A delay-differential equations model of calcium homeostasis: Effects of parathyroid hormone and vitamin D

Inthira Chaiya, Chontita Rattanakul, Sahattaya Rattanamongkonkul, Wannapa Panitsupakamon,

and Sittipong Ruktamatakul

***Abstract*—**Calcium is essential for human. Apart from providing skeletal strength, calcium also plays important role in a wide range of biological functions. In this paper, calcium homeostasis, the mechanism that maintains the serum calcium level to be in the normal range, is investigated mathematically. A mathematical model is formulated to incorporate the effects of parathyroid hormone, vitamin D and time delay on calcium homeostasis. The conditions on the model parameters for which a periodic solution exists are then derived by means of Hopf bifurcation theorem. Moreover, various kinds of dynamic behavior of the model are also investigated numerically.

***Keywords*—**Calcium homeostasis, parathyroid hormone, time delay, vitamin D.

I. Introduction

OVER 99% of total body of calcium is stored in bone [1]-[5]. Calcium is essential for many mechanisms in human body. It plays a key role in the regulation of enzymatic activities and fundamental cellular events including the contraction of muscles, hormone secretion, cell division and blood clotting [1]-[5]. Serum calcium levels are regulated by three main mechanisms which are bone turnover, intestinal absorption and renal reabsorption [2]. Parathyroid hormone (PTH) and vitamin D are two major regulators that are responsible for normal calcium homeostasis [1]-[5].

The increase in serum level of PTH leads to the increase in the mobilization of calcium from bone matrix through the stimulating effect on the osteoclastic activity [1]. The initial phase can be seen within 1-2 hours and more pronounced phase becomes evident after about 12 hours [1]. PTH also increases the serum level of calcium by acting on the kidney through the promoting of the reabsorption of calcium in the distal nephron and the promoting of the conversion of vitamin D into its active form which results in the increase in the intestinal uptake of calcium [1].

On the other hand, vitamin D in its active form mediates its biological effects by binding to vitamin D receptors (VDR) located on the target organs which are bone, intestine, kidney and the parathyroid glands [1], [7]-[11]. Active vitamin D increases calcium uptake at intestine. The result can be seen within approximately 2 hours [1]. Due to the sequential hydroxylation in liver and kidney, the longer duration is needed when vitamin D is given [1]. Moreover, active vitamin D also acts on bone to increase both the number and activity of osteoclasts [1], [7]-[11].

In the next section, we then develop a delay-differential equations model to investigate the change in the serum level of calcium ion due to the change in the serum levels of parathyroid hormone and vitamin D. The time delay observed clinically in the stimulating effects of parathyroid hormone and vitamin D on calcium release will also be incorporated in the model.

II. Model Formulation

Let us denote the concentration of PTH above the basal level in blood at time t by $P(t)$, the concentration of PTH above the basal level in blood at time $t-\tau$ by $P(t-\tau)$, the concentration of the active form of vitamin D in blood at time t by $D(t)$, the concentration of the active form of vitamin D in blood at time $t-\tau$ by $D(t-\tau)$, and the concentration of calcium in blood at time t by $C(t)$.

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I. Chaiya is with the Department of Mathematics, Faculty of Science, Mahidol University, Thailand and the Centre of Excellence in Mathematics, the Commission on Higher Education, Thailand (e-mail: g5438789@student.mahidol.ac.th).

C. Rattanakul is with the Department of Mathematics, Faculty of Science, Mahidol University, Thailand and the Centre of Excellence in Mathematics, the Commission on Higher Education, Thailand (corresponding author, phone: 662-201-5340; fax: 662-201-5343; e-mail: chontita.rat@mahidol .ac.th).

S. Rattanamongkonkul is with the Department of Mathematics, Faculty of Science, Burapha University, Thailand and the Centre of Excellence in Mathematics, the Commission on Higher Education, Thailand (e-mail: sahattay@buu.ac.th).

W. Panitsupakamon is with the Department of Mathematics, Faculty of Science, Silpakorn University, Thailand and the Centre of Excellence in Mathematics, the Commission on Higher Education, Thailand (e-mail: wannapa@su.ac.th).

S. Ruktamatakul is with the Department of Mathematics, Faculty of Liberal Arts Science, Kasetsart University, Thailand and the Centre of Excellence in Mathematics, the Commission on Higher Education, Thailand (e-mail: faasspr@nontri.ku.ac.th).

Firstly, PTH secreted from the parathyroid glands is one of the major regulators of calcium homeostasis. Parathyroid cells are unusual in the respect that hormone synthesis and degradation are adjusted due to physiological demand for secretion [1]. As much as 90% of the hormone synthesized may be destroyed within the chief cells, which degrade PTH at an accelerated rate when serum level of calcium is high [1]. On the other hand, the release of PTH is stimulated by the low level of calcium in blood [1]-[6]. PTH increases the serum level of calcium by various direct and indirect actions on bone, intestine and kidney as discussed in the previous section in order to maintain the normal range of calcium concentration in blood. Moreover, in the absence of PTH, the serum level of calcium decreases dramatically over a period of several hours [1]. In addition, the chief cells of the parathyroid glands are also targets for the active vitamin D and response to it in a negative feedback manner [1]. The equation for the rate of change of PTH concentration above the basal level in blood is then assumed to have the form

$$\frac{dP}{dT} = \frac{u_1}{(w_1 + w_2 D)(w_3 + w_4 C)} - v_1 P \tag{1}$$

where the parameters u_1, w_1, w_2, w_3, w_4 and v_1 are assumed to be positive. The first term on the right hand side represents the secretion rate of PTH from the parathyroid glands corresponding to the serum levels of active vitamin D and calcium. The last term represents the removal rate of PTH from the system.

Secondly, vitamin D is another principal regulator of calcium homeostasis. The body itself produced vitamin D when it is exposed to the sun. Vitamin D is then synthesized in to an active form so that it can mediate its biological effects. Active vitamin D then binds to vitamin D receptors expressed on the target organs. It enhances calcium absorption in the intestine and increases calcium mobilization from bone [1], [7]-[11]. On the other hand, PTH also stimulates the synthesis of the active form of vitamin D [1], [7]-[11]. The equation for the rate of change of serum level of active vitamin D is then assumed to have the form

$$\frac{dD}{dT} = \frac{(u_2 + u_3 P)(u_4 - u_5 D)D}{(w_5 + w_6 P^2)(w_7 + w_8 C)} - v_2 D \tag{2}$$

where the parameters $u_2, u_3, u_4, u_5, w_5, w_6, w_7, w_8$ and v_2 are assumed to be positive. The first term on the right hand side represents the synthesis rate of active vitamin D corresponding to the serum levels of PTH, calcium and active vitamin D itself. The last term represents the removal rate of active vitamin D from the system.

Finally, the rate of change of serum level calcium is then assumed to have the form

$$\frac{dC}{dT} = u_6 P(t-\tau) + u_7 D(t-\tau) - v_3 C \tag{3}$$

where the parameters u_6, u_7 and v_3 are assumed to be positive. The first term on the right hand side represents the delay effect in the increase of serum level of calcium due to the increase in the concentration of PTH. The second term represents the delay effect in the increase of serum level of calcium due to the increase in the serum level of active vitamin D. The last term represents the removal rate of calcium from the system.

III. MODEL ANALYSIS

In order to investigate the possibility of periodic dynamics in our system of (1)-(3), we scale the variables and the parameters in the model as follows: $X = \frac{P}{P_0}, Y = \frac{D}{D_0}, Z = \frac{C}{C_0}$, $t = \frac{T}{T_0}$, $a_1 = \frac{T_0 u_1}{w_2 w_4 P_0 D_0 C_0}$, $a_2 = \frac{T_0 u_2}{w_6 w_8 P_0^2 C_0}$, $a_3 = \frac{T_0 u_3}{w_6 w_8 P_0 C_0}$ $a_4 = \frac{u_4}{w_6 w_8 P_0^2 C_0}$, $a_5 = \frac{u_5 D_0}{w_6 w_8 P_0^2 C_0}$, $a_6 = \frac{T_0 u_6 P_0}{C_0}$, $a_7 = \frac{T_0 u_7 D_0}{C_0}$, $k_1 = \frac{w_1}{w_2 D_0}$, $k_2 = \frac{w_3}{w_4 C_0}$, $k_3 = \frac{w_5}{w_6 P_0^2}$, $k_4 = \frac{w_7}{w_8 C_0}$, $d_1 = v_1 T_0$, $d_2 = v_2 T_0$, $d_3 = v_3 T_0$. The system (1)-(3) can then be written as

$$\frac{dX}{dt} = \frac{a_1}{(k_1 + Y)(k_2 + Z)} - d_1 X \tag{4}$$

$$\frac{dY}{dt} = \frac{(a_2 + a_3 X)(a_4 - a_5 Y)Y}{(k_3 + X^2)(k_4 + Z)} - d_2 Y \tag{5}$$

$$\frac{dZ}{dt} = a_6 X(t-\tau) + a_7 Y(t-\tau) - d_3 Z \tag{6}$$

Assuming that (X_S, Y_S, Z_S) is a non washout steady state of the system (4)-(6). Letting $x = X - X_S$, $y = Y - Y_S$, $z = Z - Z_S$, 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 (X_S, Y_S, Z_S), namely

$$J_S = \begin{pmatrix} -d_1 & -d_1 A & -d_1 B \\ C & D & E \\ a_6 e^{-\lambda\tau} & a_7 e^{-\lambda\tau} & -d_3 \end{pmatrix} \tag{8}$$

where

$$A = \frac{X_S}{(k_1 + Y_S)},$$

$$B = \frac{X_S}{(k_2 + Z_S)},$$

$$C = \frac{(-a_3 X_S^2 - 2a_2 X_S + a_3 k_3) d_2 Y_S}{(a_2 + a_3 X_S)(k_3 + X_S^2)},$$

$$D = \frac{d_2 Y_S (a_4 - 2a_5 Y_S)}{(a_4 - a_5 Y_S) Y_S} - d_2,$$

$$E = d_2 Y_S (k_4 + Z_S)$$

The characteristic equation of J_S can then be written as

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

where

$$\begin{aligned} a &= d_1 + d_3 - E, \\ b &= d_1 d_3 - \left(d_1 + d_3\right)D + d_1 AC, \\ c &= a_6 d_1 B - a_7 E, \\ d &= -d_1 d_3 D + d_1 d_3 AC, \\ E &= a_7 d_1 \left(BC - E\right) + a_6 d_1 \left(AE - BD\right) \end{aligned}$$

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

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

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

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

$$\omega^3 - b\omega = c\omega\cos(\omega\tau) - e\sin(\omega\tau) \tag{12}$$

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

$$\phi(\omega) = 0 \tag{13}$$

where

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

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

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

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

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

According to the work of Ruan and Wei [12], for a polynomial in the form of (14), the following lemmas are obtained and so we state them without proofs.

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

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

Lemma 2 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. Assuming that it has three positive roots denoted by 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, we obtain

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

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

Theorem 1 Suppose that

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

(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 1(b), the necessary condition for (9) to have a positive real root 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 (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 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),

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

Then,

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

and hence,

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{3\lambda^2 + 2a\lambda + b}{(c\lambda + e)\lambda e^{-\lambda\tau}} - \frac{\tau}{\lambda} + \frac{c}{(c\lambda + e)} = 0$$

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

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

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

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

Therefore,

$$\left.\mathrm{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\right|_{\tau=\tau_0} = \frac{3\omega_0^4 + (2a^2 - 4b)\omega_0^2 + (b^2 - 2ad)}{\left[\omega_0^6 + (a^2 - 2b)\omega_0^4 + (b^2 - 2ad)\omega_0^2 + d^2\right]} - \frac{c^2}{(c^2\omega_0^2 + e^2)} \tag{13}$$

implies that

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

then,

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

Hence, $\left.\mathrm{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\right|_{\tau=\tau_0} \neq 0$ 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 (18) and (24) are satisfied.

IV. NUMERICAL INVESTIGATION

A computer simulation of the system (4)-(6) is presented in Fig. 1 and 2, with parametric values chosen 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. 1a, 1b and 1c, respectively. The corresponding time courses of the PTH concentration above the basal level, the concentration of active vitamin D and the concentration of calcium are as shown in Fig. 2a, 2b and 2c, respectively, showing a periodic behavior as theoretically predicted.

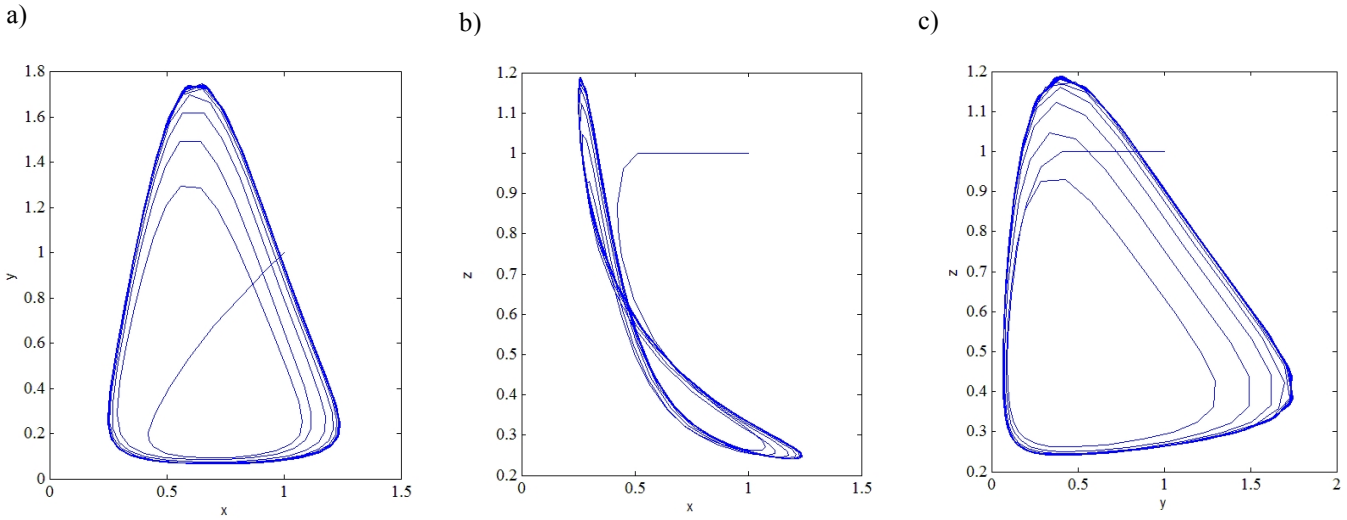

Fig. 1 A computer simulation of the model systems (4)-(6) with $a_1 = 0.007, a_2 = 0.1, a_3 = 0.8, a_4 = 0.5, a_5 = 0.01, a_6 = 0.02, a_7 = 0.08, k_1 = 0.08,$ $k_2 = 0.01,\ k_3 = 3.9,\ k_4 = 0.06,\ d_1 = 0.07, d_2 = 0.145, d_3 = 0.1, \tau$=12, $x(0) = 1,\ y(0) = 1, z(0) = 1.$ (a) The solution trajectory projected onto the (*x,y*)-plane, (b) The solution trajectory projected onto the (*x,z*)-plane and (c) The solution trajectory projected onto the (*y,z*)-plane, respectively.

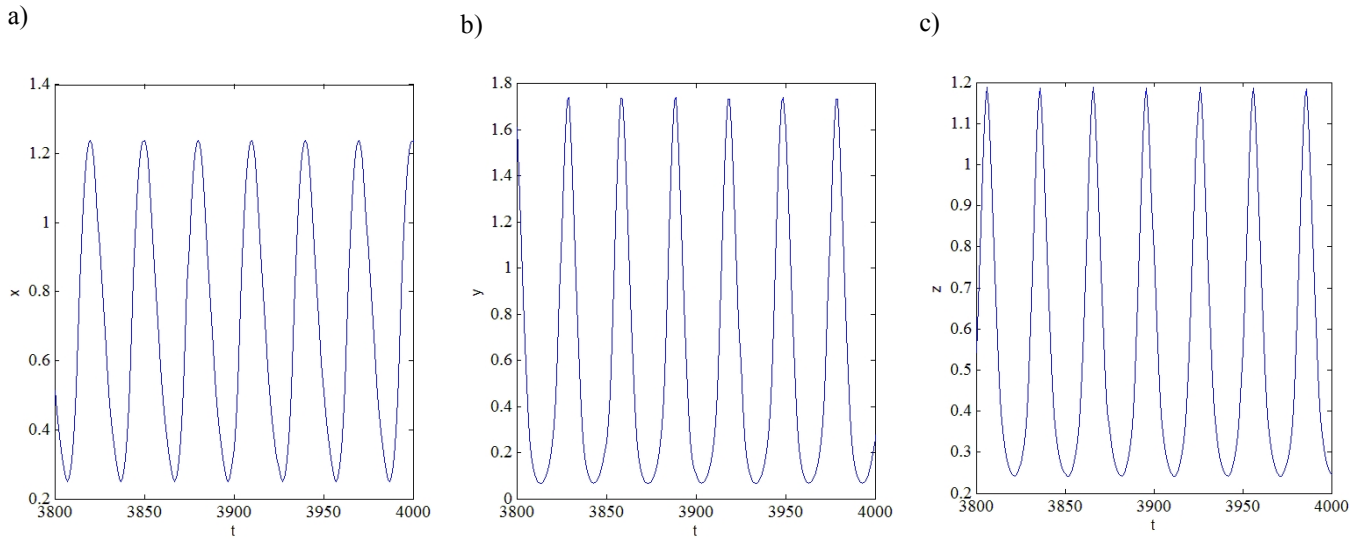

Fig. 2 A computer simulation of the model systems (4)-(6) with $a_1 = 0.007, a_2 = 0.1, a_3 = 0.8, a_4 = 0.5, a_5 = 0.01, a_6 = 0.02, a_7 = 0.08, k_1 = 0.08,$ $k_2 = 0.01,\ k_3 = 3.9,\ k_4 = 0.06,\ d_1 = 0.07, d_2 = 0.145, d_3 = 0.1, \tau = 12,\ x(0) = 1,\ y(0) = 1, z(0) = 1.$ (a) The corresponding time courses of the PTH concentration above the basal level (*x*), (b) the concentration of active vitamin D (*y*) and (c) the concentration of calcium (*z*), respectively.

A computer simulation of the system (4)-(6) is presented in Fig. 3 and 4. The solution trajectory projected onto the $(x,y)-$plane, $(x,z)-$plane and $(y,z)-$plane are as shown in Fig. 3a, 3b and 3c, respectively, showing a solution trajectory tends to a stable equilibrium solution. The corresponding time courses of the PTH concentration above the basal level, the concentration of active vitamin D and the concentration of calcium are as shown in Fig. 4a, 4b and 4c, respectively.

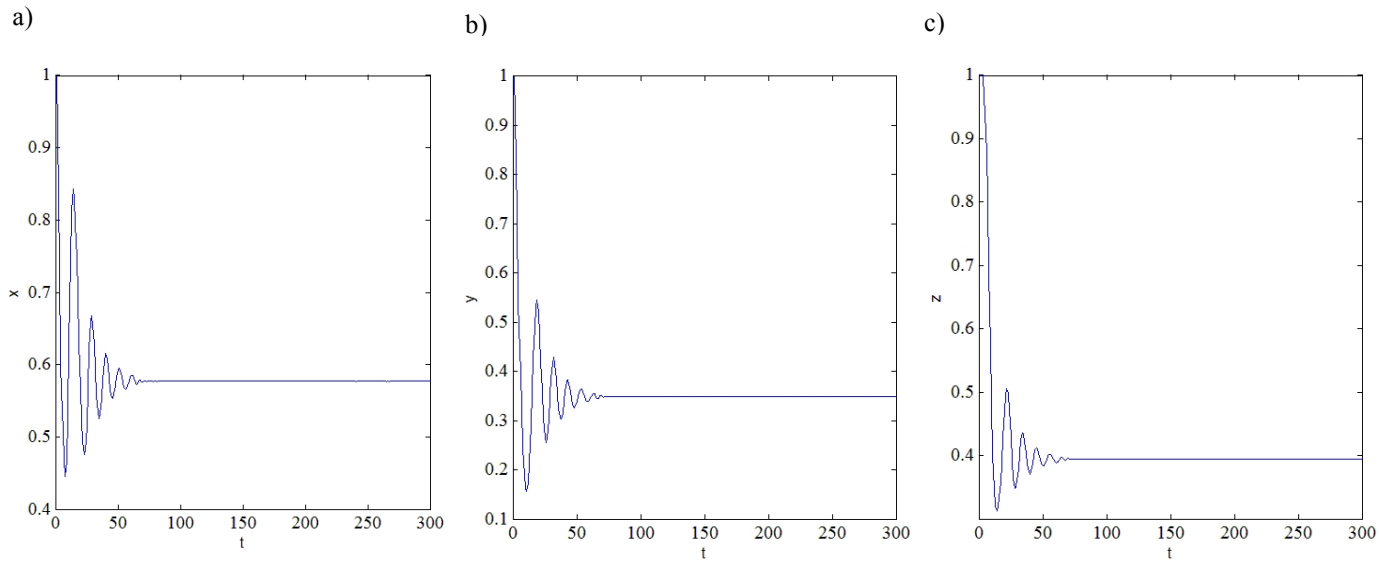

Fig. 3 A computer simulation of the model systems (4)-(6) with $a_1 = 0.007, a_2 = 0.1, a_3 = 0.8, a_4 = 0.5, a_5 = 0.01, a_6 = 0.02, a_7 = 0.08, k_1 = 0.08,$ $k_2 = 0.01,\ k_3 = 3.9,\ k_4 = 0.06,\ d_1 = 0.07, d_2 = 0.145, d_3 = 0.1, \tau = 5,\ x(0) = 1,\ y(0) = 1, z(0) = 1.$ (a) The solution trajectory projected onto the (*x*,*y*)-plane, (b) The solution trajectory projected onto the (*x*,*z*)-plane and (c) The solution trajectory projected onto the (*y*,*z*)-plane, respectively.

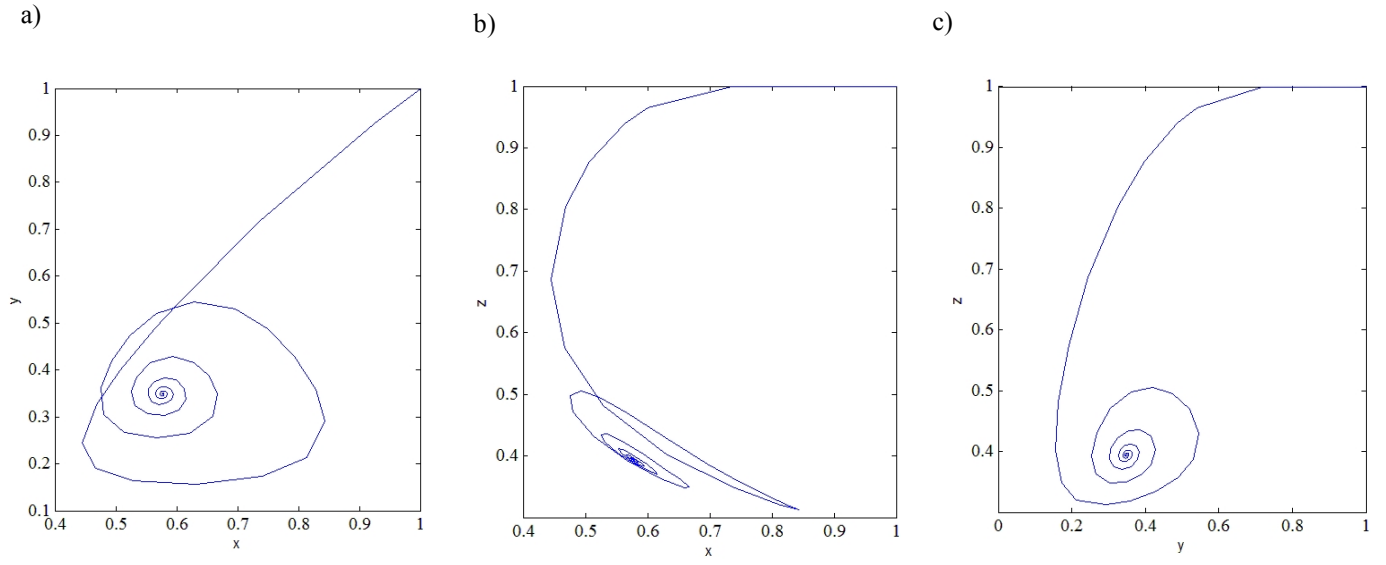

Fig. 4 A computer simulation of the model systems (4)-(6) with $a_1 = 0.007, a_2 = 0.1, a_3 = 0.8, a_4 = 0.5, a_5 = 0.01, a_6 = 0.02, a_7 = 0.08, k_1 = 0.08,$ $k_2 = 0.01,\ k_3 = 3.9,\ k_4 = 0.06,\ d_1 = 0.07, d_2 = 0.145, d_3 = 0.1, \tau = 5,\ x(0) = 1,\ y(0) = 1, z(0) = 1.$ (a) The corresponding time courses of the PTH concentration above the basal level (*x*), (b) the concentration of active vitamin D (*y*) and (c) the concentration of calcium (*z*), respectively.

A computer simulation of the system (4)-(6) is presented in Fig. 5 and 6. The solution trajectory projected onto the $(x,y)-$plane, $(x,z)-$plane and $(y,z)-$plane are as shown in Fig. 5a, 5b and 5c, respectively, showing a chaotic behavior exhibited by our model. The corresponding time courses of the PTH concentration above the basal level, the concentration of active vitamin D and the concentration of calcium are as shown in Fig. 6a, 6b and 6c, respectively.

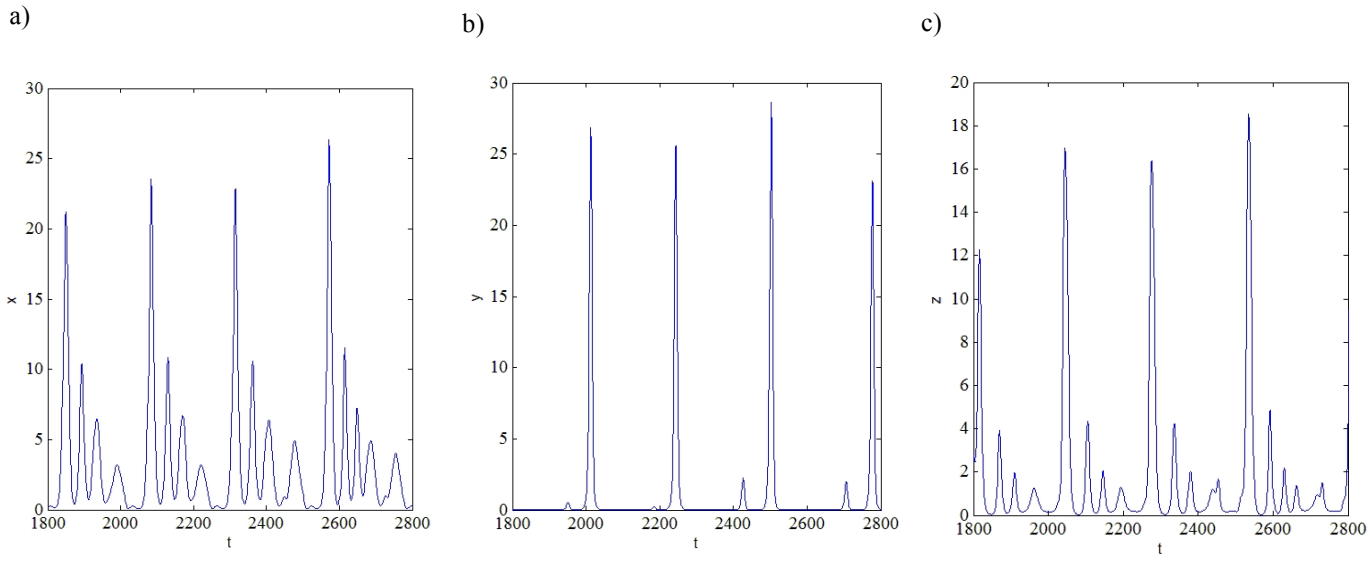

Fig. 5 A computer simulation of the model systems (4)-(6) with $a_1 = 0.007, a_2 = 0.1, a_3 = 0.8, a_4 = 0.5, a_5 = 0.01, a_6 = 0.02, a_7 = 0.08, k_1 = 0.08,$ $k_2 = 0.01,\ k_3 = 3.9,\ k_4 = 0.06,\ d_1 = 0.07, d_2 = 0.145, d_3 = 0.1, \tau = 80,\ x(0) = 1,\ y(0) = 1, z(0) = 1.$ (a) The solution trajectory projected onto the (*x*,*y*)-plane, (b) The solution trajectory projected onto the (*x*,*z*)-plane and (c) The solution trajectory projected onto the (*y*,*z*)-plane, respectively.

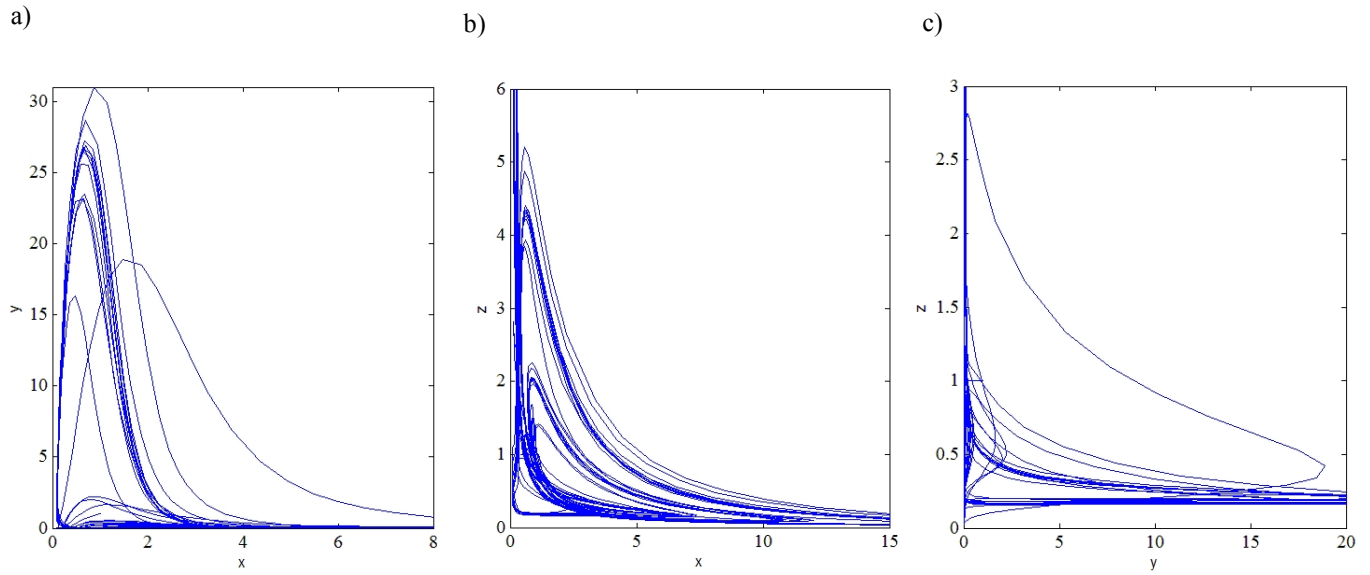

Fig. 6 A computer simulation of the model systems (4)-(6) with $a_1 = 0.007, a_2 = 0.1, a_3 = 0.8, a_4 = 0.5, a_5 = 0.01, a_6 = 0.02, a_7 = 0.08, k_1 = 0.08,$ $k_2 = 0.01,\ k_3 = 3.9,\ k_4 = 0.06,\ d_1 = 0.07, d_2 = 0.145, d_3 = 0.1, \tau = 80,\ x(0) = 1,\ y(0) = 1, z(0) = 1.$ (a) The corresponding time courses of the PTH concentration above the basal level (*x*), (b) the concentration of active vitamin D (*y*) and (c) the concentration of calcium (*z*), respectively.

V. CONCLUSION

A delay-differential equations model accounted for the effects of PTH, vitamin D and time delay is developed in order to investigate the calcium homeostasis. Hopf bifurcation theorem is then utilized in order to derive the conditions on the model parameters that guarantee the existence of a periodic solution. Numerical investigation is then carried out by using Runge-Kutta method [13]-[16]. The results indicate that our model can exhibit nonlinear behavior corresponding to the pulsatile patterns observed clinically in the serum levels of parathyroid hormone, vitamin D and calcium [17]-[19].

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