A Review of Mechanobiological Models of Bone Fracture Healing: Recent Advances and Future Directions

(Review Article)

Abstract

The healing of bone fractures is a multifaceted process that ultimately leads to the creation of new bone tissue. A significant factor influencing this process is the mechanical environment present at the site of healing. Computational models that employ mechanobiological algorithms are capable of simulating the impact of mechanical stimuli on the differentiation of stem cells into various tissue types during the bone healing process. This paper provides a review of the domain of computational mechanobiology, particularly concerning bone healing, and evaluates the existing mechanobiological models. Furthermore, it discusses recent developments and the current challenges faced in this area. Recently, there has been a growing interest in integrating mechanobiological algorithms with a more comprehensive depiction of cellular and molecular events. A primary challenge in this domain is the validation of these models through their comparison with experimental data. Such models can enhance our understanding of the bone fracture healing process and improve the design of implants and treatment analyses. However, existing mechanobiological models are still in their early stages and require ongoing updates and refinements to keep pace with the continuous advancements in the field of stem cell mechanobiology.

Keywords: Fracture healing, Mesenchymal stem cells, Finite element analysis, Bony callus.

Accepted: 50 days before printing

Yunus Rezvanifar, MSc[1], Mohammed Najafi Ashtiani, PhD[2], Gholamreza Rouhi, PhD[3]

1. Faculty of Mechanical engineering, Tarbiat Modares University, Tehran, Iran.
2. Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.
3. Faculty of Biomedical Engineering, Amirkabir University of Technology, Tehran, Iran.

Corresponding Author:
Mohammed Najafi Ashtiani, PhD
Email address:
mnashtiani@modares.ac.ir

Introduction

Bone fracture healing is a unique biological process that initiates immediately following bone tissue injury[(1)]. Unlike other tissues that heal by forming scar tissue, bone heals by forming new bone tissue. The healing process involves complex and multifactorial molecular and cellular events that can lead to the formation of new bone. New bone is continually remodeled and, after healing, the original site of injury is difficult to distinguish from the surrounding bone[(2)]. Bone healing generally occurs in a stepwise manner through a tissue differentiation process where the formation of intermediate tissues prepares the conditions for osteogenesis[(3)]. The mechanisms by which mechanical stimuli are converted into biological responses are not yet fully understood[(4)]. A deeper comprehension of these processes will facilitate the creation of more accurate strategies for fracture treatment. Mechanobiology examines the ways in which mechanical loads are conveyed to cells through signaling[(5)]. By better understanding the effects of mechanical stimuli on the formation of different tissues, it is possible to adjust physiological conditions and drug factors for better and faster formation of the desired tissue. The utilization of computer modeling has significantly influenced the domain of mechanobiology[(6)]. Computational models have enabled the investigation of the connection between mechanical loads and the local stresses and strains that influence tissue development. Numerous biological processes, such as bone healing, are inherently complex, making it frequently time-consuming, costly, or even unfeasible to ascertain their precise characteristics through experimental methods. Consequently, simplified mathematical modeling is extensively employed to replicate intricate systems within this domain.

In mechanobiology, computational models, in conjunction with in vivo and in vitro experiments, are employed to quantitatively determine the rules that link mechanical loads to the differentiation, growth, and maintenance of various tissues[5]. In these models, mechanical forces are exerted on the geometry of the model, while the mechanical properties of the tissue are evaluated through finite element analysis. The biological component of the calculations relies on several assumptions that treat particular mechanical variables as triggers for distinct cellular functions[7]. Computational models are growing more intricate due to the enhancement of computational capabilities and the expanding understanding of mechanobiology. Additionally, both experimental and computational research play a crucial role in enhancing our comprehension of mechanobiology. The convergence of these two domains is vital, as models can facilitate the analysis of experiments, while experiments can yield insights and correlations that inform the refinement of current models.

In this article, existing mechanobiological algorithms are briefly reviewed. Our focus is on studies that have used these algorithms in conjunction with the finite element analysis to study bone fracture healing. Recent advances in this field, along with existing challenges, are also presented, and future capacities are discussed. The aim of this research is to describe the most important existing works and emphasize certain advancements and prospective pathways in bone healing modeling.

Stages of Bone Fracture Healing

A bone fracture triggers a sequence of tissue reactions that eliminate bone debris, restore blood circulation, and generate a new skeletal matrix[8,9]. After the healing and remodeling process of the fracture site, the structure reverts to its condition prior to the injury (Figure 1). Bone healing may take place via either primary or secondary mechanisms. Primary healing, also referred to as direct healing or intramembranous bone formation, entails the direct generation of bone without the development of external tissue (callus)[10]. This process occurs only when displacements are very small or the fracture gap is very narrow (800 µm to 1 mm)[11]. Unlike direct healing, secondary healing, also known as endochondral bone formation, occurs more often in conditions of interfragmentary movement. Most fractures heal via endochondral ossification. Secondary healing is divided into three general stages: inflammation (hematoma formation), healing (formation of soft and then hard callus), and finally remodeling (Figure 1)[8]. In the inflammatory phase, mesenchymal stem cells move towards the fracture site to create granulation tissue[12]. These cells proliferate and subsequently differentiate into various cells that can produce fibrous, cartilaginous, or bone tissue[13]. The broken bone fragments are initially connected by an external callus of soft tissue (fibrous or cartilaginous tissue)[14]. Gradually, the cross-sectional area and stiffness of the callus increases, and the fracture site becomes mechanically more stable. Interfragmentary movements at the fracture site decreases over time as the callus stiffens, and eventually, portions of the callus are transformed into a bony bridge between the fracture fragments through the deposition of calcium[15]. Following the formation of the bony bridge within the callus and the rejoining of the fracture fragment ends, the processes of remodeling and bone resorption commence[16].

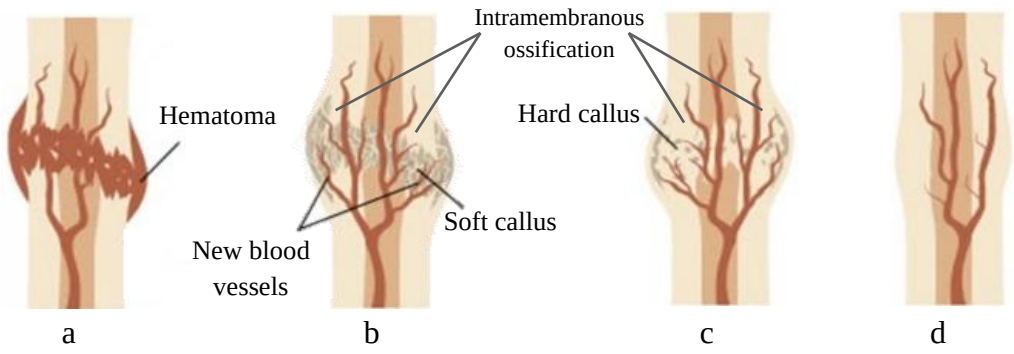

Figure 1: Stages of Bone Fracture Healing: a) Inflammation (Hematoma Formation) b) Soft Callus Formation c) Hard Callus Formation d) Bone Remodeling (Figure adapted from[9] with slight modifications)

The newly created, initially disorganized bone tissue is progressively substituted by more structured and robust lamellar bone tissue. This remodeling process reinstates the healing area to its original architecture and characteristics prior to the fracture.

Relationship between Bone Healing and Remodeling

It is crucial to note that bone healing and remodeling are two distinct yet interconnected biological processes occurring in bone tissue. Although these phenomena share similarities, they have different objectives and operate through different mechanisms. Bone remodeling is a lifelong process involving the coordinated activity of osteoclasts, osteoblasts, and osteocytes to replace old or damaged bone tissue with new bone tissue[17]. Ensuring bone strength, maintaining calcium and phosphate balance, and adapting to existing mechanical environmental conditions are the primary goals of the remodeling process. On the other hand, bone healing is the process of repairing bone tissue after a fracture. A chain of events occurs after a bone fracture to refill the fracture site with new bone. These events include an initial inflammatory response, bone healing with the formation of a soft callus, and its replacement with a hard callus and bone[18].

Newly formed bone remodeling primarily begins after the completion of the healing process and continues until its mechanical properties reach the initial state. The focus of this research is to review algorithms related to bone fracture healing, as examining algorithms related to remodeling itself requires a separate study.

Mechanobiological Models of Bone Fracture Healing

The use of mathematical modeling with numerical solution methods has significantly improved medical analysis[19]. Computational mechanobiology seeks to determine the governing laws of stem cell differentiation, tissue growth, adaptation, and maintenance under the influence of mechanical loading[5].

These processes are simulated using mechanobiological algorithms (models describing biological activities) and generally with numerical solution methods (including the finite element analysis). These models are based on the assumption that local mechanical variables (such as stress, strain, fluid velocity, etc.) are the driving force for the differentiation of stem cells into other cell types at the fracture site. In the following, some mechanobiological algorithms for bone healing are reviewed.

Early Theories

In 1960, Pauwels was the pioneer in suggesting a distinct theoretical framework regarding the impact of mechanical forces on the pathways of tissue differentiation (Figure 2a)[20].

He proposed that various tissues are adapted to endure particular mechanical conditions. For example, tension encourages the development of fibrous tissue, whereas hydrostatic pressure results in the creation of cartilaginous tissue. In his perspective, the formation of bone necessitates a relatively stable mechanical environment characterized by low stress, and ossification occurs only after the soft tissues have adequately stabilized the surroundings. Given that the direct formation of a bony bridge is initially unfeasible to connect the two sides of an unstable gap, intermediate tissues serve to stabilize the fracture gap to some extent and establish a stable mechanical environment conducive to ossification. Pauwels, for the first time, based on clinical observations and reasoning, theorized about the influence of the mechanical environment on the development of various tissues and established the groundwork for the rationale behind all contemporary models. In 1980, Perren and Cordey suggested that the formation of different tissues depends on the resistance of each tissue to strain[21]. A tissue that fails at a particular strain level cannot form in a region with the same or higher strain. Interfragmentary strain is calculated by dividing the longitudinal displacement of the fracture gap (small movements of the gap due to loading) by the initial size of the gap. As the interfragmentary strain decreases, granulation tissue differentiates into fibrous tissue, then cartilaginous tissue, and finally into bone tissue (Figure 2b). However, this hypothesis only considered axial strains and did not include the effect of other important strains, such as radial and circumferential strains, which certainly have an impact on the healing process.

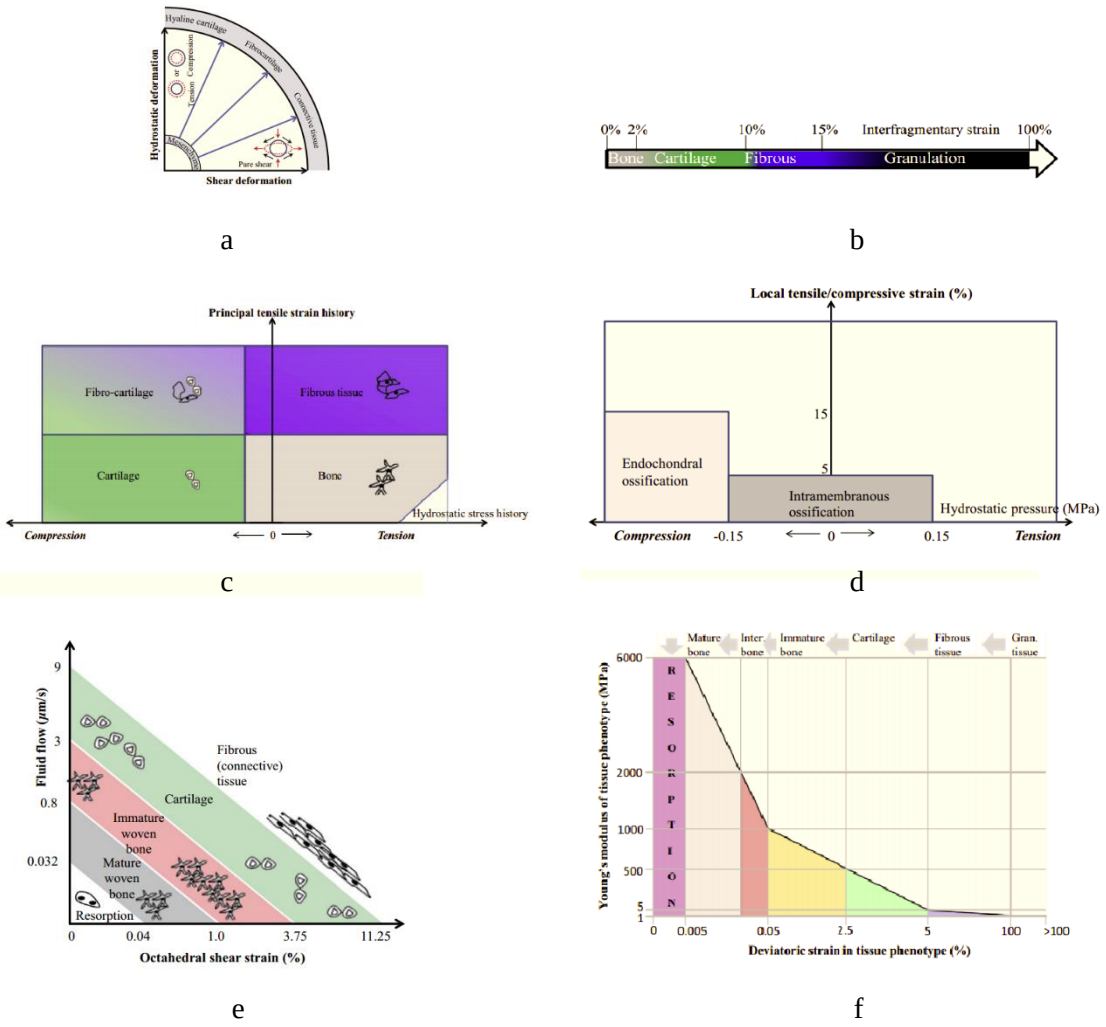

Figure 2: Different Mechanoregulation Models: a) Pauwels b) Perren et al. c) Carter et al.d) Claes and Heigele e) Lacroix and Prendergast f) Isaksson et al. (Figure adapted from[14] with slight modifications)

Single-Phasic Finite Element Models

In 1988, Carter et al. proposed a model based on Pauwels' model, in which the process of tissue differentiation over time could be predicted based on the history of local stress and strain[22]. A decade later, in 1998, they developed this model into a more general model in which, if the callus is subjected to high tensile strains, fibrous tissue is formed, and when the pressure is high, cartilaginous tissue is formed (since this tissue can withstand hydrostatic pressure)[3]. Bone is only formed when the hydrostatic pressure is low (Figure 2c). Although Carter and his colleagues did not introduce a specific threshold for tension and pressure in their research, it was the first study in which finite element analysis was used to investigate the relationships between local stress and strain levels and differentiated tissue. They stated that adequate blood flow is essential for bone formation, and insufficient blood supply leads to the formation of cartilaginous tissue.

In 1998, Claes and Heigele conducted an interdisciplinary study comparing histological data from animal experiments and finite element analysis to evaluate the effects of gap size and interfragmentary strain on bone healing[23]. Based on histological observations, Claes and Heigele developed a mechanobiological algorithm similar to that of Carter et al. and, for the first time, quantitatively defined the thresholds for stimulating the formation of different tissues (Figure 2d)[24]. To achieve this objective, the researchers employed a hyperelastic solid finite element analysis, adjusting the mechanical properties of the model at various time intervals throughout the fracture healing

process. By juxtaposing finite element analysis with histological findings, they successfully linked intramembranous ossification to local strains of under 5% and hydrostatic pressures ranging from ± 0.15 MPa. It was determined that compressive hydrostatic stresses exceeding 0.15 MPa and strains below 15% acted as catalysts for endochondral ossification. Conversely, alternative conditions resulted in the development of fibrous or fibrocartilaginous tissue. In the investigation conducted by Claes and Heigele, the tissue formation process was not modeled in an adaptive manner (i.e., gradually and incrementally); instead, the focus was on examining the mechanics of the healing tissue at designated time points to ascertain the stimulation threshold necessary for the development of each type of tissue.

Biphasic and adaptive finite element models

In a biphasic simulation of tissue differentiation around an orthopedic implant, it was observed that interstitial fluid flow had a significant effect on the stress distribution in the callus tissue under mechanical loading[25–27]. This highlighted the importance of two-phasic modeling. Therefore, in 2002, Lacroix and Prendergast based their tissue differentiation model on a finite element analysis with the properties of poroelastic materials from the process of tissue healing around an orthopedic implant[28]. They proposed two stimuli, deviatoric strain in the solid phase and fluid velocity in the interstitial fluid phase, as regulators of the cell differentiation process (Figure 2e). High values of either of these two variables led to the formation of fibrous tissue, and only when both variables were low enough did ossification occur.

Isaksson et al. in 2006, in a biphasic fracture healing model, compared and analyzed the mechanobiological algorithms of Carter et al., Claes and Heigele, and Lacroix and Prendergast, and introduced a new mechanobiological algorithm based solely on deviatoric strain (Figure 2f)[3,7,24,28]. In this work, it was observed that all the compared algorithms produced relatively similar results. This can be attributed to the presence of both a volumetric and a deviatoric component in each of these algorithms. Another interesting point in the study of Isaksson et al. was that the simulation results based solely on deviatoric strain were very close to the results of the Lacroix and Prendergast algorithm[28,29].

Therefore, they concluded that the deviatoric component may be a more important factor in predicting the outcome of the fracture healing process than the volumetric component.

Callus Growth Models

In the tissue differentiation process, not only the tissue of callus but also its geometric shape changes. In all the studies mentioned earlier, volumetric growth of the callus tissue was neglected. In 2006, Isaksson et al., using the Lacroix and Prendergast algorithm and adding volumetric growth of the callus, simulated tension-based bone formation and validated the results with experimental studies[28,30]. Also in the same year, Aznar et al. proposed a continuous mathematical model of tissue differentiation and volumetric growth of callus in fracture healing[31]. Their model simulated phenomena such as migration, proliferation, and differentiation of stem cells, and death of various cell types. They also incorporated a criterion for tissue damage and remodeling within their model. The second variable of the deviatoric stress tensor was regarded as a stimulus for the tissue differentiation process. Volumetric growth was determined by the quantity of tissue production and was simulated independently in a finite element model that utilized thermal expansion. Although the predicted callus shape was not completely physiological at its edges, the prediction regarding the alteration in callus size in response to variations in interfragmentary movements, fracture gap dimensions, and the stiffness of the fixator was executed accurately[31].

Bailon-Plaza and van der Meulen were the first to develop a mathematical framework for investigating the effect of growth factors on bone healing[32]. They employed the finite difference analysis to simulate cellular phenomena and the differentiation of tissue-specific cells in the callus. Unlike previous models, in their model, cellular differentiation was controlled by two growth factors (instead of mechanical stimulation).

In 2006, Perez and Prendergast developed a new model to simulate cell movements in the callus[33]. The model of random cell walk included both directed and undirected cell migration, leading to anisotropic cell proliferation and migration. In this study, a 2D cross-section of the implant and bone was modeled using their random cell walk model and the

mechanobiology algorithm of Lacroix and Prendergast[29]. The simulation results of both models were similar, although the random cell walk model predicted a more irregular tissue distribution compared to the diffusion model. Although the results of each simulation varied slightly due to the stochastic nature of the model, there was a good qualitative agreement between the histological data and the simulation results in simulating the data of a bone chamber experiment[34].

Greater attention to biological aspects of healing process

Although sufficient blood supply is essential for the delivery of oxygen and nutrients to cells, the previously discussed models have indicated that the mechanical environment was the only determinant of cellular functions. Given that a low-oxygen atmosphere promotes cartilage development while bone formation requires a high-oxygen environment, angiogenesis, which refers to the formation of new blood vessels, plays a crucial role in the process of bone healing[35]. Geris et al. expanded upon the Bailon-Plaza and van der Meulen model by incorporating angiogenesis influenced by growth factors, and they contrasted their findings with experimental data pertaining to normal fracture healing[32,36,37]. Oxygen diffusion is restricted to a mere few hundred micrometers surrounding the capillaries, thus the configuration of the newly formed vascular network is crucial in the process of bone healing. Checa and Prendergast expanded upon the Perez and Prendergast random cell walk model to incorporate angiogenesis as well[33,38]. They replicated tissue differentiation in the space between the implant and bone while subjected to shear loading, discovering that their model could replicate a vascular network akin to that observed in the experimental setup. This resulted in a forecast of more varied and natural tissue differentiation in contrast to earlier simulations. Furthermore, this model took into account mechanical influences and demonstrated that increased loading could diminish the rate of vascular network development and postpone the formation of bone tissue.

Given that ultrasound has the potential to markedly elevate the concentrations of cytokines, fibroblast growth factor, and vascular endothelial growth factor (VEGF), which influence angiogenesis, Vava et al. suggested a comprehensive mathematical model that incorporates partial differential equations to depict the spatiotemporal development of soft tissue, bone, and vascular networks[39]. In this model, which is grounded in prior experimental research, ultrasound was identified as the primary factor influencing VEGF. This model offers novel perspectives on the impact of ultrasound on bone development and angiogenesis[39,40].

Considering that the precise role of immune cells and their influence on fracture healing remains unclear, Kojouharov et al. introduced a novel mathematical model composed of nonlinear ordinary differential equations. This model aims to investigate the initial inflammatory responses during the bone healing process, integrating immune cells, histiocytes, and their regulatory signals[41]. Their numerical simulations indicated that administering anti-inflammatory cytokines at the onset of the healing process could potentially expedite the healing duration. The ideal dosage is contingent upon the specific type of fracture, and elevated levels of inflammatory cytokines adversely affect the healing time of fractures.

In the work of Kojouharov et al., the first attempt was made to include macrophages in a mathematical model simulating the fracture healing process[41]. Trejo et al. extended the that work by including two other types of macrophages and proposed a new mathematical model consisting of nonlinear ordinary differential equations to study macrophage-controlled inflammation in the early stages of fracture healing[42].

Zhang et al. have also recently explored the inflammatory processes that occur during the initial phases of healing. In order to examine the impact of tumor necrosis factor (TNF) on the early stages of fracture healing in both normal and diabetic conditions, the researchers developed a numerical model composed of partial differential equations that characterize the roles of cells and cytokines in fracture wounds[43].

They determined that an optimal concentration of TNF-α exists, which can enhance the healing of fractures, whereas excessively high levels (as observed in diabetic conditions) or significantly low levels of TNF-α can hinder the healing process.

Implementation of Mechanobiological Models

Mechanobiological models are commonly employed to simulate the fracture healing process in long bones (Figure 3)[44]. Initially, a numerical model (typically

finite element model) of the fracture, along with the geometry of the callus, is created. The material properties of the granulation tissue for the callus are then assigned. Subsequently, the model is subjected to a specific load, and the value of the mechanical variable or variables (mechanical stimulus) within the callus tissue is calculated. Based on the mechanobiological model and the concentration of stem cells, the type and quantity of tissue that should be formed are computed. To modify the properties of the callus tissue, one of the numerical smoothing methods is used to prevent abrupt and unnatural changes in the mechanical properties of the tissue[45]. The fracture model with the new material properties is subjected to the load again, and a new mechanical stimulus is calculated. This cycle continues until the solution converges, and the callus tissue reaches its final properties.

Discussion

Determining the external mechanical loads transferred to the fracture site through new tools is no longer challenging. Bone healing simulations can determine how these loads are converted to tissue-level stimuli through mechanobiological models. However, determining how mechanical loads at the tissue level are converted to the cellular level and the mechanical stimulus that each cell senses, as well as how these stimuli are translated into biochemical signals by these cells, has been difficult and has recently attracted the attention and focus of researchers in this field[46].

The finite element analysis is a powerful tool that allows scientists and engineers to predict the mechanical response of biological tissues using mechanobiological models and to simulate complex processes such as bone fracture healing[10]. Although new software has eliminated many time-consuming modeling steps and enabled more people to enter this field, this simplicity can also increase the likelihood of incorrect simulations or the production of inaccurate results[47].

It should be noted that computational models will never perform better than their worst initial assumptions. Adding any new mechanical or biological aspect to the model increases the number of parameters involved in the modeling, and how to determine each parameter and its accuracy can present new challenges for the researcher.

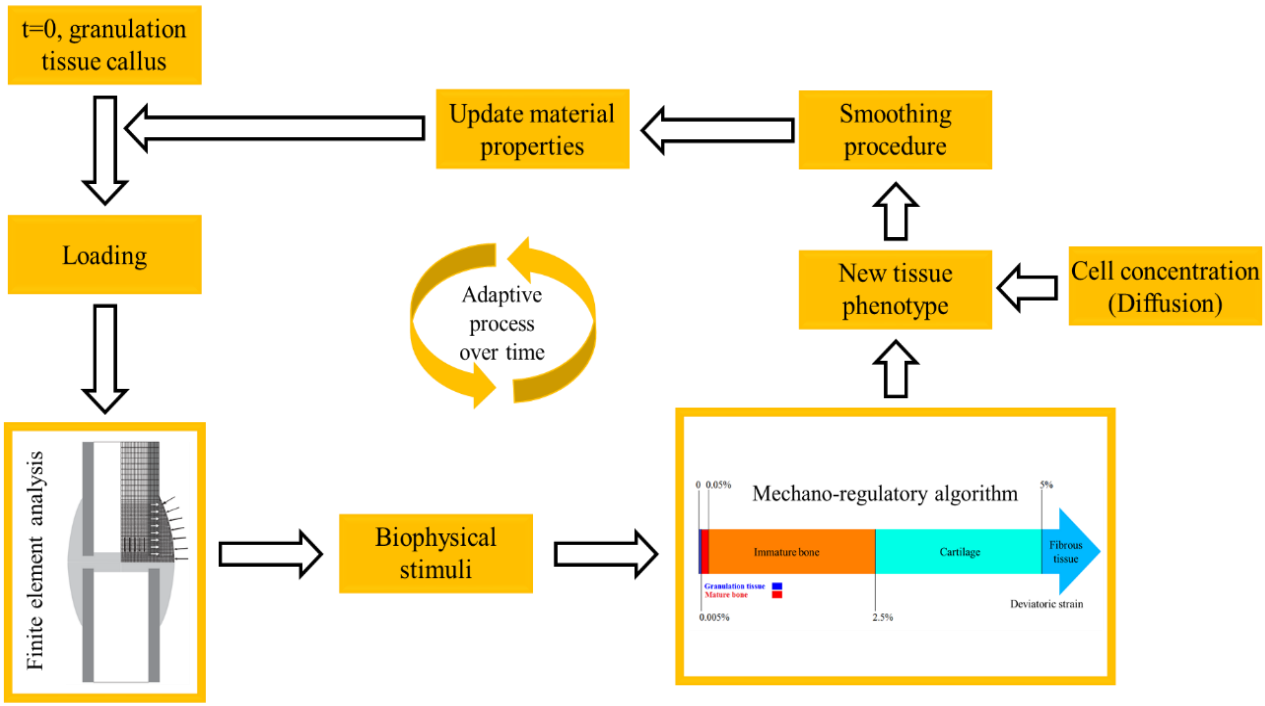

Figure 3: Flowchart of the Application of Mechanobiology Models and the Finite Element Method in Simulating the Bone Fracture Healing Process (Figure adapted from[44] with slight modifications)

Among the presented models, there are some common shortcomings that are listed as follows:

1. The exact mechanisms, functions, and cellular interactions are not fully understood, and there is no consensus yet on which mechanical stimulus (interfragmentary strain, interstitial fluid flow, shear strain, hydrostatic pressure, etc.) affects the healing process.
2. In some models, only the biological factors affecting the healing process are considered without considering the mechanical stimuli that are important for fracture healing. In another group of models, only mechanical stimuli is emphasized, and biological aspects are considered in a highly simplified manner.
3. In these models, due to the limitations of the methods used to solve the equations, simplified geometry and isotropic and homogeneous material properties are generally used, whereas bone has a complex geometric structure with anisotropic and inhomogeneous material properties.
4. In these models, only one or a few factors that may affect the healing outcome are considered, and the healing process is viewed from a specific aspect, and other factors are not included in the models or are considered with significant simplification.
5. The issue of validation of these models, which is considered one of the most important aspects of any modeling, exists as a fundamental challenge in this field, which will be discussed further below.

A key challenge in mechanobiological modeling is model validation. In other words, determining the extent to which the model's assumptions, parameters and simulation results represent reality is a significant challenge in these simulations[47]. Validation of mechanobiological models is generally achieved by comparing simulation results with experimental data. For more accurate validation, it is recommended that both the experiment and numerical analysis be conducted by the same research group[2,30,48,49].

Since this is not always feasible, comparing and matching parts of the model with experimental data from different laboratories has become common practice, which is a point worth considering. In this case, the increased possibility of error in correctly assigning numerical model parameters, corresponding to what happened in the actual experiment, exists because some details of other research groups' laboratory work, such as the mechanical properties of the tissue or boundary conditions, are not always clear and available[50].

With increasing modeling complexity, researchers often encounter situations where they cannot accurately determine parameter values. For example, the cell migration rate measured in in vitro experiments is also considered approximately the same value when interpreting in vivo experimental results. Additionally, experimental data obtained from different animal species are used for other species or humans with scaling, which is certainly not an accurate method. In these cases, to determine the degree of confidence in the simulation results, parametric analysis or sensitivity analysis should be performed. For example, to evaluate the importance of assumptions made about cell activity rates, tissue mechanical properties, and assumptions related to angiogenesis, the design of experiments or parametric analysis has been used [29,38,51]. If the model is not sensitive to parameters whose exact value is less well-known, greater confidence in the simulation results is obtained. However, if the simulation is highly dependent on a parameter for which there is insufficient experimental data for accurate determination, that simulation may not be much valuable[47].

Future Work

Although there are significant limitations in the field of numerical simulations, especially in evaluating initial assumptions, the use of mechanobiological modeling has led to significant advancements in this area. Validated mechanobiological models can contribute to improve our understanding of the biology of bone healing processes and identify areas that require further research. Validated models can be used in the design of new experiments alongside theoretical models and animal experiments and raise future research questions. One of the most important applications of mechanobiology is the development of new treatment methods (e.g., in the treatment of bone fractures). For example, Geris et al. investigated the ability of their model to predict the outcomes of certain treatments, such as the injection of stem cells and growth factors to increase bone formation[52,53].

Other areas of mechanobiological modeling application include its use in improving the design of implants and bone tissue engineering[54].

Furthermore, parametric studies of the factors affecting endochondral bone formation have identified three material properties (permeability of granulation tissue, Young's modulus of cartilage tissue and permeability of immature bone) as the most important factors affecting the numerical simulation results of this phenomenon[29].

Further experimental studies to more accurately measure these parameters, especially in relation to humans, can lead to more realistic simulations in this area. With the increasing computational power of computers, it can be expected that in future models, biological aspects (growth factors, angiogenesis, cell distribution and movement, etc.) and mechanical aspects (geometry and material properties and natural loading, etc.) of the healing process will be simultaneously considered and we will have more coupled, comprehensive, and accurate models in this area.

Conclusion

Numerous biological processes, such as bone healing, are so intricate that addressing certain related inquiries through physical experiments is often exceedingly time-consuming, expensive, and at times unfeasible. Theories in mechanobiology have demonstrated their capability to elucidate the influence of the mechanical environment on tissue differentiation, growth, maintenance, remodeling, and degradation. Over the last thirty years, computational models of bone healing have advanced significantly, evolving from basic single-phasic linear elastic models that were solely developed and resolved for a specific duration of the healing process, to more sophisticated adaptive models that incorporate the definition of porous materials[3,27].

Recently, attention has shifted from developing mechanical analyzes to considering more biological dimensions, including the effects of different cells, growth factors, and the emergence of blood vessels. Despite the remaining challenges in accurately validating the results of computer simulation-based research, mechanobiological modeling can significantly increase our knowledge of the mechanisms of biological phenomena and guide future research areas and the invention of more efficient methods and tools in this area.

Acknowledgments

The authors would like to express their sincere gratitude to Tarbiat Modares University for its support of this research.

References

1 Doblaré M, García JM, Gómez MJ. Modelling bone tissue fracture and healing: a review. Eng Fract Mech [Internet]. 2004 Sep;71(13–14):1809–40. Available from: https://doi.org/10.1016/j.engfracmech.2003.08.003
2 Isaksson H, Gröngröft I, Wilson W, van Donkelaar CC, van Rietbergen B, Tami A, et al. Remodeling of fracture callus in mice is consistent with mechanical loading and bone remodeling theory. J Orthop Res [Internet]. 2009 May 4;27(5):664–72. Available from: https://doi.org/10.1002/jor.20725
3 Carter DR, Beaupr?? GS, Giori NJ, Helms JA. Mechanobiology of Skeletal Regeneration. Clin Orthop Relat Res [Internet]. 1998 Oct;355S(SUPPL.):S41–55. Available from: https://doi.org/10.1097/00003086-199810001-00006
4 Geris L, Sloten J Vander, Van Oosterwyck H. In silico biology of bone modelling and remodelling: Regeneration. Philos Trans R Soc A Math Phys Eng Sci [Internet]. 2009;367(1895):2031–53. Available from: https://doi.org/10.1098/rsta.2008.0293
5 Van der Meulen MCH, Huiskes R. Why mechanobiology? A survey article. J Biomech [Internet]. 2002;35(4):401–14. Available from: https://doi.org/10.1016/s0021-9290(01)00184-1
6 Claes LE. Mechanobiology of FractureHealingFrom Basic Science to Clinical Application [Internet]. SpringerBriefs in Bioengineering; 2022. Available from: https://doi.org/10.1007/978-3-030-94082-9
7 Isaksson H, Wilson W, van Donkelaar CC, Huiskes R, Ito K. Comparison of biophysical stimuli for mechano-regulation of tissue differentiation during fracture healing. J Biomech [Internet]. 2006;39(8):1507–16. Available from: https://doi.org/10.1016/j.jbiomech.2005.01.037
8 Carano RAD, Filvaroff EH. Angiogenesis and bone repair. Drug Discov Today [Internet]. 2003 Nov;8(21):980–9. Available from: https://doi.org/10.1016/s1359-6446(03)02866-6
9 Giannoudis P V. Fracture Reduction and Fixation Techniques [Internet]. Giannoudis P V., editor. Fracture Reduction and Fixation Techniques: Upper Extremities. Cham: Springer International Publishing; 2018. 1–277 p. Available from: https://doi.org/10.1007/978-3-319-68628-8
10 Ghimire S, Miramini S, Edwards G, Rotne R, Xu J, Ebeling P, et al. The investigation of bone fracture healing under intramembranous and endochondral ossification. Bone Reports [Internet]. 2021;14:100740. Available from: https://doi.org/10.1016/j.bonr.2020.100740
11 Marsell R, Einhorn TA. The biology of fracture healing. Injury [Internet]. 2011 Jun;42(6):551–5. Available from: https://doi.org/10.1016%2Fj.injury.2011.03.031
12 Gerstenfeld LC, Cullinane DM, Barnes GL, Graves DT, Einhorn TA. Fracture healing as a post-natal developmental process: Molecular, spatial, and temporal aspects of its regulation. J Cell Biochem [Internet]. 2003 Apr 26;88(5):873–84. Available from: https://doi.org/10.1002/jcb.10435

13 Ghiasi MS, Chen J, Vaziri A, Rodriguez EK, Nazarian A. Bone fracture healing in mechanobiological modeling: A review of principles and methods. Bone Reports [Internet]. 2017 Jun;6:87–100. Available from: https://doi.org/10.1016%2Fj.bonr.2017.03.002
14 Ito K, Perren SM. Biology and biomechanics in bone healing. In: AO principles of fracture management: 2 Expanded edition [Internet]. Stuttgart / New York: Georg Thieme Verlag KG; 2007. p. 8–31. Available from: https://doi.org/10.1308%2F003588409X432419f
15 Rouhi G, Epstein M, Sudak L, Herzog W. Free surface density and microdamage in the bone remodeling equation: Theoretical considerations. Int J Eng Sci [Internet]. 2006 Apr;44(7):456–69. Available from: https://doi.org/10.1016/j.ijengsci.2006.02.001
16 Rouhi G, Herzog W, Sudak L, Firoozbakhsh K, Epstein M. Free Surface Density Instead of Volume Fraction in the Bone Remodeling Equation : Theoretical Considerations. Forma [Internet]. 2004;19(3):165–82. Available from: https://api.semanticscholar.org/CorpusID:138704224
17 Rouhi G, Tahani M, Haghighi B, Herzog W. Prediction of Stress Shielding Around Orthopedic Screws: Time-Dependent Bone Remodeling Analysis Using Finite Element Approach. J Med Biol Eng [Internet]. 2015 Aug 19;35(4):545–54. Available from: https://doi.org/10.1007/s40846-015-0066-z
18 Long F. Building strong bones: molecular regulation of the osteoblast lineage. Nat Rev Mol Cell Biol [Internet]. 2012 Jan 22;13(1):27–38. Available from: https://doi.org/10.1038/nrm3254%0A%0A
19 Mehboob H, Chang S-H. Application of composites to orthopedic prostheses for effective bone healing: A review. Compos Struct [Internet]. 2014 Dec;118(1):328–41. Available from: https://doi.org/10.1016/j.compstruct.2014.07.052
20 Pauwels F. [A new theory on the influence of mechanical stimuli on the differentiation of supporting tissue. The tenth contribution to the functional anatomy and causal morphology of the supporting structure]. Z Anat Entwicklungsgesch [Internet]. 1960;121:478–515. Available from: pmid: 14431062
21 Perren SM, Cordey J. The concept of interfragmentary strain. In: Uhthoff HK, Stahl E. In: Current Concepts of Internal Fixation of Fractures. Berlin: Springer; 1980. p. 63–77.
22 Carter DR, Blenman PR, Beaupré GS. Correlations between mechanical stress history and tissue differentiation in initial fracture healing. J Orthop Res [Internet]. 1988 Sep 18;6(5):736–48. Available from: https://doi.org/10.1002/jor.1100060517
23 Claes L, Augat P, Suger G, Wilke HJ. Influence of size and stability of the osteotomy gap on the success of fracture healing. J Orthop Res [Internet]. 1997;15(4):577–84. Available from: https://doi.org/10.1002/jor.1100150414
24 Claes LE, Heigele CA. Magnitudes of local stress and strain along bony surfaces predict the course and type of fracture healing. J Biomech [Internet]. 1999;32(3):255–66. Available from: https://doi.org/10.1016/s0021-9290(98)00153-5
25 Prendergast P. Finite element models in tissue mechanics and orthopaedic implant design. Clin Biomech [Internet]. 1997 Sep;12(6):343–66. Available from: https://doi.org/10.1016/s0268-0033(97)00018-1
26 Prendergast P. Finite element models in tissue mechanics and orthopaedic implant design. Clin Biomech [Internet]. 1997 Sep;12(6):343–66. Available from: https://doi.org/10.1016/s0268-0033(97)00018-1
27 Prendergast P. Biophysical stimuli on cells during tissue differentiation at implant interfaces. Clin Biomech [Internet]. 1997 Sep;12(6):343–66. Available from: https://doi.org/10.1016/s0268-0033(97)00018-1
28 Lacroix D, Prendergast PJ. A mechano-regulation model for tissue differentiation during fracture healing: analysis of gap size and loading. J Biomech [Internet]. 2002 Sep;35(9):1163–71. Available from: https://doi.org/10.1016/S0021-9290(02)00086-6
29 Isaksson H, van Donkelaar CC, Huiskes R, Yao J, Ito K. Determining the most important cellular characteristics for fracture healing using design of experiments methods. J Theor Biol [Internet]. 2008 Nov;255(1):26–39. Available from: https://doi.org/10.1016/j.jtbi.2008.07.037
30 Isaksson H, Comas O, van Donkelaar CC, Mediavilla J, Wilson W, Huiskes R, et al. Bone regeneration during distraction osteogenesis: Mechano-regulation by shear strain and fluid velocity. J Biomech [Internet]. 2007;40(9):2002–11. Available from: https://doi.org/10.1016/j.jtbi.2008.07.037
31 García-Aznar JM, Kuiper JH, Gómez-Benito MJ, Doblaré M, Richardson JB. Computational simulation of fracture healing: Influence of interfragmentary movement on the callus growth. J Biomech [Internet]. 2007 Jan;40(7):1467–76. Available from: https://doi.org/10.1016/j.jbiomech.2006.06.013
32 Bailon-Plaza, Alicia van der Meulen MCH. A Mathematical Framework to Study the Effects of Growth Factor Influences on Fracture Healing. J Theor Biol [Internet]. 2001 Sep;212(2):191–209. Available from: https://doi.org/10.1006/jtbi.2001.2372
33 Pérez MA, Prendergast PJ. Random-walk models of cell dispersal included in mechanobiological simulations of tissue differentiation. J Biomech [Internet]. 2007 Jan;40(10):2244–53. Available from: https://doi.org/10.1016/j.jbiomech.2006.10.020
34 Byrne DP, Lacroix D, Prendergast PJ. Simulation of fracture healing in the tibia: Mechanoregulation of cell activity using a lattice modeling approach. J Orthop Res [Internet]. 2011 Oct;29(10):1496–503. Available from: https://doi.org/10.1002/jor.21362
35 Keramaris NC, Calori GM, Nikolaou VS, Schemitsch EH, Giannoudis PV. Fracture vascularity and bone healing: A systematic review of the role of VEGF. Injury [Internet]. 2008 Sep;39:S45–57. Available from: https://doi.org/10.1016/s0020-1383(08)70015-9
36 Geris L, Gerisch A, Sloten J Vander, Weiner R, Oosterwyck H Van. Angiogenesis in bone fracture healing: A bioregulatory model. J Theor Biol [Internet]. 2008 Mar;251(1):137–58. Available from: https://doi.org/10.1016/j.jtbi.2007.11.008
37 Geris L, Gerisch A, Maes C, Carmeliet G, Weiner R, Vander Sloten J, et al. Mathematical modeling of fracture healing in mice: comparison between experimental data and numerical simulation results. Med Biol Eng Comput [Internet]. 2006 Apr 22;44(4):280–9. Available from: https://doi.org/10.1007/s11517-006-0040-6
38 Checa S, Prendergast PJ. A Mechanobiological Model for Tissue Differentiation that Includes Angiogenesis: A Lattice-Based Modeling Approach. Ann Biomed Eng [Internet]. 2009 Jan 15;37(1):129–45. Available from: https://doi.org/10.1007/s10439-008-9594-9

39 Vavva MG, Grivas KN, Carlier A, Polyzos D, Geris L, Van Oosterwyck H, et al. Effect of ultrasound on bone fracture healing: A computational bioregulatory model. Comput Biol Med [Internet]. 2018 Sep;100:74–85. Available from: https://doi.org/10.1016/j.compbiomed.2018.06.024
40 Cowin SC. Bone poroelasticity. J Biomech [Internet]. 1999 Mar;32(3):217–38. Available from: https://doi.org/10.1016/s0021-9290(98)00161-4
41 Kojouharov H V, Trejo I, Chen-Charpentier BM. Modeling the effects of inflammation in bone fracture healing. In 2017. p. 020005. Available from: https://doi.org/10.1063/1.5007359
42 Trejo I, Kojouharov H, Chen-Charpentier B. Modeling the Macrophage-Mediated Inflammation Involved in the Bone Fracture Healing Process. Math Comput Appl [Internet]. 2019 Jan 17;24(1):12. Available from: https://doi.org/10.3390/mca24010012
43 Zhang E, Miramini S, Patel M, Richardson M, Ebeling P, Zhang L. Role of TNF-α in early-stage fracture healing under normal and diabetic conditions. Comput Methods Programs Biomed [Internet]. 2022 Jan;213:106536. Available from: https://doi.org/10.1016/j.cmpb.2021.106536
44 Rezvanifar Y, Ashtiani MN, Rouhi G. Investigation on the effects of insertion torque on osseointegration in dental implants with immediate loading: Computer simulation using a mechanobioregulatory model. Tarbiat Modares University; 2024.
45 Irandoust S, Müftü S. The interplay between bone healing and remodeling around dental implants. Sci Rep [Internet]. 2020 Mar 9;10(1):4335. Available from: https://doi.org/10.1038/s41598-020-60735-7%0A%0A
46 García-Aznar JM, Nasello G, Hervas-Raluy S, Pérez MÁ, Gómez-Benito MJ. Multiscale modeling of bone tissue mechanobiology. Bone [Internet]. 2021 Oct;151:116032. Available from: https://doi.org/10.1038/s41598-020-60735-7%0A%0A
47 Jacobs CR, Kelly DJ. Cell mechanics: The role of simulation. In: Fernandes PR, Bártolo PJ, editors. Advances on Modeling in Tissue Engineering [Internet]. Dordrecht: Springer Netherlands; 2011. p. 1–14. Available from: https://doi.org/10.1007/978-94-007-1254-6_1%0A%0A
48 Khayyeri H, Checa S, Tägil M, Prendergast PJ. Corroboration of mechanobiological simulations of tissue differentiation in an in vivo bone chamber using a lattice-modeling approach. J Orthop Res [Internet]. 2009 Dec 9;27(12):1659–66. Available from: https://doi.org/10.1002/jor.20926
49 Khayyeri H, Checa S, Tägil M, Aspenberg P, Prendergast PJ. Variability observed in mechano-regulated in vivo tissue differentiation can be explained by variation in cell mechano-sensitivity. J Biomech [Internet]. 2011 Apr;44(6):1051–8. Available from: https://doi.org/10.1016/j.jbiomech.2011.02.003
50 Isaksson H, van Donkelaar CC, Huiskes R, Ito K. A mechano-regulatory bone-healing model incorporating cell-phenotype specific activity. J Theor Biol. 2008;252(2):230–46.
51 Isaksson H, van Donkelaar CC, Ito K. Sensitivity of tissue differentiation and bone healing predictions to tissue properties. J Biomech [Internet]. 2009 Mar;42(5):555–64. Available from: https://doi.org/10.1016/j.jbiomech.2009.01.001
52 Geris L, Reed AAC, Vander Sloten J, Simpson AHRW, Van Oosterwyck H. Occurrence and Treatment of Bone Atrophic Non-Unions Investigated by an Integrative Approach. Bourne PE, editor. PLoS Comput Biol [Internet]. 2010 Sep 2;6(9):e1000915. Available from: https://doi.org/10.1371/journal.pcbi.1000915
53 Geris L, Sloten J Vander, Oosterwyck H Van. Connecting biology and mechanics in fracture healing: an integrated mathematical modeling framework for the study of nonunions. Biomech Model Mechanobiol [Internet]. 2010 Dec 24;9(6):713–24. Available from: https://doi.org/10.1007/s10237-010-0208-8%0A%0A
54 Boccaccio A, Ballini A, Pappalettere C, Tullo D, Cantore S, Desiate A. Finite Element Method (FEM), Mechanobiology and Biomimetic Scaffolds in Bone Tissue Engineering. Int J Biol Sci [Internet]. 2011;7(1):112–32. Available from: https://doi.org/10.7150/ijbs.7.112