Journal of Theoretical Biology 260 (2009) 13–26

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

Bone ingrowth on the surface of endosseous implants. Part 2: Theoretical and numerical analysis

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ARTICLE INFO

Article history:
Received 14 August 2008
Received in revised form
21 May 2009
Accepted 24 May 2009
Available online 12 June 2009

Keywords:
Osseointegration
Travelling wave
Groove
Finite element simulation

ABSTRACT

The study of osseointegration of endosseous implants is a matter of great interest, mostly due to the increase in the use of many types of implants in clinical practice. Bone ingrowth results from a complex process, in which mechanics and biology play a major role. A wide variety of diverse factors can affect the development of the process, such as the properties or geometry of the implant surface, the mechanical stimulation or the initial cell conditions. In the first part of this article [Moreo, P., García-Aznar, J.M., Doblaré, M., 2008. Bone ingrowth on the surface of endosseous implants. Part 1: mathematical model. J. Theor. Biol., in press] a model composed of a set of reaction–diffusion equations was proposed to simulate the formation of bone around implants, specially focused on the early stages of bone healing, that was able to contemplate the effects of surface microtopography. The goal of this second part is to use the model to analyse the effect of factors such as cell stimulation, the initial cell concentration in the host bone and the geometry of the implant. For this purpose, two different simplified versions of the model are here analysed theoretically and further insight is gained from the study of the stability of fixed points and existence of travelling waves. Additionally, numerical simulations by means of the finite element method have been performed to examine the osseointegration of a dental implant with grooves at the surface of the threads. Results obtained from the analysis and simulations show that the model can reproduce some features of peri-implant bone ingrowth.

1. Introduction

In Part 1 of this work a model to study the formation of bone around endosseous implants was presented (Moreo et al., 2008). This model is composed of a set of coupled nonlinear reaction–diffusion equations, one for each of the eight variables of the model: three types of cells (platelets, osteogenic cells and osteoblasts), two generic types of growth factors (secreted by platelets and secreted by osteogenic cells and osteoblasts) and the volume fractions of the extracellular matrix constituents (fibrin network, woven inmature bone and lamellar mature bone).

Compared to current literature this work presented a novel aspect: it aimed to model the first biological phenomena that occur after implantation. In particular, it reproduces the activation of platelets after contacting the surface of the implant. This activation depends on the level of plasma protein adsorption, which in turn is determined by the microtopography of the implant surface, among other factors (Park et al., 2001; Kikuchi et al., 2005). This scheme allows taking into account in a simple and efficient manner the effect of surface roughness on the whole osseointegration process. In fact, in Moreo et al. (2008) finite element simulations of bone deposition around a dental implant were performed and the model successfully reproduced the differences between contact and distance osteogenesis, which appear when the topography of the surface is changed from rough to polished (Berglundh et al., 2003; Davies, 2003).

The goal of the second part of this study is (i) to analyse the effect that the following factors have upon peri-implant bone ingrowth: initial cell conditions, implant geometry and different levels of cell stimulation; and (ii) to study how the composition of the matrix is altered as the ossification front propagates.

The first issue to be studied is the influence of the *initial cell concentration at the surface of the host bone* that depends on the type of bone one considers. It is known that there are significant differences between cortical and trabecular bone. For example, cortical bone presents higher mechanical properties than

DOI of original article: 10.1016/j.jtbi.2008.07.040
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0022-5193/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2009.05.036

trabecular bone, hence providing better primary stability for endosseous implants. However, trabecular bone presents other advantages, since the marrow that fills its pores is an excellent source of progenitor cells and contains a rich vasculature necessary for angiogenesis. Therefore, in order to fully evaluate the influence of the type of surrounding bone both mechanical and biological aspects have to be considered. Since this subject is rather complicated, we chose to focus on examining how the number of osteogenic cells at the surface of the host bone can drive the osteoconduction phase.

Secondly, we evaluate how the *implant geometry* can affect the formation of bone, not only by changing the stresses and strains of the surrounding tissue, what has been experimentally verified (Vandamme et al., 2007), but also by altering certain biological phenomena, such as growth factor diffusion or the direction of cell migration.

Thirdly, we also study how *the composition of the matrix* is altered as the ossification front crosses a region which is affected by the kinetics of the different phenomena involved in the ossification process.

Finally, we also look into the effect of *cell stimulation* upon the global process of peri-implant bone healing.

To address all these points, two different methods are presented. On the one hand, finite element simulations of bone deposition around a dental implant are performed. On the other hand, two different simplified versions of the mathematical model are proposed and examined analytically. This second procedure is an attractive option, since it allows acquiring useful information about the qualitative behaviour of specific parts of the model. This would be more difficult to do through numerical simulation, given the complexity of the model and the large number of parameters involved.

Specifically, the analysis of the simplified models will consist in the determination of the existence and stability of fixed points and the appearance of travelling wave-like solutions. Travelling waves are particular solutions of reaction–diffusion systems, consisting in the propagation through the domain of a wave, which travels at constant speed with constant shape. They are a recurring topic in mathematical biology since there is a vast number of biological phenomena in which a key element seems to be the appearance of travelling waves (see, for example, Murray, 2005). Their analytical study is useful, because it provides information about the speed of propagation of the wave and the concentrations of the variable before and after the propagation. In peri-implant bone healing, the invasion of the cavity between an implant and the host bone by osteogenic cells and the subsequent propagation of an ossification front are two examples of travelling wave-like phenomena.

The article is organised as follows. In Section 2, the main features of the model are briefly discussed. In Sections 3 and 4, two different simplified versions of the model are proposed and studied analytically. Next, two-dimensional numerical simulations of bone ingrowth around a dental implant with grooves at the surface of the threads are presented in Section 5. Finally, a discussion on the results is given in Section 6.

2. Mathematical modelling of bone ingrowth

In this section we describe the most relevant characteristics of the mathematical model for peri-implant bone ingrowth that was developed in Part 1 of the paper (Moreo et al., 2008). In this model a continuum approach is adopted and therefore reaction–diffusion equations are used to compute the spatio-temporal evolution of the volumetric concentration of each specie.

Specifically, the model has eight variables, which can be classified into three groups:

Cell densities: Three different types of cells are considered: platelets, osteogenic cells and osteoblasts, whose respective densities are denoted by c, m and b. The inclusion of platelets in the model is noteworthy, since it allows taking into account early stages of bone healing and the influence of the implant surface microtopography. Osteogenic cells and osteoblasts are included, since they are known to be the two most important types of cells involved in peri-implant bone ingrowth (Davies, 2003). By osteogenic cells here we mean mesenchymal stem cells, which have the potential to differentiate into a variety of mesenchymal tissues, such as bone, cartilage, tendon, muscle, marrow, dermis and fat.

Growth factors: A large number of growth factors and signalling molecules are known to intervene in the mediation of bone healing (Dimitriou et al., 2005). Hence, in order to obtain a tractable model some simplification has to be done. Since many growth factors have a similar effect in the process, it is possible to group them into families that have the same influence. In our case two generic families are distinguished: s_1 stands for the concentration of the growth factors secreted by platelets (PDGF, TGF-β and others), which are known to stimulate the proliferation and migration of osteogenic cells (Kark et al., 2006); s_2 represents the concentration of osteogenic growth factors (BMPs, TGF-β superfamily), which have a stimulating effect on the secretion of bone and on the proliferation of osteogenic cells (Linkhart et al., 1996).

Volume fractions of the matrix: The extracellular matrix can be composed of three different constituents: first, the fibrin network, whose volume fraction is denoted by ν_f, that is assumed to be the initial constituent of the matrix; second, woven or inmature bone, ν_w, that is laid down by osteoblasts and, third, lamellar or mature bone, ν_l, that comes from remodelling of woven bone.

Finally, the concentration of adsorbed proteins, p, appears in the formulation but is not a model variable but an input data, since its value is assumed to be known a priori as a function of the microtopography of the implant surface.

The model equations and a concise description of the biological interpretation of the model parameters can be found in Appendix A. The reader is referred to Part 1 of the paper (Moreo et al., 2008) for a more thorough discussion on the model.

3. Osteoconduction: analysis and simulation of a first simplified model

The goal of this section is to examine in detail the phenomenon of osteoconduction and, in particular, analyse how this process can be influenced by the level of cell stimulation and the number of osteogenic cells available at the surface of the host bone. We recall that osteoconduction consists in the invasion of the cavity between the host bone and the implant by osteogenic cells. In fact, it is the most important phase in bone healing (Davies, 2003), since the following stages of bone formation and remodelling critically depend on the speed of migration of osteogenic cells and the level of cell density achieved after osteoconduction.

Within this section, we are only interested in osteoconduction. Therefore we focus exclusively on the equations that are involved in this process. With this in mind, a reduced version of the model was obtained. From this model we can extract analytical information regarding the existence of fixed points and travelling waves. Finally, the performance of numerical simulations of the simplified model permits to gain further insight into the dynamic behaviour of the model.