Comput. Methods Appl. Mech. Engrg. 253 (2013) 117–145

Contents lists available at SciVerse ScienceDirect

Comput. Methods Appl. Mech. Engrg.

journal homepage: www.elsevier.com/locate/cma

Numerical method for the bone regeneration model, defined within the evolving 2D axisymmetric physical domain

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ARTICLE INFO

Article history:
Received 14 February 2012
Received in revised form 5 July 2012
Accepted 28 September 2012
Available online 18 October 2012

Keywords:
Advection–diffusion–reaction system
Finite volume method
Method of lines
Bone regeneration
Moving boundary
Level set method
Embedded boundary
Distance and contact osteogenesis

ABSTRACT

A numerical algorithm, used to obtain a solution for a peri-implant osseointegration model is constructed. The model is formulated in terms of a system of three nonlinear coupled time-dependent advection–diffusion–reaction equations, which are defined within the irregular two dimensional physical domain, which evolves in time. The embedded boundary method and the level set function, which is approximated on the fixed regular rectangular grid, are used to track the changes of the irregular geometry of the physical domain. The method of lines is applied to separate the discretizations in time and in space. The advection, diffusion and reaction terms are discretized separately by means of the cell-centered finite volume method. The exact solution of the Riemann problem for the nonstrictly hyperbolic system without genuine nonlinearity, is obtained. An approach for the determination of the gradients of the unknown variables on the edges of the irregular control volumes is proposed. The explicit second order trapezoidal rule is used for the time integration, since it allows to maintain positivity of the solution, which is critical for the considered problem. Some results of the numerical simulations are presented. Contact and distance osteogenesis are predicted for micro-rough and smooth implants.

1. Introduction

Bone regeneration is an important biological process in the osseointegration of implants that are placed into bone tissue. The process of bone regeneration can be summarized roughly in the following way. Right after the placement of the implant into the bone, a blood clot forms within the wound site between the the implant and bone. Blood platelets attach to the implant surface and start releasing cytokines and growth factors. Osteogenic cells, recruited from the old bone surface, migrate towards the implant surface and differentiate into osteoblasts. Osteoblasts attach to a solid surface (the implant surface or the old bone surface) and release new bone matrix though a direct apposition on a pre-existing surface. Therefore, the concept of a newly formed bone front or bone-forming surface is used. The last phase of bone regeneration – remodeling of woven bone into mature bone – is not considered in the present model, although other works have widely analyzed this phase (see for example [1]). The aim of the mathematical model is to describe how changes of the environment within the peri-implant site, which are represented in the model by the initial and boundary conditions and by various sets of parameter values, influence the path of new bone formation.

In the present paper, a numerical approach for the solution of the mathematical model, which is constructed by Prokharau et al. [2] to simulate early stages of bone healing around endosseous implants, is described.

The model consists of a system of time-dependent advection–diffusion–reaction equations defined within the changing in time domain. The equations model migration of osteogenic cells from the old bone surface to the implant surface, cell differentiation and proliferation. These processes are assumed to be regulated by growth factors. Diffusion, decay and release of growth factors by osteogenic cells are also taken into account. The unknowns in the model are the densities of immature and mature osteogenic cells and the concentration of growth factors. New bone is formed through apposition on a pre-existing surface [3]. The advance of the ossification front, which was observed in experiments by Berglundh et al. [4], Abrahamsson et al. [5] and Meyer [6] is modeled by the movement of the boundary of the physical domain.

A robust method is constructed, which allows to get a numerical solution in case, when the physical domain is defined in 2D axisymmetric coordinates. First, an appropriate discretization in physical space, maturation space and time should be chosen, such

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http://dx.doi.org/10.1016/j.cma.2012.09.017

that a stable nonnegative solution of the nonlinear advection–diffusion–reaction equations will be obtained. The movement of the domain boundary, determined from the internal solution, is tracked with use of the level set method. The embedded boundary method and some auxiliary interpolation techniques are elaborated in order to adapt the finite volume discretization, which is in general defined on the structured rectangular grid, to the evolving irregular physical domain.

The present approach is developed for the solution of the considered mathematical model for peri-implant osseointegration. Due to specific features of the model and some requirements on the numerical solution, the current numerical method possesses some characteristics, which distinguish it from the existing numerical approaches for various problems in the field of biomechanics. The set of internal governing equations of the present model forms the nonlinearly coupled system of advection–diffusion–reaction type, which is a common type of the systems constructed in the classical models for bone regeneration [7,8]. An extended review of modeling approaches in the field of bone regeneration is presented in Geris et al. [9]. The Finite Volume Method (FVM) is usually used to get a solution for such problems. However, the classical models for bone regeneration are not of the moving boundary type. Hence, classically the governing equations are solved within fixed domains. For example, Amor et al. [7] employ a custom FVM on a fixed rectangular structured grid. In the present moving boundary model, we consider an irregular and time-evolving domain, within which the numerical solution is obtained. Therefore, an adaptation of the custom FVM for an unstructured grid containing non-rectangular control volumes near the domain boundary is presented in the current work, which distinguishes it from the numerical algorithm employed by Amor et al. [7]. Moving boundary problems are also considered, for example, in the models for wound healing [10] and tumor growth [11]. Javierre et al. [10] apply the level set method to track the evolution of the wound domain and the Finite Element Method (FEM) with linear elements to solve the internal diffusion-reaction equations formulated for the wound healing model. The finite element grid is updated in time in a similar way as it is done in our approach. Due to the presence of strongly hyperbolic terms in the governing equations, we use the finite volume method (FVM), which is more effective than FEM, where the solution is approximated with continuous functions. The FVM also makes it easier to meet a positivity requirement, which is essential for the current problem (see Section 3.1). The level set method is also used in Hogea et al. [11] for the simulation of tumor growth. The authors use the Finite Difference Method (FDM) to discretize the governing model equations within a fixed domain, which contains a time-dependent 'inner region' occupied by the tumor mass. Hence the equations are discretized on a structured uniform grid, which is not applicable for our model.

Therefore, in Section 2, a short description of the model for peri-implant osseointegration is given. The numerical algorithm, developed for the two dimensional physical domain is described in Section 3. The importance of positivity of the numerical solution is outlined in Section 3.1. In Section 3.2 the construction of the computational mesh within the irregular physical domain is presented. The level set function is used to track the temporal changes of the domain. The level set equation and the solution method are presented in Section 3.3. The equations for averaged quantities, derived from the initial governing equations, are constructed in Section 3.4. The discretization of the advection–diffusion terms is considered in Section 3.4.1 The approximation of the the reaction terms and the boundary conditions, and the time integration of the discretized ordinary differential equations are discussed in Sections 3.4.2 and 3.5, respectively. In Section 4, some results of the two dimensional numerical simulations are presented. Final conclusions are drawn in Section 5.

2. Mathematical model

The model for bone regeneration, constructed in Prokharau et al. [2], consists of three partial differential equations (PDEs), defined for the densities of immature and mature osteogenic cells, denoted as c_i and c_m, and for the concentration of growth factors g. The peri-implant interface Ω is divided into two subdomains Ω_s and Ω_b, which are occupied by soft connective tissue (fibrin network of blood clot) and new bone respectively. Osteogenic cells and growth factors are found within the soft tissue region. The boundary between subdomains Ω_s and Ω_b is the bone-forming surface. This interface moves in time and is denoted as $\Gamma(t)$. At time $t = 0$, the whole peri-implant region is filled with soft tissue, and the bone-forming surface $\Gamma(0)$ is defined as the external boundary of the whole peri-implant region Ω, which consists of the implant surface $\partial\Omega_i$ and the old bone surface $\partial\Omega_b$, i.e., $\Gamma(0) = \partial\Omega_i \cup \partial\Omega_b$ (see Fig. 1). New bone forms by apposition on the rigid surface, which is represented by surface $\Gamma(t)$. Hence, the interface $\Gamma(t)$ moves, so that subdomain Ω_b grows, and region Ω_s shrinks.

The approximate 2D geometry of the physical domain Ω shown in Fig. 1 corresponds to the cross-section of the 2D axisymmetric peri-implant region, which is depicted in Fig. 2.

Immature osteogenic cells within the soft tissue region differentiate into mature cells. Cell differentiation is introduced by means of maturation level (or differentiation level) a, which is considered as an additional dimension of the problem domain, and it takes values from 0 to 1. Fully non-differentiated cells are related to the differentiation level $a = 0$. If an immature osteogenic cell reaches differentiation level $a = 1$, it becomes a mature osteogenic cell.

The evolution of the unknown variables is determined by the following PDEs

$$\frac{\partial c_i}{\partial t} = \underbrace{-\nabla_s \cdot (-D_c \nabla_s c_i + \chi(g, c_{\text{tot}})\, c_i \nabla_s g)}_{\text{Migration}} \underbrace{- \frac{\partial}{\partial a}(u_b(g) c_i)}_{\text{Differentiation}} + \underbrace{A_c(g) c_i (1 - c_{\text{tot}})}_{\text{Proliferation}}, \tag{1}$$

$$\frac{\partial c_m}{\partial t} = -\nabla_s \cdot (-D_c \nabla_s c_m + \chi(g, c_{\text{tot}})\, c_m \nabla_s g) + u_b(g) c_i(\vec{x}, 1, t) + A_c(g) c_m (1 - c_{\text{tot}}), \tag{2}$$

$$\frac{\partial g}{\partial t} = \underbrace{\nabla_s \cdot (D_g \nabla_s g)}_{\text{Diffusion}} + \underbrace{E_c(g)\left(c_m + \int_0^1 \gamma(a) c_i \, da\right)}_{\text{Production}} - \underbrace{d_g g}_{\text{Degradation}}, \tag{3}$$

where $c_{\text{tot}} = \int_0^1 c_i da + c_m$ is the total density of osteogenic cells per unit of volume, and c_i is the density of immature cells per unit of

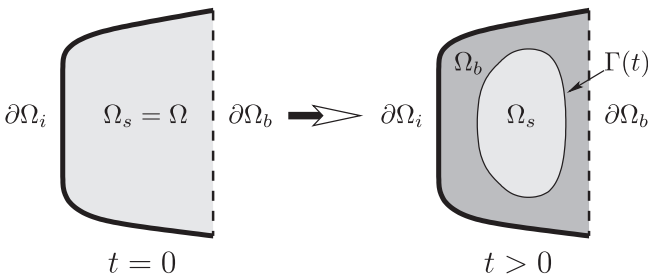

Fig. 1. Sketch of the problem domain Ω. The old bone and implant surfaces are denoted by $\partial\Omega_b$ and $\partial\Omega_i$ respectively. Subdomains Ω_b and Ω_s correspond to regions within the healing site, filled with newly formed bone and soft tissue, respectively. They are separated by the bone-forming surface, denoted by $\Gamma(t)$. At $t = 0$, soft tissue occupies the whole peri-implant space $\Omega_s = \Omega$, and the bone-forming surface is defined as the external boundary of the whole peri-implant region Ω, which consists of the implant interface and the old bone surface, i.e., $\Gamma(0) = \partial\Omega_i \cup \partial\Omega_b$.