A novel mechano-regulatory bone healing model based on cell phenotype specific activity

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Introduction

- The hypothesis is that during tissue regeneration, cells act as sensors. The cells proliferate, differentiate, migrate, and produce extracellular matrix based on the local mechanical stimulation. This response is cell phenotype specific. In this study, a mechanistic computational model is developed taking these processes into account, and its predictive capacity is evaluated.

Methods

- The computational cell model consists of seven coupled non-linear partial differential equations. The first four of variables describe the concentrations of mesenchymal stem cells (MSC), fibroblasts (FB), chondrocytes (CC), and osteoblasts (OB), as

$$\frac{\partial c_i}{\partial t} = \nabla D(c_i)_i \nabla c_i + f_P(\Psi)_i c_i \left(1 - \frac{c_i}{c_{space}}\right) - F_D(\Psi, c_{j\neq i})_i c_i - f_A(\Psi)_i c_i \quad \text{Eq 1}$$

- Each cell type can migrate (D), proliferate (f_P), differentiate (f_D) and/or apoptose (f_A), depending on their mechanical stimulation and the surrounding cells. They can also produce matrix (f_{MP}), or stimulate degradation (f_{MD}) (Eq 2).

$$\frac{\partial m_j}{\partial t} = f_{PM}(\Psi)_j c_i \left(1 - \frac{m_j}{m_{space}}\right) - f_{DM}(\Psi)_j c_i m_j \quad \text{Eq 2}$$

- To solve the equations, a 4 noded linear FE formulation was written, including seven degrees of freedom, and implemented into ABAQUS as a user-defined element (Fig 1). The system was solved as a transient heat transfer problem, using backward difference time integration. Coupling of the freedom degrees was done individually, to permit phenotype specific differentiation.

- A 1 Hz load (300 N) was applied, and the deviatoric strain and fluid velocity were calculated at maximal load [1], Material properties were based on actual matrix production.

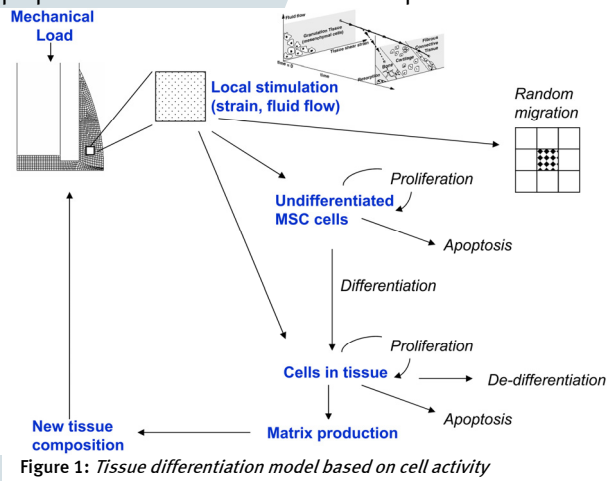

Figure 1: *Tissue differentiation model based on cell activity*

Results

The new cell model successfully captured various characteristic events of fracture healing, including normal bone healing (Fig 2), delayed and non-union due to excessive mechanical loading (Fig 3), and delayed union due to biological alterations such as periosteal stripping and impaired cartilage remodeling (Fig 4).

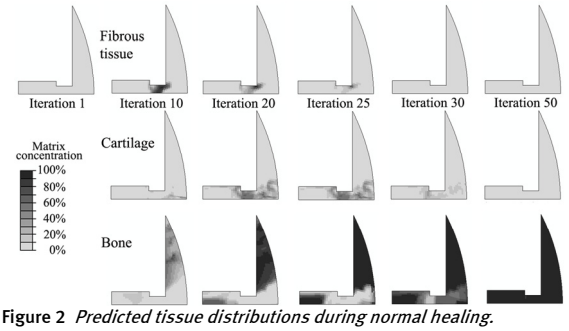

Figure 2 *Predicted tissue distributions during normal healing.*

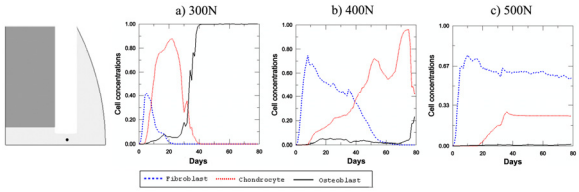

Figure 3 *Alteration of predicted cell concentrations in the gap due to increased mechanical loading.*

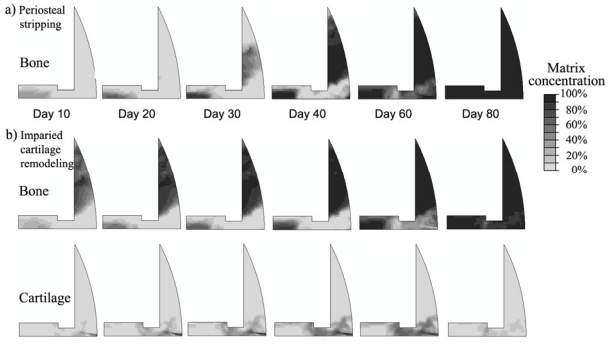

Figure 4 *Alteration of predicted tissue distributions due to periosteal stripping and impaired cartilage remodeling capacity.*

Discussion

A promising mechanistic model of bone fracture repair have been developed. The model can capture events due to altered biological environment, such as periosteal stripping and impaired endochondral ossification, which has not previously been possible.

References

[1] Prendergast et al., J Biomech, 1997