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An Overview of Developments in Computational Modeling of Bone Healing Processes

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ABSTRACT

One healing involves a complex interplay of cellular and molecular processes, heavily influenced by the mechanical environment. Computational models incorporating mechanoregulation algorithms are employed to predict the impact of mechanical stimuli on tissue differentiation and bone formation during healing. This paper reviews the evolution of mechanoregulatory modeling in bone healing, highlighting recent advancements and ongoing challenges. Recent developments focus on integrating mechanoregulation algorithms with more detailed cellular and molecular descriptions. Validation remains a significant hurdle, with efforts centered on comparing existing models with well-characterized experimental data to identify shortcomings and refine computational models. The ultimate goal of these models is to elucidate the fundamental principles of cell and tissue differentiation, optimize implant design, and investigate treatments for non-union and other bone healing complications.

Keywords: Bone Healing; Tissue Generation; Computational Modeling; Mechanoregulation Algorithms

Abbreviations: FEA: Finite Element Analysis; FE: Finite Element; FEM: Finite Element Modeling

Introduction

Bone regeneration and fracture healing are remarkable processes that are often taken for granted due to their ubiquity. Unlike other adult tissues that heal by forming scar tissue, bone heals with a remarkable ability to regenerate itself. This intricate process involves a cascade of cellular and molecular events that culminates in the formation of new bone tissue. The newly formed bone is continuously remodeled until its mechanical properties are fully restored, effectively erasing the evidence of the original fracture. Bone healing typically follows a sequential pattern of tissue differentiation, where several intermediate tissue types emerge to stabilize the fracture site and facilitate the eventual formation of a bony bridge [1]. This fundamental mechanism of bone fracture healing is also shared by other bone-forming and regenerative processes, such as long bone growth during fetal development, limb lengthening techniques, bone ingrowth on implants, and tissue engineering approaches aimed at regenerating bone tissue [2,3]. Bone healing abnormalities are attributed to various factors, including mechanical and biological conditions. Mechanical stimulation has been recognized to promote fracture healing or modulate its biological pathway, but the mechanisms underlying this process remain partially obscure [4]. A comprehensive understanding of these mechanisms would pave the way for more precise and rational fracture treatment strategies and unlock boundless avenues for research in regenerative medicine.

Mechanobiology, distinct from biomechanics, focuses on the mechanisms by which mechanical forces regulate biological processes via signals to cells. By comprehending these mechanisms, we can develop physiological conditions and pharmacological agents to enhance and accelerate bone tissue formation. Computer modeling plays a transformative role in mechanobiology [5]. Computational models are employed to decipher the intricate relationship between global mechanical forces and the localized stresses and strains that shape tissue formation [6]. Since many biological processes, including bone repair, are too intricate to effectively study through traditional experimentation, the use of mathematical models has become increasingly widespread [7,8]. In mechanobiology, computational models have been instrumental in conjunction with *in vivo* and *in*

vitro experiments to rigorously elucidate the principles governing the influence of mechanical loading on cellular and tissue differentiation, growth, adaptation, and the maintenance of bone. Computational mechanobiology utilizes finite element analysis (FEA) to simulate the mechanical environment of bone tissue and its influence on cellular activities [9]. These models incorporate various biological assumptions, such as how mechanical stimuli regulate cell division (proliferation) or bone structure remodeling [9]. Advances in computational power and mechanobiological knowledge have led to the development of increasingly sophisticated models [10].

Both experimental and computational approaches are essential for expanding our understanding of mechanobiology. Combining these methods allows models to guide experimental interpretation while experiments provide data for model development. This article provides a comprehensive overview of mechanoregulatory algorithms used in the context of bone repair, with a particular focus on studies that have combined these algorithms with finite element modeling (FEM). It delves into recent advancements in the field, identifies associated challenges, such as effectively validating the underlying assumptions, and explores the potential of corroborated mechanobiological models. The discussion highlights how mechanical modeling can enhance our understanding of basic bone regeneration biology, inform clinical fracture healing protocols, and guide tissue engineering applications. Given the vast body of research in this area, it is not feasible to cover all literature in detail. Instead, the focus is to establish the foundational context and emphasize recent advancements and future avenues particularly relevant to bone regeneration.

Broken Bone Reestablishment

Bone fractures when excessive strain exceeds its inherent limits, typically induced by physical trauma. This event triggers a cascade of tissue responses aimed at removing damaged tissue remnants, restoring vascular supply, and generating new skeletal matrix. Once the fracture heals and undergoes remodeling, the structure effectively reverts to its pre-injury state. Bone healing primarily follows two mechanisms: primary and secondary healing. Primary fracture healing, also known as direct healing or intramembranous bone formation, entails direct remodeling of the cortical bone without external tissue (callus) formation [9]. It occurs only under minimal displacement, with either a small gap or direct contact between the fractured cortical bone ends. This process is relatively slow, taking months to years to complete. In contrast, secondary fracture healing takes place in the presence of interfragmentary movement between the fractured bones ends and is the predominant mode of natural bone healing. It involves a sequential series of tissue differentiation events that initially stabilize the bone fragments with the formation of an external callus (Figure 1). This process was first described by perren [11,12]. Fracture healing is facilitated by the formation of a callus, a temporary tissue structure that bridges the gap between the fractured bone fragments. The callus initially provides stability through its gradual enlargement and stiffening, reducing interfragmentary movement. Eventually, a hard callus forms, further enhancing stability and allowing bone formation to occur at the fracture site.

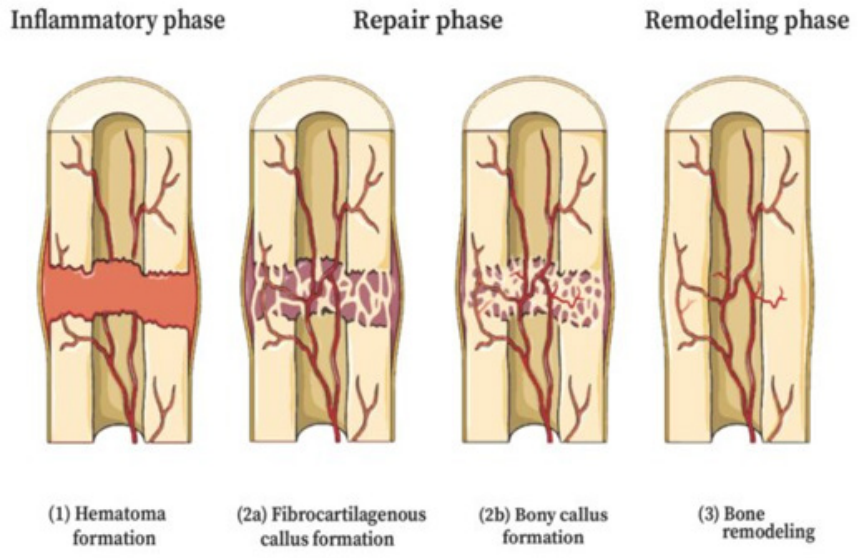


Figure 1: Secondary Bone Fracture Healing: A Journey from Injury to Restoration [16].

The process of bone repair by secondary healing can be broadly divided into three overlapping stages: inflammation, repair (soft and hard callus formation), and remodeling (callus resorption). This review focuses on the mechanical environment's crucial role in the reparative phase, where mechanical stimuli play a critical role in guiding the differentiation and deposition of bone tissue. Upon fracture, a cascade of cellular events initiates to restore bone continuity. Mesenchymal stem cells, recruited by the inflammatory response, migrate towards the fracture site and form a loose granulation tissue. These cells undergo proliferation and differentiation into tissue-specific cells, either generating fibrous tissue, cartilage, or bone, depending on the local environment. Intramembranous bone formation, characterized by rapid woven bone formation, occurs at a distance from the fracture gap. This process begins several millimeters away from the fracture site and contributes to overall bone repair. Simultaneously, endochondral ossification, involving cartilage formation and subsequent ossification, takes place at and around the fracture gap, forming the primary callus. The initial stage of bone healing involves the formation of a soft callus, a loose connective tissue structure that bridges the fracture site. This callus is primarily composed of fibrous and/or cartilaginous components, derived from mesenchymal tissue. The extent of cartilage formation depends on the level of mechanical stimulation applied to the fracture site [13,14].

Cartilage formation typically initiates at the cortical bone ends and expands outwards. Subsequently, the cartilage transitions into a calcified state, allowing for bone ingrowth. This process of bone formation progresses gradually towards the fracture plane. Once the fracture ends are securely reunited by bony bridging, the callus undergoes active remodeling and resorption to refine the structure and strength of the newly formed bone. Following the initial formation of woven bone, a less organized and less dense type of bone, the healing process transitions to the production of lamellar bone, a more organized and stiffer type of bone. This transition, known as remodeling, involves the removal and replacement of woven bone with lamellar bone, ultimately restoring the original shape and structure of the fractured bone. This process was first described by Einhorn, [15,16].

The Interplay between Mechanical Stimuli and the Process of Bone Regeneration

Mechanical forces play a critical role in regulating fracture healing, influencing its biological pathway and overall success. Among these factors, fracture geometry, interfragmentary motion, and the distribution of local strain in the healing tissue hold significant influence. Small fracture gaps promote rapid and robust healing, while larger gaps hinder the process, leading to delayed healing and reduced bone formation. The amount of movement between fractured bone ends, known as interfragmentary movement, is determined by external load and the stability of fixation. Stiff fixation restricts the formation of callus, the initial bone-like tissue that bridges the fracture gap, while flexible fixation promotes callus formation. However, excessively unstable fixation can lead to excessive movement and hinder healing, resulting in delayed bone formation and the risk of non-union, a condition where the fracture fails to heal properly. The direction of interfragmentary movement also influences the healing process. Moderate axial movement, which mimics the compression forces experienced during normal activities, is generally considered beneficial for fracture repair. It stimulates the formation of periosteal callus, the outer layer of callus that contributes to bone bridging, and accelerates healing. In contrast, shear movement, which involves sideways sliding of the bone ends, has yielded conflicting results. Some studies suggest that shear movement hinders healing by reducing external callus formation, delaying bone formation in the fracture gap, and compromising mechanical stability compared to axial movement.

However, other studies have shown that controlled shear movement may have a positive effect on bone healing, suggesting a more nuanced relationship between shear movement and fracture repair. Bone healing is a complex process involving numerous cellular and molecular events. While axial motion is generally considered beneficial for bone healing, recent studies have demonstrated that shear forces can also play a crucial role in promoting healing [17,18]. However, the precise impact of shear forces appears to be highly dependent on the timing, magnitude, and gap size of the applied forces [19]. For a comprehensive overview of experimental methods used to investigate the effect of mechanical loading on bone healing, refer to the review by Epari [20]. Despite substantial experimental knowledge, the mechanisms underlying how global mechanical stimuli translate into localized tissue- and cell-level effects remain unclear. Computational tools offer a promising approach to unravel these mechanisms. Successful bone healing is contingent upon a multitude of factors, including the mechanical environment, biological signaling, and the presence of sufficient vascular supply and oxygenated tissue. The mechanical environment, as described by Aspenberg [21], plays a pivotal role in regulating the differentiation of osteogenic cells and influencing the deposition of extracellular matrix proteins. Biological signaling, involving the balance of pro- and anti-inflammatory factors, is crucial for the initiation and progression of bone healing [22,23].

Additionally, the presence of sufficient soft tissue coverage is essential to restore vascularity and provide the necessary oxygen and nutrients for cellular proliferation and differentiation. For more in-depth information on the biochemical milieu and growth factors involved in bone healing, the reader is referred to the review articles by Nauth et al [24].

Mechanical Regulation of Bone Formation and Regeneration

Computational modeling using Finite Element Analysis (FEA) has revolutionized the design process in biomedical applications, significantly enhancing the methodology and outcomes [5]. Computational mechanobiology, an emerging field at the intersection of engineering and biology, aims to quantify the intricate relationships between me-

chanical loading and tissue differentiation, growth, adaptation, and maintenance [25]. By employing FEA models in conjunction with models representing biological processes, these dynamic interactions can be simulated adaptively (Figure 2). Computational mechanobiology models bone healing by incorporating the concept that mechanical stimuli from the local environment regulate cellular behavior and influence tissue composition, density, or structure. These models encompass various aspects, including force application at the boundary of the bone tissue, force transmission through the extracellular matrix, mechanosensation and transduction by cells, and the transformation of extracellular matrix characteristics (Figure 2). Each of these components is represented by variables, parameters, and mathematical relationships in a finite element (FE) model. While some variables can be directly measured or known (e.g., tissue morphology, mechanical properties, external loading characteristics), others require estimation based on empirical data or assumptions. Several mechano-regulatory algorithms have been proposed and employed to study tissue differentiation and bone healing, and some of these are discussed in detail below.

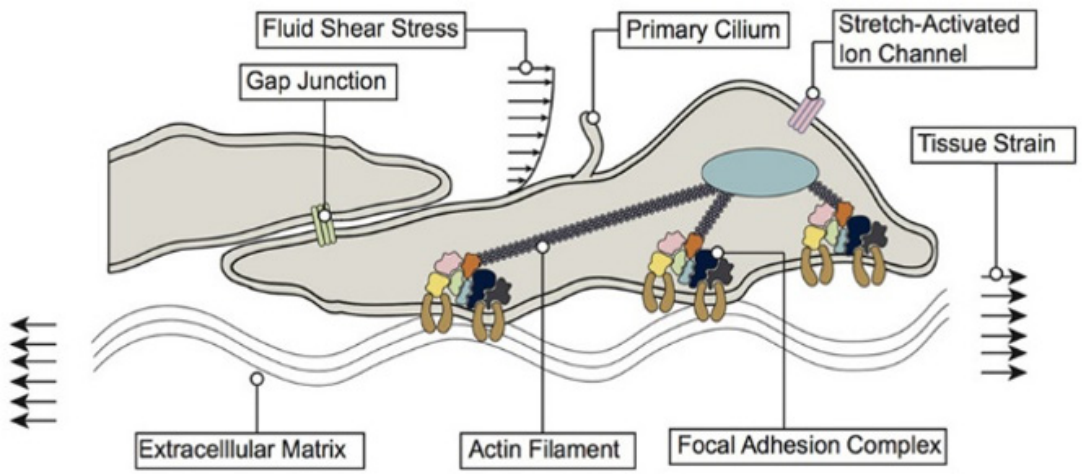
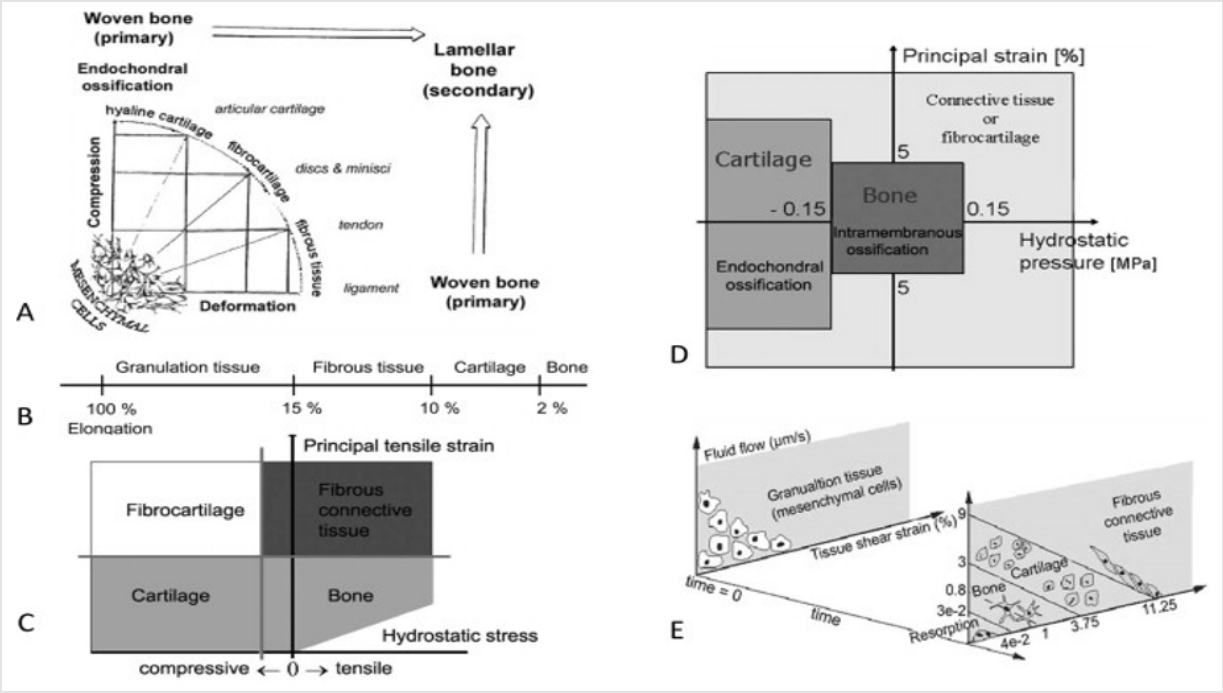


Figure 2: A modeling strategy that adapts to changing biomechanical conditions during bone restoration.

Mechanotransduction Algorithms

In 1960, Pauwels introduced a novel theoretical framework that explained how mechanical forces influence tissue differentiation through tissue deformation. He proposed that tissues were suited to withstand distinct mechanical stresses: fibrous tissue forms in regions of tension, while cartilaginous tissue is adapted to support hydrostatic pressure. Pauwels identified strain and pressure as the two primary stimuli that induce the formation of fibrous tissue and cartilage, respectively. He also asserted that primary bone formation required a stable, low-strain mechanical environment. Endochondral bone formation would only commence after the soft tissues had adequately stabilized the fracture gap and created this low-strain environment [26-29] (Figure 3a). The fundamental concept was that in the case of a healing fracture, direct bone formation across an unstable gap would be impossible without being disrupted. Consequently, the primary role of intermediate tissues is to stabilize and stiffen the fracture callus, creating a mechanically undisturbed environment conducive to bone formation. Pauwels' theory was grounded in clinical observations and logic, but he lacked the tools to meticulously measure or calculate tissue strains and stresses. In 1980, Perren and Cordey [11] advanced a different hypothesis, suggesting that tissue differentiation is regulated by the resilience of callus tissues to strain. Their premise was that a tissue that ruptures or fails at a certain strain level cannot be formed in a region experiencing strains greater than that threshold (Figure 3b).

Interfragmentary strain is determined by dividing the longitudinal fracture-gap movement by the gap size. As a tissue in the fracture gap stiffens, interfragmentary strain is reduced, permitting healing through progressive tissue differentiation from the initial granulation tissue to fibrous tissue, cartilaginous tissue, and ultimately bone. However, this hypothesis solely considered axial strains, neglecting the significant strain contributions from radial and circumferential strains.



Note: Figure A–D are adapted based on Pauwels [26], Perren and Cordey [11], Carter et al. [27], Claes and Heigele [28], figure E is reprinted from Lacroix and Prendergast [29].

Figure 3: Mechanical stimuli influence the differentiation of mesenchymal cells into musculoskeletal tissues. Pauwels [26] proposed a scheme that considers the combination of volumetric and deviatoric deformation.

Modeling Single-Phase Phenomena using Finite Element Techniques

Skeletal regeneration and bone fracture repair involve intricate cellular and molecular events leading to the formation of new bone tissue. Crucial steps in the bone healing process are profoundly impacted by the mechanical environment within the healing tissue. Computational models, coupled with mechano-regulation algorithms, are utilized to predict the influence of mechanical stimuli on the tissue differentiation process during bone healing [30]. This paper extensively reviews the field of computational mechanobiology, with a specific focus on bone healing. It delves into the history of mechanoregulatory modeling, highlighting both recent advancements and current challenges. Recent developments have focused on integrating mechano-regulatory algorithms with more sophisticated descriptions of cellular and molecular events. The most significant hurdle remains achieving suitable validation for these models. Efforts to corroborate mechanoregulatory models have primarily involved comparing existing models with well-characterized experimental data, identifying shortcomings, and refining computational models of bone healing. Ultimately, these models aim to unravel the fundamental principles of cell and tissue differentiation, optimize implant design, and potentially aid in investigating treatments for non-union and other bone healing pathologies. Building upon proposed a model that links local stress or strain patterns to tissue differentiation over time. Subsequently, they refined this model into a more generalized mechano-transduction model [27] (Figure 3c).

This model suggests that high tensile strains promote fibrous tissue formation, while high hydrostatic pressure, as indicated by the pressure line, and stimulates cartilaginous tissue production. Bone formation, on the other hand, occurs under low hydrostatic pressure. However, no specific threshold values for tension or pressure lines were specified. Carter et al. [27,31,32] were the pioneers in employing finite element analysis (FEA) to examine the relationship between local stress/strain levels and distinct tissue types. They modeled the callus tissue as a single solid (linear elastic) phase. Their model was applied to various scenarios, including joint development, endochondral ossification during fracture healing, and healing around orthopedic implants. Carter's studies emphasized the crucial role of adequate blood supply in bone formation, while compromising blood flow favored cartilaginous tissue formation. Carter's mechanobiological model has been further utilized to investigate oblique fractures [33], pseudoarthrosis formation [34], asymmetric fractures (Gardner et al., 2004), and distraction osteogenesis [35]. However, none of these studies provided adaptive predictions of tissue differentiation over time. Claes and colleagues conducted a comprehensive study to examine the effects of gap size and interfragmentary strain on bone

healing by analyzing data from animal studies, finite element analysis (FEA), and cell cultures [13,36]. Based on histological observations, Claes and Heigele [28] developed a mechano-regulation algorithm akin to Carter's model.

They were the first to quantify thresholds for when various tissues develop (Figure 3d). To determine these thresholds, the FEA employed solid hyperelastic analysis at specific time points during fracture healing. By comparing the mathematical analysis of stress and strain with histology, they could attribute intramembranous bone formation to local strains of less than 5% and hydrostatic pressure between ±0.15 MPa [36]. Compressive hydrostatic pressures greater than −0.15 MPa and strains less than 15% seemed to stimulate endochondral ossification, while all other conditions corresponded to areas of fibrous tissue or fibrocartilage [28]. Their theory was based on the observation that bone formation predominantly occurs near calcified surfaces [13]. This algorithm has also been integrated with other bone healing principles using an iterative FE model guided by 'fuzzy logic' to investigate trabecular bone fracture healing [37,38].

Multiphase Finite Element Models with Adaptivity

A study analyzing tissue differentiation around an orthopedic implant revealed that the stresses on the tissues arise from both the tissue matrix and the drag forces from interstitial fluid flow. This finding underscored the importance of biphasic models in accurately capturing the mechanical environment experienced by the tissues. Prendergast et al [5] introduced a biphasic poroelastic finite element (FE) model of the tissues and proposed two biomechanical stimuli: shear strain in the solid phase and fluid velocity in the interstitial fluid phase, as the mechano-transduction variables. High magnitudes of either stimulus favor the formation of fibrous tissue, while only when both stimuli are low enough can bone formation occur (Figure 3e). Lacroix et al [29] applied this algorithm to investigate tissue differentiation during fracture healing using a 2D axisymmetric FE model. Their adaptive poroelastic model successfully simulated direct periosteal bone formation, endochondral ossification in the external callus, stabilization upon bridging of the external callus, and resorption of the external callus [29]. The model also predicted slower healing with increasing gap size and increased connective tissue production with increased interfragmentary strain. These studies introduced the first biological representations by prescribing stem cell concentrations initially at the external boundaries and using a diffusive mechanism to collectively simulate migration, proliferation, and differentiation of cells. This model has subsequently been employed for successful predictions of tissue differentiation in a rabbit bone chamber and during osteochondral defect healing [39-41].

Comparative Analysis of the Biological Effects of Physical Forces

Although the mechano-regulation algorithms described above differ in theory, they have all been shown to predict normal bone healing with reasonable accuracy. Geris et al [42] compared the ability of two mechano-regulation algorithms, one developed by Claes and Heigele [28] and the other by Prendergast et al [5], to predict bone formation inside a rabbit bone chamber. The study used a single geometrical model for both algorithms but employed different material descriptions for each. The results indicated that fluid flow is crucial for the predicted differentiation patterns in the bone chamber. However, the study was unable to establish a clear distinction between the validity of the two algorithms [42]. Bone healing involves a complex interplay of cellular and molecular processes, heavily influenced by the mechanical environment. Computational models incorporating mechanoregulation algorithms are employed to predict the impact of mechanical stimuli on tissue differentiation and bone formation during healing [43].

This paper reviews the evolution of mechanoregulatory modeling in bone healing, highlighting recent advancements and ongoing challenges. Recent developments focus on integrating mechanoregulation algorithms with more detailed cellular and molecular descriptions. Validation remains a significant hurdle, with efforts centered on comparing existing models with well-characterized experimental data to identify shortcomings and refine computational models. The ultimate goal of these models is to elucidate the fundamental principles of cell and tissue differentiation, optimize implant design, and investigate treatments for non-union and other bone healing complications. None of the established algorithms properly predicted the spatial and temporal tissue distributions observed experimentally under all loading modes and time points. However, the algorithm based on deviatoric strain and fluid flow, proposed by Prendergast et al [5], showed the most promising results.

Computational Modeling of Callus Formation and Development

During bone healing, the callus undergoes a complex process that involves not only changes in stiffness and cell density but also significant shape alterations. While previous studies have neglected the role of volumetric growth, so they incorporated this factor into an adaptive finite element (FE) model of distraction osteogenesis (limb lengthening) using Prendergast et al [5] algorithm. This approach accurately predicted the observed spatial and temporal distributions of tissues during distraction osteogenesis, as well as the effects of alterations in distraction rate and frequency. Volumetric growth was modeled based on the matrix production rates of each tissue type, utilizing the biphasic swelling model [44] to simulate matrix production through the application of a swelling pressure and subsequent volume expansion. The tissue was allowed to swell for 24 hours and then assumed stress-free for the next increment. This approach successfully replicated the experimentally observed relaxation behavior of the tissue. However, the predicted reaction forces over time were not fully corroborated by experimental data. Garcia-Aznar et al [45] developed a continuum mathematical model that simulated the process of tissue regulation and callus volumetric growth during fracture healing adaptively. Their model aimed to capture events like stem

cell migration, proliferation, differentiation, and cell death of all the cell types involved, as well as the production and degradation of the different tissues involved. They also incorporated criteria for tissue damage, calcification, and remodeling.

For the tissue differentiation process, they employed the second invariant of the deviatoric strain tensor as the guiding stimulus. A volumetric growth model was proposed by Garcia-Aznar et al [45] based on tissue production. It was modeled using a separate finite element (FE) model based on thermal expansion. The predicted callus geometries in this model were not completely physiological at the boundaries, but it was able to predict increased callus size for increased interfragmentary movements (Figure 4). [45], as well as realistic variations when gap size and fixator stiffness were varied [46,47]. This model was improved by Reina-Romo et al [48] with respect to how it accounts for load history and used to simulate distraction osteogenesis. This study also assumed complete stress relaxation after each increment. However, in a second study, Reina-Romo et al [49] presented a macroscopic growth mixture formulation and showed that by accounting for the pre-traction stresses that are generated during distraction osteogenesis, both variations in distraction rate and the evolution of the resulting reaction forces over time can be predicted. A recent study by Garcia-Aznar et al [45] developed a computational model that simulates bone healing, including volumetric growth.

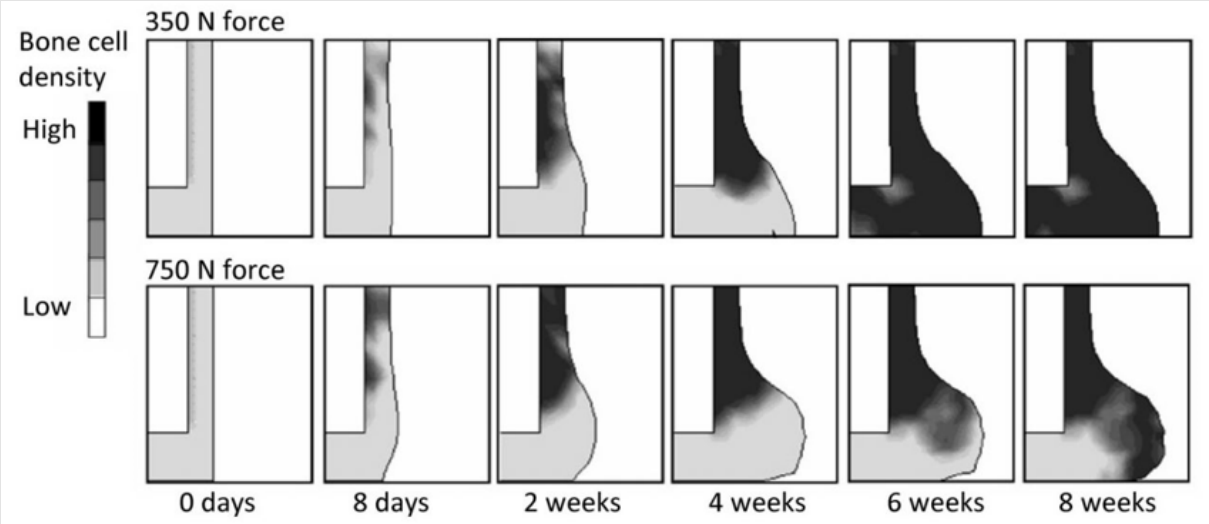


Figure 4: Bone healing involves a complex interplay of cellular and molecular processes, heavily influenced by the mechanical environment.

The study found that increased load led to delayed bone healing and somewhat larger callus growth. This finding suggests that mechanical loading can have both positive and negative effects on bone healing, and that a balance is needed for optimal healing Integrating Biological Factors into Computational Models of Bone Healing Despite the inclusion of a diffusion mechanism to simulate the migration, proliferation, and differentiation of cells, the studies mentioned above provided a very limited description of cellular mechanisms. The model by Lacroix and Prendergast [29] used a diffusion mechanism to collectively simulate migration, proliferation, and differentiation of cells. This model identified that the healing speed was most sensitive to cell diffusion rate. However, as real cell activity and tissue production rates were not considered, the "model time" held little physical significance. Several cell and tissue types contribute to bone healing, each with varying rates for different activities such as migration, proliferation, and matrix production. Consequently, recent advancements in this area have focused on a more detailed description of these cellular activities during bone healing [29].

Mathematical Models that Incorporate Biochemical Factors to Simulate Bone Healing

A mathematical framework to study the effects of growth factors during fracture healing was developed by Bailon-Plaza and van der Meulen [50]. They employed finite difference methods to simulate sequential tissue regulation and cellular events, examining the evolution of tissue-specific cells in the callus. In their model, cell differentiation was regulated by the presence of two growth factors (as opposed to mechanical stimulation, as in the models described earlier). The model incorporated the rate of change of cell density, matrix density, and growth factor concentrations, as well as matrix synthesis and degradation and growth factor diffusion.

Specific Cellular Functions Related to Cell-Specific Characteristics

In a pioneering effort, they developed a mechanistic model of cellular activity in bone healing that incorporated mechanical modulation of cell phenotype and tissue-specific activities. This model

accurately predicted the normal fracture healing process, delayed and non-union due to excessive loading, and the effects of specific biological perturbations and pathological situations, such as periosteal stripping or impaired cartilage remodeling (endochondral ossification). The model's performance was validated against experimental observations, demonstrating its ability to capture the intricate interplay between mechanical stimuli, cellular behavior, and tissue formation. However, the model required extensive parametric data as input, which was primarily obtained from literature. Since many parameter values were not well established, a factorial analysis was conducted using design of experiments and Taguchi orthogonal arrays to identify key cellular factors influencing bone healing. These factors, related to bone formation, cartilage production, and degradation, aligned with the crucial biological steps proposed in bone healing [51]. The model also revealed the sensitivity of bone healing to parameters governing fibrous tissue and cartilage formation, suggesting an optimal range for these parameters to ensure optimal healing. Notably, these studies modeled cell activities on an element basis, neglecting the anisotropy of cell movement, which could be incorporated in future models to enhance their realism.

Probabilistic Cell Modeling

Pérez and Prendergast [52] developed a new model for cell dispersal in the callus, which is the tissue that forms around a fracture site and aids in healing. The model uses a "random walk" approach to simulate cell migration, with or without a preferred direction, to account for anisotropic cell proliferation and migration. The model also incorporates a lattice structure within each element to represent the differences between the tissue and cell levels. In a 2D simulation of an implant–bone interface, the model was compared to a mechano-regulatory model developed by Prendergast et al [5]. The predictions of both models were similar, with the "random walk" model producing a more irregular tissue distribution than the diffusion model. However, due to the stochastic nature of the model, each simulation yielded slightly different results. A simulation of experimental data from a bone chamber experiment showed qualitative agreement with histological data [53]. However, the full variability observed in the experiment could not be reproduced by the mechanoregulation algorithm alone. This required the introduction of individual differences in mechano-sensitivity, which were modeled as differences in cell activity rates [54]. The model was also used in a 3D computational simulation of bone healing in a human tibia, with more realistic loading conditions [55]. The main phases of healing, including the resorption phase, were predicted with qualitative agreement to known clinical outcomes.

Blood Vessel Formation in the Tissue

Previously, the mechanical environment was the sole regulator of cell activity. However, sufficient blood supply is crucial for delivering nutrients and oxygen to cells. Angiogenesis, the growth of new blood vessels, plays a critical role in bone healing [23]. Low oxygen levels favor cartilage formation, while bone formation is only possible in high oxygen environments [23]. Geris et al [56,57] further developed the model by Bailon-Plaza and van der Meulen [50] to incorporate angiogenesis into the model by regulating the growth of a growth factor, and compared the results to experimental data on normal fracture healing. The diffusion of oxygen is limited to a few hundred micrometers from capillaries, emphasizing the importance of the vascular network's morphology in bone healing [56,57]. Checa and Prendergast [58] extended the stochastic cell model by Pérez and Prendergast [52] to account for angiogenesis. They simulated tissue differentiation in a bone/implant gap under shear loading, finding that their model could predict capillary networks similar to those observed experimentally. This also resulted in more "heterogenous" patterns of tissue differentiation [58]. Their model also considered the mechanical influence, demonstrating that higher loads lead to slower vascular development and delayed bone tissue formation [58]. Their model has also been used to evaluate the effects of cell seeding and mechanical loading on scaffolds, demonstrating the potential of these models for tissue engineering applications [59].

Challenges and Opportunities

The Finite Element Model (FEM) is a powerful tool that has enabled scientists and engineers to accurately predict the mechanical responses of biological tissues and simulate complex processes such as bone healing. Moreover, modern software has made the process of creating FEM models more efficient, allowing for wider adoption of this methodology. However, the ease of use also increases the risk of using the method incorrectly, potentially leading to inaccurate results [60]. It is crucial to remember that the validity of a computational model is ultimately determined by the accuracy of its assumptions. As described above, mechanobiological models are becoming increasingly complex, requiring more assumptions to be made for each additional mechanical or biological process that is incorporated into the model. The key challenge in mechanobiological modeling is therefore validation, which requires assessing the extent to which the assumptions and parameters of the model reflect reality [60].

Accuracy of Computational Models

Currently, validation in this field primarily focuses on comparing simulation outcomes with experimental data. Ideally, the experimental data should be obtained by the same research team to ensure consistency and accuracy [53,54]. However, this may not always be feasible, and in such cases, it is still common to corroborate specific aspects of the model against experimental data from other laboratories. However, this approach carries the risk of discrepancies due to variations in experimental setups, such as tissue mechanical properties or boundary conditions. As models become more complex, the challenge of accurately determining parameter values increases. For instance, migration rates measured in vitro are often used as estimates for in vivo conditions, and data from different species may need to be scaled. In these situations, parametric analysis or sensitiv-

ity analysis becomes crucial.

These methods, such as design of experiments or factorial analysis, allow for evaluating the impact of various assumptions, including cell activity rates, tissue mechanical properties, and angiogenesis-related parameters [58]. By identifying parameters with minimal impact on the simulation, higher confidence can be placed in the results. Conversely, if simulation outcomes are strongly dependent on a parameter lacking experimental data, the specific simulation may lack validity [60]. Parametric studies have highlighted the importance of cellular parameters associated with endochondral bone formation and three material properties – the permeability of granulation tissue, Young's modulus of cartilage, and permeability of immature bone – for accurate simulation. These findings should encourage further experimental studies to quantify these parameters.

Suggestions

Validation of computational models in mechanobiology has primarily involved comparing simulation results with experimental data. Ideally, the experimental data should be generated by the same research group [53,54]. However, when this is not possible, it is also common to corroborate specific aspects of the model with experimental data from other laboratories. This approach carries the risk of discrepancies due to differences in experimental setups, such as tissue mechanical properties or boundary conditions. Additionally, as the complexity of models increases, it becomes challenging to accurately determine parameter values. Despite these limitations, mechano-biological modeling has significantly advanced our understanding of bone regeneration. Corroborated models can guide experimental design, identify areas for further research, and contribute to the development of new therapies. Mechano-biological modeling also holds promise for improving implant design and optimizing bone tissue engineering scaffolds [61]. A critical challenge for the future is to establish the capabilities and limitations of mechano-biological modeling in hypothesis testing and predictive modeling [60]. While descriptive research has demonstrated associations between mechanical and biological parameters, the ability to rigorously test hypotheses and make robust predictions remains an ongoing area of research. In conclusion, computational modeling of tissue differentiation and bone regeneration is a promising field with the potential to advance our understanding of bone biology, improve implant design, and develop novel therapeutic strategies.

Conclusion

The complexity of biological processes such as bone healing often makes physical experimentation impractical or impossible. As a result, computational models have become increasingly valuable tools for studying these processes. Mechanoregulation theories have been developed to explain how mechanical forces influence tissue differentiation, growth, maintenance, remodeling, and degeneration. Over the past two decades, computational models of bone healing have evolved from simple linear elastic models [27] to more sophisticated poroelastic models [5] that incorporate adaptive tissue distribution predictions [28]. Poroelasticity is particularly important for describing the soft tissues involved in early bone healing, but some of their material properties remain poorly characterized. Recent advancements have focused on incorporating more intricate biological aspects, such as the effects of different cell types, growth factors, directed cell movement, and blood vessel ingrowth. As our understanding of bone healing deepens, these models are becoming increasingly multifaceted. The possibility of simulating patient-specific data and incorporating genetic or inter-specimen variability is also on the horizon. Despite the ongoing challenge of validation, mechanobiology represents a promising field where mechanical modeling can significantly enhance our comprehension of fundamental physiological and pathological processes.

Credit Authorship Contribution Statement

Pourya Bazyar: Conceptualization, Writing – original draft. Ehsan Sheidaee: Methodology, Visualization, Writing-Review & Editing.

Declaration of Competing Interest

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Data Availability

No data was used for the research described in the article.

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