Journal of Computational and Applied Mathematics 291 (2016) 76–84

Contents lists available at ScienceDirect

Journal of Computational and Applied Mathematics

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

A mathematical model of bone remodeling with delays

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ARTICLE INFO

Article history:
Received 31 July 2014
Received in revised form 12 November 2014

Keywords:
Delay differential equations
Bone remodeling
Mathematical modeling

ABSTRACT

In all vertebrates, bone tissue is constantly regenerated. As part of a very complicated process, osteoclasts reabsorb bone tissue and then osteoblasts reconstruct it. The process is regulated by several chemical signals, and there are also other cells involved. Mathematical models try to reproduce the main characteristics of the process while keeping it simplified. One of the most important part of the remodeling is the periodicity of the process. Here we will consider a simplified model consisting of three ordinary differential equations and introduce delays. The delays appear because there is a lag in the change of the population of osteoblasts due to changes in the population of osteoclasts, and vice versa. We study the properties of the system, including stability and bifurcation and find that the delay differential equations have Hopf bifurcations that give periodic solutions. We calculate numerical solutions to illustrate the behavior of the solutions.

1. Introduction

In vertebrates, the skeleton formed by bones provides support and protection to all other organs. Bone tissue is constantly being destroyed and reconstructed. Bone remodeling is a life-long process where mature bone tissue is removed from the skeleton (bone resorption) and new bone tissue is formed (ossification or new bone formation). This regeneration allows the bone to heal itself, for example in the case of fractures, and to adapt to stresses caused by normal activity that produce micro-damage. The study of these processes is of great importance especially to be able to understand and cure bone diseases such as osteoporosis and myeloma [1]. There are two types of cells that are mainly in charge of the reconstruction, osteoclasts and osteoblasts. An imbalance in the regulation of bone remodeling's two sub-processes results in many metabolic bone diseases, such as osteoporosis. The destruction and reconstruction of bone tissue is a periodic process that involves groups of cells working together in a basic multicellular unit (BMU). Spatial movement inside the BMU is small so models based on ordinary differential equations can be used. There are delays present due to the time it takes signals to be produced and transmitted and for cells to react to them. Bone remodeling is a very complicated process and not all mechanisms are known or completely understood.

It is known that there are two main groups of cells: osteoclasts and osteoblasts. Osteoclasts consist of precursor cells, active cells and dead cells. Osteoblasts consist of responding cells, active cells, differentiated cells (osteocytes and bone lining cells) and dead cells. There is a series of hormones and other signaling factors that control these processes including RANK, RANKL, OPG, vitamin D, calcitonin and estrogen, among others. For reviews of the factors involved see [2–4] and the references cited there. Clinical experiments, both in vitro and in vivo are very hard to do due to the complexity of the processes, the time periods involved and all the complications of doing experiments with living cells. As can be seen in the

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http://dx.doi.org/10.1016/j.cam.2014.11.025
0377-0427/

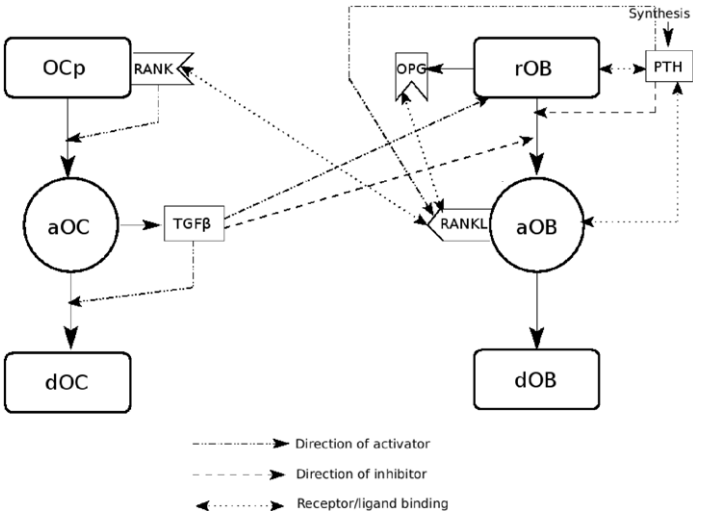

Fig. 1. Schematic diagram of main processes involved, OCp are the precursors of the osteoclasts, aOC, the active osteoclasts and dOC the dead osteoclast; rOB are the responding cells that transform into osteoblasts, aOB the active osteoblasts and dOB differentiated and dead osteoblasts. Continuous lines indicate the changes in the cells, dashed lines give the direction of positive effects, dotted–dashed lines the direction of negative effects, and dotted double arrows show receptor/ligand bindings.

above mentioned references, most of the work considers only one type of cells and one factor and the interaction between osteoblasts and osteoclasts is derived indirectly. Fig. 1 is a diagram of the principal interactions involved in bone remodeling, based on [5]. As seen from Fig. 1 there are factors that affect the same group of cells that produce them (autocrine factors) and factors that affect the other group of cells (paracrine factors).

Clinical work reports a wide range of values for the duration of the bone remodeling processes. For example, [2] mentions a duration of several weeks; [6] considers three phases: resorption lasting 2 weeks, reversal lasting 4 or 5 weeks and formation lasting 4 months; [7] found that the resorption activity in adult human bone takes approximately 3 weeks and the formation response 3–4 months.

There is clinical evidence of the presence of delays in the bone remodeling processes. Most of it relates to time delays in the reaction times of osteoblasts and osteoclasts to various factors. For example [8] reports that there is an increase in the bone forming surface 24 h after a single dose of PTH; [9] mentions delays of 1–2 h in the reaction of osteoclasts and osteoblast to PTH; [10] found that osteoclast increase did not occur for 10–15 days in mice and 6–8 days in humans after treatment with G-CSF. There is also clinical evidence that the differentiation of osteoblasts and osteoclast is not instantaneous. For example [10,11] state, that differentiation of osteoblasts into osteocytes takes 5–7 days, and 10–20 days, respectively. Furthermore, irradiation is used to treat cancer tumors and pain in bone. There are also cases of low level occupational exposure and of other medical irradiation. The irradiation delays the division of the bone cells and has other effects that last from hours to years [12,13]. There is wide range of the reported delays depending on the species, age and type of bone, but is clear that delays are present.

There are several mathematical models of bone remodeling. They all involve simplifications. Some of these are those of Komarova et al., 2003, [14], Lemaire et al., 2004, [5] and Rattanakul et al., 2011, [15]. For a review of mathematical models in bone remodeling see [16]. Lemaire et al. mention that they introduced a delay in their model but that the delay necessary to obtain a periodic solution was about two months, too large to be realistic. Several extensions of the model in [15] have included delays, for example, [17], but they involve four equations included the one for bone cells. Here we will work with Komarova's model since it is the simplest involving only three equations and also has periodic solutions in the absence of delays for certain values of the parameters.

The rest of the paper is organized as follows. In Section 2, the mathematical model of Komarova is introduced. The model with delays is presented in Section 3. Section 4 is devoted to some properties of delay differential equations and to numerical methods for delay and for finding bifurcation points. Section 5 contains several illustrative examples of the effect of delays on periodic solutions. Finally, conclusions are presented in Section 6 to end the paper.

2. Mathematical models

Komarova et al.'s model involves only three types of cells explicitly, osteoclasts, osteoblasts and bone tissue. The model is

$$\frac{du_1}{dt} = \alpha_1 u_1^{\gamma_{11}} u_2^{\gamma_{21}} - \beta_1 u_1 \tag{1}$$

$$\frac{du_2}{dt} = \alpha_2 u_1^{\gamma_{12}} u_2^{\gamma_{22}} - \beta_2 u_2, \tag{2}$$