A Delay-Differential Equation Model of Bone Remodeling Process: Effects of Estrogen Supplements

Wannapa Panitsupakamon and Chontita Rattanakul

***Abstract*—**We modify a mathematical model proposed for describing bone resorption and bone formation process based on the effect of calcitonin to investigate the effect of time delay on bone remodeling process. The model is then analyzed by using Hopf bifurcation theorem. The conditions on the system parameters are then derived so that a periodic solution can be assured. A computer simulation is carried out in order to support our theoretical prediction. Moreover, the effects of estrogen supplement in different manner are also investigated numerically.

***Keywords*—**Bone remodeling process, Calcitonin, Mathematical model, Hopf bifurcation, Estrogen supplement.

I. Introduction

In postmenopausal women, one of the most common bone diseases is osteoporosis [1]. It occurs from the imbalance of bone remodeling process where the net increase of bone resorption is over bone deposition [1], [2]. Bone remodeling process consists of both bone formation process by osteoblastic cells and bone resorption process by osteoclastic cells. The process begins with osteoclasts appear on an inactive surface of bone, a lacuna on the surface of cancellous bone or a resorption tunnel in cortical bone is excavated. Osteoclasts are then replaced by osteoblasts. Finally, the resorption cavity is then refilled by osteoblasts [3], [4]. At the end of the process, if osteoblasts fill the resorption cavity incompletely, bone loss will be occurred and osteoporosis can then be expected [3], [4]. Bone remodeling process involves with several hormones such as parathyroid hormone (PTH), calcitonin (CT), estrogen, vitamin D and prolactin. There are many attempts [5]–[14] to develop mathematical models to describe bone remodeling process, however, none of them included the effects of both calcitonin and time delay observed clinically in such process. Hence, in this paper, a mathematical model of bone remodeling process that incorporates the effects of both calcitonin and time delay will be developed.

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II. Model Modification

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 osteoclasts and active osteoblasts, respectively, resulting from the differentiation, and activation of their precursors.

In 2011, Rattanakul and Rattanamongkonkul [12] proposed a mathematical model to describe bone remodeling process based on the effect of calcitonin as in (1)-(3):

$$\frac{dx}{dt} = \left(\frac{a_1 + a_2 y}{k_1 + y}\right) - b_1 x \tag{1}$$

$$\frac{dy}{dt} = \left(a_3 - \frac{a_4 x}{k_2 + x^2}\right) yz - b_2 y \tag{2}$$

$$\frac{dz}{dt} = \left(\frac{a_5 + a_6 x}{k_3 + x}\right) z - b_3 z \tag{3}$$

where all parameters $a_1, a_2, a_3, a_4, a_5, a_6, b_1, b_2, b_3, k_1, k_2$ and k_3 are positive constants. (1) represents the rate of change of the concentration of CT above the basal level in blood at time t. The dynamics of the active osteoclastic population is described by (2) while (3) stands for the dynamics of the active osteoblastic population. However, the effect of time delay observed clinically in the process [5] did not take into account.

In 2000, Kroll [5] observed that there is a delay time of 1 hour for differentiation of preosteoblast precursors into preosteoblasts and 2 hours for the differentiation of preosteoblasts into osteoblasts. We then assume that there is also a delay time of 1 hour for differentiation of preosteoclast precursors into preosteoclasts and 2 hours for the differentiation of preosteoclasts into osteoclasts.

Therefore, we modify the model developed in [12] to incorporate the effect of time delay in the differentiation of osteoclasts and osteoblasts as follows.

Firstly, calcitonin (CT) is secreted from the thyroid gland by the parafollicular C cells [15]. The release of CT is controlled by the level of calcium in blood. When the level of calcium in blood rises above the normal range, the thyroid gland will release CT in order to counter balance the high level of calcium in blood. CT has an inhibiting effect on bone resorption by inhibiting activity of osteoclastic cells [15]. CT will bind to its receptors on the surface of osteoclastic cells and results in the increase of cAMP formation immediately, the expanse and activity of the ruffled border is then diminished within minutes [15]. 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 [15]. Hence, the equation for the rate of change of the level of CT is then assumed to have the form

$$\frac{dx}{dt}=\left(\frac{c_1+c_2y}{m_1+y}\right)-d_1x \tag{4}$$

where the first term on the right-hand side of (4) represents the secretion rate of CT from parafollicular cells in the thyroid gland. The last term is the removal rate constant d_1. c_1, c_2 and m_1 are positive constants.

Secondly, osteoclasts are bone resorbing cells that derived from hemopoietic stem cells [15]. The differentiation and activation of osteoclasts require the presence of osteoblasts since osteoclasts lack of the necessary receptors for the involving hormone such as PTH [5]. Moreover, the cell-to-cell interaction of osteoclast precursors and osteoblasts are also necessary for the derivation of osteoclasts [16]. Therefore, the dynamics of the active osteoclastic population is then assumed to have the form

$$\frac{dy}{dt}=\left(c_3-\frac{c_4x}{m_2+x^2}\right)y(t-\tau)z(t-\tau)-d_2y \tag{5}$$

where the first term on the right-hand side of (5) represents the reproduction of active osteoclasts and the inhibitory effect of calcitonin on active osteoclasts reproduction. The term $y(t-\tau)$ represents the number of active osteoclasts at time $t-\tau$ and the term $z(t-\tau)$ represents the number of active osteoblasts at time $t-\tau$. The last term represents the removal rate of active osteoclasts from the system. c_3, c_4, d_2 and m_2 are positive constants.

Finally, osteoblasts are bone forming cells that derived from the mesenchymal stem cells [17]. The derivation of osteoblasts involves many factors such as fibroblast growth factor (FGF), Insulin-like growth factor-I (IGF-I),transforming growth factor-beta (TGF-beta), PTH including CT [18]. It has been observed that CT enhances osteoblastic bone formation [19], [20]. The dynamics of the osteoblastic population is then assume to have the form

$$\frac{dz}{dt}=\left(\frac{c_5+c_6x}{m_3+x}\right)z(t-\tau)-d_3z \tag{6}$$

where the first term on the right-hand side of (6) represents the stimulating effect of CT on the reproduction of active osteoblasts. The last term is the removal rate of active osteoblasts from the system. c_5, c_6, d_3 and m_3 are positive constants. Therefore, our delay-differential equations model of bone remodeling process, therefore, consists of (4)-(6).

III. HOPF BIFURCATION ANALYSIS

In order to investigate the possibility of periodic dynamics in our system of (4)-(6), we now assume that (x_S, y_S, z_S) is a non washout steady state of the system (4)-(6).

Letting $u=x-x_S, v=y-y_S,\ w=z-z_S$, we will be led to the following linearized system of (4)-(6)

$$\begin{pmatrix}\dot{u}\\ \dot{v}\\ \dot{w}\end{pmatrix}=J_S\begin{pmatrix}u\\ v\\ w\end{pmatrix} \tag{7}$$

where J_S is the corresponding Jacobian matrix evaluated at (x_S, y_S, z_S), namely

$$J_S=\begin{pmatrix}-d_1 & \dfrac{c_2-d_1x_S}{m_1-y_S} & 0\\ \dfrac{c_4\left(x_S^2-m_2\right)y_Sz_S}{\left(m_2+x_S^2\right)^2}e^{-2\lambda\tau} & 0 & \dfrac{d_2y_S}{z_S}\\ \dfrac{d_3\left(c_6m_3-c_5\right)z_S}{\left(m_3+x_S\right)\left(c_5+c_6x_S\right)} & 0 & 0\end{pmatrix} \tag{8}$$

For simplicity, we introduce new parameters by letting

$$a=d_1,$$

$$b=\frac{d_2y_S}{z_S}\left(\frac{d_1x_S-c_2}{m_1-y_S}\right)\left(\frac{d_3\left(c_6m_3-c_5\right)z_S}{\left(m_3+x_S\right)\left(c_5+c_6x_S\right)}\right),$$

$$c=\left(\frac{d_1x_S-c_2}{m_1-y_S}\right)\left(\frac{c_4\left(x_S^2-m_2\right)y_Sz_S}{\left(m_2+x_S^2\right)^2}\right)$$

Then, the characteristic equation of J_S can be written as

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

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,

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

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

$$a\omega^2 - b = c\omega\sin(2\omega\tau) \quad (11)$$

$$\omega^3 = c\omega\cos(2\omega\tau) \quad (12)$$

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

$$\phi(\omega) \equiv \omega^6 + a^2\omega^4 - (2ab + c^2)\omega^2 + b^2 = 0 \quad (13)$$

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

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

where $U = a^2, V = -2ab - c^2, W = b^2$.

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 [21], for a polynomial in the form of (14), the following lemmas are obtained and so we state them without proofs.

Lemma 1: The necessary condition for (14) to have a positive real root is that $\Theta \equiv U^2 - 3V > 0.$

Lemma 2: If

$$\Theta \geq 0 \quad (15)$$

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

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

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

Therefore, by the above lemmas, we assume that (15) and (16) hold so that (14) has positive roots. Assuming 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

$$\tau_k^{(j)} = \frac{1}{2\omega_k}\arcsin\left(\frac{ac\omega_k^2 - bc}{c^2\omega_k}\right) + \frac{(j-1)2\pi}{\omega_k} \quad (17)$$

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

Theorem 1: Suppose that

$$a > 0,\ b > 0 \quad \text{and} \quad ac > b \quad (18)$$

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

(b) If

$$\Theta \geq 0, \beta_1 > 0 \quad \text{and} \quad \sigma(\beta_1) \leq 0 \quad (19)$$

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

$$\tau_0 = \min_{1\leq k\leq 3, j\geq 1}\left\{\tau_k^{(j)}, \tau_k^{(j)} > 0\right\} \quad (20)$$

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

Proof

(a) By contradiction, if (9) has a root with zero real part for some $\tau \geq 0$, this implies that (14) has a positive real root. By Lemma 1, 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

$$\lambda^3 + a\lambda^2 + c\lambda + b = 0 \quad (21)$$

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 (20) 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) holds. Thus, $\tau_c = \tau_0$, which completes the proof.

Theorem 1 implies that if (19) is satisfied and (18) holds, the steady state (x_S, y_S, z_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 (x_S, y_S, z_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 condition (19) in Theorem 1 holds, then $\lambda = \pm i\omega$ is a pair of purely imaginary roots of (9). Moreover,

$$\left.\frac{d\,\mathrm{Re}(\lambda(\tau))}{d(\tau)}\right|_{\tau=\tau_0} \neq 0 \quad (22)$$

provided that

$$\sigma'(\beta_0) \neq 0 \quad (23)$$

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),

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

Then,

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

and hence,

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

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

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

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

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

Therefore,

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

(13) implies that

$$\omega_0^6 + a^2\omega_0^4 - 2ab\omega_0^2 + b^2 = c^2\omega_0^2$$

then,

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

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 (19) holds, then a periodic solution occurs in our model equations (4)-(6) for a positive time delay $\tau = \tau_0$ given by (20) provided (23) holds.

IV. Numerical Investigation

In order to support our theoretical prediction, a computer simulation of the system (4)-(6) is carried out here by using the Runge-Kutta-Fehlberg Method. By choosing parameters to satisfy the conditions in Theorem 3, the solution trajectory projected onto the (*x,y*)-plane, (*x,z*)-plane and (*y,z*)-plane are as shown in Fig. 1 tends to a limit cycle as theoretically predicted. The corresponding time courses of the CT concentration, the number of active osteoclasts and the number of active osteoblasts are as shown in Fig. 2, showing a periodic behavior as theoretically predicted.

V. Effect of Estrogen Supplements

Estrogen is a primary female sex hormone which is mainly produced by the ovary. It plays an important role in woman's reproductive process, the growth and maturation of bone, the regulation of bone turnover as well as maintaining the balance between the activities of osteoclasts and osteoblasts in bone remodeling process [22].

In postmenopausal women, estrogen deficiency is expected. Several researchers found that when estrogen deficiency occurs there is an increase in the activation frequency of new bone remodeling units and an increase in remodeling imbalance, resulting from the increase of osteoclastic formation which enhances bone resorption, leading to osteoporosis [23]-[27].

Estrogen replacement therapy has been accepted that it can prevent menopausal bone loss and reduces the risk of fracture [23]-[26]. In 1998, Kanatani [24] and Riggs [26] found that estrogen inhibits the activity of osteoclastic cells. Moreover, Prestwood *et al.* [23] and Albright *et al*. [25] observed the decrease in the values of biochemical markers of bone turnover due to the short-term estrogen supplement. We then investigate the effects of estrogen therapy by modify the model (4)-(6). Assuming 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

$$\frac{dx}{dt} = \left(\frac{c_1 + c_2 y}{m_1 + y}\right) - d_1 x \tag{24}$$

$$\frac{dy}{dt} = \left[\left(c_3 - \frac{c_4 x}{m_2 + x^2}\right) y(t-\tau) z(t-\tau) - d_2 y\right] - m_C y \tag{25}$$

$$\frac{dz}{dt} = \left(\frac{c_5 + c_6 x}{m_3 + x}\right) z(t-\tau) - d_3 z \tag{26}$$

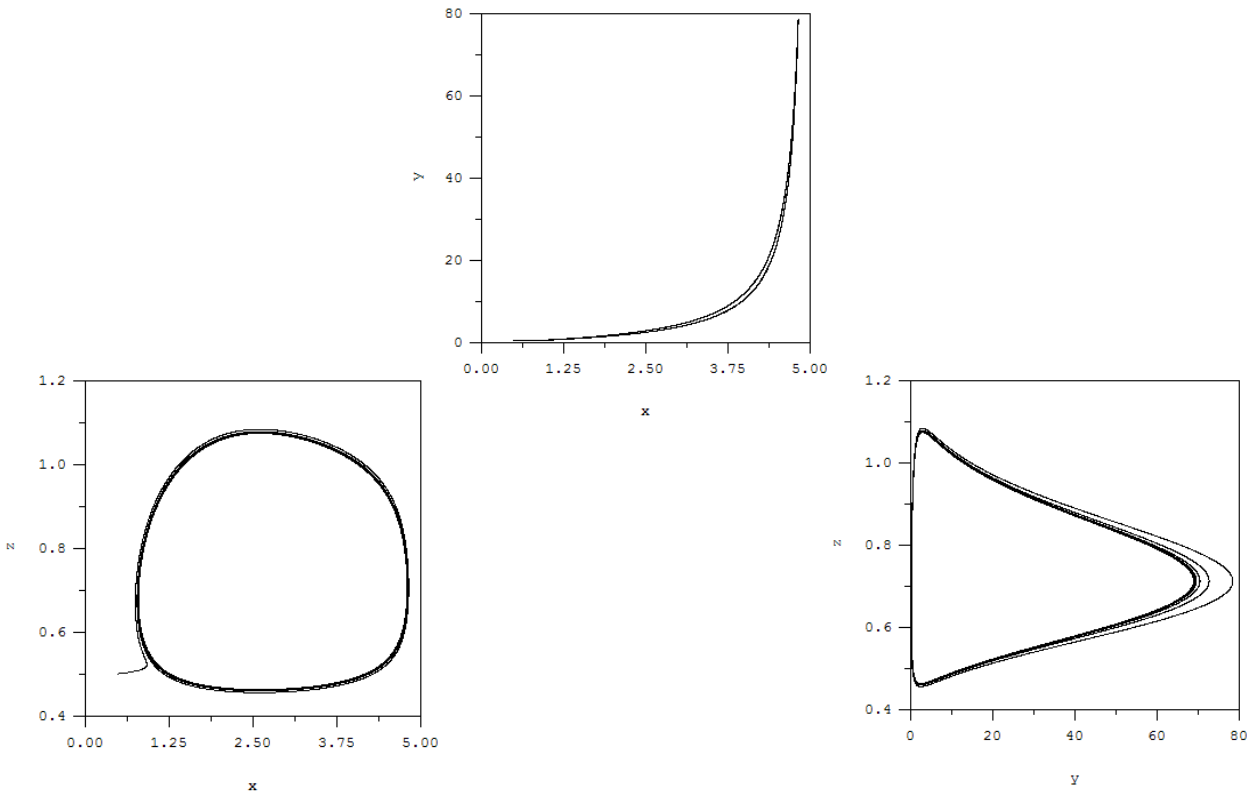

Fig.1 A computer simulation of the system (4)-(6) with $c_1 = 0.1, c_2 = 0.5, c_3 = 0.04, c_4 = 0.07, c_5 = 0.014, c_6 = 0.0017, m_1 = 3, m_2 = 5, m_3 = 2,$ $d_1 = 0.1, d_2 = 0.02, d_3 = 0.004, \tau = 3, x(0) = 0.5,\ y(0) = 0.5,$ and $z(0) = 0.5$. The solution trajectory projected onto the (x,y)-plane, (x,z)-plane and (y,z)-plane showing a periodic behavior as theoretically predicted.

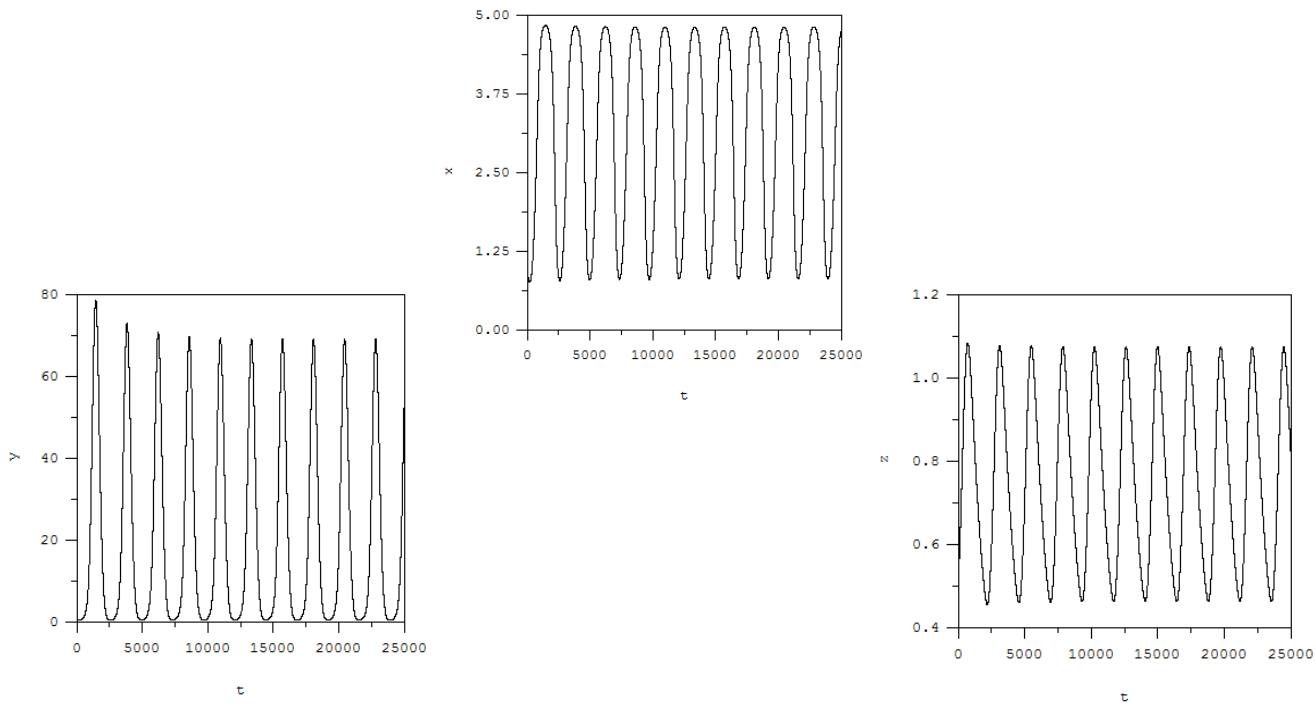

Fig.2 The corresponding time course of a) CT concentration (x) above the basal level, b) the number of active osteoclasts and c) the number of active osteoblasts of the system (4)-(6) with $c_1 = 0.1, c_2 = 0.5, c_3 = 0.04, c_4 = 0.07, c_5 = 0.014, c_6 = 0.0017, m_1 = 3, m_2 = 5, m_3 = 2,$ $d_1 = 0.1, d_2 = 0.02, d_3 = 0.004, \tau = 3, x(0) = 0.5,\ y(0) = 0.5,$ and $z(0) = 0.5$ showing a periodic behavior as theoretically predicted.

Fig. 4 shows a computer simulation of the system (24)-(26) where the term $-m_C y$ is kept in (25) as a single pulse every period of 28 days.

Fig. 5 shows a computer simulation of the system (24)-(26) where the term $-m_C y$ is kept in (25) for a duration of $\Delta T = 2$ days, every period of 28 days.

Fig. 5 shows a computer simulation where the term $-m_C y$ is kept in (25) for a duration of $\Delta T = 4$ days, every period of 28 days.

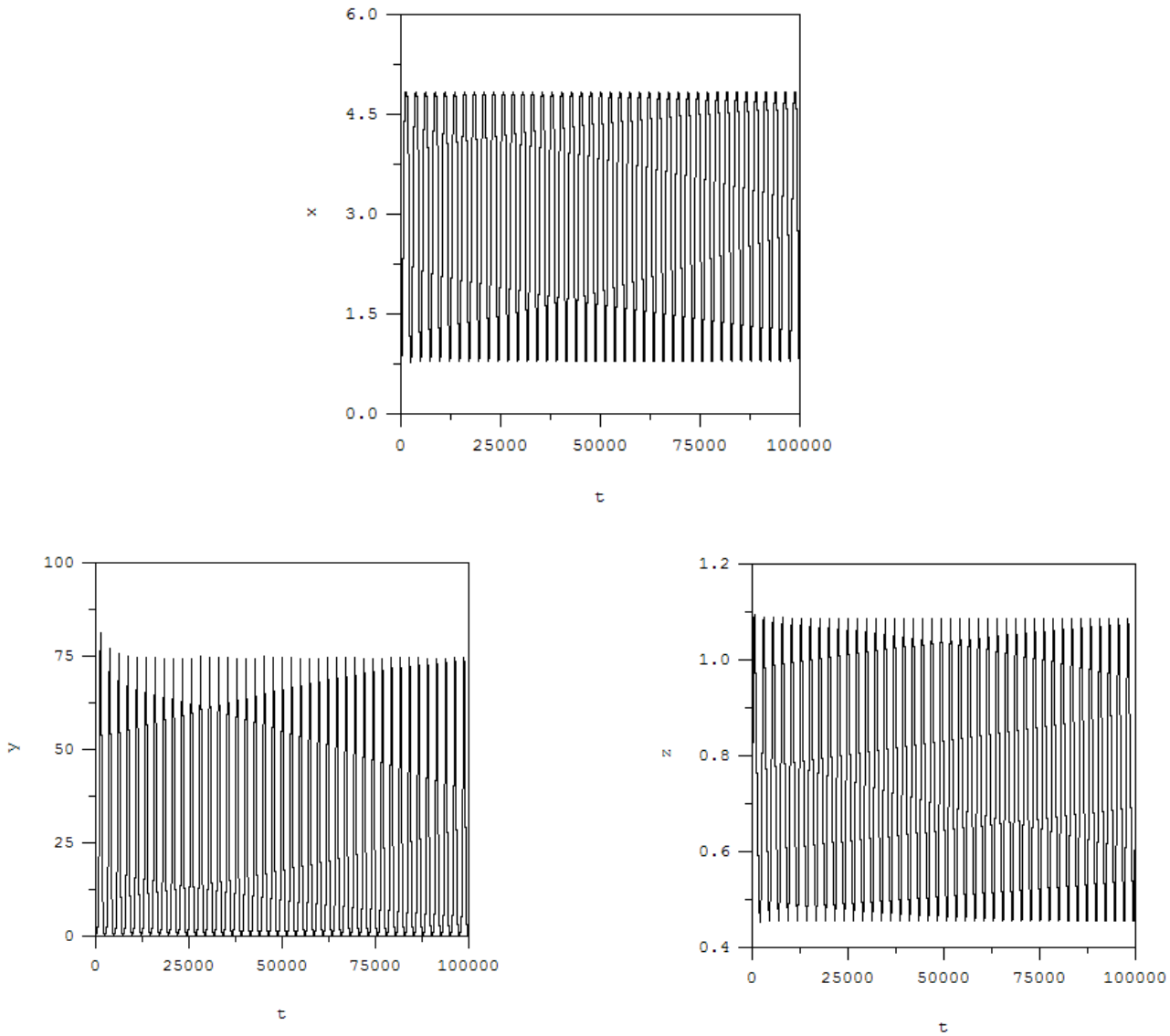

Fig.3 A computer simulation of the system (24)-(26) with $c_1 = 0.1, c_2 = 0.5, c_3 = 0.04, c_4 = 0.07, c_5 = 0.014, c_6 = 0.0017, m_1 = 3, m_2 = 5, m_3 = 2,$ $d_1 = 0.1, d_2 = 0.02, d_3 = 0.004, \tau = 5, x(0) = 0.5,\ y(0) = 0.5,\ z(0) = 0.5$, with the effect of estrogen administration $m_C = 0.005$, administered every 28 days with as a single burst initiated at the time t = 10,000.

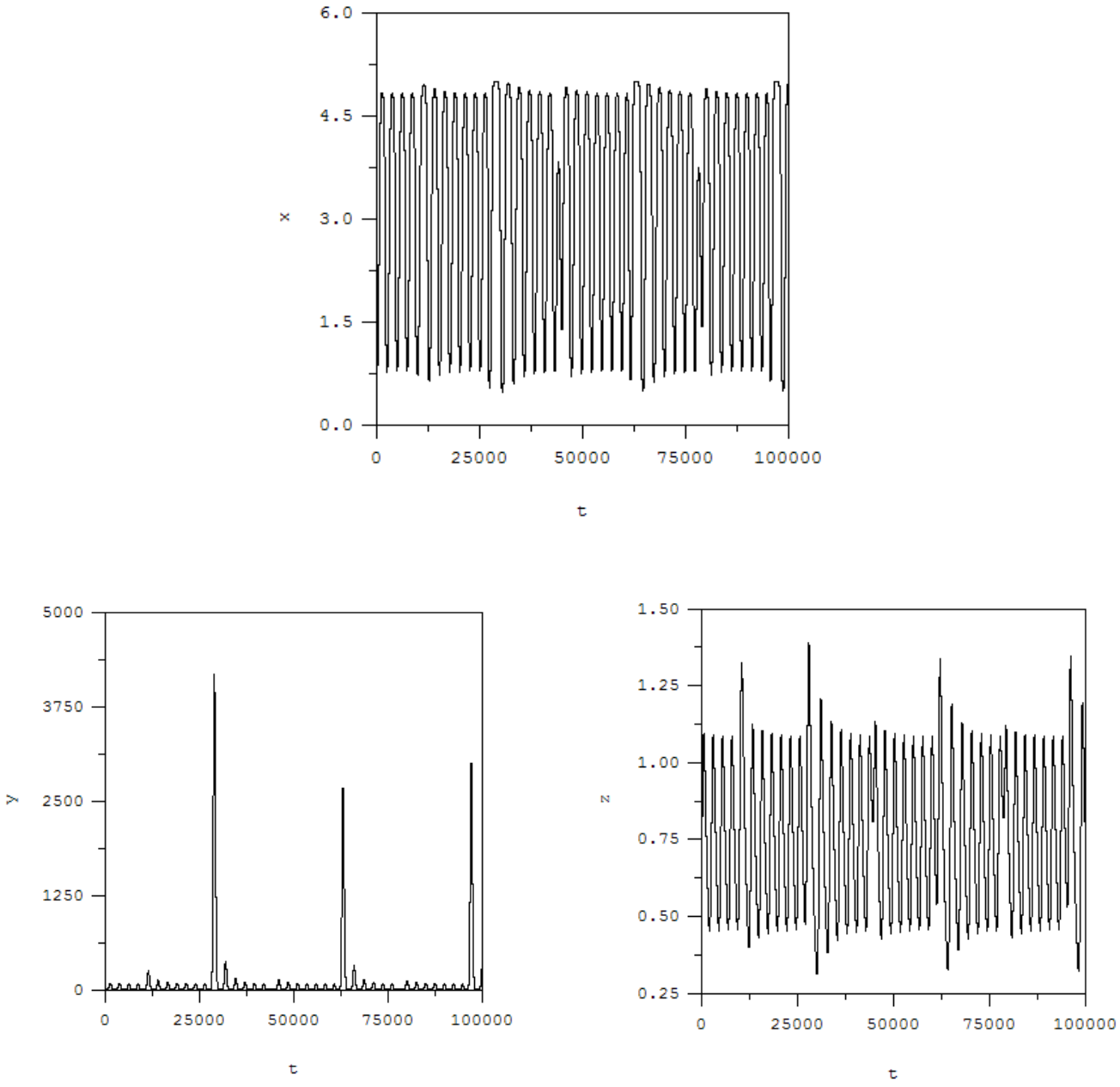

Fig.4 A computer simulation of the system (24)-(26) with $c_1 = 0.1, c_2 = 0.5, c_3 = 0.04, c_4 = 0.07, c_5 = 0.014, c_6 = 0.0017, m_1 = 3, m_2 = 5, m_3 = 2,$ $d_1 = 0.1, d_2 = 0.02, d_3 = 0.004, \tau = 5, x(0) = 0.5,\ y(0) = 0.5,\ z(0) = 0.5$, with the effect of estrogen administration $m_C = 0.005$, administered every 28 days with $\Delta T = 2$ days initiated at the time t = 10,000.

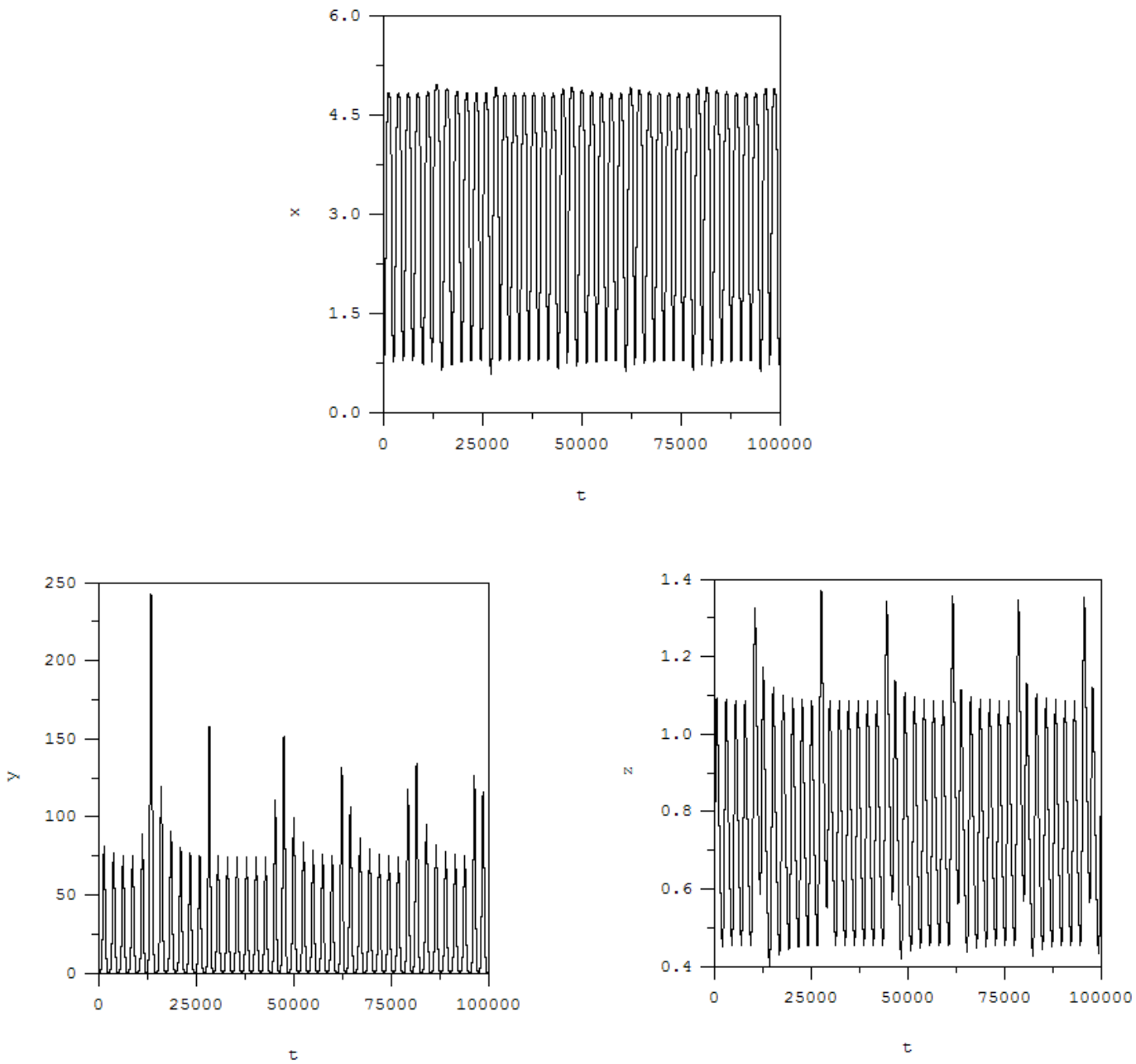

Fig.5 A computer simulation of the system (24)-(26) with $c_1 = 0.1, c_2 = 0.5, c_3 = 0.04, c_4 = 0.07, c_5 = 0.014, c_6 = 0.0017, m_1 = 3, m_2 = 5, m_3 = 2,$ $d_1 = 0.1, d_2 = 0.02, d_3 = 0.004, \tau = 5, x(0) = 0.5,\ y(0) = 0.5,\ z(0) = 0.5$, with the effect of estrogen administration $m_C = 0.005$, administered every 28 days with $\Delta T = 4$ days initiated at the time t = 10,000.

VI. CONCLUSION

The model developed by Rattanakul and Rattanamongkonkul [12] is modified to incorporate the time delay which has been observed in the clinical evidences [5]. The model is then analyzed by using Hopf bifurcation theorem [28]-[33]. The conditions on the system parameters for which a periodic behavior observed in the pulsatile secretion of CT [34] exists are then derived. Computer simulation of the model is then carried out. Both

theoretical and numerical results show that the periodic behaviour can be exhibited by our model which closely resembles to the serum level of CT that has been observed clinically in [34]. Moreover, the effects of estrogen supplements are then investigated numerically.

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