A Delay-Differential Equations Model of Bone Remodeling Process

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***Abstract*—**A mathematical model of bone remodeling process is modified here in order to incorporate the effect of time delay which has been observed clinically in such process. Hopf bifurcation theorem is then applied to the model so that the conditions on the system parameters for which a periodic solution exists are derived.

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

I. Introduction

BONE is a dynamic tissue which is constantly in a process of turnover or self-renewal, in response to mechanical stress and hormonal changes and to maintain mineral homeostasis [1], [2]. This process is known as bone remodeling process consisting of three stages: activation of the remodeling site, resorption of bone by osteoclasts, and bone formation by osteoblasts [3]. Bone imbalance can occur if the osteoclasts produce an excessively deep resorption space, if the osteoblasts fail to completely refill the resorption space, or if both events occur resulting in the increase of bone loss leading to the osteoporosis [4]-[6]. Osteoporosis is a most common bone disease. It is a bone disease which is characterized by low bone mineral density, the structural deterioration of bone and an increased risk of fracture [7], [8]. There are several factors that involve bone remodeling process such as parathyroid hormone, calcitonin, vitamin D and estrogen [2], [4]-[6].

There are many attempts to develop mathematical models to describe bone remodeling process [9]-[12]. There is only one attempt [10] to investigate the effect of time delay observed clinically in [1], [10]. However, the model that proposed in [10] did not incorporate the effects of parathyroid and osteoblasts on the osteoclastic differentiation. Therefore, in this paper, we then investigate the effect of time de lay in bone remodeling process by modifying the model that has been proposed by Rattanakul *et al.* [9].

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II. Model Modification

We now modify the nonlinear mathematical model proposed by Rattanakul *et al.* [9] to incorporate the effect of time delay 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.

Osteoclasts resorb bone and liberate calcium, therefore the increase in the number of active osteoclastic cells results in the increase in the calcium level in blood. On the other hand, parathyroid hormone (PTH) secreted from the parathyroid gland plays an important role in maintaining the extracellular Ca^{2+} concentration within the very narrow range [13]. The decrease in the serum level of calcium leads to the increase in the secretion of PTH [13]. However, low levels of PTH are secreted even when blood calcium levels are high [13]. 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 $X(t)$ in order to counter balance the high level of calcium in blood resulted from the large 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.

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Osteoclasts are derived from hemopoietic stem cells of the monocyte/macrophage lineage [2]. The differentiation and activation of osteoclasts are regulated principally by osteoblasts through the cell-to-cell interaction with osteoclasts [10], [14]. It has also been observed clinically that there is a time delay in bone formation and resorption process [1], [10]. On the other hand, PTH also plays an important role on the osteoclastic differentiation. It stimulates the differentiation of osteoclasts indirectly through the activation of osteoblasts since osteoclasts and their precursors do not possess PTH receptors while osteoblasts and their precursors possess those [10], [14], [15]. However, it has been observed that when the level of PTH increases further, the production of osteoclasts will be decreased [10]. Therefore, the dynamics of the active osteoclastic population can be described by the following equation

$$\frac{dY}{dT}=\left(\frac{u_2X}{w_3+w_4X^2}\right)Y(t-\tau)Z(t-\tau)-v_2Y \qquad (2)$$

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 since they respond to hormones and paracrine messengers which are necessary for the differentiation of osteoclasts [16]-[18]. 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 proliferation and differentiation of osteoblasts involve many factors such as FGF, IGF-I, TGF-beta and PTH [19]. Moreover, it has also been observed clinically that there is a time delay in bone formation and resorption process [1], [10]. 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 [20], [21]. However, it has been clinically observed that PTH exerts both stimulating and inhibiting effects on the osteoblastic differentiation process depending on the differentiation stages [7]. The dynamics of the osteoblastic population can be described by the following equation

$$\frac{dZ}{dT}=u_3X-\left(\frac{u_4X}{w_5+w_6X}\right)Z(t-\tau)-v_3Z \qquad (3)$$

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 [22]. The last term, it is assumed that osteoblasts is removed from the system with the removal rate constant v_3. u_3, u_4, w_5 and w_6 are positive constants.

III. HOPF BIFURCATION 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

$$\frac{dP}{dt}=\frac{a_1}{k_1+C}-d_1P \qquad (4)$$

$$\frac{dC}{dt}=\left(\frac{a_2P}{k_2+P^2}\right)B(t-\tau)C(t-\tau)-d_2C \qquad (5)$$

$$\frac{dB}{dt}=a_3P-\left(\frac{a_4P}{k_3+P}\right)B(t-\tau)-d_3B \qquad (6)$$

We now assume that (P_S, C_S, B_S) is a non washout steady 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)

$$\begin{pmatrix}\dot{x}\\ \dot{y}\\ \dot{z}\end{pmatrix}=J_S\begin{pmatrix}x\\ y\\ z\end{pmatrix} \qquad (7)$$

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

$$J_S=\begin{pmatrix}-d_1 & \frac{-d_1P_S}{k_1+C_S} & 0\\ \frac{a_2\left(k_2-P_S^2\right)B_SC_S}{\left(k_2+P_S^2\right)^2}e^{-2\lambda\tau} & 0 & \frac{d_2C_S}{B_S}\\ a_3-\frac{a_3k_3}{k_3+P_S}+\frac{d_3k_3B_S}{(k_3+P_S)P_S} & 0 & \frac{-a_3P_S}{B_S}\end{pmatrix} \qquad (8)$$

For simplicity, we introduce new parameters by letting

$$a=-D-E$$

$$b=DE$$

$$c=-F$$

$$d=-GH+GI-GJ$$

$$e=EF$$

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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

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

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,

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

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

$$a\omega^2 - d = e\cos(2\omega\tau) + c\omega\sin(2\omega\tau) \qquad (11)$$

$$\omega^3 - b\omega = c\omega\cos(2\omega\tau) - e\sin(2\omega\tau) \qquad (12)$$

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

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

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

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

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 [23], 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

$$W \geq 0 \quad \text{and} \quad \Theta \geq 0 \qquad (15)$$

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

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

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

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

where $k = 1, 2, 3,$ and $j = 1, 2, \ldots$

Theorem 1 Suppose that

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

(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

$$W < 0 \qquad (19)$$

or $W \geq 0,\ \Theta \geq 0,\ \beta_1 > 0$ and $\sigma(\beta_1) \leq 0$ (20)

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

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

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

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

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

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

Therefore,

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

(13) implies that

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

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then,

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

$$= \frac{\sigma'\left(\omega_0^2\right)}{2\left(c^2\omega_0^2+e^2\right)}$$

$$\neq 0$$

Hence, $\operatorname{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\Big|_{\tau=\tau_0} \neq 0$ 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. CONCLUSION

We modify the model proposed by Rattanakul *et al.* [9] to incorporate the time delay which has been observed in the clinical evidences [1], [10]. The conditions on the system parameters for which a periodic behavior observed in the pulsatile secretion of PTH [24] exists are then derived.

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