Investigating possible pathways of tissue development to predict endochondral ossification during bone fracture healing using mechano-regulation algorithms

Jalil Nourisa [a], **Ghadir Shayegan** [b], **and Gholamreza Rouhi** [a]

[a] Amirkabir University of Technology, Faculty of Biomedical Engineering, Tehran, Iran
[b] Iran University of Science and Technology, Faculty of Mechanical Engineering, Tehran, Iran

Abstract

Bone secondary healing process consists two different ossification mechanisms, i.e. intramembranous ossification and endochondral ossification (EO). EO is distinguished by differentiation of mesenchymal stem cells (MCs) into chondrocytes and sequential tissue differentiation of: fibrous tissue (FT); cartilage (CT); immature bone (IB); and mature bone (MB). Several mechano-regulation (MR) algorithms have been proposed in the literature to date in order to predict the healing process exclusively followed EO. Some clear differences were observed among possible pathways of tissue development proposed in different algorithms. The aim of this study was to address the question of which pathways can predict EO the best by investigating the impact of different pathways on the EO. For This purpose, a 2D model of a broken tibia, with a 3mm fracture gap, was constructed, and differentiation of stem cells and development of tissues in the determined pathways was implemented as a biofeedback loop through using Python scripting in Abaqus software. Results of this study showed that the algorithm which restricts tissue differentiation from granulation tissue (GT) to CT, failed to predict bony bridge and some small islands of bone were left in some area of internal and peripheral callus. On the other hand, healing patterns predicted by algorithms which allow pathway of jumping from GT and FT to IB without passing through the CT, showed no differences in comparison with the original theory in which no constraints were applied in tissue differentiation processes. However, by considering the constraint that in order to develop BT, CT should already exists, it significantly improves our prediction, which is in agreement with experimental evidence showing that EO can take place though calcification of CT. Based on this investigation, two pathways should be considered crucial for correct prediction of EO: first, GT to CT, and second, GT and FT should not be allowed to directly differentiate into bone phase. Results of this work suggest new regulatory algorithm by defining development pathways according to biological events, and is able to correctly predict EO.

Introduction

Long bone fractures treated with non-rigid fixators heals via the pathway of secondary healing, which consists of two different processes of intramembranous ossification (IMO) and endochondral ossification (EO). EO is distinguished by differentiation of mesenchymal stem cells (MCs) into chondrocytes and sequential tissue differentiation of: fibrous tissue (FT); cartilage (CT); immature bone (IB); and mature bone (MB). This process produces large amount of cartilage and causes development of external callus, and is regarded as the principal mode of secondary healing. There are considerable studies reported that mechanical signal can drive healing process. The correlations between mechanical environment and tissue differentiation have been known as mechano-regulation (MR) algorithms. The well-accepted theory proposed by Prendergast et al. [4] considers callus as a poroelastic medium with two components of fluid and solid, and suggests a differentiation algorithm based on the two parameters of interstitial fluid velocity and deviatoric strain of solid phase. The implementation of this algorithm by Lacroix and Prendergast [2] showed its ability to predict normal fracture healing process in which both pathways of IMO and EO included, and it is not able to predict EO solely. Therefore, in order to predict tissue development only by the pathway of EO ossification, some restrictions on the tissue differentiation is needed.
Several algorithms in the literature [1, 5, 3] have been used to predict EO, but there is no basic study to show correctness of their predictions. Furthermore, there are clear differences between these algorithms with regards to the possible passways of tissue development.
The aim of this study was to investigate influence of each possible passways on the prediction of EO healing process. For this purpose, a comparison between different algorithms was done to show differences in the results, and then a new algorithm was proposed according to the biological evidences.

Materials and Methods

A two dimensional biphasic finite element model was developed. The model consists of three parts: cortical bone, bone marrow, and callus (Figure 1). The gap length was considered 3mm, and the peripheral surface of external callus and bone marrow assumed to be impermeable [1, 2]. An 8-node bilinear pore pressure element (CPE8RP) was used. Analysis was done in Abaqus (6.11-1) by transient Soil step as a consolidation of fluid and solid, and load applied on the cortical bone as an axial ramp for 0.5 s. The procedure divided into two steps: 1: Modelling of cellular processing; 2: Iterative simulation of callus maturation.

Considering fibrous tissue (FT), cartilaginous tissue (CT), immature bone (IMB), and mature bone (MB) as tissues that can be produced in the fracture healing proess, five different mechano-regulation algorithms were implemented as:
(a) Original algorithm proposed used by Lacroix and Prendergast [2] which predicts both IMO and EO.
(b) Algorithm used by Kim et al.[1], which differentiation form GT and FT to MB is restricted.
(c) Algorithm used by Son et al.[5], which no jump allowed and sequential order should be followed.
(d) Algorithm used by Mehboob et al.[3], which differentiation form GT, FT, and CT to MB is restricted.
(e) Algorithm proposed by this study, which in addition to restrictions posed by the algorithm used by Kim et al, differentiation from GT and FT to bone phase is also prevented

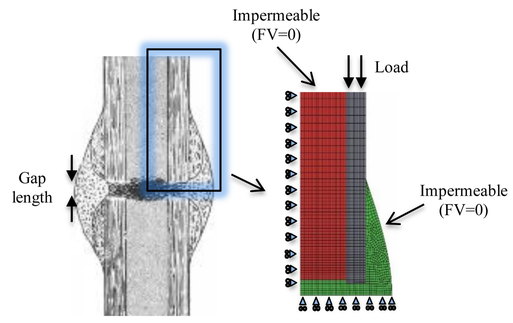

Figure 1: Axisymmetric FEM of a fracture ovine tibia with a 3mm fracture gap. Load applied at the end of cortical bone.

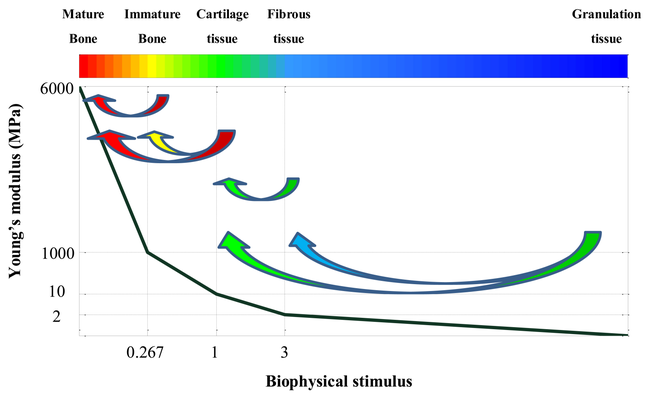

Figure 2: The algorithm proposed by this study. The arrows show possible passways for tissue differentiation.

Results

Predicted healing patterns for two loading regimes of 300N and 500N were presented in figure 3 and 4, respectively. It is shown that algorithm used by Son et al. .[5] failed to predict bony bridge and some small islands of bone were left in some area of internal and peripheral callus (figure 3 and 4-c). On the other hand, the algorithms used by Kim et al. [1] and Mehboob et al. [3] showed no differences in comparison with the original theory in which no constraints were applied in tissue differentiation processes (figure 3 and 4-b,d). The algorithm proposed by this study (figure 2) predicted healing pattern correctly, as well as a delay was shown compared to original theory.

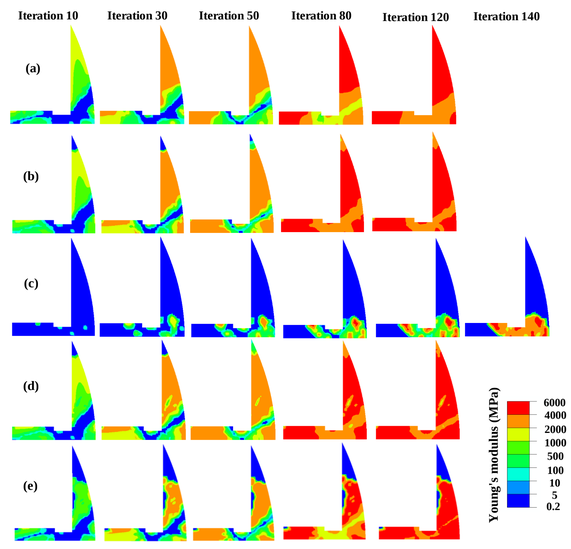

Figure 3: Fracture healing process predicted by different algorithms for loading 300N.

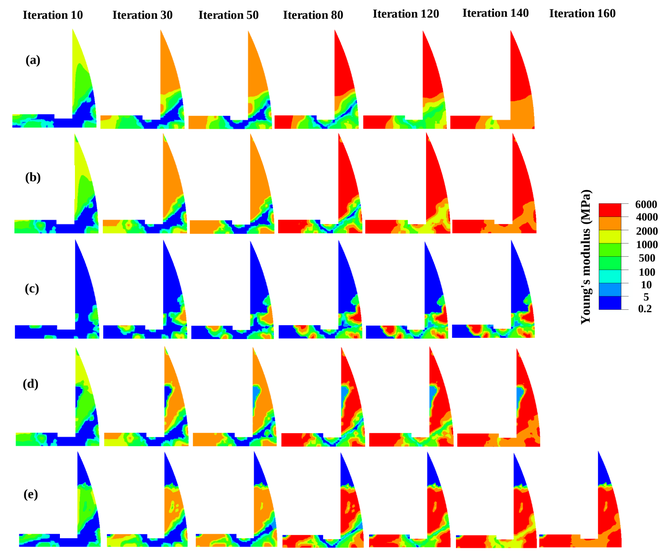

Figure 4: Fracture healing process predicted by different algorithms for loading 300N.

Conclusions

- Possibility of differntiation from GT to CT plays an crucial role in the correct prediction of healing process.
- Restriction of the tissue differentiation from CT to IMB has marginal effect on the predictions.
- In order to predict EO solely, GT and FT should not be allowed to directly differentiate into bone phase (IMB and MB), which is in agreement with experimental evidence showing that EO can take place though calcification of CT.

References

[1] Hyun-Jun Kim, Seung-Hwan Chang, and Ho-Joong Jung. The simulation of tissue differentiation at a fracture gap using a mechano-regulation theory dealing with deviatoric strains in the presence of a composite bone plate. *Composites Part B: Engineering*, 43(3):978–987, 2012.

[2] D Lacroix and PJ Prendergast. A mechano-regulation model for tissue differentiation during fracture healing: analysis of gap size and loading. *Journal of biomechanics*, 35(9):1163–1171, 2002.

[3] Hassan Mehboob and Seung-Hwan Chang. Evaluation of the development of tissue phenotypes: Bone fracture healing using functionally graded material composite bone plates. *Composite Structures*, 117:105–113, 2014.

[4] PJ Prendergast, R Huiskes, and K Sballe. Biophysical stimuli on cells during tissue differentiation at implant interfaces. *Journal of biomechanics*, 30(6):539–548, 1997.

[5] Dae-Sung Son, Hassan Mehboob, and Seung-Hwan Chang. Simulation of the bone healing process of fractured long bones applied with a composite bone plate with consideration of the blood vessel growth. *Composites Part B: Engineering*, 58:443–450, 2014.

Acknowledgements

The authors would like to thanks Amirkabir University of Technology, Iran.