Computational Modelling of the Mechanical Environment of the Early Stage of Fracture Healing Using Structural Engineering Techniques

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Abstract

Bone healing is a complex biological process which is regulated by mechanical micro-environment caused by inter-fragmentary movement (IFM). IFM generated interstitial fluid flow within the fracture callus could potentially not only affect the mesenchymal stem cells migration and differentiation during the healing, but also enhance nutrient transport within the callus tissue.

In this study, a three dimensional poroelastic finite element model of a human tibia was developed to study the mechanical behaviour of the fracture callus due to IFM at the early stage of fracture. The biophysical stimuli were characterised with three main parameters involved in the healing process: octahedral shear strain, interstitial fluid velocity and pressure. The proposed algorithm represents a first step towards to the development of a powerful simulation tool for fracture healing.

Keywords: fracture healing, mechanoregulation, finite element analysis

1. Introduction

Bone fracture healing is a complicated process that involves biological, physical and chemical mechanisms in the fracture site. To achieve the desired healing outcome, a comprehensive understanding of the healing process is required not only at macroscopic level but also at microscopic level. Experimental studies are of critical importance for this purpose, however they are normally expensive and some parameters could be immeasurable due to the limitation of current technology. Further, due to the complexity and integrity of biological systems, it is rather challenging to experimentally define the synergistic biological effects of various parameters. Like different biological processes, bone fracture healing can be simulated and analysed using an experimentally validated computational model, which will allow the identification and optimisation of critical model parameters and so enhancing the healing process.

Bone is a specialized form of connective tissue that has a remarkable structure and mechanical properties. It is composed of extracellular matrix (ECM), cells and interstitial fluid. The bone ECM consists of organic (mainly collagenous and non- collagenous proteins) as well as mineral (mainly hydroxyapatite crystals) which provides the structural functions of the bone. Bone cells regulate the process of bone modeling (construction) during the growth and bone remodeling (reconstruction) throughout life (Bilezikian et al. 1996) and thereby provide the homeostasis and biological functions of the bone tissue. These processes are regulated by the biochemical and biophysical microenvironment within the bone tissue (Doblare 2004).

Immediately after a bone fracture occurs, hematoma formes in the fracture site and prevents further bleeding. In the next stage, clot dissolves and granulation tissue is generated. This is the early stage of formation of fracture callus. This specific tissue stabilizes the fracture site and provides a suitable environment for migration, proliferation and differentiation of mesenchymal stem cells as well as formation of new bone tissue. The mechanical and biochemical conditions at this stage of fracture healing are the initial stimuli for cells migration and differentiation and therefore have a significant effect on the healing process (Doblare 2004).

It is believed that the mesenchymal stem cells in the callus are from periosteum, bone marrow, and surrounding extracortical soft tissues (Geris et al. 2004). However the actual origin of the stem cells depends on the types of the bone fracture and the fracture fixation device (Lacroix et al. 2002). The cell activities during the fracture healing are regulated by biochemical stimuli (e.g. growth factors and cytokines released during the healing process) (Bailón-Plaza & van der Meulen 2001; M Raschke et al. 2002; Gerhard Schmidmaier et al. 2004; Simpson et al. 2006) as well as biophysical stimuli (e.g. tissue strain, fluid velocity and pressure) (Prendergast et al. 1997; Carter et al. 1998; Claes et al. 1998; Claes & C. A. Heigele 1999; Kelley 2008; Huang & Ogawa 2010). Growth factors molecules (e.g., insulin like growth factors (IGFs) and transforming growth factors (TGF-B)) are the main biochemical regulators that modulate proliferation and differentiation of cells as well as ECM synthesis (Simpson et al. 2006; Okazaki et al. 2003; Derynck & Feng 1997; Grimaud et al. 2002). However growth factors and mesenchymal stem cells diffuse into the callus and their transport might be regulated and accelerated by dynamic loading. Recent studies of Zhang et al have shown that physiological relevant dynamic loading could significantly influence the protein transport in a biological tissue (e.g. cartilage) (Zhang et al. 2007; Zhang et al. 2008).The mechanical loading can also directly regulate the tissue differentiation in fracture callus. This biophysical stimuli is sensed by the cells within the callus and modulate their activities (Carter et al. 1998; Claes et al. 1998; Claes & C. A. Heigele 1999; Kelley 2008; Huang & Ogawa 2010; Prendergast et al. 1997). Prendergast et al

proposed a mechanoregulation concept to describe the tissue differentiation pattern during the fracture healing (Prendergast et al. 1997). They considered the fracture callus as a poroelastic model that comprises both solid and fluid phases. Base on this theory, the tissue differentiation depends on two biophysical stimuli: octahedral shear strain of the solid phase and fluid flow in the interstitial fluid phase. Their research was further extended to predict tissue differentiation over time under different loading conditions and fracture geometries (Lacroix & Prendergast 2002b; Lacroix & Prendergast 2002a; Lacroix et al. 2002). However the effect of mechanical loading on cell transport in callus was not considered in the above models.

2. Modeling biomechanical stimuli for bone fracture healing

As shown in Figure 1, physical activities and mechanical properties of the fracture callus determine the mechanical microenvironment of the fracture. This biophysical microenvironment influences the behaviour of callus cells either directly by regulating tissue differentiation through the deformation and fluid flow or indirectly by affecting the cell migration and growth factors distribution through advective nutrient transport. These cell activities change the callus tissue phenotype and thereby modify its mechanical properties as a feedback loop.

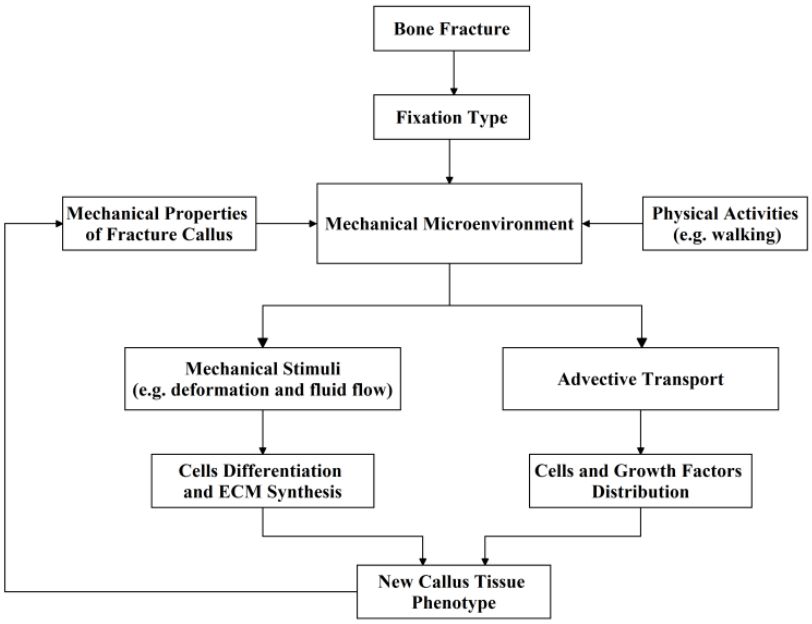

Figure 1: Schematic of biophysical and biochemical stimuli during the fracture healing process

In order to analyse the mechanical environment of the early callus, an axisymmetric poroelastic finite element model of a human tibia was developed using COMSOL MULTIPHYSICS (Figure 2). Cortical bone was considered as a cylinder with 18 mm internal diameter and 30 mm external diameter with 10 mm fracture gap. The callus had 48 mm maximum diameter and developed 24 mm along the diaphysis. The fracture callus was meshed with 4548 quadrilateral elements. Cortical bone, marrow and callus were considered as poroelastic materials with solid and fluid phases. Table 1 shows the material properties of the model. The external boundary of callus, cortical bone and

intramedullary canal were assumed to be impermeable to fluid flow. A 500 N axial ramp load in 0.5 s was applied on the cortex and the mechanical stimuli were analysed at the top of the ramp.

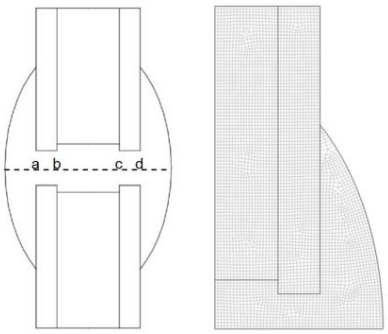

Figure 2: Axisymmetric finite element model of a fracture in human tibia

Table : Material properties

	Young's modulus (MPa)	Poisson's ratio	Porosity	Permeability m^4/Ns	Fluid compression modulus (MPa)	Solid compression modulus (MPa)
Granulation Tissue	1[a]	0.167[a]	0.8[a]	10^{-14}[a]	2300[a]	2300[a]
Marrow	2[a]	0.167[a]	0.8[a]	10^{-14}[a]	2300[a]	2300[a]
Cortical Bone	15750[b]	0.325[c]	0.04[d]	10^{-17}[e]	2300[a]	17660[a]

[a](Isaksson et al. 2006); [b](Smit et al. 2002); [c](Cowin 1999); [d](Schaffler & Burr 1988); [e](Johnson et al. 1982)

3. Results and Discussion

We calculated three mechanical parameters of the callus that have a significant role on the fracture healing pattern: tissue strain, interstitial fluid velocity and pore pressure. Octahedral shear strain of fracture callus can be considered as a factor which determines the pattern of cell differentiation during fracture healing (Prendergast et al. 1997). Octahedral shear strain for 500 N axial loading and 10 mm fracture gap varied between 0.09 and 0.37 across the osteotomy gap (Figure 3). It reached to maximum value between the cortical bone fragments and minimum value in external callus.

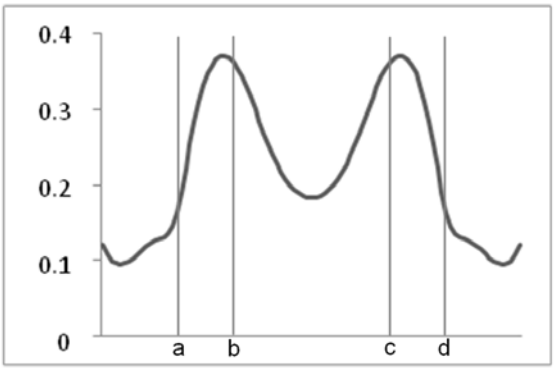

Figure 3: Octahedral shear strain in the osteotomy gap

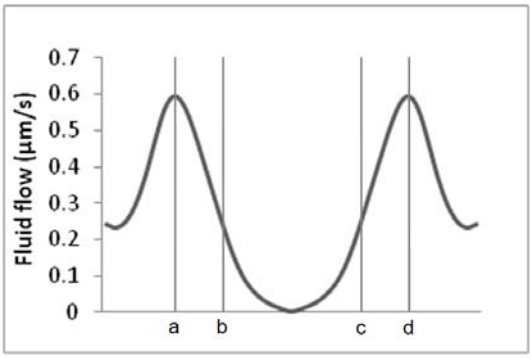

Figure 4: Fluid velocity in the osteotomy gap

Fluid velocity profile across the osteotomy gap is shown in Figure 4. As it can be seen in Figure 4, the maximum fluid velocity in the osteotomy gap was observed between the external sides of cortical bone fragments. Tissue differentiation in the initial stage of fracture healing can be predicted according to the model results and tissue differentiation theory proposed by Prendergast et al (Prendergast et al. 1997). Owing to the high shear strain, only fibrous tissue can form between the bone fragments. Cartilage tissue is expected to form within the mid-callus as well as external callus regions. After the initial tissue differentiation, the mechanical properties of the callus improve and the interfragmentary movement decreases. Therefore the tissue differentiation pattern will change during the healing.

Figure 5 illustrates the path plot of interstitial fluid pressure in the osteotomy gap. It can be seen that the peak pressure was produced at middle of internal callus. This parameter can be used as a differentiation regulator in the mechanoregulation theory of Claes and Heigele (Claes & C. A. Heigele 1999). This theory predicts the differentiation pattern based on hydrostatic pressure and strain. However the tissue differentiation pattern simulations of the both theories are similar.

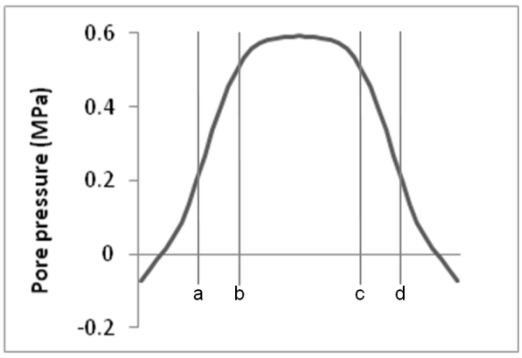

Figure 5: Fluid pressure in the osteotomy gap

Understanding the mechanobiology of the fracture healing is a key factor for enhancing the healing process. Different biophysical and biochemical stimuli along the mechanoregulation hypotheses can be applied on the model and thereby different types of fracture healing can be analysed in-silico. The fracture healing process can be simulated using the sophisticated CT scan-based finite element model of individual patients (figure 6). In this way we will be able to predict the healing pattern and select the most suitable treatment (e.g. fixation type, physiotherapy).

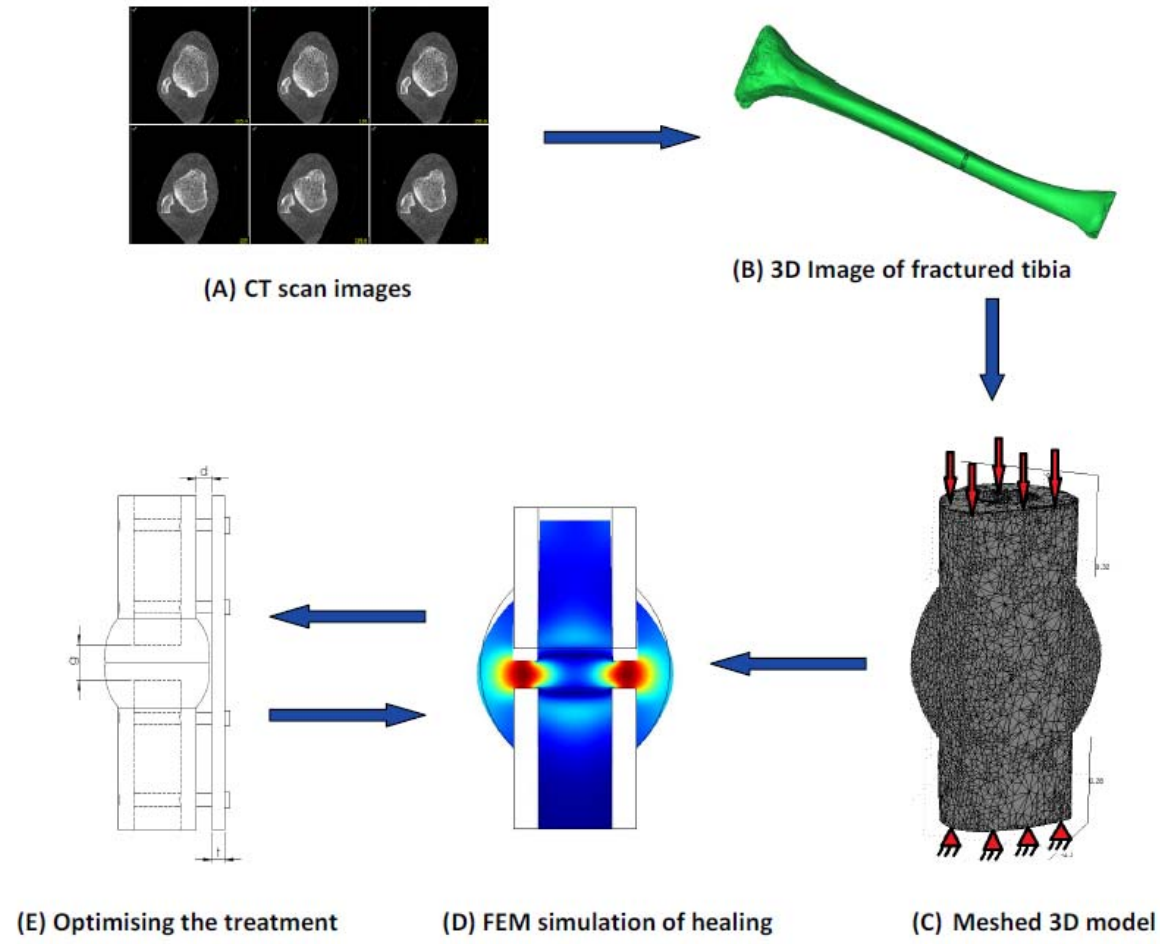

Figure 6: Optimising the fracture healing treatment using the CT scan image of the individual patients

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