Advanced Computational Methods in Science and Engineering

Bearbeitet von
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ISBN 978 3 642 03343 8
Format (B x L): 15,5 x 23,5 cm
Gewicht: 918 g

Weitere Fachgebiete > Mathematik > Numerik und Wissenschaftliches Rechnen

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A Suite of Mathematical Models for Bone Ingrowth, Bone Fracture Healing and Intra-Osseous Wound Healing

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Abstract In this paper, some modeling aspects with respect to bone ingrowth, fracture healing and intra-osseous wound healing are described. We consider a finite element method for a model of bone ingrowth into a prosthesis. Such a model can be used as a tool for a surgeon to investigate the bone ingrowth kinetics when positioning a prosthesis. The overall model consists of two coupled models: the biological part that consists of non-linear diffusion-reaction equations for the various cell densities and the mechanical part that contains the equations for poro-elasticity. The two models are coupled and in this paper the model is presented with some preliminary academic results. The model is used to carry out a parameter sensitivity analysis of ingrowth kinetics with respect to the parameters involved. Further, we consider a Finite Element model due to Bailon-Plaza and Van der Meulen for fracture healing in bone. This model is based on a set of coupled convection-diffusion-reaction equations and mechanical issues have not been incorporated. A parameter sensitivity analysis has been carried out. Finally, we consider a simplified model due to Adam to simulate intra-osseous wound healing. This model treats the wound edge as a moving boundary. To solve the moving boundary problem, the level set method is used. For the mesh points in the vicinity of the wound edge, a local adaptive mesh refinement is applied.
1 Introduction

In osteoporosis, fracture risk is high, after a hip fracture a prosthesis that replaces the joint is often the only remedy. In the case of osteoarthritis and rheumatoid arthritis, the cartilage degrades and moving the joints becomes painful. Ultimately, most patients will receive a prosthesis to restore the function of a diseased joint. Prostheses are usually attached to the host bone by means of surgical screws to obtain sufficient initial stability. A schematic of a prosthesis of the shoulder cavity, embedded within an artificial joint is shown in Figure 1. In the course of time, bone will grow into a porous tantalum layer and hence more stability of the prosthesis is obtained. To investigate the quality and life time of such an artificial joint, one needs to study the effects of the placement of the prosthesis and of the materials that are involved in the joint. At present, these effects are often studied using large amounts of data derived from patients. To predict the life span and performance of artificial joints, numerical simulations are of great value since these simulations give many qualitative insights by means of parameter sensitivity analysis. These insights are hard to obtain by experiments. In Figure 2, an X-ray picture of the prosthesis of the shoulder cavity is shown.

In the case of a shoulder prosthesis, the angle at which the prosthesis is positioned by the surgeon is crucially important. The angle is important for the ability of moving the arm by the patient, but also to have the right strain pattern for (optimal) bone ingrowth. The latter fact is due to the fact that the mammalian bone is only generated if a certain strain is exceeded, but also smaller than a certain upper bound. For the surgery on the shoulder, the incision on the shoulder is made at the front in order to save crucial organs and muscles of the patient. The location of the incision is shown in Figure 3.

As a result of a limited visibility of the orthopaedic surgeon, the angle of placement of the prosthesis is a crucial issue. Currently the stress and strain behavior of the shoulder blade is studied at the Delft University of Technology, using three-dimensional Finite Element simulations as a function of the angle of placement of the prosthesis. An example of a computational domain is shown in Figure 4.

Several studies have been done to simulate bone-ingrowth or fracture healing of bones. To list a few of them, we mention the model due to Adam [1], Ament and Hofer [3], Bailon-Plaza et al. [7], Prendergast et al. [10] and recently by Andreykiv [4]. The model due to Prendergast et al. and LaCroix et al. [10, 13] will be treated in more detail, since we expect that this model contains most of the biologically relevant processes, such as cell division and differentiation, tissue regeneration, and cell mobility. Many ideas from modeling fracture healing of bones are used in these models, since bone-ingrowth into a prosthesis resembles the fracture healing process. In the model due to Prendergast, the influence of the mechanical properties on the biological processes are incorporated. Further, we note that Prendergast’s model has been compared to animal experiments.

Next to bone-ingrowth into a prosthesis, we present the model due to Bailon-Plaza and Van der Meulen [7] for fracture healing in bone. This model is not coupled with the equations from (poro-)elasticity. Andreykiv [6] applies the model for
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bone-ingrowth to fracture healing in which coupling with mechanics has been accomplished.

Finally, the issue of intra-osseous wound healing is modeled using the simplified formalism due to Adam [1]. An intra-osseous wound may result from surgery (think of a wound on a skull due to brain surgery) or an injury caused by an accident. The equations have a rather simple nature, though obtaining a numerical solution is challenging since the wound edge is treated as a moving boundary.

In this paper, we will see a calibrated existing bone ingrowth model in terms of a system of nonlinearly coupled diffusion-reaction equations, for which the mechanical strain and fluid flow are important input parameters. In order to compute the aforementioned parameters, the poro-elasticity equations are solved. These two classes of models will be treated separately. This paper concerns a compilation of preliminary results, with some data for a shoulder prosthesis. Further, the paper considers a model for fracture healing in bone and finally a model for healing of an intra-osseous wound is described.
2 The bone- ingrowth model

We consider a prosthesis for the shoulder cavity. A sketch of the prosthesis is given in Figure 5. The top part of the prosthesis consists of polyethylene. This part is in actual contact with the upper arm, which exerts a loading on it. The second part consists of a tantalum mesh and polyethylene. In these two parts, we solve an equation for mechanical equilibrium combined with Hooke’s Law only. The third part contains the porous tantalum. Into this part, bone ingrowth takes place from the glenoid, which is the part of the scapula, in which the humeral head rotates. We denote the entire computational domain by $\Omega$, which consists of $\Omega_E$ (the elastic domain) and $\Omega_P$ (the poro-elastic domain), hence $\Omega = \Omega_E \cup \Omega_P \cup (\overline{\Omega_E} \cap \overline{\Omega_P})$. The overlines indicate the closure of the (sub) domain. Further, we assume $\Omega_E$ and $\Omega_P$ to be disjoint, that is $\Omega_E \cap \Omega_P = \emptyset$. The domain $\Omega_E$ represents the part of the computational domain on which only the elastic equations are solved. On $\Omega_P$, one solves the poro-elastic equations. Further, in $\Omega_P$, we solve the equations for bone-ingrowth, which is referred to as the biological part of the model.

Further, we note that $\Omega_E = \Omega_E^P \cup \Omega_E^B$, where $\Omega_E^P$ and $\Omega_E^B$ are the elastic part of the prosthesis and bone respectively. Further, $\overline{\Omega_E^P} \cap \overline{\Omega_E^B}$ are separated by $\overline{\Omega_P}$, hence
Fig. 3 The location at which the incision to put the shoulder prosthesis is carried out by the surgeon.

$\overline{\Omega}_E \cap \overline{\Omega}_E^B = \emptyset$. The boundary of the computational domain, $\Omega$, is denoted by $\Gamma$, and of the subdomains $\Omega_E$ and $\Omega_P$, their respective boundaries are represented by $\Gamma_E$ and $\Gamma_P$.

The biological part of the model involving cell growth, division, differentiation and formation of bone and cartilage, applies for the porous tantalum. The coefficients in the biological part of the model depend on the local strains and fluid flow velocity, which establishes a nonlinear coupled problem. First, the mechanical model is presented and subsequently we give the biological model.

2.1 The mechanical model

Assuming mechanical equilibrium in both the poro-elastic part and the elastic part of the domain, we solve

$$- \text{div } \sigma = f, \quad x \in \Omega. \quad (1)$$

In the above equation, $\sigma$ and $f$ respectively denote the stress tensor $\sigma = \begin{pmatrix} \sigma_{xx} & \sigma_{xy} \\ \sigma_{yx} & \sigma_{yy} \end{pmatrix}$ in two dimensions and $f$ represents the internal body force. In our application, we disregard the internal body force, hence we take $f = 0$. At a part of the top boundary of the prosthesis, which is a part of the computational domain, a quadratic loading is exerted, that is
Here, $\mathbf{t}$ denotes the exerted loading on $\Gamma_l$, which is the part of $\Gamma$ on which the external loading is applied. On the bottom boundary of the computational domain, which is on the glenoid, we assume that the displacement is zero, that is

$$\mathbf{u} = \mathbf{0}, \quad \mathbf{x} \in \Gamma_c.$$  

Here $\Gamma_c$ denotes the part of the outer boundary that is fixed to the host bone. On all the other parts of the boundary, it is assumed that there is no loading, that is

$$\mathbf{t} \cdot \mathbf{n} = \mathbf{0}, \quad \mathbf{x} \in \Gamma \setminus (\Gamma_l \cup \Gamma_c).$$  

The material properties vary strongly over the various parts of the computational domain. The displacement and traction are assumed to be continuous.
Fig. 5 A schematic of the prosthesis for the glenoid. From left to right: The metal backing, the poro-ethylene part, the porous tantalum, in which bone-ingrowth takes place and the bone.

2.1.1 The elasticity domain

In this part of the domain, only the equations for the mechanical balance are solved. For the link between the stresses and strains, Hooke’s Law is used, which reads as follows in the two-dimensional case

\[ E \varepsilon_{xx} = \sigma_{xx} - \nu \sigma_{yy}, \]
\[ E \varepsilon_{yy} = -\nu \sigma_{xx} + \sigma_{yy}, \]
\[ E \varepsilon_{xy} = \frac{1}{2} (1 + \nu) \sigma_{xy}. \] (5)

Here \( E \) and \( \nu \) represent the Young’s modulus and Poisson ratio. The strain tensor is denoted by \( \varepsilon = \begin{pmatrix} \varepsilon_{xx} & \varepsilon_{xy} \\ \varepsilon_{yx} & \varepsilon_{yy} \end{pmatrix} \). The relation between the strains and displacements \( \mathbf{u} = [u \ v] \) is given by

\[ \varepsilon_{xx} = \frac{\partial u}{\partial x}, \quad \varepsilon_{yy} = \frac{\partial v}{\partial y}, \quad \varepsilon_{xy} = \frac{\partial u}{\partial y} + \frac{\partial v}{\partial x}. \] (6)
2.1.2 The porous tantalum

In this part of the domain, the two-phase (poro-elasticity) equations are solved. We write

\[ \sigma = \sigma^e - pg \] (7)

where \( \sigma \) is the effective stress that gives the deformations and \( p \) is the pressure. Further, \( I \) is the identity tensor. This implies that also in this domain, we solve

\[ -\text{div} \sigma = 0, \quad \text{div} \sigma^e = \text{div} (pg), \quad x \in \Omega_p. \] (8)

Furthermore, for the fluid flow, we get

\[ \frac{\partial}{\partial t} (n_f \beta_f p + \text{div} u) - \text{div} \left( \frac{\kappa}{\eta} \text{grad} p \right) = 0, \quad x \in \Omega_p. \] (9)

Here, \( n_f, \beta_f, \kappa, \eta \) respectively denote the porosity, compressibility of the fluid, permeability of the tantalum and viscosity of the fluid. The Lamé parameters, which are linked to the stiffness and Poisson’s ratio of the material are defined by

\[ \lambda = \frac{\nu E}{(1 + \nu)(1 - 2\nu)}, \quad \mu = \frac{E}{2(1 + \nu)}. \] (10)

Using the abovementioned Lamé parameters, we arrive at the following form of the poro-elastic equations

\[ -\text{div} (\mu \text{grad} u) - \frac{\partial}{\partial x} ((\lambda + \mu) \text{div} u) + \frac{\partial p}{\partial x} = 0, \quad x \in \Omega_p, \]

\[ -\text{div} (\mu \text{grad} v) - \frac{\partial}{\partial y} ((\lambda + \mu) \text{div} u) + \frac{\partial p}{\partial y} = 0, \quad x \in \Omega_p, \] (11)

\[ \frac{\partial}{\partial t} (n_f \beta_f p + \text{div} u) - \text{div} \left( \frac{\kappa}{\eta} \text{grad} p \right) = 0, \quad x \in \Omega_p. \]

At the bone-implant interface, the displacement and stresses are continuous. The parameters in the equations (\( E \) and \( \nu \)) have to be updated as bone grows into the prosthesis. The Rule of Mixtures is applied to update the mechanical properties (see Lacroix & Prendergast [13]). For more information on the derivation of the above equations, we refer to Bear [8]. As an initial condition \( p \) is prescribed and set equal to zero. The boundary conditions for the pressure are

\[ p = 0, \quad x \in \overline{\Omega_p} \cap \overline{\Omega_E^b}, \]

\[ \frac{\kappa}{\eta} \frac{\partial p}{\partial n} = 0, \quad x \in \Gamma_p \setminus (\overline{\Omega_p} \cap \overline{\Omega_E^b}). \] (12)

Here \( \Gamma_p \) denotes the boundary of the porous tantalum \( \Omega_p \). At the boundary between the porous tantalum and the metal backing, we require continuity of the displacements and traction. In other words, these subdomains are fixed to each other.
Next, we consider a scaled version of equations (11), in which we draw our attention to the third equation. In this scaling argument, we assume that the coefficients in the equations (11) are constant in time and space. Division of this equation by \( n_f \beta_f \) (under the assumption that \( n_f \) and \( \beta_f \) are constant), and using the dimensionless variables

\[
X, Y := \frac{x, y}{L}, \quad \tau := \frac{\kappa}{\eta \beta_f n_f L^2} t, \quad \text{and} \quad U, V := \frac{u, v}{L},
\]

where \( L \) is a characteristic length, such as the length or width of the prosthesis. Then equations (11) change into

\[
\begin{align*}
- \nabla \cdot (\mu \nabla U) - \frac{\partial}{\partial X} ((\lambda + \mu) \nabla U) + \frac{\partial p}{\partial X} &= 0, \\
- \nabla \cdot (\mu \nabla V) - \frac{\partial}{\partial Y} ((\lambda + \mu) \nabla U) + \frac{\partial p}{\partial Y} &= 0, \\
\frac{\partial}{\partial \tau} (\nabla \cdot U) &= n_f \beta_f \left( \lambda p - \frac{\partial p}{\partial \tau} \right),
\end{align*}
\]

where \( \nabla (.) := \frac{1}{L^2} \nabla (.) \), \( \Delta (.) := \frac{1}{L^2} \Delta (.) \) and \( U := \frac{1}{L} u \). We see that as \( n_f \beta_f \rightarrow 0 \), then, we reach the incompressible limit, which gives a saddle-point problem, similar to the Stokes equations, where one has to consider LBB condition satisfying elements or a stabilization. Note also that for the incompressible limit, the boundary conditions for the pressure vanishes. The situation becomes analogous to the Stokes’ equations.

### 2.2 The biological part

Prendergast et al. [14] consider the behavior of mesenchymal cells, that originate from the bone marrow and differentiate into fibroblasts, chondrocytes and osteoblasts. These newly created cell types respectively generate fibrous tissue, cartilage and bone. In Prendergast’s model, it is assumed that fibroblasts may differentiate into chondrocytes, chondrocytes may differentiate into osteoblasts. The differentiation processes are assumed to be irreversible. The differentiation pattern has been sketched in Figure 6. This biological model applies for the porous tantalum. The accumulation at a certain location of all the cell types is determined by cell mobility, cell division and cell differentiation. Let \( c_m, c_c, c_f \) and \( c_b \) respectively denote the cell density of the mesenchymal cells, chondrocytes, fibroblasts and osteoblasts, in the poro-elastic tantalum of the prosthesis in which bone ingrowth takes place. Then, the dynamics of the mesenchymal cell density is described by

\[
\begin{align*}
\frac{\partial c_m}{\partial t} = & \text{div } D_m \text{ grad } c_m + P_m(1 - c_{\text{tot}}) c_m \\
& - F_f(1 - c_f) c_m - F_c(1 - c_c) c_m - F_b(1 - c_b) c_m, \quad \mathbf{x} \in \Omega_p, \quad (15)
\end{align*}
\]

where \( D_m = D_m^b(1 - m_c - m_b) \).
Fig. 6 The scheme of cell differentiation of mesenchymal cells, fibroblasts, chondrocytes and osteoblasts.

The first term in the right-hand side of the above equation represents the transport of mesenchymal cells. The diffusivity of mesenchymal cells, $D_m$, is determined by the amount of bone and cartilage present. It is assumed that cartilage and bone inhibit diffusion. The second term represents mesenchymal stem-cell production due to cell division, with production rate constant $P_m$. The other terms incorporate differentiation of mesenchymal stem cells to fibroblasts, chondrocytes and osteoblasts, with their respective differentiation rate constants $F_f$, $F_c$ and $F_b$. The dynamics of the fibroblasts, which are the cells that produce fibrous tissue, is represented by

$$\frac{\partial c_f}{\partial t} = \text{div} D_f \text{ grad } c_f + P_f (1 - c_{\text{tot}}) c_f + F_f (1 - c_f) c_m - F_c (1 - c_c) c_f - F_b (1 - c_b) c_f, \quad x \in \Omega_P, \quad (16)$$

where $D_f = D_f^0 (1 - m_c - m_b)$.

The description of the terms of the right-hand side of the above equation is similar to the previous equation for the mesenchymal stem cells. They express cell division (with production rate constant $P_f$), transport (with fibroblast diffusivity $D_f$) and differentiation to other cell types (chondrocytes and osteoblasts with their respective differentiation rate constants $F_c$ and $F_b$). The mesenchymal stem cells and fibroblasts are the only cell types that are mobile. The chondrocytes and osteoblasts, respectively producing cartilage and bone, are assumed to be immobile. Their reaction processes are modeled by
\[
\begin{align*}
\frac{\partial c_c}{\partial t} &= P_c (1 - c_{\text{tot}}) c_c + F_c (1 - c_c) (c_m + c_f) - F_b (1 - c_b) c_c, \\
\frac{\partial c_b}{\partial t} &= P_b (1 - c_{\text{tot}}) c_b + F_b (1 - c_b) (c_m + c_f + c_c). \\
\end{align*}
\]
\(x \in \Omega_p.\) \hspace{1cm} (17)

The first terms of the right-hand side in the above equations represent cell division (with production rate constants \(P_c\) and \(P_b\) for the chondrocytes and osteoblasts respectively), the second term describes the addition due to differentiation from mesenchymal stem cells and fibroblasts. The last term in the top equation represents the differentiation of chondrocytes to osteoblasts. The tissues, fibrous tissue, cartilage and bone are immobile. The volume accumulation of these tissues, denoted by \(m_f\) and \(m_c\), respectively, are modeled by

\[
\begin{align*}
\frac{\partial m_f}{\partial t} &= Q_f (1 - m_{\text{tot}}) c_f - (D_b c_b + D_c c_c) m_f m_{\text{tot}}, \\
\frac{\partial m_c}{\partial t} &= Q_c (1 - m_b - m_c) c_c - D_b c_b m_c m_{\text{tot}}, \\
\frac{\partial m_b}{\partial t} &= Q_b (1 - m_b) c_b. \\
\end{align*}
\]
\(x \in \Omega_p.\) \hspace{1cm} (18)

Here, both production (with rate constants \(Q_f, Q_c\) and \(Q_b\) for the fibroblasts, chondrocytes and osteoblasts and decay rates (with rate constants \(D_b\) and \(D_c\)) are incorporated. The quantity \(m_{\text{tot}}\) denotes the maximum allowable volume fraction of the tissues. In the above equations, a maximum allowable volume fraction of the tissues and decay rates has been incorporated.

The initial concentrations of all tissues and cell types are zero. As boundary conditions, a Dirichlet condition for the mesenchymal cell density at the bone implant and homogeneous Neumann conditions at all other boundaries are applied, that is

\[
\begin{align*}
c_m &= 1, \hspace{1cm} x \in \overline{\Omega_p \cap \Omega_E^B}, \\
D_m \frac{\partial c_m}{\partial n} &= 0, \hspace{0.5cm} x \in \Gamma_p \setminus (\overline{\Omega_p \cap \Omega_E^B}), \\
D_f \frac{\partial c_f}{\partial n} &= 0, \hspace{0.5cm} x \in \Gamma_p. \\
\end{align*}
\]
\hspace{1cm} (19)

In the present paper, the influence of the micro-motions is neglected. For the fibroblasts homogeneous Neumann boundary conditions are imposed for all boundary segments. The equations for the mesenchymal cells, fibroblasts, chondrocytes and osteoblasts were introduced by Andreykiv [4, 6, 5]. The proliferation, differentiation and diffusion parameters, which are coefficients in the above Prendergast model, depend on the mechanical stimulus. The mechanical stimulus is given by a linear combination of the maximum shear strain and the fluid velocity relative to the rate of displacement of the solid, that is
\[ S = \frac{\gamma}{a} + \frac{v}{\beta}, \quad (20) \]

where \( \gamma \) represents the maximum shear strain and \( v \) denotes the relative fluid/solid velocity. Here \( \gamma := \frac{1}{2}(\lambda_1 - \lambda_2) \), where \( \lambda_{1,2} \) represent the eigenvalues of the strain tensor. The rates of tissue regeneration and differentiation qualitatively depend on the mechanical parameters such that:

- Low strain has a stimulatory effect (in relation to no strain) on the fibroblast proliferation and bone regeneration (if \( 0 < S < 1 \));
- For intermediate values of the strain, cartilage formation is more favorable (if \( 1 < S < 3 \));
- High strains favor the proliferation of fibrous tissue (if \( S > 3 \)).

This gives a coupling of the poro-elasticity model to this biological model.

The above set of partial differential equations poses a nonlinearly coupled set of equations. Standard Galerkin Finite Element methods provide a straightforward method to obtain solutions. For the dependencies of the parameters involved on the mechanical stimulus, that is \( S \), we refer to the thesis due to Andreykiv [4].

### 2.3 The numerical method for the ingrowth model

To solve the equations, we use a Finite Element method. To derive the weak form for both the metal backing part and the porous tantalum, we express the equations for mechanical equilibrium in terms of the stresses. The equations for poro-elasticity (in the porous tantalum) become the same as for the metal backing. The diagonal entries of the stress tensor change:

\[ \sigma_{xx} = \overline{\sigma}_{xx} - p, \quad \sigma_{yy} = \overline{\sigma}_{yy} - p, \quad (21) \]

where \( \overline{\sigma}_{xx} \) and \( \overline{\sigma}_{yy} \) denote the effective stresses as in the metal backing region. A weak form for the equations for mechanical equilibrium is given by

Find \( u, v \in H^1(\Omega) \), subject to \( u = 0 \) on \( \Gamma_c \), such that

\[
- \int_{\Gamma_1} t_1 \phi'^{u} d\Gamma + \int_{\Omega} \left\{ \sigma_{xx} \frac{\partial \phi'^{u}}{\partial x} + \sigma_{xy} \frac{\partial \phi'^{u}}{\partial y} \right\} \, d\Omega = 0,
\]

\[
- \int_{\Gamma_1} t_2 \phi'^{v} d\Gamma + \int_{\Omega} \left\{ \sigma_{xy} \frac{\partial \phi'^{v}}{\partial x} + \sigma_{yy} \frac{\partial \phi'^{v}}{\partial y} \right\} \, d\Omega = 0,
\]

\[ \forall \phi'^{u}, \phi'^{v} \in H^1(\Omega), \text{ subject to } \phi'^{u} = \phi'^{v} = 0 \text{ for } x \in \Gamma_c. \]

In the above formulation, we avoided the tensor representation to keep the text readable for researchers that are unfamiliar with mechanical problems. For the pressure,
one obtains the following weak form

\[
\text{Find } p \in H^1(\Omega), \text{ subject to } p = 0 \text{ on } \Omega_p \cap \Omega_E^B, \text{ such that }
\int_{\Omega} \frac{\partial}{\partial t} (n_f \beta_f p + \text{div } \mathbf{u}) \psi d\Omega = -\int_{\Omega} \frac{\kappa}{\eta} \nabla p \cdot \nabla \psi d\Omega,
\]
\[
\forall \psi \in H^1(\Omega), \text{ subject to } \psi = 0 \text{ whenever } p \text{ on } \Omega_p \cap \Omega_E^B.
\]

For a rather recent comprehensive overview of Finite Element methods applied to solid state mechanics, we refer to the book due to Braess [9]. The above poro-elasticity equations are often solved using Petrov-Galerkin Finite element methods, such as the Taylor-Hood family: if the pressure is approximated with elements of polynomials of \(P_n\), then, the displacements are approximated using polynomials of \(P_{n+1}\). In the Taylor-Hood elements, one usually uses linear and quadratic basis functions for the pressure and displacements respectively. On the other hand, Crouzeix-Raviart elements, which are often used for Stokes flow problems, are based on a discontinuity of the pressure. Since \(p \in H^1(\Omega) \subset C(\Omega)\), the Crouzeix-Raviart elements are not suitable here. As long as the compressibility is sufficiently large, one can also make use of linear-linear elements for the pressure and displacement. This was done successfully in the study due to Andreykiv [4]. If \(\beta_f = 0\), which is the incompressible case, then the issue of oscillations and the use of appropriate elements or a stabilization becomes more important. For \(\beta_f = 0\), the third equation in equation (11) reduces to the version that is solved by Aguilar et al. [2].

A Galerkin formulation of the above equation with

\[
p = \sum_{j=1}^{m} p_j \psi_j(x,y), \text{ and } \mathbf{u} = \sum_{j=1}^{n} \mathbf{u}_j \phi_j(x,y),
\]

is applied to equations (11). For consistency, we require \(m \leq 2n\) as \(n_f \beta_f \to 0\). This case resembles the classical Stokes’ equations. For the classical Taylor-Hood elements, we use \(\psi_j \in P_1(\Omega)\) and \(\phi_j \in P_2(\Omega)\).

By numerical experiments and the argument that the discretization matrix no longer remains an \(M\)-matrix if \(\Delta t < \frac{h}{\sigma}\), Aguilar et al. [2] demonstrate for the one-dimensional Terzaghi problem that the numerical solution becomes mildly oscillatory. Aguilar et al. [2] use a stabilization term \(\gamma \frac{\partial}{\partial \tau} \Delta p\) (with \(\gamma = \frac{\sigma h^2}{4(\lambda + 2\mu)} = O(h^2)\), where \(\sigma = 1\)) to suppress the spurious oscillations. In our application, the stabilization coefficient is given by \(\gamma \approx 1.2 \cdot 10^{-18}\). In this study, we use linear-linear elements to solve poro-elasticity equations. We verified numerically that these elements gave the same results as the Taylor-Hood elements. A possible reason for this is that for our settings the compressibility term is given by \(n_f \beta_f \approx 2.5 \cdot 10^{-16}\), which is larger than the stabilization coefficient \(\gamma\) that was introduced by Aguilar et al. [2]. Since this term, and in particular the \(\frac{\partial \tau}{\partial \tau}\)-term (also as \(\Delta \tau \to 0\)), gives an additional contribution to the diagonal entries of the discretization matrix, the \(M\)-matrix prop-
The property of the discretization matrix is probably preserved. Hence, this term stabilizes the solution. Note that linear-linear elements are always allowable if the stabilization term due to Aguilar is used. Our approach, which is motivated physically, stabilizes in a similar way as Aguilar’s term does. We admit that this issue needs more investigation in mathematical rigor. For the concentrations and densities, linear elements are used too.

The equations for poro-elasticity were solved using the Euler backward time integration method in which the data for the material parameters such as the permeability, Young’s modulus and Poisson ratio were determined from the bone, cartilage and fibrous tissue densities that were obtained at the previous time step. Using this approach, there is hardly any limitation with respect to the time step. The nonlinear partial differential equations for the differentiation of several cell types were integrated in time using a first order IMEX method. Further, the material properties that depend on local strain and fluid flow were adapted using the data from the previous time step. This approach hardly influences stability as in the previous case of poro-elastic equations. The IMEX method for the reaction-diffusion equations yields good solutions, but here time step with respect to stability becomes more important. The first order IMEX time integration was applied to the reaction terms and to the diffusivity that depends on the cartilage and bone densities. As an example, we present the semi-discretization with respect to the time integration of the equation for the mesenchymal cell density:

\[
    c_{p}^{m+1} = c_{m}^{p} + \Delta t \cdot \left\{ \text{div} D_{m}^{p} \text{grad} c_{m}^{p+1} \right\} + \\
    \Delta t \cdot \left( P_{m}(1 - c_{f_{tot}}^{p}) - F_{f}(1 - c_{f}^{p}) - F_{c}(1 - c_{c}^{p}) - F_{b}(1 - c_{b}^{p}) \right) c_{m}^{p+1},
\]

where \( p \) denotes the time index, where \( t = p \Delta t \) is the actual time. The maximum allowable time step becomes dependent on the local solution at the time step considered. One can analyze the stability using the eigenvalues of the Jacobi matrix (left multiplied by the mass matrix) from the reaction terms. Using upper bounds and lower bounds of the solution, one can investigate the allowable time steps for the integration. This was not done in this study. We compared the solutions by halving the time step and observed that there was hardly difference when a time step of the order of an hour was taken.

The diffusion part of the equations for the mesenchymal cells and fibroblasts were solved using an IMEX method, where the diffusivities of the mesenchymal cells and fibroblasts were taken from the previous time step. The reaction parts in all the equations were treated using an IMEX time integration method too. The coupling was treated by the use of information from the previous time step. Until now, no iterative treatment of the coupling has been done in the current preliminary simulations. A state-of-the-art book on several numerical time integrators for stiff problems is the work due to Hundsdorfer & Verwer [11].

To determine the stimulus in equation (20), the strain is computed from the spatial derivatives of the displacements. To determine the strains at the mesh points, we proceed as follows: consider the equation for \( \varepsilon_{xx} \), then multiplication by a test-
function gives
\[ \int_{\Omega} \varepsilon_{xx} \phi \, d\Omega = \int_{\Omega} \frac{\partial u}{\partial x} \phi \, d\Omega, \quad \text{for } \phi \in H^1(\Omega), \tag{23} \]
where \( \varepsilon_{xx} \in H^1(\Omega) \). Using the set of basis functions as in our finite element solution, gives
\[ \sum_{j=1}^{n} \varepsilon_{xx}^{j} \int_{\Omega} \phi_i \phi_j \, d\Omega = \sum_{j=1}^{n} u_j \int_{\Omega} \frac{\partial \phi}{\partial x} \phi_j \, d\Omega, \quad \text{for } i \in \{1, \ldots, n\}. \tag{24} \]
This gives a system of \( n \) equations with \( n \) unknowns. This is applicable for any type of element. For piecewise linear basis functions, the mass matrix is diagonal (lumped) after applying Newton-Cotes’ integration rule. Then, the strains and fluid velocities are used for the mechanical stimulus at the mesh points for the ordinary differential equations, which are solved using an IMEX time integrator only.

### 2.4 Numerical experiments on the ingrowth model

In Figure 7, the distribution of the stimulus, osteoblast density, mesenchymal stem cell density and the bone fraction in the porous tantalum layer after 100 days have been plotted. The prosthesis is assumed to consist of two parts: the top part being the functional part on which an external force is exerted from the outer motion. The bottom part is the porous tantalum, in which bone is allowed to grow in from the bottom layer. The size of the prosthesis is given by 40 × 10 mm, in which the prosthesis is divided into the top and bottom layer of the same size. The upper force is given by 165.84 N, corresponding to an arm abduction of 30 degrees. In this paper, it is assumed that this force is exerted constantly. In future, we will consider more realistic oscillatory forces. In the top part of the prosthesis, the elasticity equations are solved. The prosthesis has been approximated by a two-dimensional geometry, which can be done with the use of cylindrical co-ordinates. The latter has not been done yet.

It can be seen that the osteoblast density is maximal where the stimulus is maximal. This implies that bone develops at the positions where the osteoblast density and stimulus is maximal. This can be seen clearly from the figures. Furthermore, the mesenchymal cell density shows a decrease where the cells differentiate into osteoblasts. The conditions are such that the model only allows the differentiation into osteoblasts and the development of other cell types and tissues is prohibited. To have bone ingrowth in the other parts of the tantalum, it is necessary that the upper arm moves allowing for the stimulus to increase at various positions within the tantalum. This has been observed to take place in preliminary simulations that are not shown in this paper. For arm abductions of 90 degrees, cartilage is also allowed to develop in the tantalum due to a higher outer force that is exerted on the top of the prosthesis. It can be seen that bone develops in the high stimulus domain. Bone
can only remain at locations where it has been generated. Bone resorption has been disregarded in the model since its effect seems to be of second order only.

![Graphs showing distributions in porous tantalum](image)

**Fig. 7** Some distributions in the porous tantalum after 100 days, from top to bottom: The stimulus, the osteoblasts (bone cells) density, the mesenchymal stem cell density and the bone density.

Some preliminary results reveal that the model is rather insensitive to the diffusion parameters near the current values. There is a high sensitivity with respect to $F_b$ and $Q_b$ in the present loading regime, where $F_b$ and $Q_b$ can be considered as the differentiation rate of mesenchymal cells to osteoblasts and the bone production rate respectively. Physically, this means that the bone ingrowth pattern is severely influenced by the mesenchymal to osteoblast differentiation rate and osteoblast activity to produce bone. Hence, it is important to have a loading pattern and chemical environment that favor osteoblast and bone production.
3 The fracture healing model due to Bailon-Plaza

An interesting model that is somewhat similar to the previous model due to Prendergast is the model due to Bailon-Plaza and Van der Meulen [7]. Bailon-Plaza and van der Meulen formulated this model and solved the involved partial differential equations. Since this paper concerns an overview of bone ingrowth, fracture healing and intra-osseous healing, the equations due to Bailon-Plaza and van der Meulen are repeated for completeness. This model is used to simulate healing of a bone fracture. The geometry is sketched in Figure 8. This model does not take into account the generation of fibroblasts and fibrous tissue, but it incorporates the production and decay of growth factors that stimulate or inhibit cell production. Growth factors are hormones that influence the rate differentiation of several cell types to other cell types (such as the differentiation of mesenchymal stem cells to chondrocytes). Unlike in the previous model, it is assumed that the formation of bone and cartilage as solid materials introduces an additional nonlinear convective term to the mesenchymal stem cells. The convective velocity is proportional to, and towards the gradient of $m$, which is defined as $m = m_c + m_b$. This changes the nature of the equation of the mesenchymal cell profile in the following way.
\[ \frac{\partial c_m}{\partial t} = \text{div} \{ D_m \text{ grad } c_m - \frac{C_k}{(K_k + m)^2} c_m \text{ grad } m \} + \frac{A_{m0} m}{(K_m^0 + m^2)^2} c_m (1 - \alpha_m c_m) \]

\[ - \left( \frac{Y_1 g_b}{H_1 + g_b} - \frac{Y_2 g_c}{H_2 + g_c} \right) c_m, \quad x \in \Omega_p. \]

(25)

The first term in the right-hand side models diffusive and convective transport of mesenchymal cells. The quantity \( D_m \) is also referred to as the haptotatic cell migration speed. The second term takes care of convective transport resulting from bone and cartilage formation. The quantity \( C_k \) is called the haptokinetic migration speed. Further, \( g_b \) and \( g_c \) are growth factors that enhance the differentiation of mesenchymal cells to chondrocytes and osteoblasts respectively. The quantities \( C_k, A_{m0}, Y_1 \) and \( Y_2 \) are constants. The diffusion coefficient \( D_m \) is given by

\[ D_m = \frac{D_h}{K_h^2 + m^2} m, \]

(26)

where \( D_h \) and \( K_h \) are constants. The PDE for \( c_m \) is a nonlinear convection-diffusion-reaction equation. The PDE for \( c_m \) is supplemented with a Dirichlet boundary for \( c_m \) at the interface between the internal callus and the marrow region and at the peristome layer. At the other boundaries of the computational domain, which consists of the internal callus, fracture gap and callus, homogeneous Neumann boundary conditions are applied. Andreykiv et al. [6] use the model as in the previous section to study bone-ingrowth. A comparison between the two models is an interesting topic for future research. The equations for the chondrocytes and osteoblasts look similar to the ones in the model in the previous section, and read as

\[ \frac{\partial c_c}{\partial t} = A_c c_c (1 - \alpha_c c_c) + \frac{Y_2}{H_2 + g_c} g_c c_m - \frac{m_c^6}{B_{cc}^0 + m_c^6} \frac{Y_3}{H_3 + g_b} g_b c_c, \quad x \in \Omega_p. \]

(27)

The first terms in the above equations represent the logistic growth due to cell mitosis. The second terms take into account the differentiation from mesenchymal cells to chondrocytes and osteoblasts. The quantities \( A_c, A_b, Y_3, \alpha_c, \alpha_b, H_1, H_2, H_3, d_d \) and \( B_{cc} \) are considered as given constants. These differentiation processes are triggered by the presence of growth factors. In the equations, a maximum for the differentiation rate with respect to the growth factor concentration is incorporated. The other terms take differentiation of chondrocytes to osteoblasts and decay into account. The changes in cartilage and bone density are modeled by
\[
\frac{\partial m_c}{\partial t} = P_{cs}(1 - \kappa_c m_c)(c_m + c_c) - Q_{cd} m_c c_b, \quad x \in \Omega_p.
\]
\[
\frac{\partial m_b}{\partial t} = P_{bs}(1 - \kappa_b m_b) c_b, \quad x \in \Omega_p.
\]

Here, \(P_{cs}, P_{bs}, Q_{cd}, \kappa_c\) and \(\kappa_b\) are constants. The growth factors for the generation of bone and cartilage are subject to diffusional transport within the callus, formation due to the presence of chondrocytes, osteoblasts and tissues, and decay. The PDE’s for the growth factors are the following:

\[
\frac{\partial g_c}{\partial t} = \text{div} (D_{gc} \text{ grad } g_c) + \frac{G_{gc} g_c}{H_{gc} + g_c} \frac{m}{K_{gc} + m} c_c - d_{gc} g_c, \quad x \in \Omega_p.
\]
\[
\frac{\partial g_b}{\partial t} = \text{div} (D_{gb} \text{ grad } g_b) + \frac{G_{gb} g_b}{H_{gb} + g_b} c_b - d_{gb} g_b, \quad x \in \Omega_p.
\]

Here \(D_{gc}, D_{gb}\) are the diffusivities of the cartilage and bone growth factors, respectively. Further, \(G_{gc}, G_{gb}, H_{gc}, d_{gc}, H_{gb}\) and \(d_{gb}\) are assumed to be known constants. Further, \(g_c\) and \(g_b\) denote the growth factor concentration for the cartilage and bone regeneration. For the boundary conditions, one uses Dirichlet conditions for \(g_c\) at the interface between bone and the fracture gap for \(t < \tau\). Here, \(\tau\) represents the time after which no growth factors appear at the interface between bone and the gap. Typically, it is observed that \(\tau\) is approximately 24 hours. Further, for \(g_b\) a Dirichlet boundary condition is applied along the interface between bone and the (external) callus, at a part away from the fracture gap for \(t < \tau\). For \(t > \tau\), the Dirichlet conditions are replaced with homogeneous Neumann boundary conditions. At all other boundaries, homogeneous Neumann boundary conditions are applied. The initial conditions for \(g_c\) and \(g_b\) are \(g_b(x,0) = g_c(x,0) = 20\), and \(m(x,0) = 0.1 = m_c(x,0)\), which reflect inflammatory conditions.

In Figure 9, the evolution of the integral over the bone- and cartilage density is presented. First, cartilage is developed as an intermediate stage and finally the callus is filled with bone. The disappearance of the callus is not taken into account here. For the values of the parameters involved, we refer to Bailon and Van der Meulen [7]. For this model, we looked at the influence of the parameters involved. The most important parameter for bone ingrowth seems to be \(P_{bs}\). A low value gives a slow bone growth process. An increase of the value of \(D_{gc}\) gives a high concentration of cartilage growth factors, which slightly enhances cartilage formation. However, bone formation is hardly influenced. An increase of \(d_{gb}\) leads to an increased cartilage formation and a delayed bone formation. Changing \(F_3\) hardly has any influence, but an increase of \(F_1\) reduces the growth of cartilage and growth of bone starts a little earlier. An increase of \(A_{po}\) leads to a higher osteoblast density and a lower peak density of cartilage, whereas bone grows faster.
Fig. 9 The evolution of the cartilage and bone densities (top-left), where $m_b \to 1$ as $t \to \infty$, and the evolution of the growth factor concentrations (cartilage top-right; bone bottom) at a point on the middle of the fracture gap. The time is presented in days.

4 The model due to Adam

The model due to Adam is based on the so-called critical size, which is defined as the smallest intra-osseous wound that does not heal. The model is applied to wound healing both on skin tissue and bone. Wound healing, if it takes place, proceeds by various processes: chemotaxis (cell movement up a concentration gradient), neovascularization, synthesis of extracellular matrix proteins and scar remodeling. Growth factors likely play a crucial role in bone regeneration as in the model due to Bailon-Plaza and Van der Meulen. Furthermore, the supply of oxygen is crucially important for the rate and quality of wound healing. Hence, angiogenesis, which is the formation of capillaries in the vicinity of the wound, is crucially important for the healing process. In the model due to Adam, it is assumed that around the wound periphery, there is a thin band of tissue where tissue regeneration takes place. This thin band is referred to as the active layer.
4.1 The model equations

Let \( \Omega_1 \) be a regular simply connected domain, surrounded by \( \Omega_2 \), which is surrounded by \( \Omega_3 \), with \( \Omega = \cup_{p=1}^{3} \Omega_p \cup_{p=1}^{2} (\overline{\Omega}_p \cap \overline{\Omega}_{p+1}) \), see Figure 10. The model for wound healing due to Adam is governed by the following equations:

\[
\frac{\partial c}{\partial t} - D \Delta c + \lambda c = P f(x,y), \quad \text{for} \ (x,y) \in \Omega, \tag{30}
\]

\[
\frac{\partial c}{\partial n}(x,y,t) = 0, \quad \text{for} \ (x,y) \in \Gamma, \tag{31}
\]

\[
c(x,y,0) = 0, \quad \text{for} \ (x,y) \in \Omega, \tag{32}
\]

Further \( f(x,y) = 1_{\Omega_2} = \begin{cases} 1, & \text{for} \ (x,y) \in \Omega_2 \text{ open domain}, \\ 0, & \text{for} \ (x,y) \in \Omega_1 \cup \Omega_3. \end{cases} \tag{33} \]

Here \( c \) is the concentration of a generic growth factor that stimulates cell division and hence healing of an epidermal or intra-osseous wound, and \( f \) can be seen as an indicator function on \( \Omega_2 \) over \( \Omega \). The term with \( \lambda c \) represents a decay of the growth factor. The PDE is supplemented with a homogeneous Neumann condition. Further, the outer boundary is denoted by \( \Gamma = \overline{\Omega} \setminus \Omega \). In the present study we use the assumption that the wound heals if and only if the growth factor concentration exceeds a threshold concentration \( \hat{c} \), at the wound edge \( W(t) = \overline{\Omega}_1 \cap \overline{\Omega}_2 \). Hence

\[
v_n > 0 \text{ if and only if } c(x,y,t) \geq \hat{c} \text{ for } (x,y) \in W(t), \tag{34}\]

This implies that in order to determine whether the wound heals at a certain location at \( W \) at a certain time \( t \), one needs to know \( c \) there. We assume that the healing rate is an affine function of the local curvature, \( \hat{k} \), at the wound edge \( W(t) \), hence

\[
v_n = -\frac{1}{2}(\alpha + \beta \hat{k})w(c(x,t) - \hat{c}), \quad \text{for} \ x \in W, \tag{35}\]

where \( \alpha, \beta \geq 0 \ (\alpha + \beta \geq 0) \). Here the function \( w(s) \) falls within the class of Heaviside functions, that is \( w(s) \in H(s) \), where \( H(\cdot) \) represents the family of Heaviside functions, for which we have

\[
H : s \rightarrow \begin{cases} 0, & \text{if } s < 0, \\ [0,1], & \text{if } s = 0, \\ 1, & \text{if } s > 0. \end{cases} \tag{36}\]

Until now, some mathematical analysis on the existence, uniqueness and conditions for (retarded) healing has been performed. Further, a Finite Element solution has been obtained where the level set method has been used to track the wound edge, \( W(t) \). To determine the concentration at the wound edge, local mesh refinement is
used in the vicinity of the wound edge to enhance the numerical accuracy. Some results are shown Figure 11, 12 and 13. For more details concerning this issue, we refer to Javierre [12]. In Figure 11, we see the initial shape of a hypothetical star-shaped wound. This peculiar geometry is only used to illustrate the potential of the level set method to treat this moving boundary problem. In Figures 12 and 13, we see the gradual breaking up of the wound, which illustrates the topological changes, which are undergone by the healing wound.

5 Conclusions

A model has been developed for bone-ingrowth into a prosthesis. Parameters that were used were obtained from literature and animal experiments. For small forces exerted, bone develops mainly near the interface, between the prosthesis and host bone, and close to the applied force. For large forces, bone develops far away from the interface. For a complete ingrowth, oscillatory forces are to be applied. Linear-linear (displacement-pressure) elements are applicable for this two-dimensional problem.

Further, an accepted model for the healing of a bone fracture has been presented and some results have been shown. A parameter sensitivity analysis has been shown.

Finally, a model for the healing of an intra-osseous wound has been described and some results were shown. The model, being simple in its nature, poses a challenging
Fig. 11 The initial shape of the star-shaped wound and a local mesh refinement around the wound edge.

numerical problem due to the incorporation of a moving boundary to model wound closure.

References

Fig. 12 The shape of the star-like wound once the initial wound area has healed for 40%.


Fig. 13 The shape of the star-like wound once the initial wound area has healed for 90 %. The topology of the wound changes due to breaking up.


