scales is a novel strategy which is emerging as a thriving working methodology [38,145]. The systematic synergy of multiscale simulations and image processing techniques will also provide a useful tool for model validation and testing.

In this work, it has been highlighted that multiscale modeling is a promising technology to advance in the understanding of bone mechanobiology, but it requires the development of novel techniques and numerical schemes to couple bone mechanobiological models at different scales in a rigorous manner.

## CRediT authorship contribution statement

JMGA prepared the organization of this review work. All authors contributed to the preparation of the document: JMGA wrote the Introduction, the Physiological Bone Remodeling and Conclusions section; MJGB wrote the Bone Fracture Healing and Distraction section; MAP prepared the Bone Ingrowth and Remodeling around Implants section; GN wrote the Bone Regeneration section and SHR prepared all the figures of the paper. All authors reviewed and approved the final manuscript.

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## Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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