A Finite Element Approach for a Mechanically Stimulated Biochemical Bone Fracture Healing Model

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Abstract

Following the fracture of a bone, a well orchestrated cascade of cellular events usually leads to the reunion of the fractured bone ends and to the recovery of its original functionality. Suitable biochemical and mechanical conditions within the fracture region are required for a successful regeneration. Recent computational approaches attempt to combine biochemical and mechanical stimuli. The simulation of the chemical events involve the concurrent solution of several non-linear hyperbolic differential equations. The arising stability issues within the finite element framework have been approached in this work by utilizing the time-discontinuous Galerkin (TDG) and the Finite Calculus (FIC) methods.

1 Introduction

When a bone is fractured, bloodvessels located in the periosteum, endosteum, bone marrow and the surrounding soft tissues are ruptured. A haematoma forms around the fracture gap and an inflammation replaces the resulting blood clot with granulation tissue. The expression of growth factors recruits stem cells, which differentiate depending on mechanical environment and growth factor concentrations to e.g. chondrocytes or osteoblast. At the same time, osteoblasts located at the periosteum activate and produce woven bone tissue adjacent to the cortical cortex in some distance from the fracture gap. This immediate bone formation is called primary ossification. In the regions surrounding the fracture gap mechnical conditions and the lack of oxygen and nutrient supply in the absence of blood vessels, cause the formation of fibrous and cartilage tissue, which form a soft callus stabilizing the fracture. After calcification of the cartilage tissue new blood vessels are formed, enabling osteoclasts and osteoblasts to replace the cartilage with new woven bone. When this secondary ossification successfully bridges the fracture gap and the two fracture ends are joined, the healing process ends. Following the ossification, the callus is slowly remodelled by replacing the woven bone with lamellar bone and by degradation of the callus during the usual bone turn-over. Finally the bone is remodelled to its prefracture condition.

Simulations of the tissue formation patterns during the healing process were developed in the last two decades. Most of the numerical models focused on tying the mechanical conditions within the callus to the observed tissue patterns and on defining a mechanical stimulus, which promotes healing. But also revascularization and the biochemical cell stimulation through growth factors were investigated. Recently the coupling of biochemical and mechanical stimulation were explored. Here, a sophisticated biochemical model [1] coupled with a mechanical stimulation is solved within a finite element framework.

2 Mathematical Formulation

The fracture healing model consists of two distinct simulations, i.e. a static mechanical simulation, where the bone is exposed to a predefined load and local stimulation factors are computed. Then a biochemical problem is solved for the participating cells, tissues and growth factors. Certain cell activities, mainly the differentiation of the stem cells and the tissue production, are weighted by the stimulation factors resulting from the mechanical simulation.

Mechanical Stimulation At the beginning of the computation a predefined displacement is acting on the axisymmetric model of the fracture gap region (see figure 2). The local mechanical properties of the callus are calculated by a rule of mixture of the properties of the tissue types. As a measure for the resulting deformation a parameter η is defined by the principal stretches

$$\eta = \frac{\sqrt{2}}{6}\sqrt{(\lambda_1^2-\lambda_2^2)^2+(\lambda_2^2-\lambda_3^2)^2+(\lambda_3^2-\lambda_1^2)^2}. \tag{1}$$

Three stimulation parameters $\psi_{osteo}, \psi_{fibro}$ and $\psi_{chondro}$ are defined for certain levels of deformation measure η, see figure 1. The stimulation parameters take values between 0

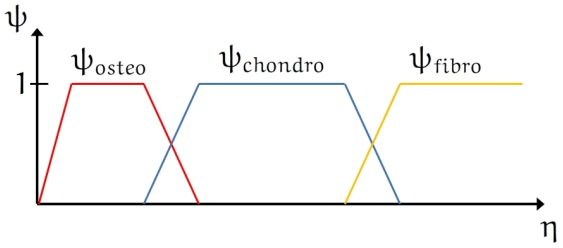

Figure 1: Definition of stimulation factors ψ_{osteo}, $\psi_{chondro}$ and ψ_{fibro} according to a deformation level η

and 1, while influencing the cell differentiation by multiplication with the suitable reaction terms, e.g. in equation 2. In the following biochemical simulation, the tissue concentrations develop according to the local mechanical and biochemical milieu. This changes the material properties of the callus and thus the mechanical stimulation, leading the tissue development down a certain evolution path. When the reaction forces to the enforced displacement exceed the day-to-day load of a limb, the further computation is then carried out by replacing the displacement with this maximum load.

Biochemical Model The biochemical model, presented by Geris et al. in [1], is given here in an abbreviated form. It incorporates five cell types i.e. mesenchymal stem cells (c_m), fibroblasts (c_f), chondrocytes (c_c), osteoblasts (c_b) and endothelial cells (c_v), four tissues, i.e. fibrous tissue (m_f), cartilage (m_c), woven bone (m_b) and vasculature (m_v) and three growth factor groups, i.e. chondrogenic growth factors (g_c), osteogenic growth factors (g_b) and angiogenic growth factors (g_v). The evolution of the concentrations of the cell types are given by

$$\begin{aligned}\frac{\partial c_m}{\partial t} &= \nabla(D_m(m)\nabla c_m) - C_m(g_b,g_v,m)c_m) + A_m(m)c_m(1-c_m) \\ &\quad - (\psi_{osteo}F_1(g_b,g_v) + \psi_{chondro}F_2(g_c) + \psi_{fibro}F_4)c_m,\end{aligned} \tag{2}$$

$$\frac{\partial c_f}{\partial t} = \nabla(D_f \nabla c_f - C_f(g_b)c_f) + A_f(m)c_f(1-c_f) + \psi_{fibro}F_4 c_m - F_3(m_c, m_v, g_b)d_f c_f, \tag{3}$$

$$\frac{\partial c_c}{\partial t} = A_c(m)c_c(1-c_c) + \psi_{chondro}F_2(g_c)c_m - F_3(m_c, m_v, g_b)c_c, \tag{4}$$

$$\frac{\partial c_b}{\partial t} = -\nabla(C_b(g_b)c_b) + A_b(m)c_b(1-c_b) + \psi_{osteo}F_1(g_b, g_v)c_m + F_3(m_c, m_v, g_b)c_c - d_b c_b, \tag{5}$$

$$\frac{\partial c_v}{\partial t} = \nabla(D_v(m)\nabla c_v - C_v(g_v, m_v)c_v) + A_v(m)c_v(1-c_v) - d_v c_v, \tag{6}$$

where D denotes a diffusion coefficient, C an advection coefficient, A the proliferation and d the absorption of the cells. Furthermore, F describes the cell differentiation. The evolution of tissue formation is given by

$$\frac{\partial m_f}{\partial t} = P_{fs}(1-m)c_f - Q_f m_f m_c c_b, \tag{7}$$

$$\frac{\partial m_c}{\partial t} = P_{cs}(1-m)c_c - Q_c m_c c_b, \tag{8}$$

$$\frac{\partial m_b}{\partial t} = P_{bs}(1-m)c_b, \tag{9}$$

$$\frac{\partial m_v}{\partial t} = P_{vs}(1-m_v)c_v, \tag{10}$$

with P and Q denoting the tissue production and absorption, respectively. Finally, the growth factor concentrations are defined as

$$\frac{\partial g_c}{\partial t} = \nabla(D_{gc}\nabla g_c) + E_{gc}c_c - d_{gc}g_c, \tag{11}$$

$$\frac{\partial g_b}{\partial t} = \nabla(D_{gb}\nabla g_b) + E_{gb}(g_b)c_b - d_{gb}g_b, \tag{12}$$

$$\frac{\partial g_v}{\partial t} = \nabla(D_{gv}\nabla g_v) + E_{gvb}(g_v, m_v)c_b + E_{gvc}(g_v, m_v, m_c)c_c - (d_{gv} + d_{gvc}c_v)g_v, \tag{13}$$

where E are the productive terms. The total tissue density can be written as $m = \sum_j m_j \quad j = f, b, c$, neglecting the marginal contribution of the vasculature m_v.Thus, in general an instationary advection-diffusion-reaction problem consisting of twelve non-linear, coupled equations has to be solved.

Stabilization It is well known, that solutions of hyperbolic partial differential equations are polluted by spurious oscillations, when standard finite element schemes are applied. Such oscillations result from the dominance of advective and reactive terms, when steep gradients occur in the solution and in the vicinity of Dirichlet boundaries. In the last decades numerous stabilization schemes were developed, in order to smooth out these oscillations. In this work such instabilities are especially crucial, as some of the coefficients

depend on one or more of the concentrations. Negative values would then destroy the physical meaning of these equations and a meaningful solution can no longer be obtained.

The Finite Calculus (FIC) method [2] is applied in this context to obtain a stable and accurate solution. The main idea of the FIC is to derive a flux balance on a *finite* control volume and to truncate the Taylor expansion after the first term of higher order. The resulting equation can be written as

$$\frac{dq}{dx} - \frac{h}{2}\frac{d^2q}{dx^2} = 0 \tag{14}$$

for a flux q in a finite volume with the characteristic length h. The general diffusion-advection-reaction problem can then be rewritten as

$$r - \frac{h}{2}\frac{dr}{dx} = 0 \tag{15}$$

with

$$r := -u\frac{d\phi}{dx} + \frac{d}{dx}\left(k\frac{d\phi}{dx}\right) + s\phi, \tag{16}$$

where u, k and s are the advection, diffusion and reaction coefficients, respectively.

The FIC method is combined here with the time-discontinuous Galerkin scheme, which provides stable and highly accurate solutions of transient problems even when several time scales have to be treated numerically [3].

3 Results

The fracture healing simulation is applied to the axisymmetric callus model shown in figure 2. A healing period of 30 days has been simulated by solving the mechanical problem at the beginning of each day, followed by the transient biochemical simulation influenced by the computed mechanical stimulus.

Figure 3 shows the soft (fibrous and cartilage) tissue formation at several days during the healing period. In the early days the fracture gap is encapsulated by the soft tissues stabilizing the callus to a degree, that the maximum daily load can be sustained. Afterwards bone formation becomes the dominant process and the soft tissues are replaced along an ossification front, which originates from the endosteum and periosteum. Some cartilage and fibrous tissue remains at the rim of the callus, where the mechanical stimulus is too marginal to incite bone formation in this region.

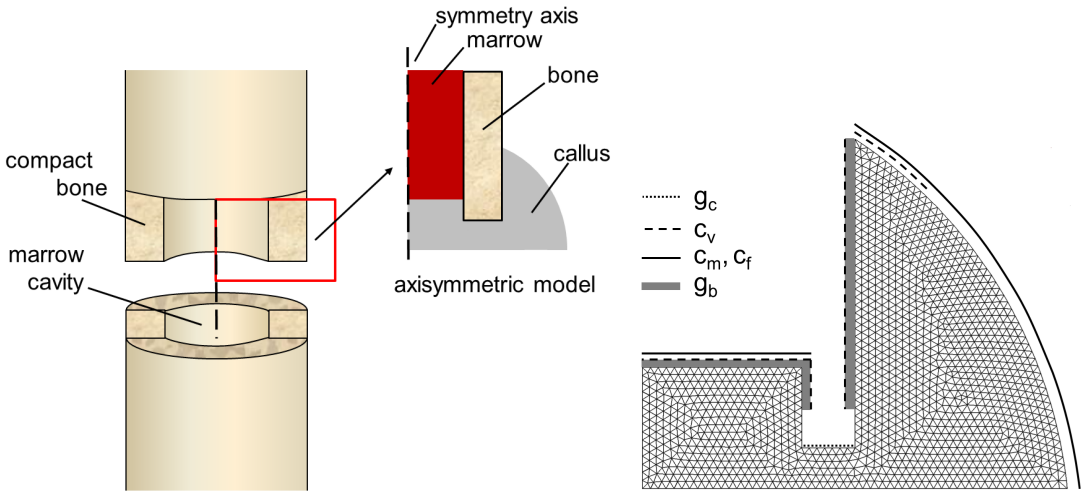

Figure 2: Axisymmetric model of the fracture gap region including a predefined callus geometrie (left), example of the meshed callus with boundary conditions for cells and growth factors entering the region from the surrounding areas (right).

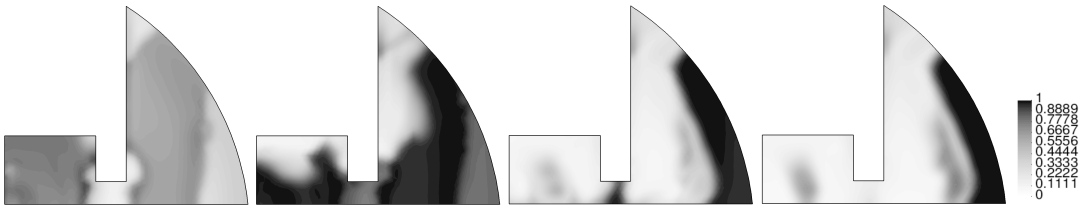

Figure 3: Formation of soft tissues, i.e. fibrous tissue and cartilage at 7 days, 14 days, 21 days and 30 days of healing (left to right).

The bone tissue density evolution is shown in figure 4. The ossification of the callus area starts at the periosteum and endosteum, in some distance to the fracture gap. This is in agreement with the observations of primary ossification in clinical studies. Bone formation then continues by replacing the soft tissues discussed earlier. The ossification path follows the vascularization of the area, which is shown in figure 5. After 30 days of healing the fracture gap is bridged by young bone and displacements resulting from daily loads are reduced to natural levels.

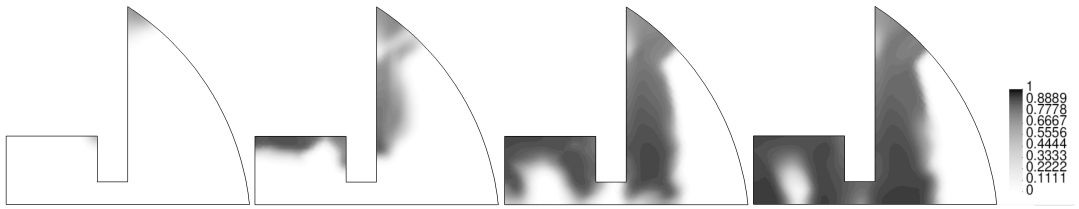

Figure 4: Bone formation in the callus region at 7 days, 14 days, 21 days and 30 days of healing (left to right).

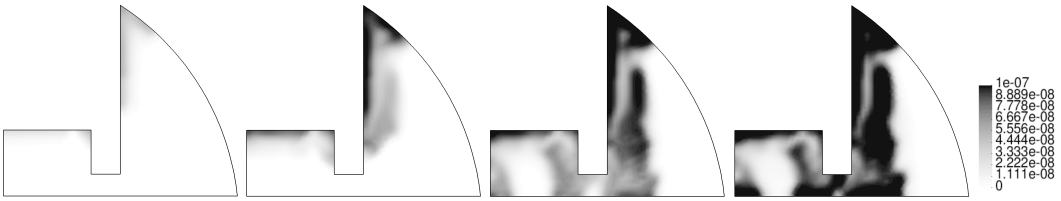

Figure 5: Vascularization, i.e. formation of new blood vessels, in the callus region at 7 days, 14 days, 21 days and 30 days of healing (left to right).

4 Discussion

A mathematical model for fracture healing, consisting of twelve hyperbolic differential equations, has been combined with the computation of a mechanical stimulus. The results show that the computed tissue formation patterns are in good agreement with clinical observations. The proposed FIC-FEM approach coupled with a time-discontinuous Galerkin scheme proved to be sufficient to obtain stable and accurate results, without severe oscillations arising in the solutions.

Acknowledgements

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