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Mathematical Modeling and Analysis of Force Induced Bone Growth

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Abstract— **Bone is a dynamic living tissue that undergoes continuous adaptation of its mass and structure in response to mechanical and biological environment demands. Studies of bone adaptation have focused on metabolic or mechanical stimulus, but mathematical models of bone adaptation considering both, are not available by now. In this paper, we propose a mathematical model of bone adaptation during a remodeling cycle due to mechanical stimulus with the introduction of osteocytes as mechanotransducers. The model captures qualitatively very well the bone adaptation and cell interactions during the bone remodeling.**

keywords: Mathematical modeling, Bone cells, Mechanotransduction, NO, PGE_2, Bone adaptation.

I. Introduction

Bone is a dynamic living tissue that adapts its mass and structure due to mechanical and biological changes. Recent reports have shown the ability of bone cells to respond to mechanical stimulus. The objective of this paper is to derive a mathematical model for force induced bone growth.

At cellular level, bone consists of highly specialized cells for the metabolic mechanisms [5], [14], [23]. Osteoclasts (OCs), are multinucleated cells with hematopoietic origin that resorb bone [16], [19], [23]. Osteoblasts (OBs), are the bone formers which differentiate from mesenchymal precursors. Osteocytes (OCys) are matured OBs which remain buried in the bone matrix when mineralization occurs.

In the mechanostat theory [6], bone is presented as a feedback system where bone strength, mass, structure and architecture is adapted due to mechanical demands and local factors [22]. This adaptation is obtained by a continuous bone resorption and formation activity. In bone modeling, the bone formation and resorption takes place at different sites, leading to a bone morphology change. In bone remodeling, formation and resorption are executed at the same site by a basic multicellular unit (denoted by BMU). The balance of these activities ensure the maintenance of bone mechanical integrity [6], [8], [9], [11], [12]. However, the mechanotransduction is not captured. Osteocytes, located and distributed in bone tissue, have been suggested to play an important role in mechanotransduction [10], [25], [26].

By now, only few attempts to mathematically model the interactions between bone cells during the bone remodeling cycle have been proposed. Komarova et al. [11] proposed a mathematical model of the bone remodeling cycle considering autocrine and paracrine interactions among OBs and OCs. Moroz et al. [15] introduced OCys in the BMU control regulation loop. Rattanakul et al. [21] proposed a model with the Parathyroide Hormone (PTH) as a regulator of bone formation and resorption. Lemaire et al. [12] proposed the RANK-RANKL-OPG pathway to control the interactions between OCs and OBs during the bone remodeling cycle. These mathematical approaches offer cell based models to study BMU behavior during a remodeling process considering metabolic factors. However, in order to improve the understanding of bone adaptation it is important to include the biological and the mechanical influences.

In this article we present a mathematical model of bone adaptation introducing osteocytes as mechanotransducers. In addition, biological effects are used to describe bone adaptation and remodeling induced by mechanical stimuli.

II. Proposed Model

Mathematical modeling provides a useful approach to integrate the existing knowledge of the bone cells regulation and interactions, to elucidate the bone formation and resorption response to mechanical demands.

Recent works have shown the importance of the RANK-RANKL-OPG pathway in the cellular regulation of bone remodeling [11], [12], [14]. OBs express RANKL and OPG which influence osteoclastogenesis. OCs differentiation is stimulated by RANKL. Osteoprotegerin (OPG) inhibits bone resorption by diminishing the interaction of RANKL with its receptor RANK (expressed by OCs) In addition, the transforming growth factor β (TGF-β) promotes bone formation by stimulating osteoblasts differentiation [14], [12], [11]. PTH promotes bone resorption inhibiting OPG and increasing RANKL expression [14], [12], [21]. The nitric oxide (NO) and prostaglandin E_2 (PGE_2) factors have been reported to promote bone formation by inhibiting osteoclastogenesis [1], [2], [3], [4], [10], [17], [18], [24], [27], [28], [29]. Regulation of bone remodeling is complex and involves simultaneous and concurrent actions of a large number of metabolic and mechanobiologic factors. In our model we try to capture the described effects.

A. Basic Bone Adaptation and Mechanotransduction

The scheme of the proposed generalized bone adaptation model is shown in Fig. 1. There is one main feedback loop for the bone strength and structure maintenance regulation system. This loop considers a mechanical stimuli input acting on the bone tissue. In this loop the osteocytes are the key elements introduced in the model.

The metabolic part of the model builds the inner loop of bone formation/resorption activities that is activated through

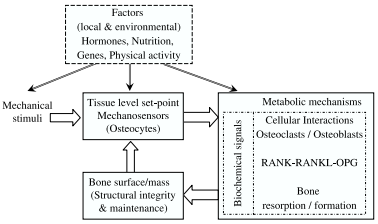

Fig. 1. Schematic representation of the basic structure of the model.

biochemical signals. Bone adaptation is the result of resorption and formation activities due to modeling or remodeling. Bone remodeling is achieved by a coupled activity between OCs and OBs [6], [11], [12], [14], [22]. Thus, it is required to model the synchronized cell activities of bone resorption and formation during a remodeling cycle. The model used for describing the interactions between osteoclasts and osteoblasts population during a remodeling cycle is based on the proposed in [12].

In the proposed model, the bone structural and mechanical integrity is obtained keeping the bone deformation, induced by mechanical loads, close to a predefined set point.

B. Mathematical Model development

In [12], a mathematical model for the cellular interactions between osteoblasts and osteoclasts during bone remodeling is proposed. However, this model does not include the bone adaptation due to mechanical stimuli. Thus, we propose a generalized model to capture the bone adaptation during a remodeling cycle initiated by a mechanical stimuli using the osteocytes as the key mechanotransduction elements.

In the proposed model, bone is considered as an ideal cylinder with the circular area A_B,

$$A_B = r_B^2 \pi. \tag{1}$$

The bone radius r_B, describes the bone "growth" with dynamics:

$$\frac{dr_B}{dt} = \frac{-k_{res}}{X_c} x_c + \frac{k_{for}}{X_b} x_b + \frac{1}{X_y} x_y - k_{rB} r_B. \tag{2}$$

The radius r_B depends on the activity of osteoclasts population x_c with resorption rate k_{res}, the active osteoblasts population x_b with formation rate k_{for} and the osteocytes population x_y. The parameters X_c, X_b and X_y correspond to nominal values for osteoclasts, osteoblasts and osteocytes.

The osteocytes population depends on the osteoblasts population differentiation. It is given by:

$$\frac{dx_y}{dt} = k_{byp}(x_b - X_{bss}) - k_{yd}(x_y - X_{yss}). \tag{3}$$

Constant rates of osteoblasts differentiation and osteocytes apoptosis are assumed. They are denoted by k_{byp} and k_{yd}, respectively. The osteocytes apoptotic behavior due to fatigue or microdamage is not considered.

By mechanotransduction, osteocytes sense stress describing a force stimuli F_{sti} to release NO and PGE_2 factors [1], [4], [10], [17], [27], [28], [29]. The F_{sti} depends on the osteocytes x_y population located on the bone area,

$$F_{sti} = \frac{F_s x_y}{(1 + exp(-(k_{Fs} F_s + k_y x_y)))}. \tag{4}$$

The mechanical load F_a is applied axially on the bone area A_B producing a stress magnitude F_s,

$$F_s = \frac{F_a}{A_B}. \tag{5}$$

The nitric oxide dynamics x_{no} depends on the force stimuli, a constant rate of NO released by osteocytes k_{yno}, a degradation term with constant rate k_{nod} and an external input X_{noe},

$$\frac{dx_{no}}{dt} = k_{yno} F_{sti} - k_{nod} x_{no} + X_{noe}. \tag{6}$$

The PGE_2 dynamics x_{pge} is influenced by the force stimuli and osteocytes with constant rate k_{ypge}. In addition, PGE_2 is increased by NO with constant rate k_{nopge}. A degradation term with constant rate k_{pged} and an external input X_{pgex} are also considered. The PGE_2 dynamics is given by

$$\frac{dx_{pge}}{dt} = k_{ypge} F_{sti} + k_{nopge} x_{no} - k_{pged} x_{pge} + X_{pgex}. \tag{7}$$

In the model, local factors NO and PGE_2 used the RANK-RANKL-OPG pathway to influence the OCs and OBs interactions. NO increases the OPG levels when mechanical loads are applied to the bone. OPG depends on x_r, a degradation term, an external input and TGF-β receptor occupancy π_c [12]. The OPG dynamics x_{opg} is described by

$$\frac{dx_{opg}}{dt} = K_o^p \pi_c x_r + I_o + k_{nopg} x_{no} - k_{opgd} x_{opg}. \tag{8}$$

NO decreases RANKL levels in the presence of mechanical loads. RANKL x_{kl} is influenced by the RANK-RANKL occupancy ratio and an external input [12]:

$$\frac{dx_{kl}}{dt} = r_l + I_l - k_{nokl} x_{no} - r_l \frac{1 + \frac{k_1}{k_2} x_{opg} + \frac{k_3}{k_4} K}{K_l^p \pi_p x_b} x_{kl}. \tag{9}$$

Furthermore, PGE_2 has been reported to promote bone formation [1], [4], [20]. Thus, the responding osteoblasts x_r are increased by PGE_2,

$$\frac{dx_r}{dt} = D_R \pi_c - \frac{D_B}{\pi_c} x_r + k_{pger} x_{pge}. \tag{10}$$

The OBs and OCs dynamics remain as proposed in [12]:

$$\frac{dx_b}{dt} = \frac{D_B}{\pi_c} x_r - k_B x_b \tag{11}$$

$$\frac{dx_c}{dt} = D_c \pi_L - D_A \pi_c x_c. \tag{12}$$

The osteoblasts dynamics x_b is influenced by x_r and the TGF-β receptor occupancy π_c. The osteoclasts population x_c depends on TGF-β receptor occupancy and the RANK occupancy ratio π_L [12].

TABLE I

MODEL PARAMETER VALUES

Symbol	Reference Value	Description
k_{rB}	1.000e0 day^{-1}	Radius degradation rate
k_{res}	10.000e-3 mm/day	Rate of bone resorption
k_{for}	1.000e-3 mm/day	Rate of bone formation
F_{ass}	1.000e0 N	Force reference value
X_{rss}	7.734e-4 pM	ROBs reference value
X_{bss}	7.282e-4 pM	OBs reference value
X_{css}	9.127e-4 pM	OCs reference value
X_{yss}	7.300e-3 pM	OCys reference value
k_{byp}	1.000e-1 day^{-1}	OCys production rate
k_{yd}	1.000e0 day^{-1}	OCys degradation rate
k_{yno}	2.000e4 $mm^2 day/dyn$	NO released rate
k_{nod}	1.000e3 day^{-1}	NO elimination rate
k_y	1.000e0 pM^{-1}	OCys influence rate
k_{Fs}	1.000e0 mm^2/N	Stress influence rate
X_{noe}	0.000e0 $pM day^{-1}$	NO external administration rate
k_{ypge}	1.000e2 $mm^2 day/dyn$	PGE_2 released rate
k_{pged}	1.000e2 day^{-1}	PGE_2 elimination rate
k_{nopge}	1.000e0 day^{-1}	PGE_2 rate increased by NO
X_{pgex}	0.000e0 $pM day^{-1}$	PGE_2 ext administration rate
k_{nopg}	1.000e1 day^{-1}	Rate of OPG increased by NO
k_{opgd}	3.500e-1 day^{-1}	Rate of elimination of OPG
k_{nokl}	1.000e2 day^{-1}	Rate of RANKL decreased by NO
k_{pger}	1.000e-4 day^{-1}	Rate of ROB increased by PGE_2

III. PARAMETER IDENTIFICATION AND ADAPTATION

A first group of the model parameters has a physicochemical meaning. They are kept constant. The values of k_{res}, k_{for}, k_{byp}, k_{opgd} are given in literature. The remaining parameters are adjusted considering experimental observations reported [1], [2], [3], [4], [6], [7], [10], [12], [14], [18], [24], [27], [28], [29]. A second group of parameters are external inputs used to change the physiological environment. A detailed description of the parameters can be found in [13].

The parameter values in steady state are defined keeping the ratio x_c/x_b in 1.25 for a healthy condition and increasing up to 5 for an osteoporotic condition [13]. Table I gives the parameter values used.

IV. PRELIMINARY RESULTS

The reference force value is set to 1N. Preliminary results are obtained applying a force beginning the day 200. The force magnitudes inputs are increased in 1N, 5N and 10N for the use case (shown in solid lines), and decreased in 0N, -0.5N and -1N for the disuse case (shown in segmented lines). Preliminary results are shown in Fig. 2 and 3. There is a transient, due to initial conditions, but the steady state is achieved after 50 days. Bone diseases conditions are also simulated to study the bone adaptation response. The force input is increased in 1N and -1N. Results are shown in Fig. 4.

Fig. 2 shows bone cells response during the bone remodeling cycle initiated by mechanical stimuli. There is a proportional response of x_r, x_b and x_y population when the mechanical force level is increased or decreased, indicating that bone cells adapt their activity to compensate the change of the load level. If an increased mechanical force is applied x_c is diminished by the NO and PGE_2 inhibition effect. Concerning the x_c/x_b ratio, it reaches a lower value for the use case, and shows an increment for the disuse case. This anabolic and catabolic effect is also observed in the bone turnover $x_c + x_b$.

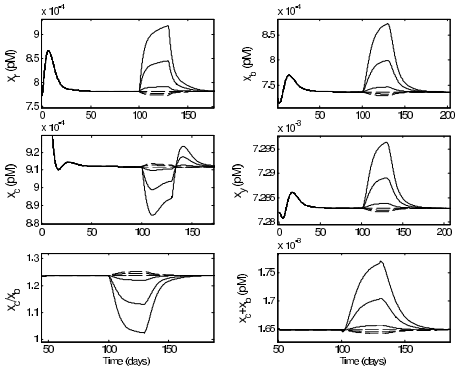

Fig. 2. Bone cells during the remodeling cycle.

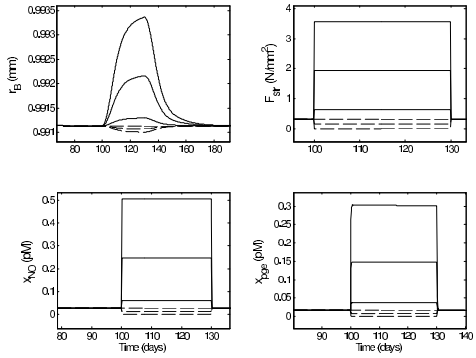

Fig. 3. Bone variables during the remodeling cycle.

Fig. 3 shows the bone radius, the force stress and the local factors. NO and PGE_2 show a proportional response to the mechanical stimuli. NO presents a very fast dynamic which is activated by the mechanical force, but PGE_2 remains longer in the bone microenvironment after the mechanical force has been removed. As can be seen, the bone remodeling cycle takes around 100 days for completing bone formation and resorption activity. The radius r_B changes in the order of μm. The resulting stress changes, influenced by the change in the area.

Fig. 4 shows the response when a bone disease condition is considered. Specifically, BD0 corresponds to a healthy condition, BD1 corresponds to a Estrogen deficiency condition, BD2 corresponds to a Vitamin D deficiency, BD3 represents the response for a senescence condition and BD4 corresponds to a Glucocorticoid excess condition. Further details can be found in [13]. The ratio x_c/x_b increases from 1.25 (healthy condition) to 5 (osteoporotic condition). As can be seen the bone remodeling cycle is initiated by the mechanical stimuli in the presence of the bone disease condition. These results are comparable with the ones obtained by Lemaire et al. [12], which match clinical observations.

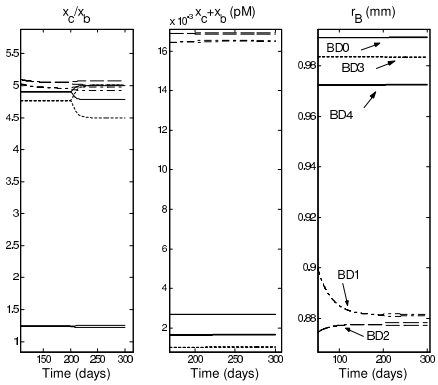

Fig. 4. Bone diseases condition during the remodeling cycle.

V. Discussion and Conclusion

In this article we have developed an expanded model for bone adaptation incorporating the local effects of metabolic and mechanical factors. Our model introduced osteocytes as part of the bone adaptation control loop. Osteocytes are the mechanotransducers which activate the bone resorption and bone formation activity as a response of a mechanical force stimulation.

Preliminary results show that the bone adaptation during a remodeling cycle promoted by mechanical forces matches clinical and experimental observations. In this sense, physical activity among other factors can be used to capture their influence on bone adaptation and thereby the development of new therapeutic treatments to bone diseases can be achieved.

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