Effects of Prolactin and Time Delay on Bone Resorption: Mathematical Modeling Approach

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***Abstract*—**A mathematical model is developed in order to investigate the effect of prolactin on the mechanism of bone formation and resorption. By applying the singular perturbation technique to our model, we then obtain the explicit conditions on the system parameters which ensure the existence of limit cycle behavior corresponding to the oscillatory behavior observed in the clinical data. Numerical simulations are then carried out to support our theoretical analysis. In addition, we extend our model to investigate the effects of estrogen and parathyroid hormone supplements in patients with osteoporosis.

***Keywords*—**bone resorption, parathyroid hormone, prolactin, estrogen.

I. Introduction

OSTEOPOROSIS is now recognized as a major health disorder of bone remodeling, requiring costly medical treatment. It is a bone disease which is characterized by low bone mass, the structural deterioration of bone and an increased risk of fracture [1], [2]. Literally, osteoporosis means an increased porosity of bone. It can be more accurately defined as a clinical condition in which a progressive diminution of skeletal mass renders bone increasingly vulnerable to fracture [3]. Osteoporosis can affect both men and women of all ages, including children, but it occurs most frequently in the older population, particularly in postmenopausal women [1]. It is estimated that women have lost 10% of their bone mass by the time they go through menopause and that 35% of cortical bone and 50% of trabecular bone are lost over a life time [4]. Prevention and reversal of bone loss require a thorough understanding of bone remodeling process, the mechanism of bone formation, and resorption, including the action of hormones such as parathyroid hormone (PTH) and prolactin (PRL).

In bone remodeling, osteoclasts and osteoblasts differentiate from less mature precursors, which line bone surfaces in an inactive state [5]. Bone remodeling 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 [6]. 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 [7]. Thus, the number of osteoblasts determines the rate of bone deposition while the number of osteoclasts determines the rate of bone resorption, the balance between the number and activity of osteoblasts and of osteoclasts determines whether net bone deposition or net bone resorption occurs [8]. 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 even occur. 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 [6].

Bone, being a major reservoir of body calcium, is under the hormonal control, principally of parathyroid hormone (PTH) [5]. The overall effect of PTH is to raise plasma levels of calcium, partly through bone resorption, by the activation of osteoclasts. Osteoclasts resorb bone and liberate calcium but they lack PTH receptors while preosteoblast precursors and preosteoblasts possess them. Therefore, PTH will increase the number of osteoclasts only after having increased the osteoblastic population [8].

PTH is directly controlled by the level of calcium in blood. The decrease of calcium level in blood results in an increase in the secretion of PTH from the parathyroid grand. PTH inhibits the differentiation of preosteoblasts to form osteoblasts [9], [10]. Moreover, PTH stimulates osteoblasts to produce interleukine-6 (IL-6) and in turn, IL-6 stimulates the activity and differentiation of osteoclasts resulting in increased bone resorption [11]. On the other hand, osteoblasts and stromal cells express an osteoclast differentiation factor (ODF) and osteoclasts precursors possess RANK, a receptor of the TNF (tumor necrosis factor) family, which recognizes ODF through the cell-to-cell interaction with osteoblasts [12], [13]. In addition, the binding of ODF by RANK in the presence of macrophage colony-stimulating factor causes preosteoclasts to differentiate into osteoclasts and pre-existing osteoclasts to become activated which also resulted in increased bone resorption and then the level of calcium in blood will be increased [14].

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PRL is a polypeptide hormone that is synthesized and secreted from the lactotroph cells in the anterior pituitary gland. Aside from its action on reproduction and lactation, PRL plays a role in maintaining the constancy of the internal environment by regulation of the immune system, osmotic balance and angiogenesis [15]. Moreover, PRL-receptors have been found on the receptors of the osteoblastic cells [16] which are the cells that play a crucial role in the bone remodeling process. Hence, PRL can have significant effects on the bone remodeling process as well. It has been found that PRL enhances bone resorption in part by increasing RANKL and decreasing OPG expressions by osteoblasts [17].

There are several attempts such as [8], [18]-[21] to describe bone remodeling process mathematically, however the effect of PRL on the process did not take into account.

Thus, a better understanding of the roles of PTH and PRL in the mechanism of bone remodeling process is crucial to the study of how these secretion systems of physiological importance may be monitored and controlled or regulated for effective preventive therapy measures.

II. MODEL DEVELOPMENT

We now develop a mathematical model of bone formation and resorption based on the effects of PTH and PRL as follows where $T(t)$, $P(t)$, $C(t)$ and $B(t)$ denote the level of PTH above the basal level, the level of PRL above the basal level, the number of activated osteoclasts and the number of activated osteoblasts, respectively.

Firstly, osteoclasts resorb bone and liberate calcium, in order to counter balance the high level of calcium in blood the rate of PTH secretion will decrease [22]. Moreover, the increase of the level of PRL results in the increase of the level of PTH [23]. Therefore, the equation for the rate of PTH secretion is then assumed to take the form

$$\frac{dT}{dt} = \frac{c_1}{k_1 + C} + c_2 P - e_1 T \tag{1}$$

where c_1, c_2, k_1 and e_1 are positive constants.

Secondly, PRL secretion is controlled by the negative feedback of the anterior pituitary gland, when the level of PRL rises to the high level the secretion of PRL will be decreased [15]. Moreover, PTH inhibits the uptake and release of dopamine which is PRL inhibiting factor and hence increases the level of PRL [22]. Therefore, the equation for the rate of PRL secretion is then assumed to take the form

$$\frac{dP}{dt} = \left(c_3 - c_4 P\right) P + c_5 TP - e_2 P \tag{2}$$

where c_3, c_4, c_5 and e_2 are positive constants.

The dynamics of the osteoclastic population can be described by the following equation

$$\frac{dC}{dt} = \left(\frac{\left(c_6 + c_7 T\right)}{k_2 + T^2} + c_8 P \right) BC - e_3 C \tag{3}$$

where the first term on the right-hand side represents the reproduction of active osteoclasts which requires the production of osteoclast differentiation factor (ODF) and its receptor on osteoclasts [8]. The more C means the more ODF receptors available for the reproduction of active osteoclasts, and hence the term is taken to depend on the number of osteoclasts C at that moment in time.

Moreover, osteoclasts precursors possess RANK, a receptor of TNF (tumor necrosis factor) family that recognizes ODF through a cell-to-cell interaction with osteoblasts [12]-[14], hence the rate of reproduction is taken to depend also on the number of active osteoblastic cells $B(t)$ at any time t. However, the rate of reproduction of C increases with the increase in the level of PTH [11], [24]. On the other hand, it has been clinically observed [8] that as PTH level increases further, it begins to inhibit osteoclastic reproduction, and hence the saturation expression $\frac{\left(c_6 + c_7 T\right)}{k_2 + T^2}$ is assumed for the stimulating effect of PTH. In addition, it has been found that PRL enhances bone resorption in part by increasing RANKL and decreasing OPG expressions by osteoblasts [17]. Hence, the increase in the level of PRL results in the increase of the activated osteoclasts and therefore the term $c_8 P$ is also taken in to account where c_6, c_7, c_8, e_3 and k_2 are positive constants.

Finally, the dynamics of the active osteoblastic population B(t) can be described by the following equation

$$\frac{dB}{dt} = c_9 T - \frac{c_{10} TB}{k_3 + T} - e_4 B \tag{4}$$

where c_9 is the specific rate at which PTH stimulates reproduction of active osteoblasts [5],[10]. The second term on the right-hand side of (4) accounts for the inhibiting effect of PTH on osteoblastic differentiation through the process of down-regulation of the PTH receptors on osteoblasts [8] where c_9, c_{10}, k_3 and e_4 are positive constants.

The last terms in the above four equations are the removal rates of the four components of the remodeling process with rate constants e_1, e_2, e_3 and e_4, respectively.

Our model therefore consists of (1)-(4), 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. SINGULAR PERTURBATION ANALYSIS

To analyze the nonlinear mathematical model (1)-(4) by the singular perturbation method, we scale the dynamics of the four components of the system by means of two small dimensionless positive parameters ε, δ and η, as follows.

Letting $x = T,\ y = P,\ z = C,\ w = B,\ a_1 = c_1,\ a_2 = c_2,\ a_3 = \frac{c_3}{\varepsilon}$,

$a_4 = \frac{c_4}{\varepsilon}, a_5 = \frac{c_5}{\varepsilon}, a_6 = \frac{c_6}{\varepsilon\delta}, a_7 = \frac{c_7}{\varepsilon\delta}, a_8 = \frac{c_8}{\varepsilon\delta}, a_9 = \frac{c_9}{\varepsilon\delta\eta}, a_{10} = \frac{c_{10}}{\varepsilon\delta\eta}$,

$d_1 = e_1,\ d_2 = \frac{e_2}{\varepsilon},\ d_3 = \frac{e_3}{\varepsilon\delta}$ and $d_4 = \frac{e_4}{\varepsilon\delta\eta}$, we are led to the following system of differential equations.

$$\frac{dx}{dt} = \frac{a_1}{k_1 + z} + a_2 y - d_1 x \equiv f\left(x, y, z, w\right) \tag{5}$$

$$\frac{dy}{dt} = \varepsilon\left[\left(a_3 - a_4 y\right)y + a_5 xy - d_2 y\right] \equiv \varepsilon g\left(x,y,z,w\right) \tag{6}$$

$$\frac{dz}{dt} = \varepsilon\delta\left[\left(\frac{\left(a_6 + a_7 x\right)}{k_2 + x^2} + a_8 y\right)zw - d_3 z\right] \equiv \varepsilon\delta h\left(x,y,z,w\right) \tag{7}$$

$$\frac{dw}{dt} = \varepsilon\delta\eta\left[a_9 x - \frac{a_{10} xw}{k_3 + x} - d_4 w\right] \equiv \varepsilon\delta\eta k\left(x,y,z,w\right) \tag{8}$$

This means that, if ε,δ and η are small, the dynamics of PTH, PRL, activated osteoblasts and activated osteoclasts are assumed to be fastest, intermediate, slow and slowest, respectively. The system of (5)-(8) can be analyzed by applying the singular perturbation technique in the following manner [25] which are based on simple geometric characteristics of the equilibrium manifolds, allowing one to derive conditions that ensure the existence of a limit cycle.

The shapes and relative positions of the manifolds $\{f=0\}$, $\{g=0\}$, $\{h=0\}$ and $\{k=0\}$ determine the directions, speeds, and shapes of the resulting solution trajectories. Therefore, we shall analyze each of the equilibrium manifolds in detail. The delineating conditions for the existence of limit cycle are arrived at from the close inspection of these manifolds.

The manifold { f = 0 }

This manifold is given by the equation

$$y = \frac{1}{a_2}\left(d_1 x - \frac{a_1}{k_1 + z}\right) \equiv U\left(x,z\right) \tag{9}$$

We see that this manifold is independent of *w*. It intersects the $(x,z)-$ plane along the curve

$$x = \frac{a_1}{d_1\left(k_1 + z\right)}$$

which intersects the *x*-axis at the point where $z = 0$ and

$$x = \frac{a_1}{d_1 k_1} \equiv x_1 \tag{10}$$

Moreover, $U\left(x,z\right)$ is an increasing function of x and z.

The manifold { g = 0 }

This manifold consists of two sub-manifolds. One is the trivial manifold $y = 0$ while the other one is the nontrivial manifold

$$y = \frac{1}{a_4}\left(a_5 x + \left(a_3 - d_2\right)\right) \equiv V\left(x\right) \tag{11}$$

which is independent of z and w. $V\left(x\right)$ is an increasing function of x, it intersects the *x*-axis at the point where $y = 0$ and

$$x = \frac{1}{a_5}\left(d_2 - a_3\right) \equiv x_2 \tag{12}$$

The manifold { h = 0 }

This manifold consists of two sub-manifolds. One is the trivial manifold $z = 0$ while the other one is the nontrivial manifold

$$y = \frac{1}{a_8}\left(\frac{d_3}{w} - \frac{a_6 + a_7 x}{k_2 + x^2}\right) \equiv W\left(x,w\right) \tag{13}$$

which is independent of z. For a fixed value of w, the nontrivial manifold $y = W\left(x,w\right)$ intersects the *y*-axis at the point where $x = 0$ and

$$y = \frac{1}{a_8}\left(\frac{d_3}{w} - \frac{a_6}{k_2}\right) \equiv y_1\left(w\right) \tag{14}$$

It attains its minimum at the point where

$$x = \frac{-a_6 + \sqrt{a_6^2 + a_7 k_2}}{a_7} \equiv x_3 \tag{15}$$

and

$$y = \frac{1}{a_8}\left(\frac{d_3}{w} - \frac{a_6 + a_7 x_3}{k_2 + x_3^2}\right) \equiv y_3\left(w\right) \tag{16}$$

Moreover, $y \to \frac{d_3}{a_8 w} \equiv y_2\left(w\right)$ as $x \to \infty$ and $W\left(x,w\right)$ is a decreasing function of w.

The manifold { k = 0 }

This manifold is given by the equation

$$w = \frac{a_9 x^2 + a_9 k_3 x}{\left(a_{10} + d_4\right)x + d_4 k_3} \equiv \Psi\left(x\right) \tag{17}$$

This manifold is independent of y and z. It intersects the *x*-axis at the point where $w = 0$ and $x = 0$ or $x = -k_3$, while it intersects the *w*-axis at the point where $x = 0$ and $w = 0$. Moreover, $\Psi\left(x\right)$ is an increasing function of x in the first octant and $w \to \infty$ as $x \to \infty$.

Theorem 1 If ε,δ and η are sufficiently small, and

$$0 < x_2 < x_3 < x_1 \tag{18}$$

$$0 < y_3\left(w\right) < y_1\left(w\right) \tag{19}$$

where all parametric values are defined as above, then a limit cycle exists for the system of (5)-(8).

The proof of the theorem is based on a geometric singular perturbation method, which were elaborated by [26] and [27] and utilized successfully in many applications [28], [29]. Under the conditions identified in the theorem, the shapes and relative positions are as in Fig. 1. where the fast parts are indicated by three arrows, the intermediate parts by two arrows, and the slow parts by a single arrow.

In Fig. 1, starting from a generic point A in front of the manifold $\{f=0\}$ and above the manifold $\{h=0\}$, the solution trajectory develops at constant *y* and *z* in the direction of decreasing x since $f < 0$ here, and reaches a point B on the fast manifold $\{f=0\}$ at high speed. Then, a transition develops at intermediate speed along manifold $\{f=0\}$ in the direction of decreasing y, since $g < 0$ here, towards the point C on the stable branch of the curve $\{f = h = 0\}$. A transition develops along this curve at intermediate speed in the downward direction, since $g < 0$ here, until it reaches some point D, where the stability of the manifold is lost followed by a jump to the point E on the other stable branch of the curve

$\{f = h = 0\}$ with a fast speed in the direction of increasing x. Here, $g > 0$ and thus a transition will develop at intermediate speed from the point E in the direction of increasing y to the point F where the stability of the manifold is lost followed by a jump to the point G on the other stable branch of the curve $\{f = h = 0\}$ with a fast speed in the direction of decreasing x. A transition develops along this curve at intermediate speed in the downward direction, since $g < 0$ here, until it reaches some point D resulting in a closed cycle DEFG. Therefore, a limit cycle has been identified for the system of (5)-(8).

A computer simulation of (5)-(8) is presented in Fig. 2, with parametric values chosen to satisfy the inequalities identified in Theorem 1. The solution trajectory, shown in Fig. 2 projected onto the (x,y)-plane, (x,z)-plane, (y,z)-plane and (x,w)-plane tends to a limit cycle as theoretically predicted. The corresponding time courses of PTH, PRL, activated osteoclasts and actived osteoblasts are shown in Fig. 3. Such oscillatory behavior in the level of PTH and PRL has often been observed in clinical data [30]-[32].

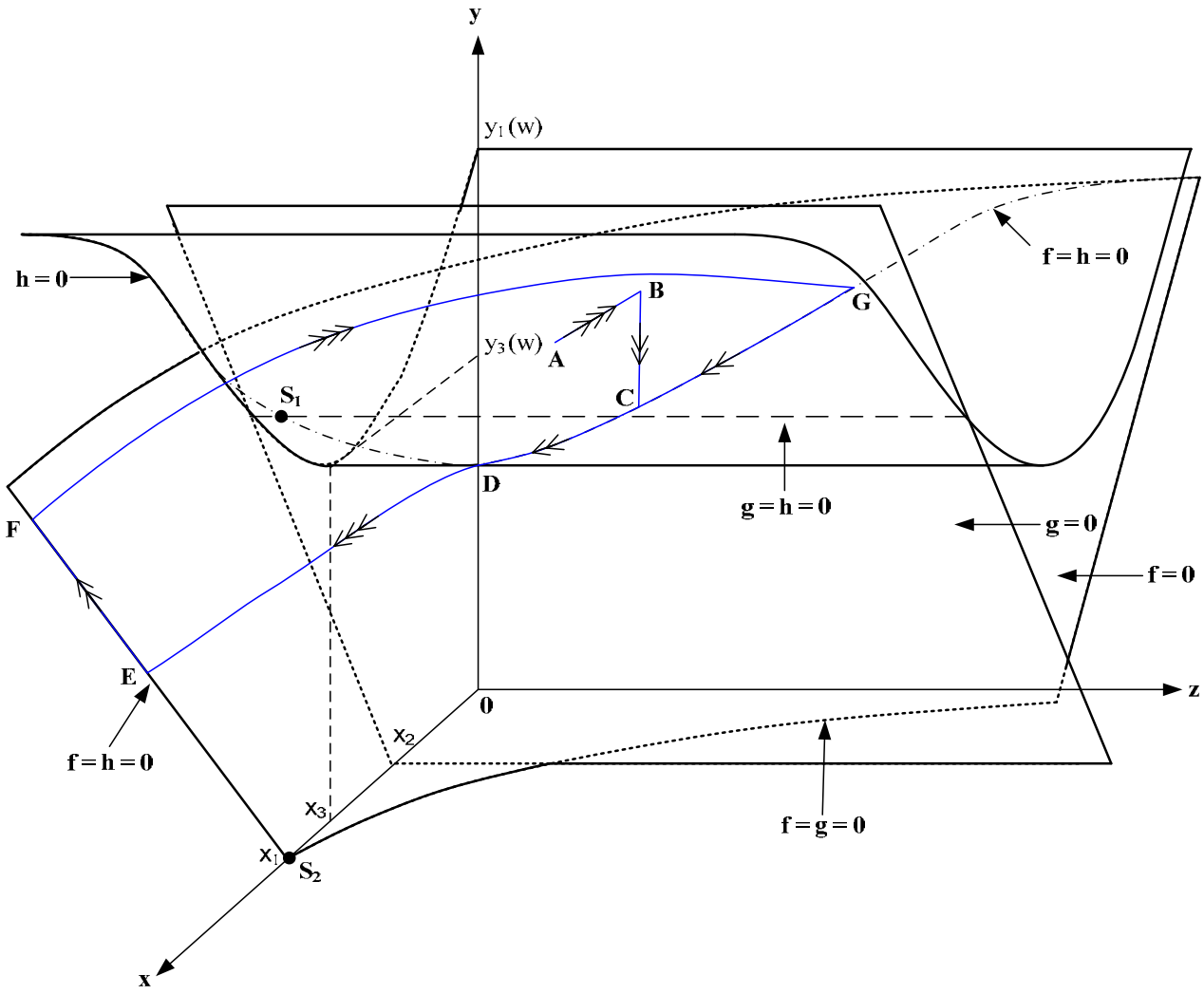

Fig. 1 The three equilibrium manifolds $\{f = 0\}, \{g = 0\}$ and $\{h = 0\}$ in the $(x, y, z)-$space for a particular value of w. and a solution trajectory of the system of (5)-(8) for which the attractor is a limit cycle where all conditions in theorem 1 are satisfied.

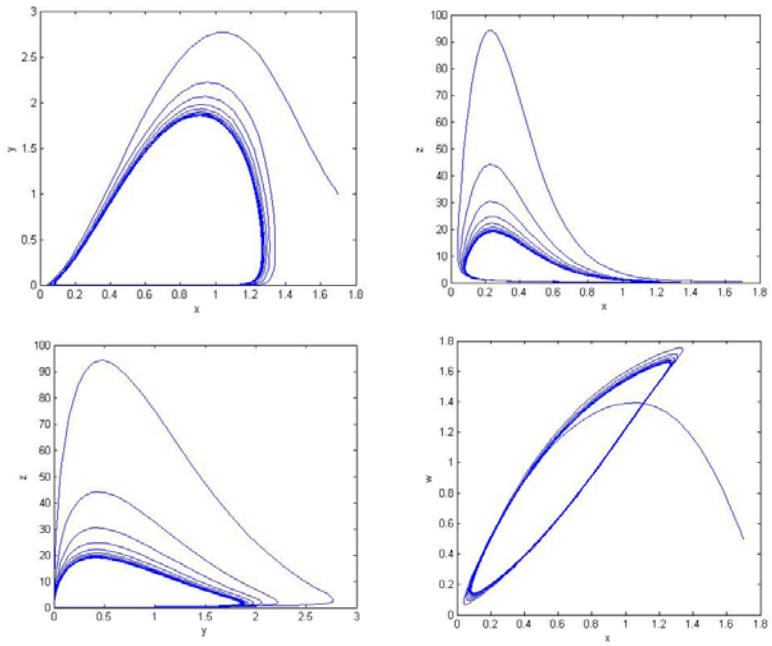

Fig. 2 A computer simulation of the model system (5)-(8) with $a_1 = 0.1, a_2 = 0.01, a_3 = 0.05, a_4 = 0.1, a_5 = 0.7, a_6 = 0.2, a_7 = 0.1,$ $a_8 = 0.25, a_9 = 0.7, a_{10} = 0.1, k_1 = 0.3, k_2 = 0.5, k_3 = 3.2, d_1 = 0.2, d_2 = 0.5, d_3 = 0.3, d_4 = 0.5, \varepsilon = 0.85,$ $\delta = 0.97$ and $\eta = 0.75$ where $x(0) = 1.7, y(0) = 1, z(0) = 0.5,\ w(0) = 0.5$. The solution trajectory projected onto the (x,y)-plane, (x,z)-plane, (y,z)-plane and (x,w)-plane tends to a limit cycle.

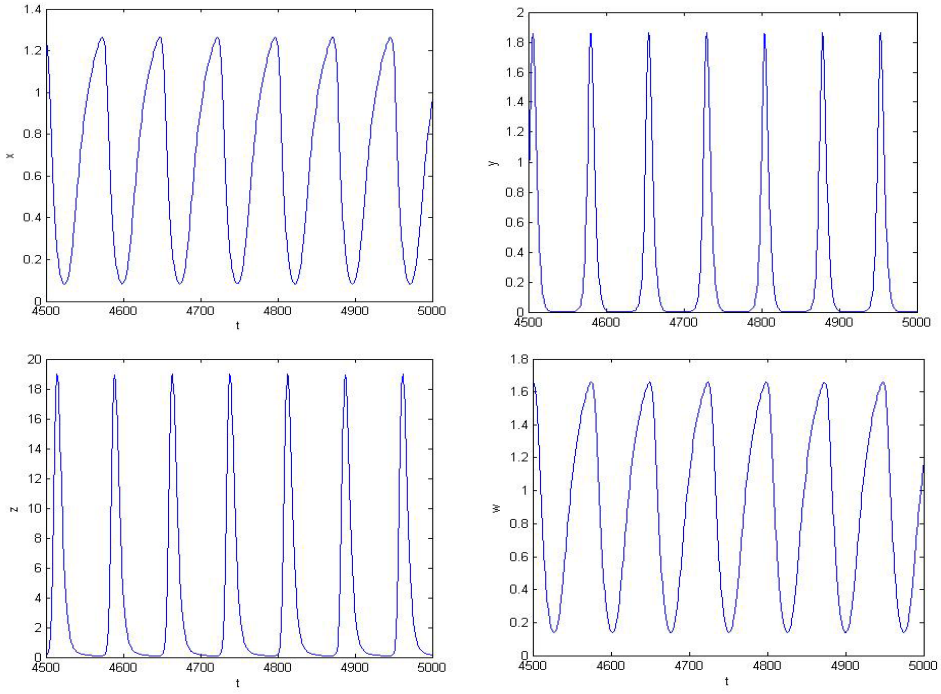

Fig. 3 A computer simulation of the model system (5)-(8) with $a_1 = 0.1, a_2 = 0.01, a_3 = 0.05, a_4 = 0.1, a_5 = 0.7, a_6 = 0.2, a_7 = 0.1,$ $a_8 = 0.25, a_9 = 0.7, a_{10} = 0.1, k_1 = 0.3, k_2 = 0.5, k_3 = 3.2, d_1 = 0.2, d_2 = 0.5, d_3 = 0.3, d_4 = 0.5, \varepsilon = 0.85,$ $\delta = 0.97$ and $\eta = 0.75$ where $x(0) = 1.7, y(0) = 1, z(0) = 0.5,\ w(0) = 0.5$. The corresponding time courses of PTH, PRL, activated osteoclasts and activated osteoblasts exhibit a periodic solution as theoretically predicted.

IV. Responses to Estrogen therapy

Estrogen is a sex steroid hormone produced by the ovary. It plays an important role in the growth and maturation of bone as well as in the regulation of bone turnover [3]. In the adult woman, estrogen exerts a tonic suppression of cancellous bone remodeling and maintains remodeling balance between osteoclastic and osteoblastic activities. When estrogen is deficient, many researchers [33]-[37] observed an increase in the activation frequency of new bone remodeling units and an increase in remodeling imbalance, especially resulting from the increase of osteoclastic formation which enhances bone resorption, leading to osteoporosis.

It has been widely accepted that estrogen replacement therapy can prevent menopausal bone loss and reduces the risk of fracture [33]-[36]. Moreover, Kanatani [34] and Riggs [36] have suggested that the presence of estrogen results in the decrease of bone resorption by inhibiting the activity of osteoclasts. The works of Albright *et al*. [35] and Prestwood *et al.* [33] indicated the decrease in the values of biochemical markers of bone turnover due to the short-term estrogen treatment. However, there are some risks and side effects from the estrogen replacement therapy such as breast cancer and heart disease [37], [38]. High doses of estrogen results in weight loss in rats, and an increase in tumor formation was observed in aging rats with long-term treatment of estrogen [39].

In order to investigate the effects of estrogen therapy, we then assume that estrogen remains effective in the human body accumulatively over a long enough period so that daily intake of estrogen can be taken as equivalent to continuous application of the steroid, all through the time period ΔT, during which time the model equations then become

$$\frac{dx}{dt} = \frac{a_1}{k_1 + z} + a_2 y - d_1 x \tag{20}$$

$$\frac{dy}{dt} = \varepsilon\left[\left(a_3 - a_4 y\right) y + a_5 xy - d_2 y\right] \tag{21}$$

$$\frac{dz}{dt} = \varepsilon\delta\left[\left(\frac{\left(a_6 + a_7 x\right)}{k_2 + x^2} + a_8 y\right) zw - d_3 z\right] - k_C z \tag{22}$$

$$\frac{dw}{dt} = \varepsilon\delta\eta\left[a_9 x - \frac{a_{10} xw}{k_3 + x} - d_4 w\right] \tag{23}$$

In Fig. 4, the term $-k_C z$ is kept in (22) for a duration of ΔT = 10 days, every period of 28 days. We observe that when the administration period ΔT is over, the effect still lasts for quite some time before the system recovers itself and there is a resetting of oscillatory behavior in the active osteoblastic population. The "plateau" is much wider than ΔT. This is a result of the diversified time responses of the 4 components in this nonlinear system. Since osteoblast is the very slow variable, it takes a long time to respond to the change in the proliferation rate of osteoclast. In particular, the plateau width is inversely proportional to ε, δ and η. We also found, upon experimenting with different values, that different dosage (or k_C) will yield different plateau width.

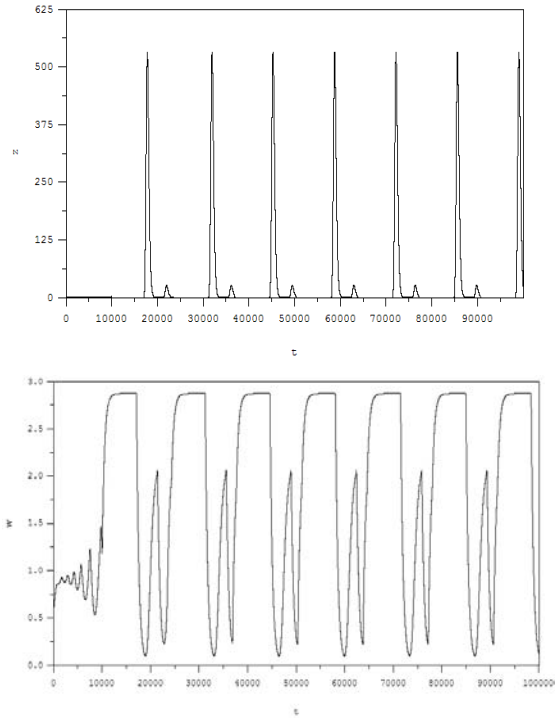

Fig. 4 A computer simulation of the model system (20)-(23) with $a_1 = 0.1, a_2 = 0.01, a_3 = 0.05, a_4 = 0.1, a_5 = 0.7, a_6 = 0.2,$ $a_7 = 0.1, a_8 = 0.25, a_9 = 0.7, a_{10} = 0.1, k_1 = 0.3, k_2 = 0.5, k_3 = 3.2,$ $d_1 = 0.2, d_2 = 0.5, d_3 = 0.3, d_4 = 0.5, \varepsilon = 0.1, \delta = 0.2, \eta = 0.2, k_c = 0.22$ and $\Delta T =$ 10 days where $x(0) = 1.7, y(0) = 1, z(0) = 0.5,$ $w(0) = 0.5$.

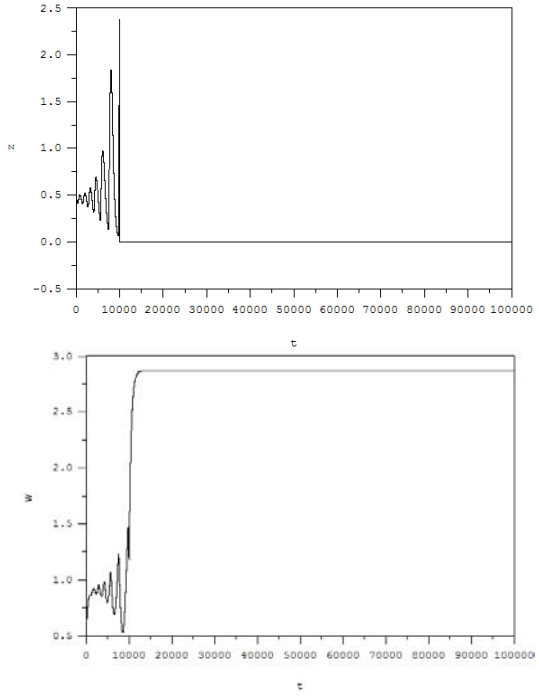

Fig. 5 A computer simulation of the model system (20)-(23) with $a_1 = 0.1, a_2 = 0.01, a_3 = 0.05, a_4 = 0.1, a_5 = 0.7, a_6 = 0.2,$ $a_7 = 0.1, a_8 = 0.25, a_9 = 0.7, a_{10} = 0.1, k_1 = 0.3, k_2 = 0.5, k_3 = 3.2,$

$d_1 = 0.2, d_2 = 0.5, d_3 = 0.3, d_4 = 0.5, \varepsilon = 0.1, \delta = 0.2, \eta = 0.2, k_c = 0.22$ and $\Delta T =$ 20 days where $x(0) = 1.7, y(0) = 1, z(0) = 0.5,$ $w(0) = 0.5$.

In Fig. 5, the term $-k_C z$ is kept in (22) for a duration of ΔT = 20 days, every period of 28 days. We see that there is no longer any resetting of oscillatory behavior. Even though estrogen has already been cut off, the dissipative effect still lasts long enough to overlap with the next application of estrogen. This seems to suggest that with appropriate choices of ΔT and the prescribed dosage, administration may not necessarily be kept on for the entire time, while a net bone surface formation can still be expected.

V. Effect of Time Delay on Bone Resorption and Bone Formation

According to Whitfield *et al.* [40], the need to repair microdamage in a patch of cortical bone is sensed by an interconnected network of cells called osteocytes, each of which is locked in a tiny cubicle inside the dense cortical bone. The damage may only strain the osteocytes or it may be severe enough for them to suicidally trigger a process called apoptosis. When osteocytes are injured or die, they stop producing a major suppressor of osteoclastic biosynthesis. This removes a major restraint on the production of new osteoclasts, each of which will live and dig for the next 2 weeks [40].

When the osteoclasts dissolve the bone mineral, a lot of Ca^{2+} is released. The Ca^{2+} concentration serves as a 2-way switch: "off" for the osteoclasts and "on" for the bone-making osteoblasts [40]. Osteoblasts take about 5 times longer to fill the tunnels and trenches than osteoclasts take to dig them. When the patch is finally repaired 6 to 9 months later, the distress signals have stopped, the approximately 3-month-old members of the last osteoblast crew are now out of work, so they "commit apoptotic suicide", as explained in great detail by [40].

In order to investigate the time delay observed in the above processes, we then modify our model as follows

$$\frac{dx}{dt} = \frac{a_1}{k_1 + z} + a_2 y - d_1 x \tag{24}$$

$$\frac{dy}{dt} = \varepsilon\left[\left(a_3 - a_4 y\right) y + a_5 xy - d_2 y\right] \tag{25}$$

$$\frac{dz}{dt} = \varepsilon\delta\left[\left(\frac{\left(a_6 + a_7 x\right)}{k_2 + x^2} + a_8 y\right) z\left(t-\tau\right) w\left(t-\tau\right) - d_3 z\right] \tag{26}$$

$$\frac{dw}{dt} = \varepsilon\delta\eta\left[a_9 x - \frac{a_{10} x w\left(t-\tau\right)}{k_3 + x} - d_4 w\right] \tag{27}$$

A computer simulation of (24)-(27) is presented in Fig. 6 and Fig. 7. The solution trajectory projected onto the (x,y)-plane, (x,z)-plane, (y,z)-plane and (x,w)-plane tends to a limit cycle as shown in Fig. 6. The corresponding time courses of PTH, PRL, activated osteoclasts and actived osteoblasts are shown in Fig. 7. Such oscillatory behavior in the level of PTH and PRL has often been observed in clinical data [30]-[32].

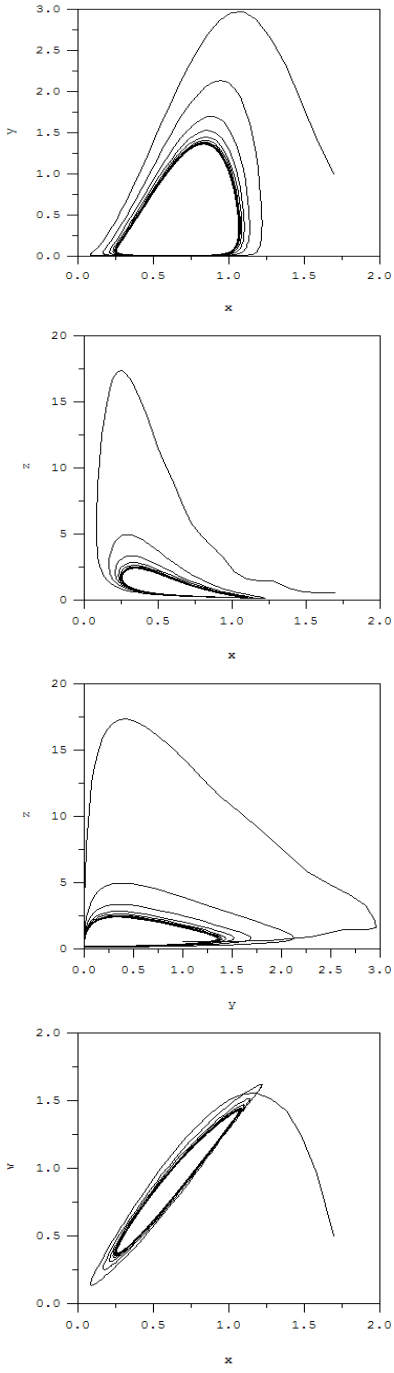

Fig. 6 A computer simulation of the model system (24)-(27) with $a_1 = 0.1, a_2 = 0.01, a_3 = 0.05, a_4 = 0.1, a_5 = 0.7, a_6 = 0.2,$ $a_7 = 0.1, a_8 = 0.25, a_9 = 0.7, a_{10} = 0.1, k_1 = 0.3, k_2 = 0.5, k_3 = 3.2,$ $d_1 = 0.2,\ d_2 = 0.5,\ d_3 = 0.3,\ d_4 = 0.5,\ \varepsilon = 0.1, \delta = 0.2, \eta = 0.2$ and $\tau = 2$ where $x(0) = 1.7, y(0) = 1, z(0) = 0.5,\ w(0) = 0.5$. The solution trajectory projected onto the (x,y)-plane, (x,z)-plane, (y,z)-plane and (x,w)-plane tends to a limit cycle.

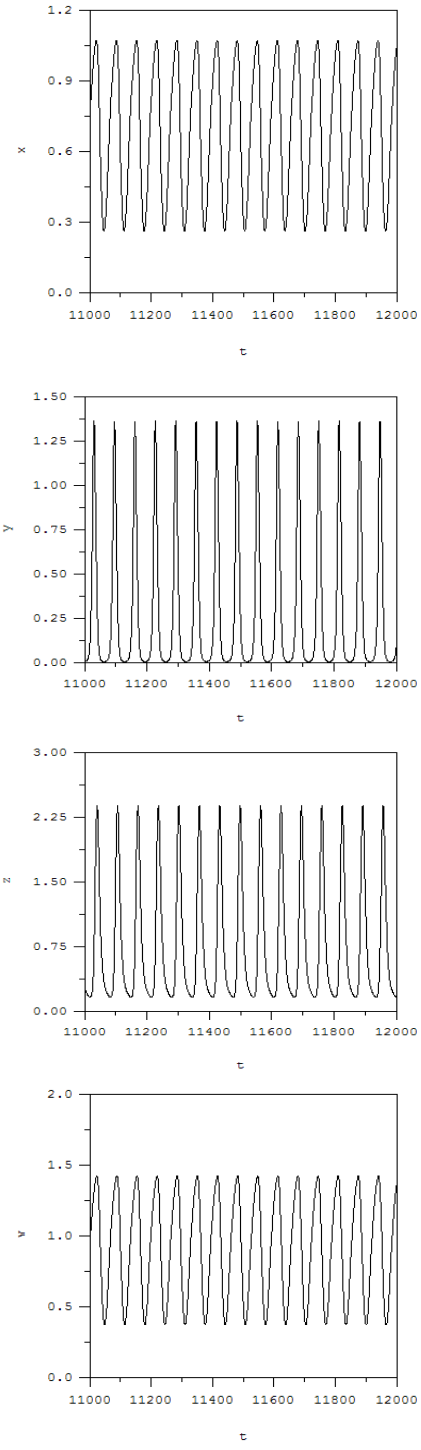

Fig. 7 A computer simulation of the model system (24)-(27) with $a_1 = 0.1, a_2 = 0.01, a_3 = 0.05, a_4 = 0.1, a_5 = 0.7, a_6 = 0.2,$ $a_7 = 0.1, a_8 = 0.25, a_9 = 0.7, a_{10} = 0.1, k_1 = 0.3, k_2 = 0.5, k_3 = 3.2,$ $d_1 = 0.2,\ d_2 = 0.5,\ d_3 = 0.3,\ d_4 = 0.5,\ \varepsilon = 0.1, \delta = 0.2, \eta = 0.2$ and $\tau = 2$ where $x(0) = 1.7, y(0) = 1, z(0) = 0.5,\ w(0) = 0.5$. The corresponding time courses of PTH, PRL, activated osteoclasts and activated osteoblasts exhibit a periodic solution.

VI. CONCLUSION

We proposed and analyzed a model of bone formation and resorption based on the effects of PTH and PRL theoretically by means of singular perturbation method and then carried out the numerical simulations by using Runge-Kutta method which has been widely used to investigate numerical solutions of differential equations [41]-[44]. We have demonstrated, through the development and analysis of the model that the nonlinear dynamic behavior can be deduced which closely resembles clinical data, even though the model is kept relatively simple. The effects of estrogen replacement therapy and the time delay on bone resorption are also investigated.

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