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A comparative analysis between different approaches for simulating the bone remodeling

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Abstract. Bones can replace old and damaged tissue with healthy new tissue in a process called bone remodeling. This process is biologically described by coordinated activity between bone formation (osteoblasts) and bone resorption (osteoclasts) by following stages of activation, resorption, and formation. From a mechanical point of view, there is formation (resorption) where there are high (low) levels of mechanical stimulus. The literature presents several models for bone remodeling simulation, which can be classified as phenomenological, biological, mechanobiological and chemomechanobiological, among others. Thus, this work aims, through numerical simulations, to compare phenomenological and mechanobiological bone remodeling models. With the phenomenological model, the objective is to obtain the density distribution that characterizes a human femur. In turn, the mechanobiological model simulates the behavior of bone tissue by evaluating the biological feedback due to different levels of external stimulus applied. It should be emphasized that in this second approach, simulation time has real physical meaning. In the end, the bone tissue behavior was simulated using both approaches. The mechanobiological model provided a distinct behavior for cortical, trabecular, and osteoporotic bones under different load conditions. This was not visualized when we used the phenomenological approach. However, the phenomenological model characterized the femoral density distribution that qualitatively represents a radiography.

Keywords: *phenomenological models, mechanobiological models, finite element method*

1 Introduction

Bone tissue is an anisotropic and heterogeneous material that modifies its structure according to the biological feedback to mechanical loading and has interesting properties [1,2]. Bone has a stress limit similar to steel but it is three times lighter and ten times more flexible [1], due to its heterogeneity. Furthermore, the tissue is in constant change, where old and damaged tissue is replaced by new and healthy one in a process denominated bone remodeling (BR) [1-3]. From a biological point of view, BR is executed by a structure called BMU (Basic Multicellular Unit), composed of specialized cells, responsible for tissue resorption and formation, and known as osteoclasts and osteoblasts, respectively. The cells follow a coordinated activity divided into three phases: activation, resorption, and formation [4-6]. Another cell, called osteocyte, acts as a type of sensor in bone tissue, "feeling" the mechanical and biochemical stimuli, and is linked to the activation phase, where signals are sent to osteoclasts for resorption to begin [2]. From a mechanical point of view, bone tissue is formed and reabsorbed at places where there are high and low levels of mechanical stimulation, respectively. This happens until system homeostasis (equilibrium) [3]. The BR process is performed mainly on the surface of trabecular bone tissue. About 80% of BR is performed on this type of tissue, although it represents only 20% of the total amount of bone in the skeleton [7]. In cortical tissue, remodeling may occur on both endosteal and periosteal surfaces and also internally. On the surfaces, cortical BR is similar to what occurs in trabecular tissue. In the intracortical process, BR is characterized by the perforation through the cortical bone by osteoclasts followed by the filling of the cavity by the osteoblasts. This process is known as the Haversian remodeling system [7-9].

Many BR models can be found in the literature. The first type is the phenomenological model [1, 10-14]. In this model, a variable associated with external loading (mechanical stimulus), changes some tissue properties such as density and orientation. These properties are used to describe the mechanical behavior of bone tissue in the macroscale. In general, this stimulus is described in terms of stress, strain, strain energy density or other mechanical quantities. Variables related to the biological processes described above are not considered in the formulations. The use of this type of model relies on obtaining the distribution that characterizes the final structural morphology of the simulated bone. In this case, except for the final distribution, all distribution obtained throughout the simulation time can be discarded, since the simulations are started from homogeneous density distributions, which have no physiological significance. Despite some limitations, phenomenological models were the first class to be implemented, contributing to a better understanding of how the tissue would adapt to the mechanical conditions and providing property distributions that qualitatively characterize different bone morphologies.

A second approach to the description the BR is biological [3, 6, 15-17]. Unlike phenomenological models, this type of model describes tissue behavior through interactions between cells (osteoblasts and osteoclasts) and biochemical feedback mechanisms for bone balance regulation, without the influence of mechanical stimuli, such as the consideration of the OPG-RANK-RANK1 [3,6], of PTH administration [3,6,16] and the catabolic and anabolic effects caused by TGF-β [3,6], among others biochemical factos. In general, the biological iteration process is described by nonlinear differential equations. Cellular behavior is assessed by changing concentrations of receptors and ligands in the tissue. Thus, there is a positive or negative evolution of bone density or volume. This type of mathematical model provides an excellent structure, which allows the insertion of mechanical variables to describe cellular behavior considering a stimulus derived from mechanical action.

One type of mathematical model that unites mechanical and biological concepts is the mechanobiological [4,5,18-22]. In this case, remodeling starts from an external mechanical agent that regulates or inhibits cellular feedback (mechanotransduction). Unlike phenomenological, the mechanobiological models consider the biological real-time of the BR process. Therefore, this variable has an effective meaning at the end of the simulations. Phenomena such as damage accumulation and bone tissue mineralization (precipitation of mineral salts, especially calcium) are often included in the formulation of the behavior of the remodeling process.

This study aims to use numerical simulations to compare two approaches for simulating the BR process. The first approach is phenomenological and it is based on the adaptation of tissue according to mechanical stimulus at tissue level [11]. The second approach is mechanobiological and it considers mechanical stimulus and microdamage as drive variables of the process, acting on the activity of BMUs [4]. The simulations was performed in one and two-dimensional models using the Finite Element Method (FEM) in a structure implemented in Matlab R2015b package.

2 Material and methods

Here we describe the methodology utilized for the BR process simulations. Initially, it is present a simple description of the BR models used. Subsequently, the information regarding the one and two-dimensional cases is presented.

2.1 Description of bone remodeling models used in this study

Jacobs's [11] phenomenological model determines the bone response according to daily tissue level stress stimulus. The model considers that BR is performed into three situations: resorption, formation, and equilibrium. Formation (Resorption) will occur when the mechanical stimulus is greater (lesser) than the reference stimulus value. Equilibrium is characterized by the dead zone [23]. Simulation time is associated with the number of cycles but without any biological consideration. The isotropic model makes it possible to obtain a density distribution that characterizes the structural morphology of the human femur.

Rüberg's [4] mechanobiological model uses mechanical stimulus and microdamage as mechanical variables responsible for the remodeling process. The biological process is modeled in terms of equations that describe the activities of BMUs. The BR process follows the sequence A-R-F (Activation - Resorption - Formation) and it considers their respective time period. The change in bone volume is determined by the number of current BMUs and their history of evolution. The number of BMUs is determined according to the signal level (conductive variable determined from mechanical stimulus and microdamage) and active surface area. The model is capable of simulating microdamage accumulation and bone repair, as well as predicting the occurrence of stress fractures. Tissue mineralization is considered, acting on both the density value and bone tissue elastic modulus. This model allows simulating different tissue types (cortical, trabecular, and osteoporotic) under different conditions (disuse, equilibrium, and overload).

2.2 One-dimensional case

Initially, bone tissue behavior, using both approaches, is simulated to a point (unidimensional model). It considers different initial density values, which characterize osteoporotic (ρ = 0.50 g/cm^3), trabecular (ρ = 1.0 g/cm^3), and cortical (ρ = 2.05 g/cm^3) tissue. The behavior of each tissue is simulated under different mechanical stimulus conditions, which is considered constant over the simulation, but with intensities 0 (disuse), 1 (equilibrium) and 7 (overload) that multiply the reference mechanical stimulus value.

2.3 Two-dimensional geometry of the femur

FEM, implemented in the Matlab R2015b package, was applied to simulate a two-dimensional human femur model. The geometry is discretized using CST (constant strain triangle) finite elements for plane stress state, resulting in 3,184 elements and 1,714 nodes. We use a load condition (Fig. 1), which is widely used in the literature [1,10-14,24], that characterizes a gait cycle and it is divided in: (1) abduction, (2) when the foot touches the floor and (3) adduction. Load condition is balanced with Dirichlet boundary conditions applied to the middle section of the femoral diaphysis. Load condition is derived from two main sources: one from femoral head compression and one of traction at the greater trochanter. Table 1 presents the intensities and directions of each considered force and also the number of cycles used at each moment. We use the nodal stress field smoothing technique in both bone remodeling models to solve the checkerboard problem [25,26].

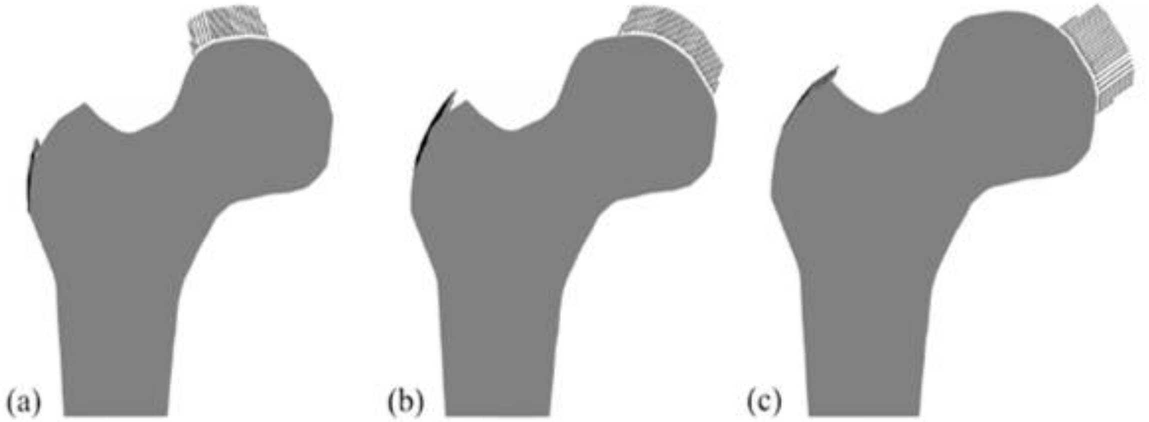

Figure 1. Load condition applied to the geometry of the human femur. Three moments are considered: (a) abduction, (b) touch of the foot on the floor, and (c) adduction.

Table 1. Magnitudes and orientations of the applied forces and number of cycles of each movement

Applied forces	Number of daily cycles	Compression		Traction	
		Magnitude (N)	Orientation (°)	Magnitude (N)	Orientation (°)
(a)	2,000	1,158	-15	351	-8
(b)	6,000	2,317	24	703	28
(c)	2,000	1,548	56	468	35

3 Material and methods

3.1 One-dimensional model

Figure 2 shows the behavior of bone tissues, for the phenomenological (Fig. 2a) and mechanobiological approaches (Fig. 2b), subjected to different levels of mechanical stimulation. Disuse and overload conditions presented excessive resorption and formation, respectively, for the phenomenological case. We note that minimum and maximum allowable values for bone density were obtained regardless of the simulated tissue. The difference is the number of iterations required to reach such values due to the initial density. Essentially, this is the behavior of BR phenomenological models. They describe the process as being dependent on the difference between current and reference mechanical stimuli.

For the mechanobiological model (Fig. 2b), the behaviors of materials are distinct. Cortical tissue feedbacks to overload stimulus by forming followed by slight bone resorption due to the microdamage accumulation. This characterizes material failure due to mechanical stress caused by mechanical stimulation. In the case of disuse, the resorption level is higher among the cases analyzed for the mechanobiological approach, but at lower levels than with the phenomenological model (Fig. 2a). For trabecular and osteoporotic tissues, bone response is similar to cortical bone, but at lower levels, both in formation and resorption. At the end of the simulations (Fig. 2b), a stable behavior is obtained. Also, we observe that bone resorption levels are much higher than those of tissue formation, as happens in reality. An individual who initiates coordinated physical activity will take longer to strengthen bone tissue and gain muscle than a second individual who, for example, has some bone tissue disease such as osteoporosis, which increases the porosity of bone tissue. That is, it is much harder to form than to reabsorb.

3.2 Two-dimensional model of the human femur

Figures 2c and 2d show the finite element mesh and density distribution obtained using the phenomenological approach for BR simulation using the two-dimensional geometry of the human femur. Numerical analyze was started with a uniform density distribution of 0.5 g/cm³ (Fig. 2c), as performed in several studies in the literature [1,11,12]. The remodeling model achieves a realistic morphological structure after 300 iterations (Fig. 2d). We note the formation of lateral and medial cortical layers along the femoral diaphysis, the proximal characteristic trabecular density distribution, and the formation of the Ward triangle in the femoral neck.

The mechanobiological model of BR simulates the process from a physiological point of view, considering the biological responses due to load condition and microdamage accumulation in the bone tissue. Thus, when starting the simulation with an unrealistic distribution and without any physiological aspect, it is not possible to obtain the correct characterization of the bone. The BR process is a complex system which is dependent not only on mechanical variables but also on genetic and metabolic factors. Therefore, the simulation using the mechanobiological model was started with the final density field (Fig. 2d) obtained using the phenomenological BR model, since it presents the main aspects that characterizes the femoral bone morphology.

Figures 2e and 2f show the initial and final results, respectively, of the 300-day simulation of bone tissue evolution using the mechanobiological model. We observe that the density distributions are practically the same since there are no modifications in the mechanical aspects. However, we note the influence of bone mineralization throughout the process on the final distribution (Fig. 2f).

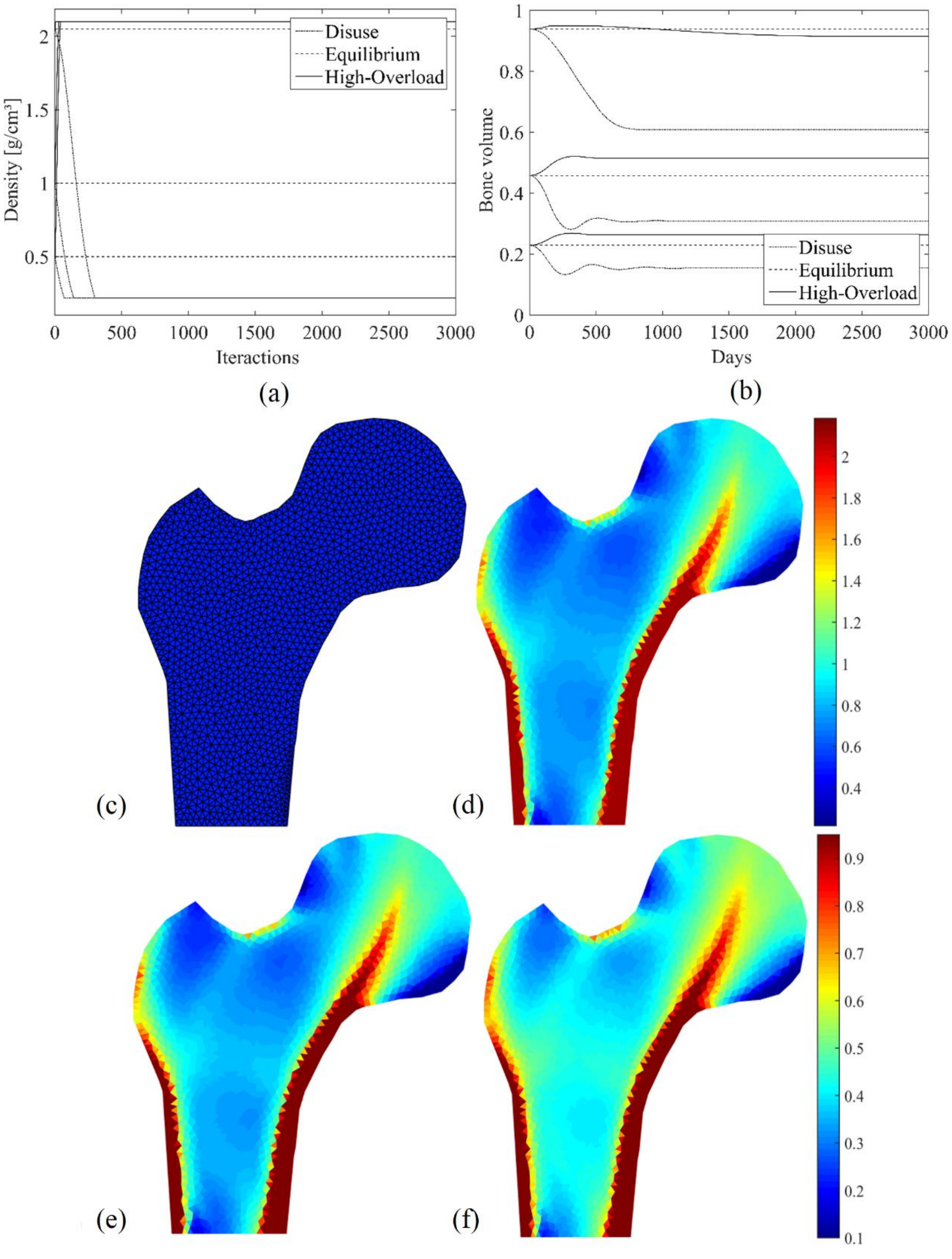

Figure 2. Results obtained using the (a, b) one-dimensional and (b, f) two-dimensional femur models for the (a, c, d) phenomenological and (b, e, f) mechanobiological BR approaches. (c, d) Density (g/cm³) and (e, f) bone volume distributions that characterize structural morphology.

4 Discussions

BR is a process of bone tissue renewal, where old and damaged tissue is replaced by a healthy new one. This is a complex system that involves coordinated cellular interactions between osteoblasts and osteoclasts, which is known as BMU. In addition, mechanical interaction is necessary since bone tissue is subjected daily to strains derived from external efforts. This stimulus acts on cells called osteocytes, which are responsible for mechanosensitivity and mechanotransduction in the BR process.

Several models are used to describe the process of tissue renewal. Among others, the phenomenological models are based on Wolff's law [1,10-14]. Biological models deal with the description of cells, ligands, and receptors in the human body [3,15-17]. Mechanobiological models describe cellular responses due to mechanical stimuli derived from external efforts [4,5,18,24]. Models range from approaches and simple descriptions, such as isotropic adaptation generated from the difference between the current stimulus level and a reference value, to more complex systems where there is a description of bone tissue anisotropy [1,18], BMU [4,5,18,24], of cell population variations over time [3,6,17], mechanical and biological interactions [4,5,18], chemical-mechanical-cellular interactions [24,27,28], among others. The use of each model, whether simple or complex, depends on the need of the user.

The phenomenological model used allows the user to understand Wolff's law [29] which says that bone tissue adapts to the stress to which it is subjected. Locations with a higher (lower) level of mechanical stimulation form (resorb) more bone tissue until the process is reached. Using this model is possible to obtain the morphological distribution of the femur (Fig. 2d), which provides a reasonable distribution when it is compared to a radiograph. However, the intermediate results of density fields of the simulation before the final iteration (equilibrium) should be discarded, since that the numerical simulation starts with a homogeneous, unrealistic field, and without any physiological meaning. An important point is that this type of model is not able to predict the actual rate of bone tissue remodeling (Fig. 2a), and the entire biological process of the process is disregarded.

The mechanobiological approach allows a better understanding of the biological bone feedback due to the applied mechanical stimulus. Unlike the phenomenological model, where the time increment of the simulation has no relation to the real-time of the BR process, when a mechanobiological model is used, the time has real meaning. With this approach, it is possible to simulate the bone tissue behavior under the effect not only of changes in the mechanical environment (such as after the installation of a prosthesis) but also in the chemical environment or the direct effect of mechanics on the distribution of biochemical substances and bone cells, which may be useful for virtual drug testing or for analyzing the long-term effect of a disease. As the model used, it is possible to simulate the behavior of bone tissue with different density and stimulus levels, as well as to evaluate variables such as microdamage accumulation, which is very important and may cause material failure (Fig. 2b). For the simulation of the BR in the femur geometry, the behavior is evaluated according to the microdamage and mechanical stimulus levels derived from the applied load condition. Without changing the boundary conditions, the tendency is that there is a mechanical equilibrium condition, which allows the properties to be maintained without large variations. However, as can be seen in Fig. 3d, bone tissue mineralization (bone calcification) influences the process, generating small variations in bone volume distribution, which cannot be verified with the first approach.

5 Conclusions

This study aimed to simulate the BR process using two distinct approaches (phenomenological and mechanobiological) in order to compare the results obtained. Both situations allow an understanding of mechanical and biological phenomena that are linked to the process. Importantly, for the phenomenological model, the idea is to obtain the density distribution that characterizes the femur. For mechanobiological, the objective is to simulate bone tissue behavior (with or without changes in boundary conditions), evaluating the biological response concerning the external stimulus generated, since the simulation begins of a heterogeneous distribution. Moreover, in this approach, the simulation time has real meaning.

The idea of this study is to show the advantages and disadvantages of each approach, and it is up to the user to decide which strategy is best for the simulated problem. Jacob's [11] model allows a quick simulation with an appropriate result to obtain the final morphology. When the simulation is performed aiming at the bone tissue behavior according to different stimuli and the simulation time has a real meaning, the Rüberg's [4] model is more adequate.

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