

MODELING THE INFLUENCE OF OXYGEN IN DELAYED BONE FRACTURE HEALING

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Introduction

The healing of a bone fracture strongly depends on the development of a new blood vessel network (angiogenesis) in the fracture zone. In this study, a previously developed hybrid model of sprouting angiogenesis during fracture healing, including Dll4-Notch1 signaling to determine tip cell selection (MOSAIC [Carlier, 2012]), is extended by modeling the influence of oxygen more accurately.

Methods

The MOSAIC model is implemented in MATLAB (The MathWorks, Inc) and consists of: (1) a *tissue level*: describing the various key processes of bone regeneration with 10 continuous variables: mesenchymal stem cells, fibroblasts, chondrocytes, osteoblasts, fibrous matrix, cartilage, bone, oxygen, morphogenic growth factor (BMP) and angiogenic growth factor (VEGF), (2) a *cellular level*: representing the developing vasculature with discrete endothelial cells (ECs), (3) an *intracellular level*: that defines the internal dynamics of every EC (Dll4-Notch1 signaling). Every EC acts as a source of oxygen which diffuses across the fracture callus and which is removed due to cellular consumption. In the MOSAIC model oxygen influences many cellular processes: the proliferation and differentiation of chondrocytes and osteoblasts, the production of VEGF by chondrocytes and cell apoptosis.

Results

The MOSAIC model (union) captures the general trends in the experimental data of Harrison et al. [2003] (Fig. 1). In a next stage the MOSAIC model was used to simulate a non-union by increasing the gap size to 2.5 mm. Around the bony ends the fracture healing processes are similar to the union case. However, in the centre of the callus all cells die due to lack of oxygen. This disrupts the VEGF production by mature chondrocytes which stops the ingression of the vasculature and ultimately the endochondral bone

formation process. Consequently, both the periosteal as well as the endosteal callus show an increased amount of cartilage and fibrous tissue (Fig. 1). After 35 days the bony ends are capped with newly formed bone but this is not sufficient to bridge the entire defect.

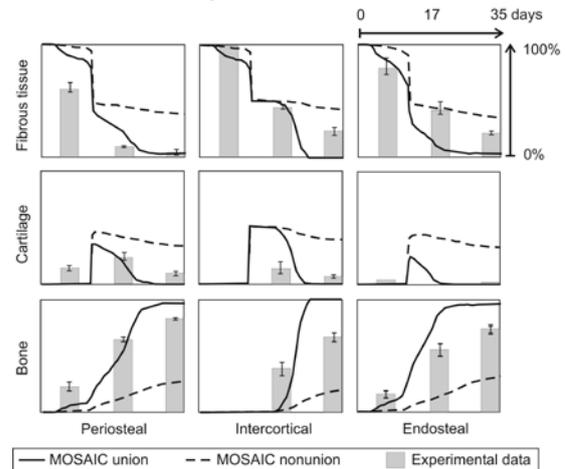


Figure 1: *In silico* and *in vivo* evolution of normal and delayed fracture healing. Temporal evolution of the bone, cartilage and fibrous tissue fractions (%) in the periosteal, intercostal and endosteal callus as predicted by the MOSAIC model and as measured by Harrison et al. [2003] in a rodent standardized fracture model.

Discussion

The proposed multiscale method, calibrated with respect to *in vivo* fracture union data, is a useful tool to investigate possible biological mechanisms across different time and spatial scales, thereby contributing to the fundamental knowledge of the bone fracture healing process. Future work will focus on the *in silico* prediction of non-unions and possible therapies thereof.

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References

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Harrison, L. et al, J Orthop Trauma, 17:11-21, 2003