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Research Progress of Computer Simulation in Fracture Healing

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Abstract:

Fracture healing represents an intricate biological process. Across various time periods, numerous factors influence this healing journey, primarily categorized into mechanical and biological stimulation factors. To enhance our understanding and simulation of fracture healing, multiple computer models have emerged, including mechanical stimulation models, biological stimulation models, integrated mechanical-biological stimulation models, and evolving multi-scale models. However, each computer model bears certain limitations in clinical application. This paper comprehensively reviews the stimulating factors and developed computer models associated with fracture healing, highlighting existing challenges. Our aim is to offer valuable insights for the clinical application of computer simulations in fracture healing.

Keywords:

Computer simulation
Fracture healing
Model

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1. Introduction

Bone injuries often result in fractures, and fracture healing is a complex process influenced by various factors. In recent years, computer simulations of these factors have enhanced our understanding of the fracture healing process. Computer simulations aim to identify the underlying rules that drive bone regeneration [1], simulate the biological and mechanical stimulation factors that affect the bone repair process during specific time periods, and simultaneously predict whether a fracture will heal. Although numerous computer simulation models have been developed, their application in clinical practice is still in its infancy, and how to better utilize these models remains a challenge. This article provides an overview of the fracture healing process, influencing factors, the classification of fracture healing models, and the difficulties and prospects of model application.

2. Fracture healing process

Fracture healing can be divided into primary healing and secondary healing. Primary healing occurs when fracture fragments are closely connected without interfragmentary movement (often after surgical fixation). It involves direct

healing through the action of osteoblasts and osteoclasts, without the formation of a bone callus between the two ends of the fracture. Secondary healing, which occurs more widely, takes place when there is micromovement between the fracture ends (often seen in external fixation or natural healing). The fracture healing process goes through four stages: the inflammatory phase, the soft callus repair phase, the hard callus formation phase, and the remodeling phase. (1) Inflammatory phase: After a fracture, surrounding blood vessels and tissue damage form a hematoma, in which inflammatory cells, white blood cells, and macrophages play a role. As the hematoma is cleared and organized, and capillaries grow, it becomes granulation tissue. In summary, the inflammatory phase provides a favorable environment for fracture repair. (2) Soft callus repair phase: Granulation tissue is replaced by fibrous tissue and cartilage tissue, called bone callus. (3) Hard callus formation phase: The bone callus generates bone through intramembranous ossification and endochondral ossification, which is the third stage of fracture repair. At the end of the hard callus formation phase, the fracture ends are covered by woven bone, making them relatively stable. However, further shaping is required for bone strength and shape. (4) Remodeling phase: The woven bone in the stress direction of the diaphysis is transformed into normally structured lamellar bone by osteoblasts, while woven bone that is not aligned with the diaphysis stress direction or has an incorrect position or shape is absorbed under the action of osteoclasts. This phase can take several months or even years. Computer simulations of fracture healing mainly focus on simulating and calculating the first three stages.

3. Factors influencing fracture healing

The process of fracture healing is influenced by multiple factors. Based on their types, these factors can be divided into mechanical stimulation factors and biological stimulation factors.

3.1. Mechanical stimulation factors

Fracture healing has a significant correlation with mechanical stimulation factors. Interfragmentary movement (IFM), which depends on fixation stability and musculoskeletal loading, is the most important mechanical stimulation factor affecting the fracture healing process [2]. Both excessively high and low IFM can delay fracture healing and even lead to nonunion. Therefore, overly rigid fixation or overly flexible fixation of locking plates can result in delayed healing or nonunion. Similarly, the IFM of the cortex close to the locking plate is much smaller than that of the far cortex, which may lead to asymmetric callus formation and delayed healing. Besides the magnitude of IFM, its direction also plays a crucial role. Shear loading is detrimental to fracture healing, while the same amount of axial loading is beneficial [3]. This is reflected in clinical practice, where angle-stable interlocking fixation reduces shear loading, thereby improving healing. In addition to these factors, the rate and frequency of cyclic loading also affect fracture healing. Early dynamization leads to significant enhancement of cartilage tissue formation, especially in the cortical and endosteal regions, and the increase in cartilage promotes callus formation and remodeling [4]. Currently, the role of dynamic loading remains controversial, with the focus being on whether it affects the quality of newly formed bone. Some animal experiments have concluded that dynamization has no effect or is even detrimental to fracture healing. Despite the insufficient understanding of dynamic loading [5], all experimental results indicate that it can increase callus formation and promote bridging of fracture ends.

3.2. Biological stimulation factors

Fracture healing is a complex biological process involving numerous biological stimulation factors. During the inflammatory phase, the most important cytokines involved in the inflammatory response are interleukin (IL) and tumor necrosis factor-alpha (TNF-α). IL-1 and TNF-α show a biphasic response and are produced immediately after injury. The main role of the IL family is to promote ossification, mediate the release of other osteogenic factors, and inhibit the differentiation of osteoclasts. TNF-α expressed by bone marrow mesenchymal stem cells inhibits osteoblasts and stimulates osteoclastogenesis. An increase in TNF-α levels leads to a reduction in cartilage and decreased stability of the callus [6]. Currently, the regulatory role of the inflammatory phase in fracture healing is still not

fully understood. Deepening the study of inflammatory factors will undoubtedly enhance our understanding of the inflammatory phase of fracture healing.

Besides inflammatory factors, many other biological factors regulate fracture healing at different times. Transforming growth factor-beta (TGF-β) induces extracellular matrix production and ossification, promotes callus development and the release of other growth factors, inhibits osteoclast activity, and induces apoptosis [7]. Bone morphogenetic protein (BMP) significantly increases bone formation and improves fracture healing strength and speed [8]. Platelet-derived growth factor (PDGF) can attract and activate neutrophils and macrophages, promoting granulation tissue formation and endochondral ossification. Parathyroid hormone (PTH) regulates mineral homeostasis while promoting osteoblast proliferation and fracture healing in a dose-dependent manner [9]. It has been developed as a drug for the treatment of osteoporosis. Fibroblast growth factor (FGF) promotes osteoblast proliferation, induction of angiogenesis, and osteoblast differentiation [10]. Vascular endothelial growth factor (VEGF) can directly affect bone progenitor cells to promote bone mineralization and increase bone density. It can also induce cell migration and differentiation. On the other hand, VEGF mediates capillary infiltration, which is a prerequisite for endochondral ossification. Overall, while it is feasible to understand the mechanism of a specific role of a biological factor, the multiple roles and interactions of biological factors make it difficult to simulate their overall effects and calculate dosages. This requires further exploration and discovery.

In addition to biological factor stimulation, vascular growth and oxygen supply also play an indispensable role in fracture healing. When a fracture occurs, the blood vessels at the fracture site are damaged. As the vascular network reconstructs, oxygen, growth factors, and nutrients can be transported to the corresponding areas, providing the energy needed for cellular activities and increasing the activity of biological enzymes to promote fracture healing. Oxygen is an important signaling molecule that regulates the expression of various angiogenic genes through the hypoxia-inducible factor pathway. Oxygen is essential for aerobic metabolism and enzyme activity in cellular activities [11]. Currently, research on the fracture healing process has gradually shifted its focus to the process of vascular reconstruction and the role of oxygen, reflecting that the fracture healing process is not a single-factor change but rather the result of multiple influencing factors working together.

4. Classification of fracture healing models

Various fracture healing models have been developed, each attempting to simulate the mechanism of fracture healing from different perspectives. These models can be broadly classified into mechanical stimulation models, biological stimulation models, and mechanobiological stimulation models based on the simulated factors.

4.1. Mechanical stimulation models

Pauwels [12] was the first to elaborate on the influence of mechanical stimulation on tissue differentiation, discovering that tension can stimulate the formation of fibrous tissue, while hydrostatic pressure can stimulate the formation of cartilage. Based on these findings, research began on how mechanical stimulation affects tissue formation. Perren and Cordey introduced a threshold for the strain experienced by tissues, beyond which tissue formation becomes impossible. Simultaneously, they proposed the concept of interfragmentary strain (IFS), defined as the ratio of fracture gap motion to gap size. A smaller IFS value indicates a higher likelihood of fracture healing [13]. Carter *et al.* [14] further refined the types of mechanical stimulation, suggesting that octahedral shear stress promotes cartilage ossification, hydrostatic compressive stress inhibits ossification, low to moderate tensile strain promotes bone formation, moderate to high tensile strain promotes fibrous tissue formation, and hydrostatic compressive stress promotes cartilage formation. This theory provided a foundation for subsequent research. Claes and Heigele [15] used finite element analysis to quantitatively describe tissue differentiation. In their theory, the formation of new tissue is related to local mechanical stimulation: intramembranous ossification occurs when the strain is less than 5% and the hydrostatic pressure is less than 0.15 MPa; cartilage formation occurs when the strain is less than 15% and the pressure is greater than -0.15 MPa. Through their

theory, people have deepened their understanding of the relationship between mechanical stimulation and tissue differentiation. Morgan *et al.* [16] raised questions about the source of mechanical stimulation and the modeling elements of callus based on this theory. They believed that shear strain may be an important regulatory factor in the bone healing process, as it can regulate the differentiation of cartilage tissue. On the other hand, they argued that bone density or elastic modulus is not a good representative of callus. Modeling callus as a solid alone can lead to decreased accuracy of simulation results. Morgan's questions made people realize that tissue modeling cannot rely on a single element but rather a mixture of solid and liquid phases. Prendergast *et al.* [17] updated the types of mechanical stimulation to include shear strain in the solid phase and relative velocity in the interstitial fluid phase. This theory was supported by *in vivo* experiments. Through a biphasic finite element model, people were able to initially understand and predict the influence of different fracture gaps on fracture healing from the stage of granulation tissue formation to bone remodeling. To investigate the effects of shear strain, Epari *et al.* [18] studied the strain, pressure, and fluid flow in early callus under different motion patterns using the finite element method. They found that shear and torsion between gaps do not produce volumetric stimulation, which differs from the mechanical stimulation caused by axial gap motion. This contradicted Morgan's conclusions. To determine which algorithm truly reflects the mechanically regulated process of tissue differentiation during bone healing, Isaksson *et al.* [19] compared the models of Carter, Claes and Heigele, and Prendergast in fracture healing research. They concluded that the algorithm based on deviatoric strain and fluid velocity predicts patterns that are closest to experimental results, and it is the only algorithm capable of predicting torsional stress after fracture. Steiner *et al.* [20] simulated the fracture healing process under translational shear and asymmetric bending loads, using deformation and dilatational strain as mechanical stimuli. They successfully predicted fracture healing in sheep. This conclusion enhances the model's ability to simulate complex loading conditions, but models solely relying on mechanical stimulation are still far from sufficient.

Ament and Hofer [21] used a set of fuzzy rules to describe tissue transformation, improving upon previous mechanical stimulation models. Instead of using mechanical properties to describe changes in bone elements, they employed a set of hypothetical rules based on weighted "truth" values to represent conditional statements. This approach simulates cellular activities during the healing process, including proliferation, migration, differentiation, and apoptosis. Fuzzy logic facilitates the integration of biological factors into the mechanical modeling of fracture healing without the use of partial differential equations. It aids medical professionals in incorporating experimental theories, medical knowledge, and clinical experience into complex models. Shefelbine *et al.* [22] calculated mechanical stimulation received by the model using volumetric strain and octahedral shear strain. Bone, cartilage, fibrous tissue, and vasculature were modeled using fuzzy rules. In Shefelbine's model, the mechanically stimulated vasculature was simulated. Although this phenomenologically mediated computational model achieved partial success in predicting experimental observations, the role of phenomenological models becomes limited when human intervention is incorporated into the model. This underscores the need for mechanical stimulation models that are not just empirically refined phenomenological models, but rather models that incorporate biological principles. To address this optimization, Isaksson *et al.* [23] integrated cellular mechanisms with mechanical stimulation during bone healing, based on the idea that cells act as sensors during tissue regeneration. They associated all cellular activities with the mechanical stimulation they experience. The accuracy of Isaksson's model was fully validated in comparison to phenomenological models. Additionally, the influence of each parameter in the model on tissue regeneration can be individually evaluated, and it has the ability to predict changes in healing patterns, which was not possible in previous computational models. Wang *et al.* [24] developed a mechanical stimulation model jointly regulated by biphasic porous elastic finite element analysis and fuzzy logic control. This model can simulate the healing process under different mechanical environments and has the potential to be extended to multi-scale healing models. This is crucial for reducing animal experiments and helping to characterize

the complex dynamic interactions between tissue differentiation within the callus region.

In addition to simulating and exploring the sources and effects of mechanical stimulation, computational models for predicting changes in callus volume during fracture healing have expanded the application scope of mechanical stimulation models. Isaksson *et al.* [25] used a biphasic expansion model to predict the growth of various tissue types during distraction osteogenesis. This model can help optimize treatment plans for distraction osteogenesis in experiments. García-Aznar *et al.* [26] proposed a more complex model for callus volume growth that includes the influence of cellular activities. With these models, it becomes possible to predict changes in callus volume under different interfragmentary movements, fracture gap sizes, and fixator stiffnesses. This has predictive value for fracture nonunion caused by insufficient callus volume.

4.2. Biostimulation models

In addition to mechanical stimulation, fracture healing involves the participation of many cell types, numerous biochemical and biomechanical regulatory factors, and the expression of thousands of genes. The first biostimulation model was designed by Bailón-Plaza and van der Meulen [27]. This model describes fracture healing as a process regulated solely by osteogenic and chondrogenic growth factors. The application of partial differential equations in the model allows for the prediction of the spatiotemporal distribution of different tissues. The proposal of this model opened up new ideas for the study of biostimulation in fracture healing. Geris *et al.* [28] continued to refine this model by adding fibroblasts and fibrous tissue as separate variables, as well as incorporating the effects of angiogenesis and directed cell migration. These factors made the simulation scope of the fracture healing model more comprehensive. However, this model cannot simulate the discreteness of angiogenesis. To improve the accuracy of blood vessel simulation, Peiffer *et al.* [29] updated the continuous variables of blood vessel simulation in Geris' model to discrete variables, which are represented by vascular activities (growth, branching, anastomosis, etc.). Along with the updated simulation of blood vessels, the role of oxygen and nutrients in the fracture healing process was also simulated in the model. This model can be used to simulate normal and impaired healing conditions, as well as to design potential treatment strategies for fracture healing. Nevertheless, the process of angiogenesis is still simulated in a phenomenal way. To achieve more accurate simulations, Carlier *et al.* [30] proposed a multiscale mathematical model (MOSAIC model) to describe the interactions between biological factors, oxygen, cells, and blood vessels. The multiscale model simulates the factors leading to angiogenesis at multiple levels. At the intracellular level, the model simulates the effects of various factors such as VEGFR-2, Notch1, DII4, and others on endothelial cells. At the cellular level, the model simulates the discrete growth process of blood vessels, and after the blood vessels anastomose with each other, the model continues to simulate the transport of oxygen and nutrients. At the tissue level, the model simulates intramembranous ossification and endochondral ossification resulting from angiogenesis. The MOSAIC model can be validated at the molecular, cellular, and tissue scales, respectively. It can be used to investigate how gene knockout, injection of vascular endothelial growth factor antibodies, or blocking of vascular endothelial growth factor receptors affect fracture healing. Moreover, the model's selection of tip cells is based on intracellular dynamics simulation rather than phenomenal simulation [31]. The multiscale model provides new ideas and methods for simulating the fracture healing process.

4.3. Mechanical-biological stimulation models

Biological stimulation models cannot explain the effects of fixation, fracture stability, or loading rate on fracture healing. Similarly, while cell proliferation, angiogenesis, and nutrient supply are crucial for bone regeneration, the mechanisms that link mechanical stimulation to these processes are poorly understood. Therefore, mechanical-biological stimulation models have been developed that use partial differential equations to simulate biological stimulation during fracture healing and the finite element method to calculate mechanical stimulation. Lacroix and Prendergast [32] made the first attempt to incorporate cellular activity mechanisms into a mechanical model, using diffusion mechanisms to simulate cell migration, proliferation, and differentiation, and determined that the healing rate is most sensitive to cell diffusion rate.

Kelly and Prendergast [33] further developed this model to include the effects of mechanical stimulation on cellular activity and the influence of existing tissue on cell diffusion rate. Isaksson *et al.* [23] established a more comprehensive mechanical-biological model by describing the temporal and spatial distribution of fibrous tissue, cartilage, and bone. In this model, cells can generate cellular activity based on mechanical and biological stimulation at each time point and location. This model has been proven to predict normal fracture healing processes and the effects of excessive loading or other biological perturbations and pathological conditions on fracture healing. However, these studies did not consider the anisotropy of cell movement. To address this issue, Pérez and Prendergast [34] developed a "random walk" model to simulate anisotropic cell proliferation and migration. Byrne *et al.* [35] used this theory to conduct three-dimensional simulations and analysis, predicting the main stages of fracture healing, including the bone resorption phase, and obtained qualitatively consistent results regarding the temporal variation of strain between fragments and bending stiffness. Checa and Prendergast [36] further developed the random walk cell model to explain angiogenesis. Their simulations confirmed that higher loads lead to slower vascular development and delayed bone tissue formation.

5. Conclusion and outlook

The research and development of computer models represent a deepening understanding of the fracture healing process. Currently, computer simulation technology for fracture healing has made significant progress, not only in terms of increased simulation factors but also in the transition from single-scale to multi-scale simulation. However, there are still some limitations.

(1) The accuracy of the parameters used in computer simulations needs to be verified. As models progress and more factors are included, computational models become increasingly complex, representing more parameters. These parameters should be calculated and verified by each research team, but a considerable portion of them is not easy to obtain. In many model designs, researchers use some parameters from other research teams, such as using *in vitro* measured cell migration rates as estimates for *in vivo* rates or combining data from different species. Therefore, sensitivity analysis of these parameters is necessary. Currently, model validation mainly focuses on comparing simulation results with experimental data, but if the model heavily relies on parameters that are difficult to obtain experimentally, the specific simulation may not be very valuable.

(2) The process of bone healing is highly complex and dynamic, involving coordination and interaction at the tissue, cellular, and intracellular levels to achieve organ-level bone repair. The current difficulty lies mainly in simulating the intracellular level, as the mechanisms of how mechanical stimulation signals are transmitted into the cell and the intracellular receptors for these signals are still being studied. On the other hand, even if an intracellular scale model is designed, it remains questionable whether incorporating such a model will improve computational accuracy or increase computational burden [37]. Nevertheless, it is undoubtedly true that with the further improvement of multi-scale models, the signal transduction pathways of fracture healing will gradually be understood and simulated.

(3) The current models have difficulties in accurately designing and understanding growth factors to align with reality. Experimenters often study individual growth factors as independent stimuli, but in the actual healing process, the effects of these growth factors are not mutually independent. Different growth factors can have synergistic or inhibitory effects, posing challenges for simulating growth factors in models. Additionally, the simulation of cell states in models is overly simplistic. The developmental and transitional states of different cells are not included in existing models, yet these different cell states have unique functions during fracture healing. Incorporating these transitional states into models could help address the issue of simulated healing times being shorter than actual

healing times.

(4) In current simulations, the specificity of the patient's own situation cannot be described. Elderly patients with fractures often suffer from various comorbidities, unhealthy lifestyle habits, and congenital deformities. For instance, patients with osteoporotic fractures are typically associated with factors such as age, smoking and drinking, obesity and diabetes, and steroid medication use. These fracture patients have longer healing times and lower success rates, posing challenges for clinicians. To ensure the specificity of computer models, patients' individual circumstances need to be incorporated. However, integrating these factors into the models remains a challenge. Although computer simulations of fracture healing still have many shortcomings, significant progress has been made in fracture healing models. Relying too heavily on a single model is far from sufficient, and combining multiple models yields better simulation results than over-reliance on a single model type. The future trend in modeling is toward mechanobiological regulatory models that consider the combined effects of mechanical stimulation and biological factors. Additionally, the development and design of multi-scale models at different levels, especially at the intracellular level, is a future trend. Signaling pathways (such as Wnt, BMP, and ER receptor pathways) have been proven to play a critical role in the bone formation response, and multi-scale models can help elucidate the interactions between signaling pathways and how they are expressed at other levels.

Beyond model development, the rational use of different types of models is also a future trend. Good fixation methods significantly impact the mechanical stability of fracture ends, further influencing healing outcomes. Preoperatively, models can be used to select the optimal type of fracture fixator, placement position, and fixation length [38]. Besides fixator selection, models can simulate fractures under different conditions and provide guidance on treatment strategies. For example, models can simulate the therapeutic effects of different concentrations of mesenchymal stem cells and growth factors on pathological fractures, thus assisting clinicians in selecting appropriate dosages. The combination with tissue engineering expands the scope of fracture healing models. These models can simulate elements such as the mechanical behavior of implanted biological scaffolds and the activity of inoculated cells [39], providing more scientifically based treatment options for patients with large bone defects [40].

In summary, current computer models can simulate the effects of independent factors on fracture healing within a fixed time frame. With the advent of the 5G era and rapid advancements in computer technology, the introduction of methods like big data, artificial intelligence, and machine learning could optimize or even transform current models, offering new approaches for fracture healing simulation and treatment planning.

Disclosure statement

The authors declare no conflict of interest.

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