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Computational techniques for the assessment of fracture repair

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ABSTRACT

The combination of high-resolution three-dimensional medical imaging, increased computing power, and modern computational methods provide unprecedented capabilities for assessing the repair and healing of fractured bone. Fracture healing is a natural process that restores the mechanical integrity of bone and is greatly influenced by the prevailing mechanical environment. Mechanobiological theories have been proposed to provide greater insight into the relationships between mechanics (stress and strain) and biology. Computational approaches for modelling these relationships have evolved from simple tools to analyze fracture healing at a single point in time to current models that capture complex biological events such as angiogenesis, stochasticity in cellular activities, and cell-phenotype specific activities. The predictive capacity of these models has been established using corroborating physical experiments. For clinical application, mechanobiological models accounting for patient-to-patient variability hold the potential to predict fracture healing and thereby help clinicians to customize treatment. Advanced imaging tools permit patient-specific geometries to be used in such models. Refining the models to study the strain fields within a fracture gap and adapting the models for case-specific simulation may provide more accurate examination of the relationship between strain and fracture healing in actual patients. Medical imaging systems have significantly advanced the capability for less invasive visualization of injured musculoskeletal tissues, but all too often the consideration of these rich datasets has stopped at the level of subjective observation. Computational image analysis methods have not yet been applied to study fracture healing, but two comparable challenges which have been addressed in this general area are the evaluation of fracture severity and of fracture-associated soft tissue injury. CT-based methodologies developed to assess and quantify these factors are described and results presented to show the potential of these analysis methods.

Introduction

The combination of high-resolution three-dimensional (3D) medical imaging, increased computing power, and modern computational methods today provide unprecedented capabilities for assessing biological processes that include the repair and healing of fractured bone. While these capabilities have to date been underutilized, that is beginning to change. This paper discusses areas of computational techniques suitable for the assessment of fracture repair in which significant advances have been made.

Computational prediction of the likelihood of successful fracture healing for a given fracture's mechanical and biological state may soon be possible. Patient-specific determination of the fixation construct optimizing the likelihood of uneventful fracture healing is likewise possible. Fully 3D assessment of the formation of fracture callus and progress towards mineralization is now conceivable using CT and/or ultrasound. Such assessments require secondary computational analysis of the source image data to extract meaningful measures. The use of such approaches for longitudinal assessments is made more plausible as lower radiation dose conebeam CT technology becomes more widely available.

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Current mechanobiological theories and models of fracture healing

Fracture healing is a natural process that restores the mechanical integrity of bone. This regenerative process involves cell differentiation and tissue remodelling, both of which are influenced by the mechanical environment. However, it is not yet completely understood how differentiation pathways are related to mechanical factors. Several mechanobiological theories have been proposed to provide greater insight into these phenomena.

Much of the present-day understanding of the regulative effect of mechanical forces on tissue differentiation is based on research performed by Pauwels [1]. He analyzed the mechanical environment within a healing fracture callus and hypothesized that hydrostatic stress and shear strain are the stimuli that guide cells to differentiate into connective tissue, which will ultimately form bone when mature and stabilized. This theory has inspired many researchers during recent decades, while computational modelling has emerged as an alternative approach to investigate biological processes. Carter and co-workers expanded Pauwels's theory by using a finite element (FE) model to explain how mechanical loading guides cell differentiation in a fracture callus [2]. Their theory related high hydrostatic stresses with cartilage ossification, and octahedral shear stress and strain with stimulation of fibrous tissue. Unlike Pauwels, they included direct bone formation corresponding with intramembranous ossification under low stresses and strains. The model was able to predict realistic tissue patterns consistent with biological observations, but there was no quantification of the magnitude of the mechanical stimuli with tissue formation [2].

Claes and Heigele extended the theory of Carter et al. by defining certain thresholds for the local stress and strain magnitudes to determine whether endochondral or intramembranous ossification takes place [3]. Their quantitative mechano-regulation theory was based on the observation that bone formation occurs mainly near calcified surfaces and that both intramembranous and endochondral ossification exist concurrently in fracture healing. Histological images from in vivo experiments were used to show that their FE model properly predicted tissue differentiation in the callus at three stages of the healing event [3].

Biological tissues are composed of a solid phase and an interstitial fluid phase. Therefore, two-phase models are required to investigate internal stresses in the fluid or at the fluid/solid interface where many cell phenotypes are present. Prendergast et al. presented a poroelastic FE model of a bone implant interface to predict tissue differentiation. The tissue phenotype was regulated by the applied biophysical stimuli; shear strain on the solid collagenous phase and relative velocity on the interstitial fluid phase (Fig. 1) [4]. This new approach was supported by in vivo results and it was found that high and intermediate levels of biophysical stimuli govern fibrous tissue and cartilage formation, respectively, and low levels of stimulus are responsible for bone differentiation. Isaksson et al. compared the mechanobiological models of Carter, Claes and Heigele, and Prendergast in a fracture healing study, and they concluded that the concept based on strain and fluid velocity as stimuli correlated best with experimental results [5]. The algorithms mentioned above predicted tissue phenotype only at specific time points, being unable to simulate tissue differentiation over the complete regeneration period. As new mechano-regulatory concepts emerged, mechano-biological computations developed into computer simulations and were able to simulate chronological tissue differentiation by employing the algorithm of Prendergast et al. in iterative FE simulations [6].

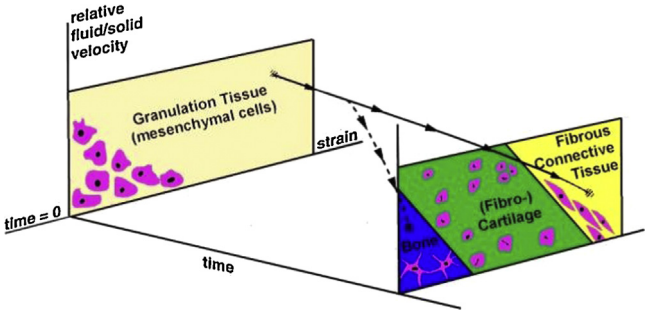

Fig. 1. Mechanoregulatory model presented by Prendergast et al. [4] that describes the hypothesis that tissue differentiation is controlled by two biophysical stimuli, shear strain on the solid collagenous phase and relative velocity on the interstitial fluid phase.

Later, Lacroix et al. adapted the Prendergast model to describe fracture healing in a time-dependent fashion adding diffusion equations to model progenitor cell dispersal in the callus [7]. This theory was able to predict tissue differentiation and bone resorption under different gap sizes and loads, and it highlights the importance of cell activities on healing patterns and rates. Diffusion is not the mechanism of cell migration and proliferation, but despite this, Lacroix's theory paved the way for many researchers to include cell activities in their mechano-regulatory algorithms. Subsequent mechano-biological models combined FE analysis with lattice models to include cell activities. Perez and Prendergast developed a 2D FE lattice model representing both cells and extracellular matrix in which individual cell activity was guided by a "random walk" [8]. Byrne adapted this model into 3D and later implemented it in fracture healing of a human tibia under realistic muscle loading, predicting healing beyond the reparative phase [9]. Another lattice approach was presented by Checa and Prendergast, incorporating angiogenesis in the modulation of cell phenotype, raising the question of whether mechanoregulatory theories must be coupled with bioregulatory networks [10].

Computer models to assess fracture healing

Mechanobiological computer models have evolved during the last two decades from simple tools only able to analyze fracture healing at a single point in time to current models that can predict tissue differentiation and remodelling over time. The predictive capacity of these models is measured by the corroborating experiments used in their validation. A model is deemed more valid as more tests are used to either corroborate or refute the model [11].

Recent models can capture many complex biological events that are involved during tissue regeneration, such as angiogenesis, stochasticity in cellular activities, and cell-phenotype specific activities. A priori, it is reasonable to assume that inclusion of a higher degree of complexity in a model will yield increasing accuracy. However, as the complexity of a model increases, more data from experiments are needed for corroboration. Jacobs and Kelly suggested that this fact could lead to a paradox of validation; the information needed for validation may obviate the model in first instance [12]. Although, as long as the field develops, the predictive power of a model can go beyond the data used for its validation, eliminating the paradox of validation. Thus, mechano-biological models can provide insight into the mechanical regulation of tissue differentiation that standard experiments are incapable of, becoming a new technique to test scientific hypotheses.

Mechanobiological researchers have made efforts developing sophisticated models to achieve greater explanatory power. Generally, these models have been corroborated without incorporating animal variability; therefore, their ability to predict tissue differentiation in animals or specimens for which they have not