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Influence of different mechanical stimuli in a multi-scale mechanobiological isotropic model for bone remodelling

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ABSTRACT

This work represents a study of a mathematical model that describes the biological response to different mechanical stimuli in a cellular dynamics model for bone remodelling. The biological system discussed herein consists of three specialised cellular types, responsive osteoblasts, active osteoblasts and osteoclasts, three types of signalling molecules, transforming growth factor beta (TGF-β), receptor activator of nuclear factor kappa-b ligand (RANKL) and osteoprotegerin (OPG) and the parathyroid hormone (PTH). Three proposals for mechanical stimuli were tested: strain energy density (SED), hydrostatic and deviatoric parts of SED. The model was tested in a two-dimensional geometry of a standard human femur. The spatial discretization was performed by the finite element method while the temporal evolution of the variables was calculated by the 4th order Runge–Kutta method. The obtained results represent the temporal evolution of the apparent density distribution and the mean apparent density and thickness for the cortical bone after 600 days of remodelling simulation. The main contributions of this paper are the coupling of mechanical and biological models and the exploration of how the different mechanical stimuli affect the cellular activity in different types of physical activities. The results revealed that hydrostatic SED stimulus was able to form more cortical bone than deviatoric SED and total SED stimuli. The computational model confirms how different mechanical stimuli can impact in the balance of bone homeostasis.

1. Introduction

Osteoporotic fractures are a major public health problem, with a high prevalence worldwide [1,2], especially in the hip joint and in particular are a serious problem in Brazil [3]. Hip fracture is the major consequence of osteoporosis among elderly people, in many Western nations, leading to chronic pain, disability, lower quality of life and lower mortality [1,4,5]. Many prospective studies have shown that bone mineral density (BMD) measurements are able to predict fracture [6].

Bone tissue is a dynamic system capable of changing its own density, in response to different biomechanical stimuli. The "mechanostat" theory of Frost states that bone adapts its strength to keep the strain, caused by physiological loads, in a certain interval [7]. Some authors consider that this interval lies outside of a "dead zone" and established that range was between 1000 and 2000 micro strain [8]. If strain is above this interval, new bone is formed, while below this interval, bone is resorbed. Osteocytes, are strain-sensitive cells and can transduce mechanical signals to groups of specialised cells, such as osteoblasts and osteoclasts, which are responsible for forming and resorbing bone matrix [9].

In the last decades, several research groups have worked in the development of new models, to describe the bone remodelling process, taking into account different stimuli in bone cell regulation, like mechanical strain, microdamage, cell biology, metabolic factors and other external contributions [8,10]. From a biochemical point of view, the first model correlated the differential activity of parathyroid hormone (PTH) as a regulator for bone resorption and formation. For example, Kroll et al. [11] found that an external administration of PTH can affect directly the time evolution of bone cells populations. Then, it was the time to demonstrate the role of hormones like autocrine and paracrine in the regulation of bone remodelling. Finally, a signalling pathway known as RANK/RANKL/OPG to regulate bone cells activities [10]. It was also found that this signalling pathway RANK-RANKL-OPG is an important regulation of the paracrine interactions between osteoblasts and osteoclast [12–15]. Wnt is a secreted family of

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glycoproteins and its pathway signalling, particularly through low-density lipoprotein receptor-related protein 5 (LRP5), is very important in the regulation of bone mass and strength. Also, the Wnt/β-catenin signalling is a normal physiological response to mechanical load, and that the activation of Wnt/β-catenin pathway can enhance the sensitivity of osteoblasts/osteocytes to mechanical loading [16,17]. Osteoprogenitor cells, stromal cells, osteoblasts, and osteocytes are the candidates for sensing and responding to mechanical stimulus. Different approaches were considered to describe the mechanisms through which bone cells are able to sense their mechanical environment, like direct matrix deformations [7,8], pressure and transient microdamage [8], accelerations, pressure waves, interstitial fluid flow, fluid drag forces, fluid shear stresses, or dynamic electric fields [18–20]. It is not clear, however, which of these stimuli are the most relevant for bone remodelling. Recently, authors developed numerical models that consider mechanoregulation functions that affect cellular activities based on the SED intensity [21]. The deviatoric and hydrostatic modes of SED interact with each other in a general anisotropic elastic material, as bone hard tissue is sometimes characterised [22]. However, in our study it was considered isotropic, linear elastic, material, so the hydrostatic and deviatoric modes of SED are non-interactive and the separation of the influence of both physical quantities is acceptable.

The aim of this study was to study the influence of different modes of the SED stimuli, in a cellular interaction model for the bone remodelling process. The main goal was to verify if the algorithm was able to predict the formation of the cortical mid diaphysis region, starting from a femur with homogeneous apparent density distribution. This is a common condition in bone remodelling simulations [23–25] and it was chosen to perform the validation of our model. The mechanical stimuli considered within the study, to update the physical properties of bone, were: SED, hydrostatic SED and deviatoric SED. Were also objectives of this study estimate the average thickness of cortical bone with different mechanical stimuli and calculate the mean apparent density of cortical and trabecular bone, after 1200 days of remodelling simulation, for each considered stimulus.

2. Equations of the model

The system of ordinary differential equations governing the coupling between osteoclasts and osteoblasts proposed by Lemaire et al. [13], has been improved by several authors [12–15,21,26].

The principal equations of the model are shown below, Eqs. (1–4) [21,26]. The variables R, B, C represent the concentrations of pre-osteoblasts, active osteoblasts and active osteoclasts, respectively, and the quantity BV represents bone volume. The variables vary with respect to time t and the first order ordinary differential equations of the system are displayed below.

$$\frac{dR}{dt} = D_R.\pi_C + P_R.R.\Pi_w - \frac{D_B}{\pi_C}.R \tag{1}$$

$$\frac{dB}{dt} = \frac{D_B}{\pi_C}.R - K_B.B \tag{2}$$

$$\frac{dC}{dt} = D_C.\pi_L - D_A.\pi_C C \tag{3}$$

$$\frac{d\mathrm{VB}}{dt} = K_{\mathrm{form}}.B - K_{\mathrm{res}}.C \tag{4}$$

In addition, the influence of mechanical stimulus, in the concentration of pre-osteoblast cells, is made by the following function:

$$\Pi_w = \Pi_{w_{\mathrm{equil}}}\left[1 + \lambda\left(\frac{w}{w_{\mathrm{equil}}} - 1\right)\right] \tag{5}$$

The terms related to RANKL are as follows:

$$\pi_L = \left(\frac{K_3}{K_4}\right)\frac{K_L^P \pi_P B}{1 + \frac{K_3}{K_4} + \frac{K1}{K_2 K_0}\left(\frac{K_0^P}{\pi_P + I_0}\right)}\left(1 + \frac{I_L + P_{\mathrm{RANKL_w}}}{r_L}\right) \tag{6}$$

$$P_{\mathrm{RANKL_w}} = K\left(1 - \frac{w}{w_{\mathrm{equil}}}\right) \tag{7}$$

The term related to PTH is:

$$\pi_P = \frac{\frac{I_P}{K_P} + \frac{S_P}{K_P}}{\frac{I_P}{K_P} + \frac{K_6}{K_5}} \tag{8}$$

and the term representing the influence of TGF-β is:

$$\pi_C = \frac{C + f_0 C^S}{C + C^S} \tag{9}$$

All parameters of the model are provided in Table 1, as well as a brief explanation of the units used.

The primary difference incorporated into Scheiner's model [21] was the use of two limits for remodelling, an upper (w_{sup}) and a lower (w_{inf}) limit, with an intermediate "dead zone" indicating a region of equilibrium [27]. The numerical values of the constants w_{sup} and w_{inf} and all parameters are shown in Mercuri et al. [26].

3. Strain energy density

When an elastic solid is deformed by an applied force, the work produced by the surface and body forces is stored within the solid under the form of deformation energy. For an ideal elastic body, this energy is completely recovered after removing the load [28,29]. The strain energy can be written as:

$$w = \frac{1}{2}\varepsilon_{ij}\sigma_{ij} \tag{10}$$

$$w = \frac{1}{2}\sigma\varepsilon \tag{11}$$

$$w = \frac{1}{2}\begin{pmatrix}\varepsilon_{xx} & \varepsilon_{xy} & \varepsilon_{xz}\\ \varepsilon_{yx} & \varepsilon_{yy} & \varepsilon_{yz}\\ \varepsilon_{zx} & \varepsilon_{zy} & \varepsilon_{zz}\end{pmatrix}.\begin{pmatrix}\sigma_{xx} & \sigma_{xy} & \sigma_{xz}\\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz}\\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz}\end{pmatrix} \tag{12}$$

$$w = \frac{1}{2}(\varepsilon_{xx}\sigma_{xx} + 2\varepsilon_{xy}\sigma_{xy} + \varepsilon_{yy}\sigma_{yy} + 2\varepsilon_{yz}\sigma_{yz} + \varepsilon_{zz}\sigma_{zz} + 2\varepsilon_{xz}\sigma_{xz}) \tag{13}$$

$$w = \frac{1}{2}(\varepsilon_{xx}\sigma_{xx} + \varepsilon_{yy}\sigma_{yy} + \varepsilon_{zz}\sigma_{zz}) + (\varepsilon_{xy}\sigma_{xy} + \varepsilon_{yz}\sigma_{yz} + \varepsilon_{xz}\sigma_{xz}) \tag{14}$$

The SED in the case of a plane stress state, $\sigma_{zz} = \sigma_{yz} = \sigma_{xz} = 0$, is defined by Eq. (15) [28]:

$$w = \frac{1}{2}(\varepsilon_{xx}\sigma_{xx} + \varepsilon_{yy}\sigma_{yy} + \varepsilon_{zz}\sigma_{zz}) + \varepsilon_{xy}\sigma_{xy} \tag{15}$$

in which σ_{xx}, σ_{yy} and σ_{xy} are the stress tensor components and ε_{xx}, ε_{yy} and ε_{xy} are the deformation tensor components, in the Cartesian coordinate system.

Any tensor can be decomposed into deviatoric and hydrostatic parts, so the strain tensor can be written as:

$$\varepsilon = \mathrm{hyd}(\varepsilon) + \mathrm{des}(\varepsilon) \tag{16}$$