A Mathematical Model of Bone Formation and Resorption: Effect of Calcitonin

Chontita Rattanakul and Sahattaya Rattanamongkonkul

***Abstract*—**We propose here a nonlinear mathematical model of bone formation and resorption process accounting for the concentration of calcitonin, the population of osteoclastic cells, and that of the osteoblastic cells. Singular perturbation technique is then applied to the model in order to obtain the conditions on the system parameters for which a periodic solution exists. Numerical simulation of the model is also carried out. The result shows that the model can exhibit a periodic behavior which has been observed in the secretion pattern of calcitonin in normal individuals. The model is then modified to investigate the effects of estrogen and calcitonin treatments in osteoporosis patients.

***Keywords*—**bone formation, bone resorption, calcitonin, mathematical model.

I. Introduction

BONE remodeling is a dynamic, life-long process in which mature bone tissue is removed from the skeleton by osteoclastic cells and new bone tissue is formed by osteoblastic cells. It can be viewed as a step by step process as follows: osteoclasts appear on a previously inactive surface of bone and then, they excavate a lacuna on the surface of cancellous bone or resorption tunnel in cortical bone. Osteoclasts are subsequently replaced by osteoblasts and finally, osteoblasts refill the resorption cavity [1]. After osteoblasts have laid down their protein-based matrix, known as osteoid, they bury themselves in bony matrix, becoming osteocytes, or revert to an inactive cell form and line the bone surfaces as surface osteocytes or resting osteoblasts [2]. Bone imbalance can result if the osteoclasts produce an excessively deep resorption space, if the osteoblasts fail to completely refill the resorption space, or if both events occur [1]-[2]. If a remodeling imbalance exists after the completion of a remodeling cycle, the degree of bone loss will be exacerbated which leads to osteoporosis [3].

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The purposes of bone remodeling are to regulate calcium homeostasis, to repair micro-damaged bones (from everyday stress) and also to shape and sculpture the skeleton during growth. As a result, bone is added where needed and removed where it is not required. In the first year of life, almost 100% of the skeleton is replaced [4]-[6]. In adults, remodeling proceeds at about 10% per year [4]-[6]. If a remodeling imbalance exists after the completion of a remodeling cycle, the degree of bone loss will be exacerbated and that leads to osteoporosis [4]-[6]. Therefore, the knowledge of how these cell types of bone are regulated and how their proliferation and differentiation are stimulated is most important to our understanding of factors regulating their number and activity in healthy or diseased human.

Osteoporosis represents a major health disorder of bone remodeling, requiring costly medical treatments. It is a bone disease where bone mass decreases over time resulting from a net increase of bone resorption over bone deposition. A research by Rosenberg [6] indicated that in osteoporosis, the overall density of the skeleton decreases with thinning of the trabeculae and a loss of interconnections that lead to microfractures and eventually the collapse of the vertebral bodies. As a result, bones become brittle and fracture easily. Moreover, osteoporosis causes women die of hip fractures more than cancer of ovaries, cervix, and uterus combined because it is disease which occurs without symptoms [5].

Several pharmacological treatments have been developed for osteoporosis such as calcium and/or vitamin D, estrogen, selective estrogen-receptor modulators (SERMs), bisphosphonates, calcitonin (CT) and parathyroid hormone (PTH) [7]. Considerations of safety and patient compliance are particularly important in the choice of drug therapy [7]. Since there are no major safety or compliance concerns with calcitonin (salmon calcitonin), calcitonin is then considered to be a potent therapy for osteoporosis. Although calcitonin has a relatively long duration of effect, its elimination half-life is short and its residence time in bone is limited [7]. No specific antidote is necessary and there is no known food or relevant drug interactions and no GI or renal issues that impose restrictions on its use [7].

Prevention and reversal of bone loss require an in-depth understanding of the remodeling process in bone, the mechanism of bone formation and resorption, including hormonal action such as parathyroid hormone (PTH), calcitonin (CT), estrogen or interleukin-6 (IL-6).

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Although there are several attempts to propose a suitable mathematical model to describe bone remodeling process, none of them concentrate on the effect of calcitonin on bone remodeling process. Therefore, we will develop a mathematical model to describe bone remodeling process based on the effect of calcitonin.

II. MODEL DEVELOPMENT

We now proceed to construct a nonlinear mathematical model to describe bone remodeling process based on the effect of calcitonin as follows. Let us denote the level of CT above the basal level in blood at time t by $X(t)$, the number of active osteoclasts at time t by $Y(t)$, and the number of active osteoblasts at time t by $Z(t)$. At first, we assume that the high levels of osteoclast and osteoblast precursors lead to the high levels of active osteoclastic and osteoblastic cells, respectively, which result from the differentiation, and activation of their precursors.

Calcitonin (CT) is synthesized by parafollicular C cells of the thyroid gland [8]. The secretion of CT is stimulated by elevated serum calcium level. CT inhibits bone resorption by inhibiting osteoclastic activity resulting in decreasing serum calcium. The decrease in blood calcium produced by CT is greatest when osteoclastic bone resorption is most intense and is least evident when osteoclastic activity is minimal [8]. Interaction of CT with receptors on the osteoclast surface promptly increases cAMP formation, and within minutes the expanse and activity of the ruffled border diminishes [8]. Osteoclasts pull away from the bone surface and begin to dedifferentiate. Synthesis and secretion of lysosomal enzymes are inhibited. In less than an hour fewer osteoclasts are present, and those that remain have decreased bone-resorbing activity [8]. Although osteoclasts express very high numbers of receptors for CT, they quickly become insensitive to the hormone because continued stimulation results in massive down-regulation of receptors [8]. Therefore, the equation for the rate of calcitonin secretion is then assumed to have the form

$$\frac{dX}{dt} = \left(\frac{a_1 + a_2 Y}{k_1 + Y} \right) - b_1 X \tag{1}$$

where the first term on the right-hand side of (1) represents the secretion rate of CT from parafollicular cells in the thyroid gland. The last term is the removal rate constant b_1. a_1, a_2 and k_1 are positive constants.

Osteoclasts are multinucleated giant cells that originate from hemopoietic stem cells of the monocyte/macrophage lineage [9]. Osteoclastic differentiation and activation are regulated principally by osteoblasts [10],[11]. There are several factors that regulate osteoclast formation and differentiation such as osteoclast differentiation factor (ODF) which was found to be identical to osteoprotegerin ligand (OPGL), TNF-related activation induces cytokine (TRANCE), receptor activator NF-kB ligand (RANKL) [10],[12],[13]. Therefore, the dynamics of the active osteoclastic population can be described by the following equation

$$\frac{dY}{dt} = \left(a_3 - \frac{a_4 X}{k_2 + X^2} \right) YZ - b_2 Y \tag{2}$$

where the first term on the right-hand side of (2) represents the reproduction of active osteoclasts and the inhibitory effect of calcitonin on active osteoclasts reproduction through the osteoclastic differentiation process which requires the presence of osteoblasts and bone marrow stromal cells since they respond to hormones and paracrine messengers which are necessary for the differentiation of osteoclasts. Also, the responsiveness of osteoblasts and their precursors to these necessary factors regulates the responsiveness of preosteoclasts and osteoclasts [14]-[16]. The last term, it is assumed that osteoclasts is removed from the system with the removal rate constant b_2. a_3, a_4 and k_2 are positive constants.

Osteoblasts are derived from the mesenchymal stem cells. The proliferation and differentiation of osteoblasts involve many factors such as FGF, IGF-I, TGF-beta. Moreover, calcitonin has been found to enhance osteoblastic bone formation [17],[18]. The dynamics of the osteoblastic population can be described by the following equation

$$\frac{dZ}{dt} = \left(\frac{a_5 + a_6 X}{k_3 + X} \right) Z - b_3 Z \tag{3}$$

The first term on the right-hand side of (3) represents the reproduction of active osteoblasts through the stimulating effect of CT on osteoblastic cells. The last term, it is assumed that osteoblasts is removed from the system with the removal rate constant b_3.

Our model therefore consists of (1)-(3), possessing highly diversified nonlinear characteristics, upon which further analysis and investigation may be carried out in an attempt to explain the mystifying empirical observations previously mentioned.

III. MODEL ANALYSIS

We assume that CT has the fast dynamics. The osteoclastic population possesses the intermediate dynamics and the osteoblastic population has the slow dynamics. Consequently, we scale the dynamics of the four components and parameters of the system in term of small positive parameters $0 < \varepsilon << 1$ and $0 < \delta << 1$ as follows.

Letting $x = X$, $y = Y$, $z = Z$, $c_1 = a_1$, $c_2 = a_2$, $c_3 = \frac{a_3}{\varepsilon}$, $c_4 = \frac{a_4}{\varepsilon}, c_5 = \frac{a_5}{\varepsilon\delta}, c_6 = \frac{a_6}{\varepsilon\delta}, d_1 = b_1, d_2 = \frac{b_2}{\varepsilon}, d_3 = \frac{b_3}{\varepsilon\delta}$, we are led to the following model equations:

$$\frac{dx}{dt} = \left(\frac{c_1 + c_2 y}{k_1 + y} \right) - d_1 x \equiv f(x, y, z) \tag{4}$$

$$\frac{dy}{dt} = \varepsilon \left(\left(c_3 - \frac{c_4 x}{k_2 + x^2} \right) yz - d_2 y \right) \equiv \varepsilon g(x, y, z) \tag{5}$$

$$\frac{dz}{dt} = \varepsilon\delta\left(\left(\frac{c_5 + c_6 x}{k_3 + x}\right)z - d_3 z\right) = \varepsilon\delta h(x, y, z) \qquad (6)$$

The system of (4)-(6), with the small parameters ε and δ can then be analyzed by using the geometric singular perturbation method which, under suitable regularity conditions, allows approximating the solution of the system with a sequence of simple dynamic transitions occurring at different speeds.

The shapes and relative positions of the manifolds $\{f = 0\}$, $\{g = 0\}$ and $\{h = 0\}$ determine the shapes, directions and speeds of the solution trajectories. We now analyze each of the equilibrium manifolds in detail. The delineating conditions of the limit cycle are described below.

The manifold $\{f = 0\}$

This manifold is given by the equation

$$x = \frac{1}{d_1}\left(\frac{c_1 + c_2 y}{k_1 + y}\right) \equiv U(y) \qquad (7)$$

which is parallel to the z-axis. It intersects the $(x,z)-$plane along the line

$$x = \frac{c_1}{d_1 k_1} \equiv x_1 \qquad (8)$$

Moreover, $U(y)$ is an increasing function of x and $U(y) \to \frac{c_2}{d_1} \equiv x_2$ as $y \to \infty$.

The manifold $\{g = 0\}$

This manifold consists of two submanifolds. One is the trivial manifold $y = 0$. The nontrivial one given by the equation

$$z = \frac{d_2\left(k_2 + x^2\right)}{c_3\left(k_2 + x^2\right) - c_4 x} \equiv V(x) \qquad (9)$$

this nontrivial manifold is independent of the variable y and thus this submanifold is parallel to the y-axis with asymptotic line

$$z = \frac{d_2}{c_3} \equiv z_2 \qquad (10)$$

Furthermore, the nontrivial manifold $\{g = 0\}$ attains its maximum at the point where

$$x = \sqrt{k_2} \equiv x_3 \quad \text{and} \quad z = \frac{2d_2 k_2}{2c_3 k_2 - c_4\sqrt{k_2}} \equiv z_1 \qquad (11)$$

The manifold $\{h = 0\}$

This consists of the trivial manifold $z = 0$ and the nontrivial one given by the equation

$$x = \frac{d_3 k_3 - c_5}{c_6 - d_3} \equiv x_4 \qquad (12)$$

Theorem 1 (Existence of a limit cycle)
If ε and δ are sufficiently small and

$$0 < x_1 < x_4 < x_2, \qquad (13)$$

$$z_2 < z_1, \qquad (14)$$

$$c_4 < 2c_3\sqrt{k_2}, \qquad (15)$$

$$c_6 < d_3, \qquad (16)$$

and

$$d_3 k_3 < c_5 \qquad (17)$$

where all the parametric values are given as before, then the system of (4)-(6) has a global attractor, in the positive octant of the phase space which is a limit cycle. The limit cycle can be constructed by concatenation of catastrophic various transitions occurring at three different speeds.

The proof of the theorem is based on geometric singular perturbation method. This method is a useful tool in the analysis of the different types of flows that clear separation in time scales: the fast flow, the intermediate flow, the slow flow, and the very slow flow. The limit cycle can consist of various parts. The fast, intermediate, and slow parts are indicated, respectively, by three, two, and one arrows.

Under the conditions in Theorem 1, without loss of generality we start from point *I* and we assume that the position of *I* is as in Fig. 1 with $\{f \neq 0\}$. A fast transition will tend to point *J* on the manifold $\{f = 0\}$. Here, $\{g < 0\}$ and a transition at intermediate speed will be made in the direction of decreasing y until point *K* on the curve $\{f = g = 0\}$ is reached. A slow transition then follows along this curve to some point *L* where the stability of submanifold will be lost. A jump to point *M* on the other stable part of $\{f = g = 0\}$ followed by a slow transition in the direction of decreasing z until the point *N* is reached since $\{h < 0\}$ here. Once the point *N* is reached the stability of submanifold will be lost. A jump to point *O* on the other stable part of $\{f = g = 0\}$ followed by a slow transition in the direction of increasing *z* since $\{h > 0\}$ here. Consequently, a slow transition will bring the system back to the point *L*, followed by flows along the same path repeatedly, resulting in the closed orbit *LMNOL*. Thus, limit cycle in the system for ε and δ are sufficiently small exists.

IV. NUMERICAL RESULT

A numerical result of the system (4)-(6) is presented in Fig. 2, with parametric values chosen to satisfy the condition in Theorem 1. The solution trajectory, shown in Fig. 2a project onto the (x,z)-plane, tends to a limit cycle as theoretically predicted. The corresponding time courses of the calcitonin concentration and the number of active osteoblasts are as shown in Fig. 2b and 2c, respectively.

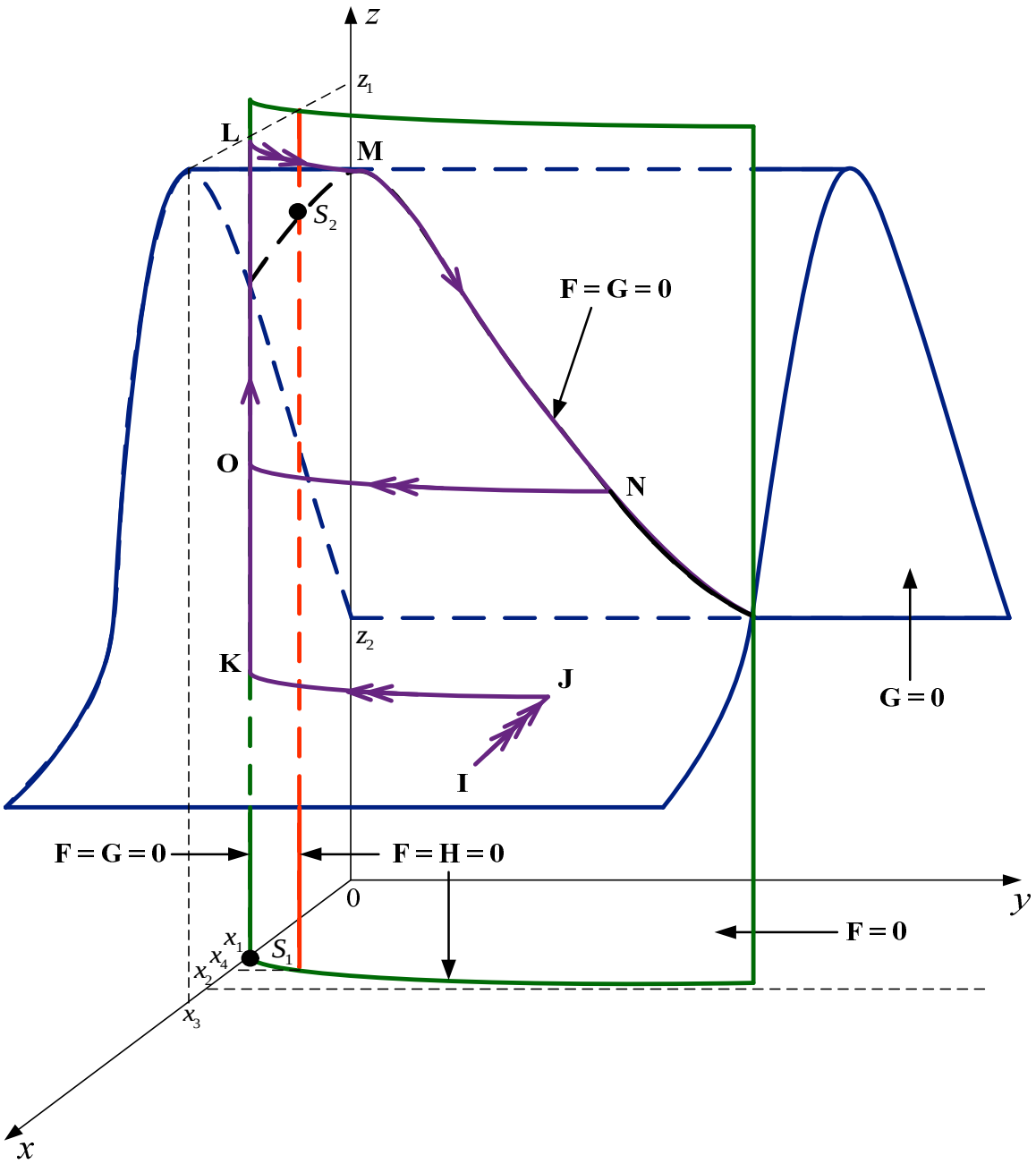

Fig. 1 The three equilibrium manifolds $\{f=0\},\{g=0\}$ and $\{h=0\}$ in the (x,y,z) – space in the case of limit cycle exists. Segments of the trajectories with one, two, and three arrows represent slow, intermediate, and fast transitions, respectively.

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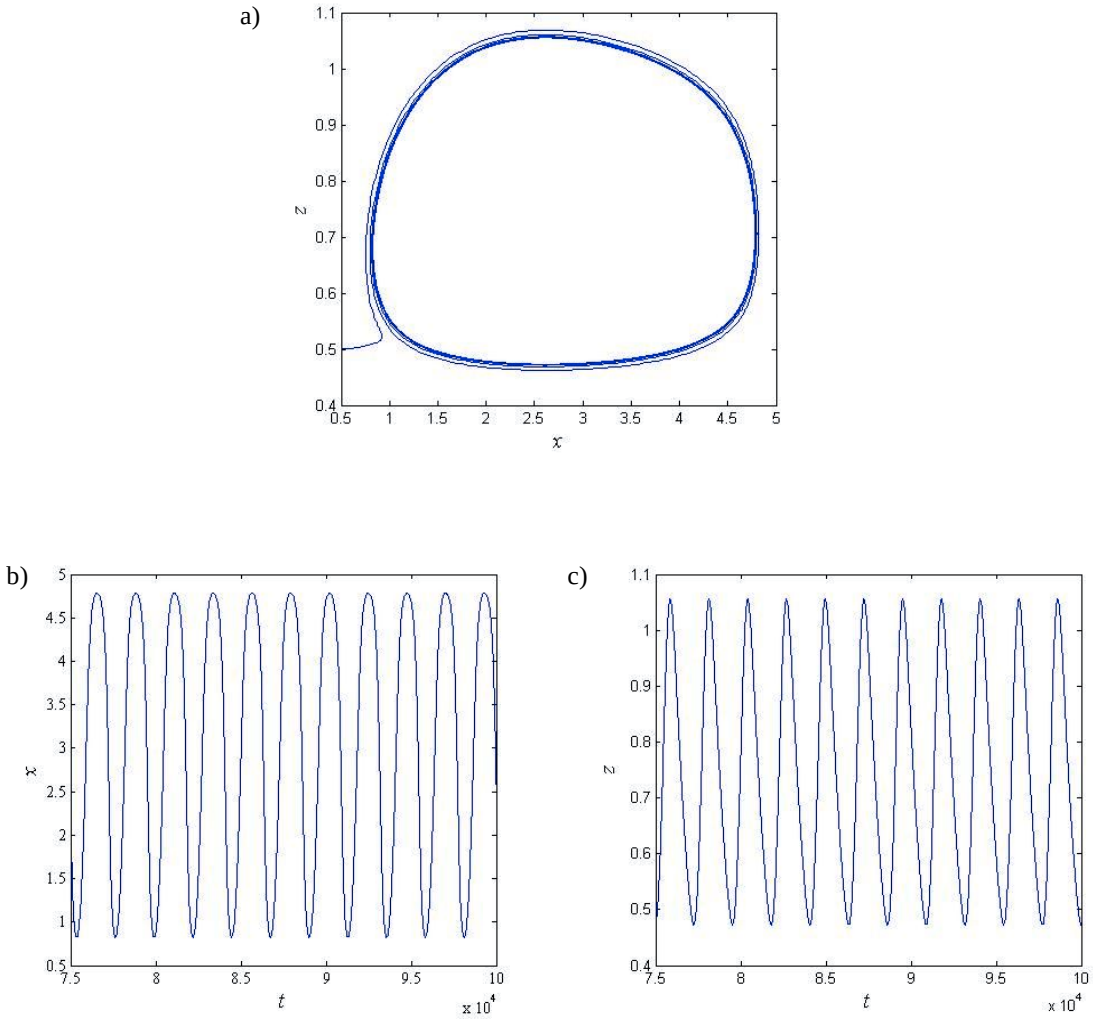

Fig. 2 A computer simulation of the model systems (4)-(6) with $c_1 = 0.1, c_2 = 0.5, c_3 = 0.4, c_4 = 0.7, c_5 = 0.7,\ c_6 = 0.085, k_1 = 3,\ k_2 = 5,$ $k_3 = 2,\ d_1 = 0.1,\ d_2 = 0.2,\ d_3 = 0.2,\ \varepsilon = 0.1,\ \delta = 0.2,\ x(0) = 0.5, y(0) = 0.5,\ z(0) = 0.5.$ (a) The solution trajectory projected onto the (*x*,*z*)-plane. (b) The corresponding time courses of calcitonin concentration (*x*), and (c) number of active osteoblastic cells (*z*).

V. CONCLUSION

Many different mathematical models have been proposed to describe bone remodeling process [19]-[22]. In this paper we have proposed a nonlinear mathematical model of bone remodeling process based on the effect of calcitonin, the population of osteoclastics cells, and osteoblastic cells and we have proved that our model can exhibit limit cycle when the parametric values satisfy the condition in Theorem 1. Moreover, the numerical result demonstrated that the limit cycle behavior of the system (4)-(6) with parametric values chosen to satisfy Theorem 1 close to the construction and analysis of our model.

We have demonstrated, through the development and analysis of a model for bone formation and resorption based on the effect of calcitonin that the nonlinear dynamic behavior can be deduced which closely resembles clinical data [23], even though the model is kept relatively simple.

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