Effect of Time Delay on Bone Remodeling Process

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***Abstract*—**We modify a mathematical model of bone remodeling process to study the effect of time delay observed clinically in the process. We then utilize the Hopf bifurcation theorem to investigate the possibility of the occurrence of periodic behavior exhibited by our model. Numerical simulation is also carried out to support our theoretical results. Theoretical and numerical results indicate that the periodic behavior observed clinically in the pulsatile secretion of parathyroid hormone can be expected in our model.

***Keywords*—**bone remodeling process, osteoblast, osteoclast, parathyroid hormone, time delay.

I. Introduction

OSTEOPOROSIS is known as a major health disorder of bone remodeling [1]. It can be occurred in both men and women especially in postmenopausal women [1], [2]. It is a bone disease resulted from the net increase of bone resorption over bone formation in bone remodeling process [1], [2]. In osteoporosis, the overall density of the skeleton decreases with thinning of the trabeculae and a loss of interconnections, as a result bones become brittle and fracture easily [3]. Bone remodeling is a continuous cycle of destruction and renewal of bone carried out by teams of bone resorbing cells called osteoclasts and bone forming cells called osteoblasts [1]. The process starts with the appearance of osteoclasts 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. After that osteoclasts are then replaced by osteoblasts and finally, osteoblasts refill the resorption cavity. After osteoblasts have laid down their protein-based matrix, known as osteoid, they bury themselves in bony matrix and become osteocytes or resting osteoblasts [4]. Hence, the rate of bone resorption can be determined by the number of osteoclasts while the rate of bone deposition can be determined by the number of osteoblasts, the balance between the number and activity of osteoblasts and of osteoclasts determines whether net bone deposition or net bone resorption occurs.

Many researchers proposed mathematical models to describe bone remodeling process [5]-[8] but only one of them [6] incorporates the effect of time delay observed clinically in [1], [6]. However, the model that proposed in [6] did not incorporate the effects of parathyroid and osteoblasts on the osteoclastic differentiation. Therefore, in this paper, we then investigate the effect of time delay in bone remodeling process by modifying the model that has been proposed by Rattanakul *et al.* [5].

II. Model Modification

We now modify the model proposed by Rattanakul *et al.* [5] to incorporate the effect of time delay in bone remodeling process as follows. Let us denote the level of PTH 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.

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PTH is secreted from the parathyroid gland. It is principally controlled by the level of calcium in blood. Since the more osteoclasts means the more calcium releases from bone into blood, therefore, in order to counter balance the high level of calcium in blood, the secretion rate of PTH from the parathyroid gland will be decreased [10], [11]. However, the secretion rate of PTH was observed to be always above the basal level. They also observed that there is a linear relationship between the rate of PTH elimination from the blood plasma and the rate of cellular production/secretion. The equation for the rate of PTH secretion above the basal level is then assumed to take the form

$$\frac{dX}{dT} = \frac{u_1}{w_1 + w_2 Y} - v_1 X \tag{1}$$

where the first term on the right-hand side of (1) represents the secretion rate of PTH from the parathyroid gland which decreases with the increase in the number of active osteoclastic cells, while u_1, w_1 and w_2 are positive constants. The last term on the right-hand side is the removal rate of PTH from the system at the rate, which is proportional to its current level with the removal rate constant v_1.

Osteoclasts are derived from the hemopoietic cells. The hemopoietic stem cells proliferate osteoclast progenitors or preosteoclast precursor cells and then preosteoclasts precursors differentiate into preosteoclasts. After that, preosteoclasts differentiate into osteoclasts [9]. The works of Kong *et al.* [12], Takahashi *et al.* [13] and Burgess *et al.* [14] suggested that the differentiation of osteoclasts requires the presence of osteoblasts and their precursors which respond to hormones and paracrine messengers necessary for the differentiation of osteoclasts. The responsiveness of osteoblasts and their precursors to those necessary factors then regulates the responsiveness of preosteoclasts and osteoclasts. It has been observed clinically that there is a time delay in the differentiation of osteoclasts [6], [15]. The proliferation and differentiation of osteoclasts are stimulated indirectly by PTH through the activation of osteoblasts since osteoclasts and their precursors do not possess PTH receptors while osteoblasts and their precursors possess those [6], [16], [17]. However, it has been observed that when the level of PTH increases further, the production of osteoclasts will be decreased [6]. Therefore, the dynamics of the active osteoclastic population can be described by the following equation

$$\frac{dY}{dT} = \left(\frac{u_2 X}{w_3 + w_4 X^2} \right) Y(t-\tau) Z(t-\tau) - v_2 Y \tag{2}$$

where the first term on the right-hand side of (2) represents the stimulating effect of PTH on the reproduction of active osteoclasts through the osteoclastic differentiation process which requires the presence of osteoblasts and bone marrow stromal cells [12]-[14]. The last term on the right-hand side is the removal rate of active osteoclasts from the system with the removal rate constant v_2. u_2, w_3 and w_4 are positive constants.

Osteoblasts are derived from the mesenchymal stem cells. The stromal stem cells proliferate osteoprogenitors or preosteoblast precursors and then preosteoblasts precursors proliferate preosteoblasts. After that, preosteoblasts differentiate into osteoblats and then osteoblasts become osteocytes [9]. There are several factors involve in the proliferation and differentiation of osteoblasts such as FGF, IGF-I, TGF-beta and PTH [18]. In addition, it has been observed clinically that there is a time delay in the differentiation of osteoblasts [6], [15]. On the other hand, PTH works by increasing the number of osteoblasts and by extending their working life by preventing their death through a suicidal process called apoptosis [19], [20]. However, it has been clinically observed that PTH has both stimulating and inhibiting effects on the osteoblastic differentiation process [1]. The dynamics of the osteoblastic population can be described by the following equation

$$\frac{dZ}{dT} = u_3 X - \left(\frac{u_4 X}{w_5 + w_6 X} \right) Z(t-\tau) - v_3 Z \tag{3}$$

where the first term on the right-hand side of (3) represents the reproduction of active osteoblasts through the stimulating effect of PTH on osteoblastic cells, while the second term on the right-hand side of (3) accounts for the inhibition of osteoblastic differentiation due to PTH as observed clinically in [21]. The last term is the removal rate of osteoblasts from the system with the removal rate constant v_3. u_3, u_4, w_5 and w_6 are positive constants.

III. MODEL ANALYSIS

In order to investigate the possibility of periodic dynamics in our system of (1)-(3), we let $P = \frac{X}{X^*}$, $C = \frac{Y}{Y^*}$, $B = \frac{Z}{Z^*}$, $t = \frac{T}{T_0}$, $a_1 = \frac{u_1}{w_2}$, $a_2 = \frac{u_2}{w_4}$, $a_3 = u_3$, $a_4 = \frac{u_4}{w_6}$, $d_1 = v_1$, $d_2 = v_2$, $d_3 = v_3$, $k_1 = \frac{w_1}{w_2}$, $k_2 = \frac{w_3}{w_4}$, $k_3 = \frac{w_5}{w_6}$, the system (1)-(3) can then be written as follows

$$\frac{dP}{dt} = \frac{a_1}{k_1 + C} - d_1 P \tag{4}$$

$$\frac{dC}{dt} = \left(\frac{a_2 P}{k_2 + P^2} \right) B(t-\tau) C(t-\tau) - d_2 C \tag{5}$$

$$\frac{dB}{dt} = a_3 P - \left(\frac{a_4 P}{k_3 + P} \right) B(t-\tau) - d_3 B \tag{6}$$

We now assume that (P_S, C_S, B_S) is a non washout steady state of the system (4)-(6). Letting $x = P - P_S$, $y = C - C_S$, $z = B - B_S$, we will be led to the following linearized system of (4)-(6)

$$\begin{pmatrix} \dot{x} \\ \dot{y} \\ \dot{z} \end{pmatrix} = J_S \begin{pmatrix} x \\ y \\ z \end{pmatrix} \tag{7}$$

where J_S is the corresponding Jacobian matrix evaluated at (P_S, C_S, B_S), namely

$$J_S = \begin{pmatrix} -d_1 & \dfrac{-d_1 P_S}{k_1 + C_S} & 0 \\ \dfrac{a_2\left(k_2 - P_S^2\right) B_S C_S}{\left(k_2 + P_S^2\right)^2} e^{-2\lambda\tau} & 0 & \dfrac{d_2 C_S}{B_S} \\ a_3 - \dfrac{a_3 k_3}{k_3 + P_S} + \dfrac{d_3 k_3 B_S}{\left(k_3 + P_S\right) P_S} & 0 & \dfrac{-a_3 P_S}{B_S} \end{pmatrix} \tag{8}$$

For simplicity, we introduce new parameters by letting

$$a = -D - E$$
$$b = DE$$
$$c = -F$$
$$d = -GH + GI - GJ$$
$$e = EF$$

where

$$D = -d_1$$
$$E = \frac{-a_3 P_S}{B_S}$$
$$F = \left(\frac{-d_1 P_S}{k_1 + C_S}\right)\left(\frac{a_2\left(k_2 - P_S^2\right) B_S C_S}{\left(k_2 + P_S^2\right)^2}\right)$$
$$G = \left(\frac{-d_1 P_S}{k_1 + C_S}\right)\left(\frac{d_2 C_S}{B_S}\right)$$
$$H = a_3$$
$$I = \frac{a_3 k_3}{k_3 + P_S}$$
$$J = \frac{d_3 k_3 B_S}{\left(k_3 + P_S\right) P_S}$$

Then, the characteristic equation of J_S can be written as

$$F(\lambda) \equiv \left(\lambda^3 + a\lambda^2 + b\lambda + d\right) + \left(c\lambda + e\right) e^{-2\lambda\tau} = 0 \tag{9}$$

According to the Hopf bifurcation theory, for a periodic solution to exist, it is necessary that (9) has a pair of purely imaginary complex roots $\lambda = \pm i\omega$ for some value of τ. In order that such a pair can be found, one must have $F(i\omega) = 0$, that is,

$$(i\omega)^3 + a(i\omega)^2 + b(i\omega) + d + \left(c(i\omega) + e\right) e^{-2(i\omega)\tau} = 0 \tag{10}$$

Equating real and imaginary parts on the left of (10) to zero, we obtain the following equations:

$$a\omega^2 - d = e\cos(2\omega\tau) + c\omega\sin(2\omega\tau) \tag{11}$$
$$\omega^3 - b\omega = c\omega\cos(2\omega\tau) - e\sin(2\omega\tau) \tag{12}$$

By squaring both sides of (11) and (12), and then adding, we obtain

$$\phi(\omega) \equiv \omega^6 + \left(a^2 - 2b\right)\omega^4 + \left(b^2 - 2ad - c^2\right)\omega^2 + \left(d^2 - e^2\right) = 0 \tag{13}$$

Letting $\beta = \omega^2$, (13) can be written as

$$\sigma(\beta) \equiv \beta^3 + U\beta^2 + V\beta + W = 0 \tag{14}$$

where $U = a^2 - 2b, V = b^2 - 2ad - c^2, W = d^2 - e^2$.

Hence, (9) will have a pair of complex solutions, $\lambda = \pm i\omega$ provided that (14) has a positive real solution $\beta = \omega^2 > 0$.

According to the work of Ruan and Wei [22], for a polynomial in the form of (14), the following lemmas are obtained and so we state them without proofs.

Lemma 1 If $W < 0$, then (14) has at least one positive root.

Lemma 2 If $W \geq 0$, then the necessary condition for (14) to have a positive real root is that $\Theta \equiv U^2 - 3V > 0$.

Lemma 3 If

$$W \geq 0 \quad \text{and} \quad \Theta \geq 0 \tag{15}$$

then (14) has a positive root if and only if

$$\beta_1 > 0 \quad \text{and} \quad \sigma(\beta_1) \leq 0 \tag{16}$$

where $\beta_1 \equiv \dfrac{-U + \sqrt{\Theta}}{3}$.

Therefore, by the above lemmas, we assume that either $W<0$ or (15) and (16) hold so that (14) has positive roots. Without loss of generality, we assume that it has three positive roots denoted β_1, β_2 and β_3. Then, (13) has three positive roots

$$\omega_k=\sqrt{\beta_k}\ ,\quad k=1,2,3.$$

Now, let $\tau_0>0$ be the smallest of such τ for which, $\lambda=\pm i\omega$. Substituting ω_k into (11)-(12) and solving for τ, one obtains

$$\tau_k^{(j)}=\frac{1}{2\omega_k}\arcsin\left(\frac{(ac-e)\omega_k^3+(be-cd)\omega_k}{c^2\omega_k^2+e^2}\right)+\frac{(j-1)2\pi}{\omega_k} \tag{17}$$

where $k=1,2,3,$ and $j=1,2,...$

Theorem 1 Suppose that

$$a>0,\ d+e>0 \qquad \text{and} \qquad a(b+c)>(d+e) \tag{18}$$

(a) If $W\geq 0$ and $\Theta<0$, then all roots of (9) have nonzero real parts for all $\tau\geq 0$.

(b) If either

$$W<0 \tag{19}$$

or $$W\geq 0,\ \Theta\geq 0,\ \beta_1>0 \quad \text{and} \quad \sigma(\beta_1)\leq 0 \tag{20}$$

then all roots of (9) have negative real parts when $\tau\in[0,\tau_0)$, where

$$\tau_0=\min_{1\leq k\leq 3,\ j\geq 1}\left\{\tau_k^{(j)},\tau_k^{(j)}>0\right\} \tag{21}$$

with $\tau_k^{(j)}$ defined in (17).

Proof

(a) By contradiction, if (9) has a root with zero real part for some $\tau\geq 0$ which implies that (14) has a positive real root. By Lemma 2, the necessary condition of this is that $\Theta\geq 0$ which contradicts the fact that $\Theta<0$. Therefore, all roots of (9) have nonzero real parts for all $\tau\geq 0$.

(b) For $\tau=0$, equation (9) is reduced to

$$\lambda^3+a\lambda^2+(b+c)\lambda+(d+e)=0 \tag{22}$$

Since the conditions in (18) hold, the Routh-Hurwitz criterion then implies that all roots of (9) have negative real parts and hence, all roots, $\lambda(\tau)$ of (9) have negative real parts at the point $\tau=0$. From the continuity of $\lambda(\tau)$, all roots of (9) will have negative real parts for values of τ in some open interval containing $\tau=0$. Therefore, all roots of (9) have negative real parts for positive values of $\tau\in[0,\tau_c)$ for some $\tau_c>0$.

However, τ_c is defined by (21) to be the minimum of all the positive $\tau=\tau_k^{(j)}$ where $\tau_k^{(j)}$ is defined as in (17). Hence, τ_0 is the minimum of such positive τ's for which the real parts of some roots of (9) vanish, provided that (19) or (20) holds. Thus, $\tau_c=\tau_0$, which completes the proof.

Theorem 1 implies that if either (19) or (20) are satisfied and (18) holds, the steady state (P_S,C_S,B_S) of our system of (4)-(6) is stable for some values of $\tau\in[0,\tau_0)$. At $\tau=\tau_0$, $\mathrm{Re}(\lambda(\tau))=0$ by the definition of τ_0 and hence the stability of the steady state (P_S,C_S,B_S) is lost at $\tau=\tau_0$. In order for a Hopf bifurcation to occur, and hence a periodic solution of our system of (4)-(6) may be expected, we still need to show that

$$\left.\frac{d\,\mathrm{Re}(\lambda(\tau))}{d(\tau)}\right|_{\tau=\tau_0}\neq 0$$

which is done in the next theorem.

Theorem 2 Suppose that conditions (19) or (20) in Theorem 1 hold, then $\lambda=\pm i\omega$ is a pair of purely imaginary roots of (9). Moreover,

$$\left.\frac{d\,\mathrm{Re}(\lambda(\tau))}{d(\tau)}\right|_{\tau=\tau_0}\neq 0 \tag{23}$$

provided that

$$\sigma'(\beta_0)\neq 0 \tag{24}$$

where $\beta_0=\omega_0^2$, $\omega_0=\omega_k\big|_{\tau=\tau_0}$.

Proof

The first part of this theorem is an immediate consequence of Theorem 1 and the definition of τ_0. In order to prove that $\left.\frac{d\,\mathrm{Re}(\lambda(\tau))}{d(\tau)}\right|_{\tau=\tau_0}\neq 0$, let us consider (9),

$$F(\lambda)=\lambda^3+a\lambda^2+b\lambda+d+(c\lambda+e)e^{-2\lambda\tau}=0$$

Then,

$$\begin{aligned}\frac{dF(\lambda)}{d\tau}&=\left(3\lambda^2+2a\lambda+b-2(c\lambda+e)\tau e^{-2\lambda\tau}\right)\frac{d\lambda}{d\tau}\\&\quad-2(c\lambda+e)\lambda e^{-2\lambda\tau}\\&=0\end{aligned}$$

and hence,

$$\left(\frac{d\lambda}{d\tau}\right)^{-1}=\frac{3\lambda^2+2a\lambda+b}{2(c\lambda+e)\lambda e^{-2\lambda\tau}}-\frac{\tau}{\lambda}+\frac{c}{2(c\lambda+e)\lambda}$$

Since $(c\lambda+e)e^{-2\lambda\tau}=-\left(\lambda^3+a\lambda^2+b\lambda+d\right)$, then

$$\left(\frac{d\lambda}{d\tau}\right)^{-1}=\frac{3\lambda^2+2a\lambda+b}{-2\left(\lambda^3+a\lambda^2+b\lambda+d\right)\lambda}-\frac{\tau}{\lambda}+\frac{c}{2(c\lambda+e)\lambda}$$

At $\tau=\tau_0$, $\lambda=i\omega_0$ and thus,

$$\left(\frac{d\lambda}{d\tau}\right)^{-1}\Bigg|_{\tau=\tau_0}=\frac{\left(-3\omega_0^2+b\right)+i\left(2a\omega_0\right)}{2\left[\left(-\omega_0^4+b\omega_0^2\right)+i\left(a\omega_0^3-d\omega_0\right)\right]}+i\left(\frac{\tau}{\omega_0}\right)+\frac{c}{2\left(-c\omega_0^2+i(e\omega_0)\right)}$$

Therefore,

$$\mathrm{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\Bigg|_{\tau=\tau_0}=\frac{3\omega_0^4+\left(2a^2-4b\right)\omega_0^2+\left(b^2-2ad\right)}{2\left[\omega_0^6+\left(a^2-2b\right)\omega_0^4+\left(b^2-2ad\right)\omega_0^2+d^2\right]}-\frac{c^2}{2\left(c^2\omega_0^2+e^2\right)}$$

(13) implies that

$$\omega_0^6+\left(a^2-2b\right)\omega_0^4+\left(b^2-2ad\right)\omega_0^2+d^2=c^2\omega_0^2+e^2$$

then,

$$\mathrm{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\Bigg|_{\tau=\tau_0}=\frac{3\omega_0^4+2\left(a^2-2b\right)\omega_0^2+\left(b^2-2ad-c^2\right)}{2\left(c^2\omega_0^2+e^2\right)}=\frac{\sigma'\left(\omega_0^2\right)}{2\left(c^2\omega_0^2+e^2\right)}\neq 0$$

Hence, $\mathrm{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\Big|_{\tau=\tau_0}\neq 0$ and the proof is complete. We thus have the following result.

Theorem 3 If either (19) or (20) holds, then a periodic solution occurs in our model equations (4)-(6) for a positive time delay $\tau=\tau_0$ given by (21) provided that (19) and (24) are satisfied.

IV. Numerical Investigations

A computer simulation of the system (4)-(6) is presented in Fig. 1, with parametric values chosen to satisfy the condition in Theorem 3. The corresponding time courses of the PTH concentration, the number of active osteoclasts and the number of active osteoblasts are as shown in Fig. 1a, Fig. 1b and 1c, respectively, showing a periodic behavior as theoretically predicted.

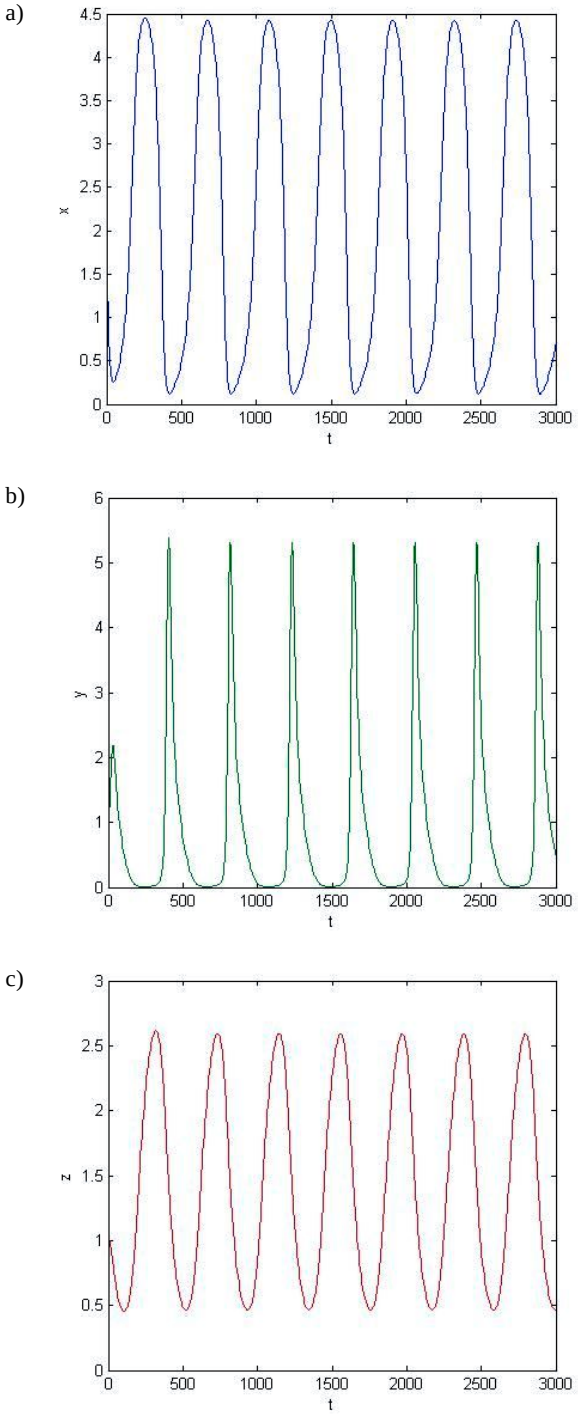

Fig. 1 A computer simulation of the model systems (4)-(6) with $a_1=0.05$, $a_2=0.675$, $a_3=0.01$, $a_4=0.005$, $k_1=0.1$, $k_2=0.5$, $k_3=0.025$, $d_1=0.1$, $d_2=0.2$, $d_3=0.2$, $\tau=10$, $x(0)=2$, $y(0)=1$, $z(0)=1$. (a) The corresponding time courses of PTH (x) (b) the number of active osteoclastic cells (y), and (c) the number of active osteoblastic cells (z), showing a periodic behavior exhibited by our model.

A computer simulation of the system (4)-(6) is presented in Fig. 2. The corresponding time courses of the PTH concentration, the number of active osteoclasts and the number of active osteoblasts are as shown in Fig. 2a, Fig. 2b and 2c, respectively, showing that the solution tends to a stable equilibrium.

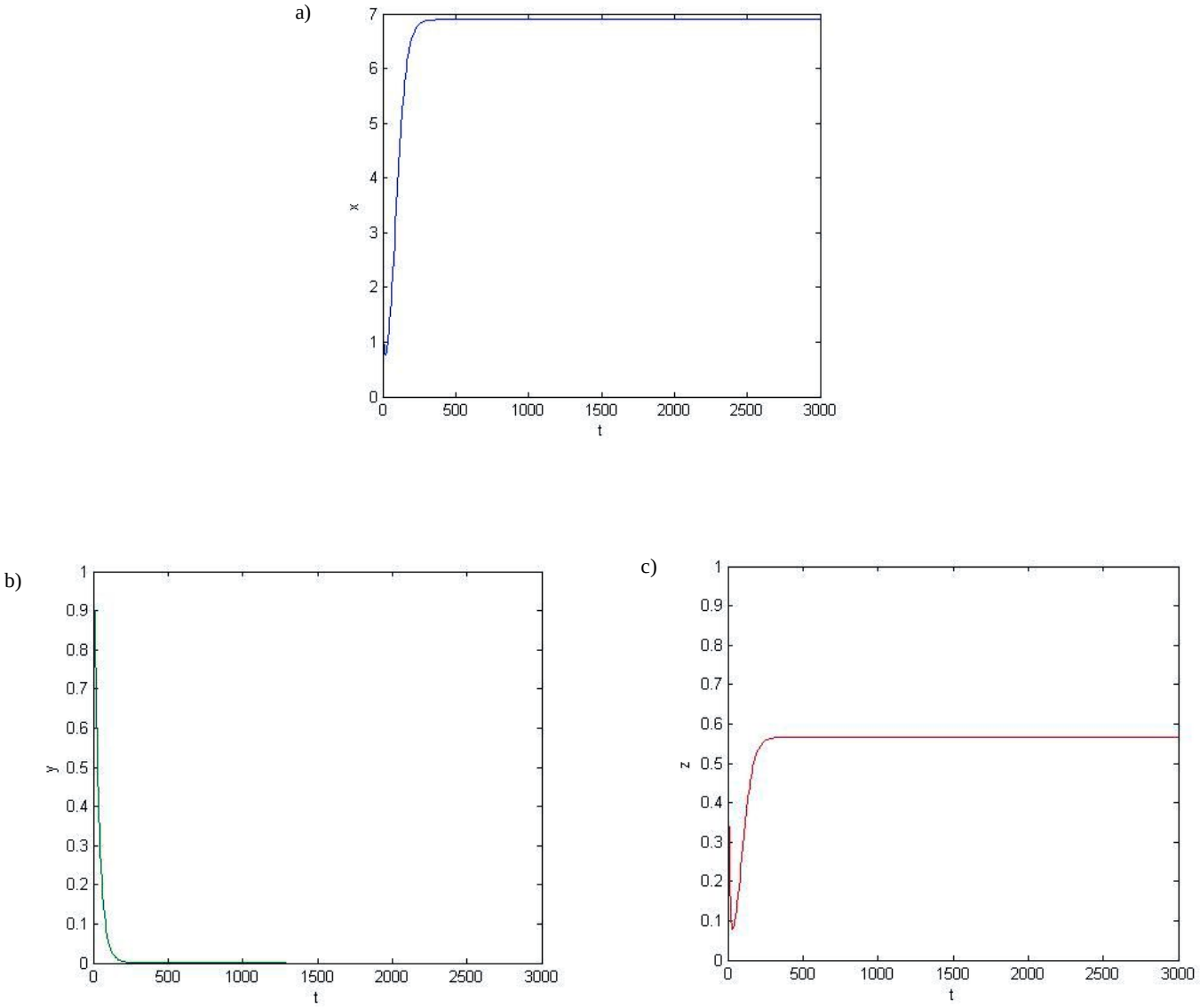

Fig. 2 A computer simulation of the model systems (4)-(6) with $a_1 = 0.05$, $a_2 = 0.8$, $a_3 = 0.01$, $a_4 = 0.007$, $k_1 = 0.01$, $k_2 = 0.05$, $k_3 = 0.01$, $d_1 = 0.1$, $d_2 = 0.3$, $d_3 = 0.01$, $\tau = 10$, $x(0) = 2$, $y(0) = 1$, $z(0) = 1$. (a) The corresponding time courses of PTH (x) (b) the number of active osteoclastic cells (y), and (c) the number of active osteoblastic cells (z), showing that the solution tends toward a stable equilibrium.

A computer simulation of the system (4)-(6) is presented in Fig. 3. The corresponding time courses of the PTH concentration, the number of active osteoclasts and the number of active osteoblasts are as shown in Fig. 3a and Fig. 3b, respectively, showing the irregular patterns exhibited by our model.

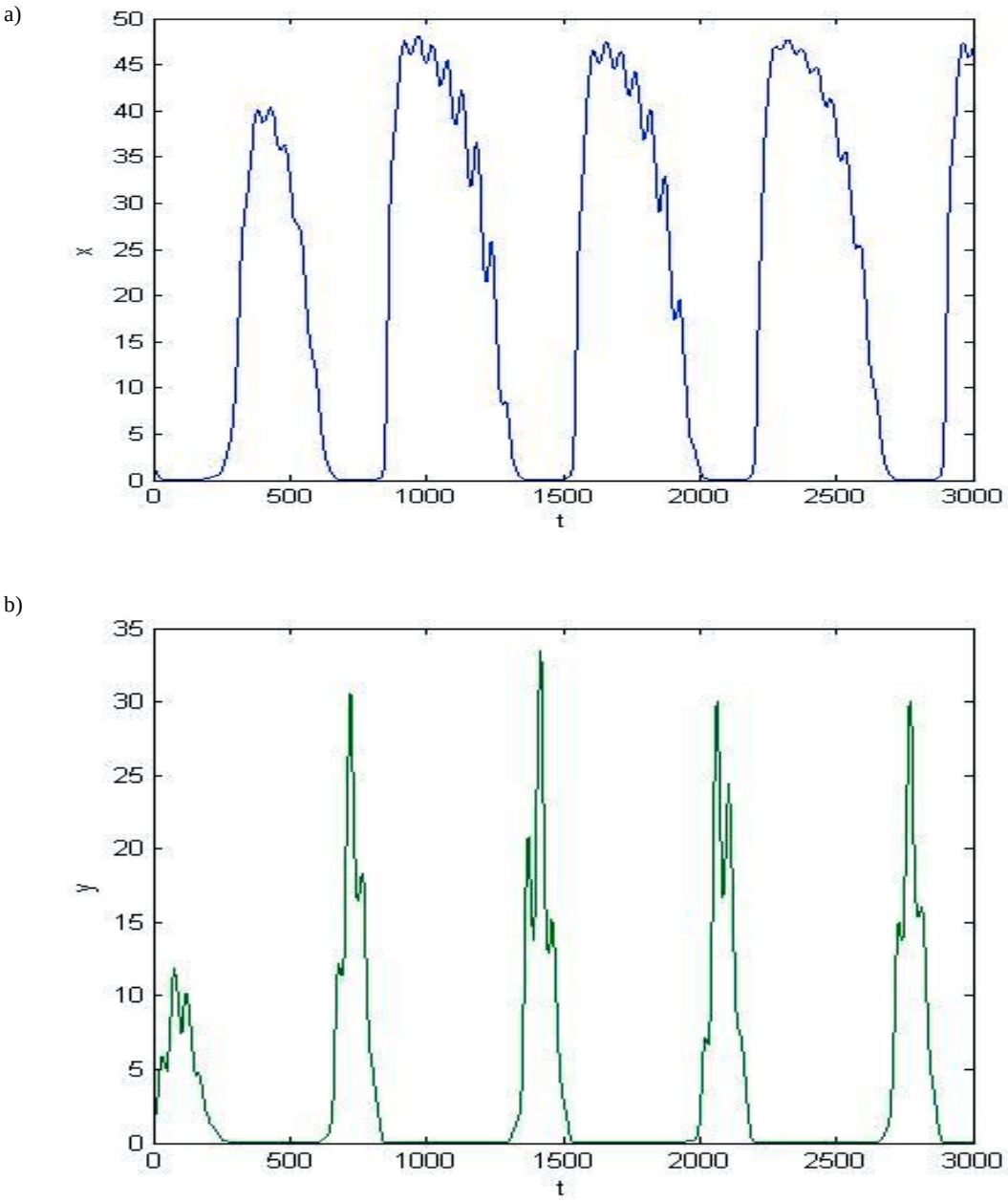

Fig. 3 A computer simulation of the model systems (4)-(6) with $a_1 = 0.09$, $a_2 = 0.08375$, $a_3 = 0.01125$, $a_4 = 0.125, k_1 = 0.087, k_2 = 1.5$, $k_3 = 0.025$, $d_1 = 0.15$, $d_2 = 0.034375$, $d_3 = 0.0125$, $\tau = 1$, $x(0) = 2$, $y(0) = 1$, $z(0) = 1$. (a) The corresponding time courses of PTH (x) and (b) the number of active osteoclastic cells (y), showing the irregular patterns exhibited by our model.

V. CONCLUSION

In this paper, we modified the model proposed by Rattanakul *et al.* [5] to incorporate the time delay which has been observed in the clinical evidences [6], [15]. Hopf bifurcation theorem [23]-[28] is then utilized to obtain the conditions on the system parameters for which a periodic behavior observed in the pulsatile secretion of PTH [29] exists. Computer simulations of the model are then carried out by using Runge-Kutta method [30]-[33]. Both of theoretical and numerical results show that the periodic behavior can be exhibited by our model which closely resembles to the serum level of PTH that has been observed clinically in [29]. Moreover, we also carried out a numerical simulation of the model to investigate the possibility that the irregular pattern observed in the pulsatile secretion of PTH can be occurred. The result shows that our model can exhibit an irregular pattern corresponding to the pulsatile secretion of PTH observed clinically in [34], [35], even though the model is kept relatively simple.

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