Effects of Vitamin D and Time Delay on Bone Resorption and Bone Formation: Mathematical Modeling Approach

Chontita Rattanakul

***Abstract*—**A mathematical model proposed by Rattanamongkonkul *et al.* [1] is modified here to study the effects of both vitamin D and time delay. Hopf bifurcation theorem is then applied to derive the conditions on the model parameters for which a periodic solution exists. Computer simulation is also carried out in order to support our theoretical result. Both theoretical and numerical results show that a periodic behavior observed clinically in the level of vitamin D can be expected in our model. Moreover, different kinds of dynamic behavior are investigated numerically.

***Keywords*—**Bone resorption, Bone formation, Vitamin D, Time delay, Hopf bifurcation.

I. Introduction

BODY calcium is derived from the diet, and daily intake is usually offset by urinary loss [2]. Bone acts as a major reservoir of calcium and can buffer the concentration of calcium in extracellular fluid by taking up or releasing calcium phosphate [2]. Appropriate amounts of calcium are required in order to maintain the normal function of all cells. Maintaining adequate amounts of calcium involves many factors including the activity of two hormones, parathyroid hormone (PTH) and a derivative of vitamin D called calcitriol [2]. About 600 mg of calcium is exchange between bone mineral and extracellular fluid everyday. Much of this exchange reflects resorption and reformation of bone as skeleton undergoes constant remodeling [2].

Bone resorption and bone formation process is carried out by teamwork of two types of cells which are bone resorbing cell (called osteoclast) and bone forming cell (called osteoblast). At the end of the process, if osteoclasts resorb too deep cavity or osteoblasts fails to refill the resorption cavity, the imbalance is occurred leading to a major bone disease called osteoporosis [2]. Therefore, the understandings of bone resorption and bone formation are needed in order to understand the calcium homeostasis.

Several mathematical models have been proposed in order to gain a better understanding of bone resorption and bone formation process [1], [3]-[11]. However, the time delay observed on bone resorption and bone formation process [3] has not been incorporated. In this paper, we therefore modify a mathematical model proposed by Rattanamongkonkul *et al.* [1] to study the effect of time delay on the process.

Manuscript received June 12, 2011. This work was supported by the Centre of Excellence in Mathematics, Commission on Higher Education, Thailand.

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II. A Mathematical Model

Let us denote the level of vitamin D above the basal level in blood at time t by $x(t)$, the number of active osteoclasts at time t by $y(t)$, the number of active osteoclasts at time $t-\tau$ by $y(t-\tau)$, the number of active osteoblasts at time t by $z(t)$ and the number of active osteoblasts at time $t-\tau$ by $z(t-\tau)$. Assuming 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, we modify the model proposed by Rattanamongkonkul *et al.* [1] to incorporate the effect of time delay as follows.

Rattanamongkonkul *et al.* [1] proposed a mathematical model to describe bone remodeling process based on the effect of vitamin D as in (1)-(3):

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

$$\frac{dy}{dt} = \left(\frac{a_2 + a_3 x}{k_2 + x^2}\right) yz - b_2 y \tag{2}$$

$$\frac{dz}{dt} = a_4 + \frac{a_5 xz}{k_3 + x} - b_3 z \tag{3}$$

where all parameters $a_1, a_2, a_3, a_4, a_5, b_1, b_2, b_3, k_1, k_2$ and k_3 are positive constants. (1) stands for the rate of change of the level of calcitriol in blood at time t. (2) stands for rate of change of the number of active osteoclastic population

while (3) stands for the rate of change of the number of active osteoblastic population. However, the effect of time delay observed clinically in the process [3] did not take into account.

Kroll [3] indicated that the differentiation of preosteoblast precursors into preosteoblasts has a delay time of 1 hour and the differentiation of preosteoblasts into osteoblasts has a delay time of 2 hours. By assuming that the differentiation of osteoclasts has the same delay time, we then modify the model developed in [1] to incorporate the effect of time delay in the differentiation of osteoclasts and osteoblasts as follows.

Firstly, vitamin D is a steroid vitamin which can be obtained from exposure to sunlight or vitamin D supplements. Its active form is called calcitriol which is synthesized in kidneys and circulates as a hormone [12]. Vitamin D has an important role in maintaining the serum calcium in the normal physiological range to preserve neuromuscular and cellular functions [13]. It enhances the efficiency of intestinal calcium absorption and increases the mobilization of stem cells to become osteoclasts that, in turn, mobilize calcium stores from bone resulting in the increase in the concentration of calcium in blood [13]-[16]. In order to maintain the normal range of calcium in blood the synthesized of calcitriol will be decreased. Therefore, the rate of change of the serum level of vitamin D is then assumed to have the form

$$\frac{dx}{dt} = \left(\frac{c_1}{m_1 + y} \right) - d_1 x \tag{4}$$

where the first term on the right-hand side of (4) stands for the rate of change in serum level of vitamin D. In order to counter balance the high level of calcium in blood resulted from the large number of active osteoclasts, the synthesized of the active form of vitamin D, calcitriol, will be decreased. The last term on the right-hand side of (4) is the removal rate constant d_1. c_1 and m_1 are positive constants.

Secondly, osteoclast is one type of bone cells. It is responsible for bone resorption in bone remodeling process [2]. Osteoclasts are large cells that arise by fusion of mononucleated hematopoietic cells. Differentiation and activation of osteoclasts require a direct physical contact with osteoblasts [2]. Moreover, there are several factors that regulate osteoclast formation and differentiation such as osteoclast differentiation factor (ODF) which was found to be identical to osteoprotegerin ligand (OPGL), tumor necrosis factor family-related activation induces cytokine (TRANCE), receptor activator NF-kB ligand (RANKL) [3], [17], [18] including several hormones such as vitamin D, PTH, calcitonin. Vitamin D interacts with its vitamin D receptor (VDR) located in osteoblast resulting in the expression of RANKL which recognized by its corresponding receptor RANK on preosteoclast. The interaction of RANKL and RANK results in signal transduction inducing the preosteoclast to be come a mature osteoclast [19]-[21]. Therefore, the rate of change of the number of active osteoclasts can be described by the following equation

$$\frac{dy}{dt} = \left(\frac{c_2 x}{m_2 + x^2} \right) y(t-\tau) z(t-\tau) - d_2 y \tag{5}$$

where the first term on the right-hand side of (5) stands for the stimulating effect of vitamin D on the differentiation and activation of active osteoclasts through the interaction of vitamin D and its receptors on osteoblasts. The last term on the right-hand side of (5) is the removal rate constant d_2. c_2 and m_2 are positive constants.

Finally, osteoblast is also a type of bone cells. It is responsible for bone formation in bone remodeling process [2]. Osteoblasts are derived from the mesenchymal stem cells [22]. The proliferation and differentiation of osteoblasts involve many factors such as fibroblast growth factor (FGF), insulin like growth factor–I (IGF-I), transforming growth factor beta (TGF-beta), including vitamin D [22], [23]. Therefore, the rate of change of the number of active osteoblasts can be described by the following equation

$$\frac{dz}{dt} = c_3 + \left(\frac{c_4 x}{m_3 + x} \right) z(t-\tau) - d_3 z \tag{6}$$

where the first term on the right-hand side of (6) stands for the stimulating effect of many factors such as FGF, IGF-I, TGF-beta on the proliferation and differentiation of active osteoblasts. The second term on the right-hand side of (6) stands for the stimulating effect of vitamin D on the reproduction of active osteoblastic cells. The last term on the right-hand side of (6) is the removal rate constant d_3. a_3, a_4 and m_3 are positive constants.

III. Model Analysis

Hopf bifurcation theorem is utilized here in order to investigate the possibility of periodic solution 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

$$J_S = \begin{pmatrix} -d_1 & -\dfrac{c_1 x_S}{m_1 + y_S} & 0 \\ \dfrac{c_2\left(m_2 - x_S^2\right) y_S z_S}{\left(m_2 + x_S^2\right)^2} e^{-2\lambda\tau} & 0 & \dfrac{d_2 y_S}{z_S} \\ \dfrac{m_3\left(d_3 z_S - c_3\right)}{x_S\left(m_3 + x_S\right)} & 0 & -\dfrac{c_3}{z_S} \end{pmatrix} \quad (8)$$

For simplicity, we introduce new parameters by letting

$$a = -A - B,$$

$$b = AB,$$

$$c = -C,$$

$$d = DE - DF,$$

$$e = BC$$

where

$$A = -d_1,$$

$$B = -\frac{c_3}{z_S},$$

$$C = -\frac{m_3}{x_S}\left(\frac{c_1 x_S}{m_1 + y_S}\right)\frac{\left(d_3 z_S - c_3\right)}{\left(m_3 + x_S\right)} e^{2\lambda\tau},$$

$$D = \frac{c_3}{z_S}\left(\frac{c_1 x_S}{m_1 + y_S}\right),$$

$$E = \frac{c_3 m_3}{x_S\left(m_3 + x_S\right)},$$

$$F = \frac{d_3 m_3 z_S}{x_S\left(m_3 + x_S\right)}$$

Then, the characteristic equation of J_S can be written as

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

According to the Hopf bifurcation theory, 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 of the system (4)-(6) can occur. In order that such a pair can be found, one must have $F(i\omega) = 0$, that is,

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

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

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

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

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

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

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

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

where

$$U = a^2 - 2b,$$

$$V = b^2 - 2ad - c^2, \ .$$

$$W = d^2 - e^2$$

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 [24], 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 $W < 0$, the necessary condition for (14) to have a positive real root is that $\Theta \equiv U^2 - 3V > 0$.

Lemma 3 If

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

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

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

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

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

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

Theorem 1 Suppose that

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

(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 $\tau\geq 0$, then (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) 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) or (20) in Theorem 1 holds, then $\lambda=\pm i\omega$ is a pair of purely imaginary roots of (9). Moreover,

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

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,

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

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,

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

Therefore,

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

(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,

$$\operatorname{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\Bigg|_{\tau=\tau_0}$$

$$=\frac{3\omega_0^4+2\left(a^2-2b\right)\omega_0^2+\left(b^2-2ad-c^2\right)}{2\left(c^2\omega_0^2+e^2\right)}$$

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

$$\neq 0$$

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 (24) is satisfied.

IV. COMPUTER SIMULATION

A computer simulation of the system (4)-(6) is presented in Fig.1 and Fig. 2, with parametric values chosen to satisfy the condition in Theorem 3. The solution trajectory projected onto the (x,y)-plane, (x,z)-plane, (y,z)-plane and the corresponding time courses of the level of vitamin D, the number of active osteoclasts and the number of active osteoblasts showing a periodic behavior as theoretically predicted.

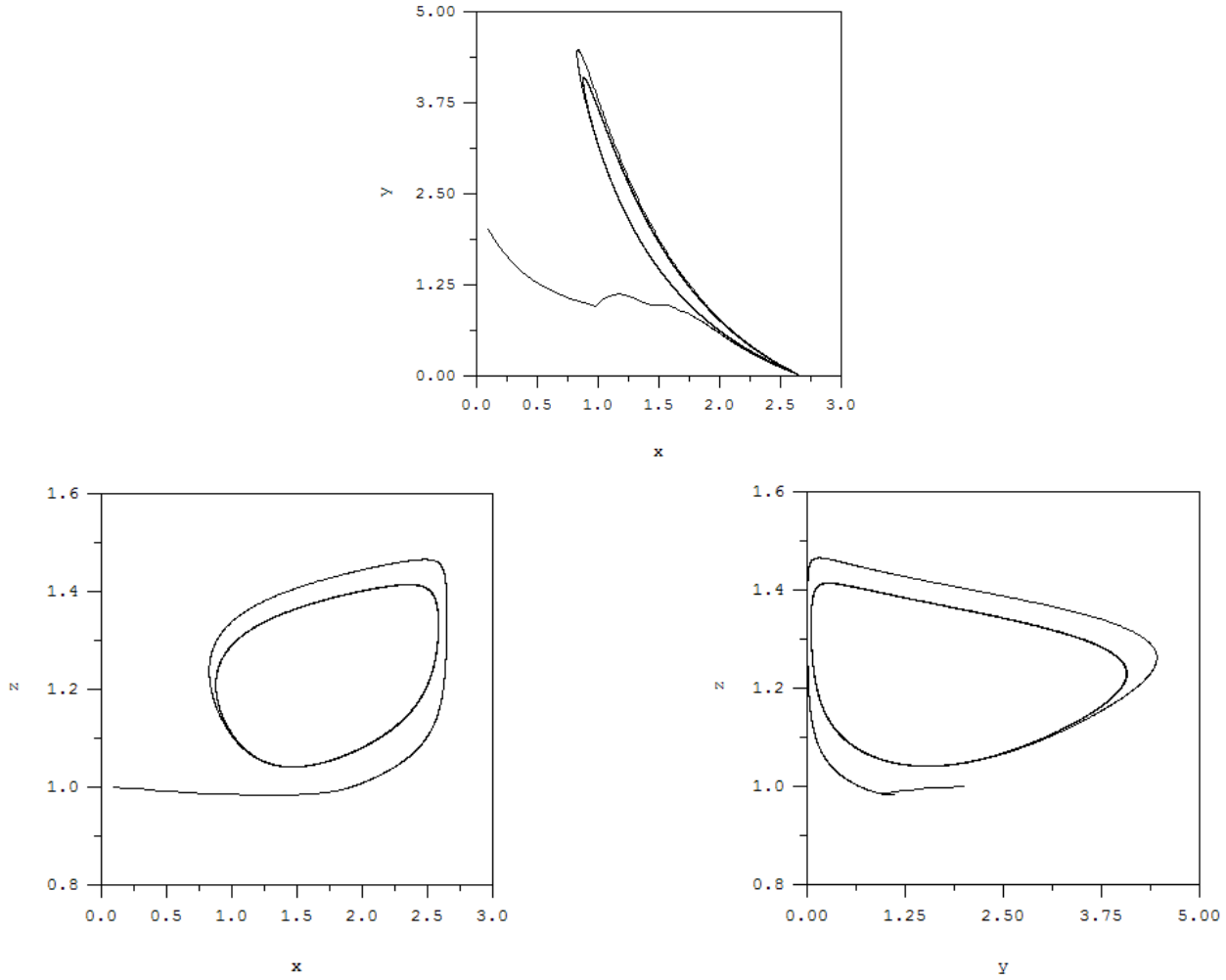

Fig. 1 A computer simulation of the system (4)-(6) with $c_1=0.8, c_2=0.81, c_3=0.0054, c_4=0.01278, m_1=2, m_2=2, m_3=1$, $d_1=0.15, d_2=0.319, d_3=0.0128, \tau=5, x(0)=0.1$, $y(0)=2$, and $z(0)=1$. The solution trajectory projected onto the (x,y)-plane, (x,z)-plane and (y,z)-plane showing a periodic behavior as theoretically predicted.

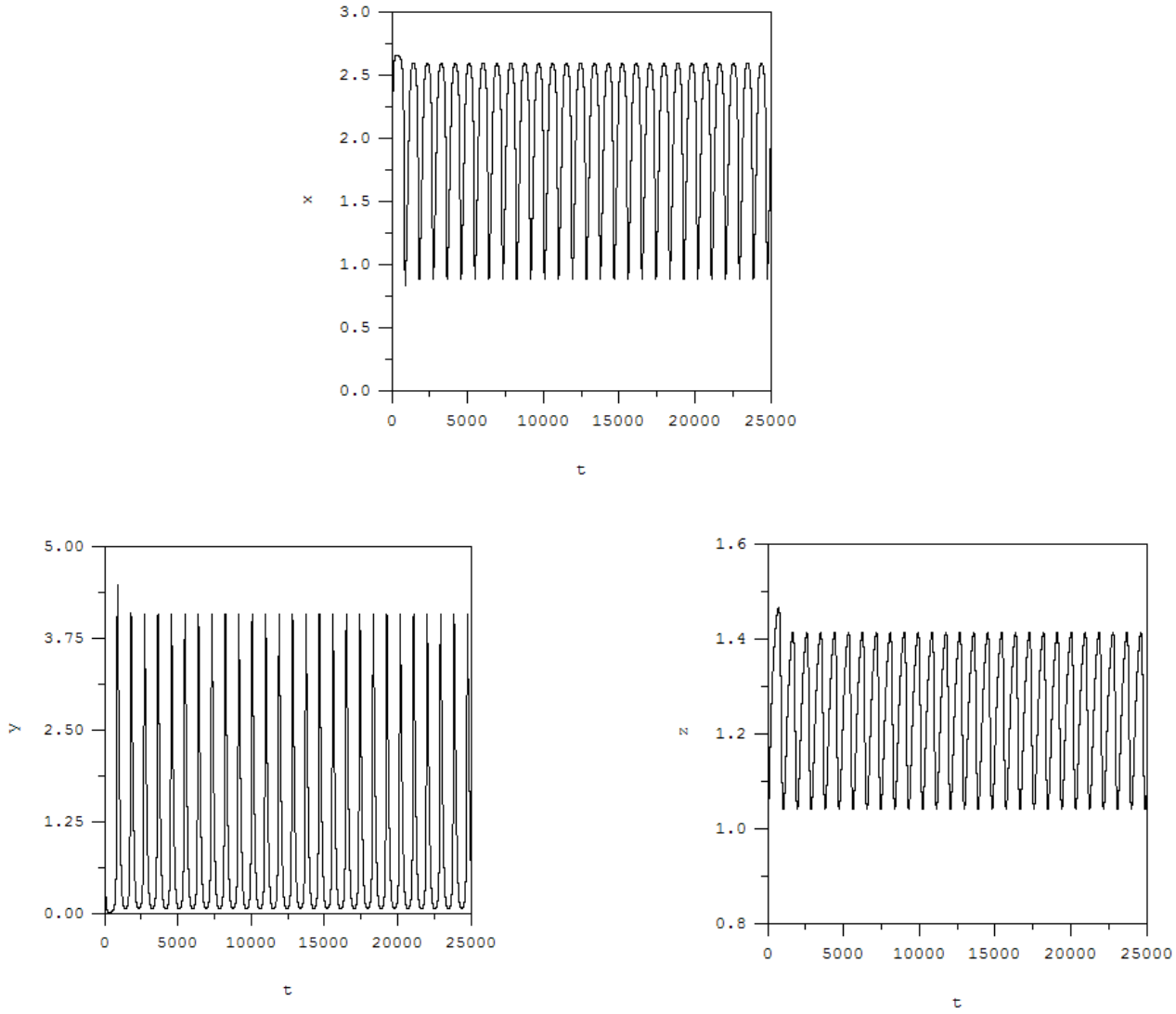

Fig. 2 The corresponding time courses of a) the level of vitamin D (x) in blood, b) the number of active osteoclasts and c) the number of active osteoblasts of the system (4)-(6) with $c_1 = 0.4, c_2 = 0.4, c_3 = 0.07, c_4 = 0.007, m_1 = 3, m_2 = 2, m_3 = 2, d_1 = 0.2, d_2 = 0.08, d_3 = 0.07, \tau = 3, x(0) = 0.5,$ $y(0) = 0.5,$ and $z(0) = 0.5$ showing a periodic behavior as theoretically predicted.

Fig. 3 shows a computer simulation of the model (4)-(6). The solution trajectory projected onto the (x, y)-plane, (x, z)-plane, (y, z)-plane while Fig. 4 shows the corresponding time courses of the level of vitamin D, the number of active osteoclasts and the number of active osteoblasts showing that the solution tends toward a non-washout steady state.

Fig. 5 shows a computer simulation of the model (4)-(6). The solution trajectory projected onto the (x, y)-plane, (x, z)-plane, (y, z)-plane while Fig. 6 shows the corresponding time courses of the level of vitamin D, the number of active osteoclasts and the number of active osteoblasts showing that the solution tends toward a washout steady state.

Fig. 7 shows a computer simulation of the model (4)-(6). The solution trajectory projected onto the (x, y)-plane, (x, z)-plane, (y, z)-plane shows an irregular pattern exhibited by the model.

V. CONCLUSION

We modify the model developed by Rattanamongkonkul *et al.* [1] to investigate the effect of time delay. The model is then analyzed by utilizing Hopf bifurcation theorem. The conditions on the system parameters for which a periodic solution exists are obtained. A computer simulation of the

model is then carried out for a set of parameters that satisfies the conditions in Theorem 3. The result indicates that a periodic solution occurs as theoretically predicted. This kind of behavior is qualitatively correspond to the pattern of the serum level of vitamin D observed clinically in [25], [26]. Moreover, the numerical simulations are carried out to show that different kinds of dynamic behaviors can be exhibited by our model.

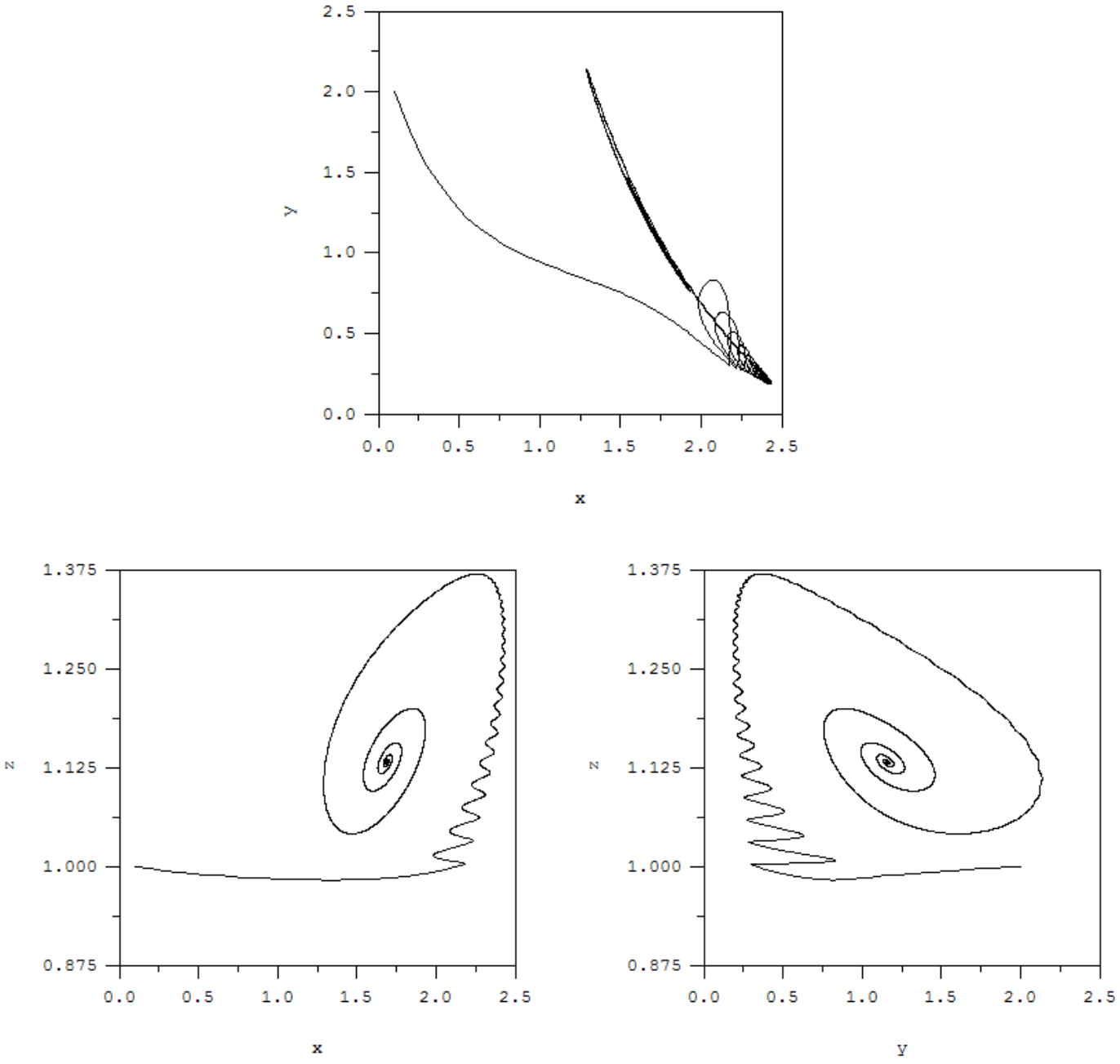

Fig. 3 A computer simulation of the system (4)-(6) with $c_1 = 0.8, c_2 = 0.81, c_3 = 0.0054, c_4 = 0.01278, m_1 = 2, m_2 = 2, m_3 = 1,$ $d_1 = 0.15, d_2 = 0.319, d_3 = 0.0128, \tau = 30, x(0) = 0.1,\ y(0) = 2,$ and $z(0) = 1$. The solution trajectory projected onto the (x,y)-plane, (x,z)-plane and (y,z)-plane showing that the solution tends toward a non-washout steady state.

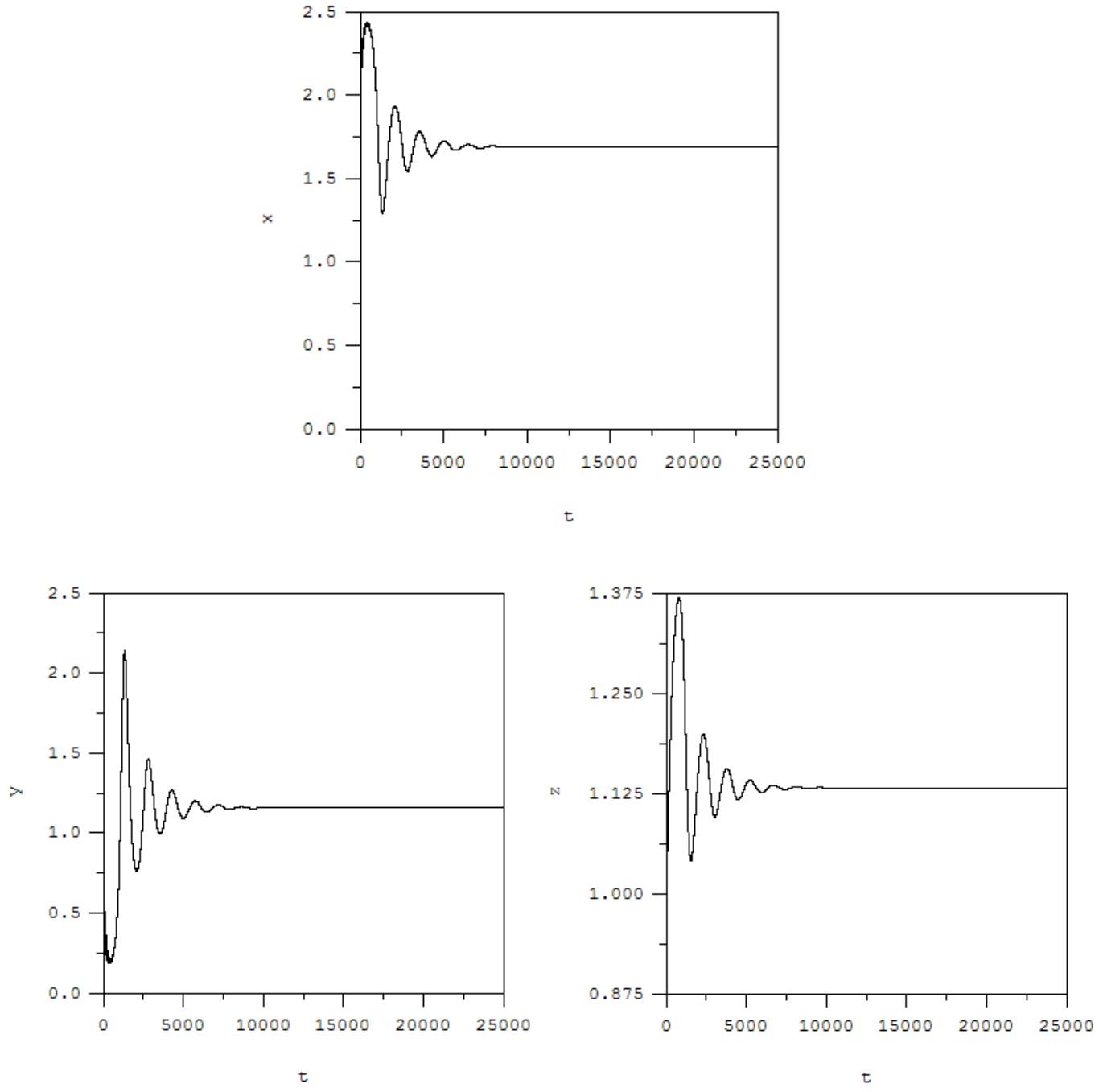

Fig. 4 The corresponding time courses of a) the level of vitamin D (x) in blood, b) the number of active osteoclasts and c) the number of active osteoblasts of the system (4)-(6) with $c_1 = 0.8, c_2 = 0.81, c_3 = 0.0054, c_4 = 0.01278, m_1 = 2, m_2 = 2, m_3 = 1, d_1 = 0.15, d_2 = 0.319, d_3 = 0.0128,$ $\tau = 30, x(0) = 0.1,\ y(0) = 2,$ and $z(0) = 1$ showing that the solution tends toward a non-washout steady state.

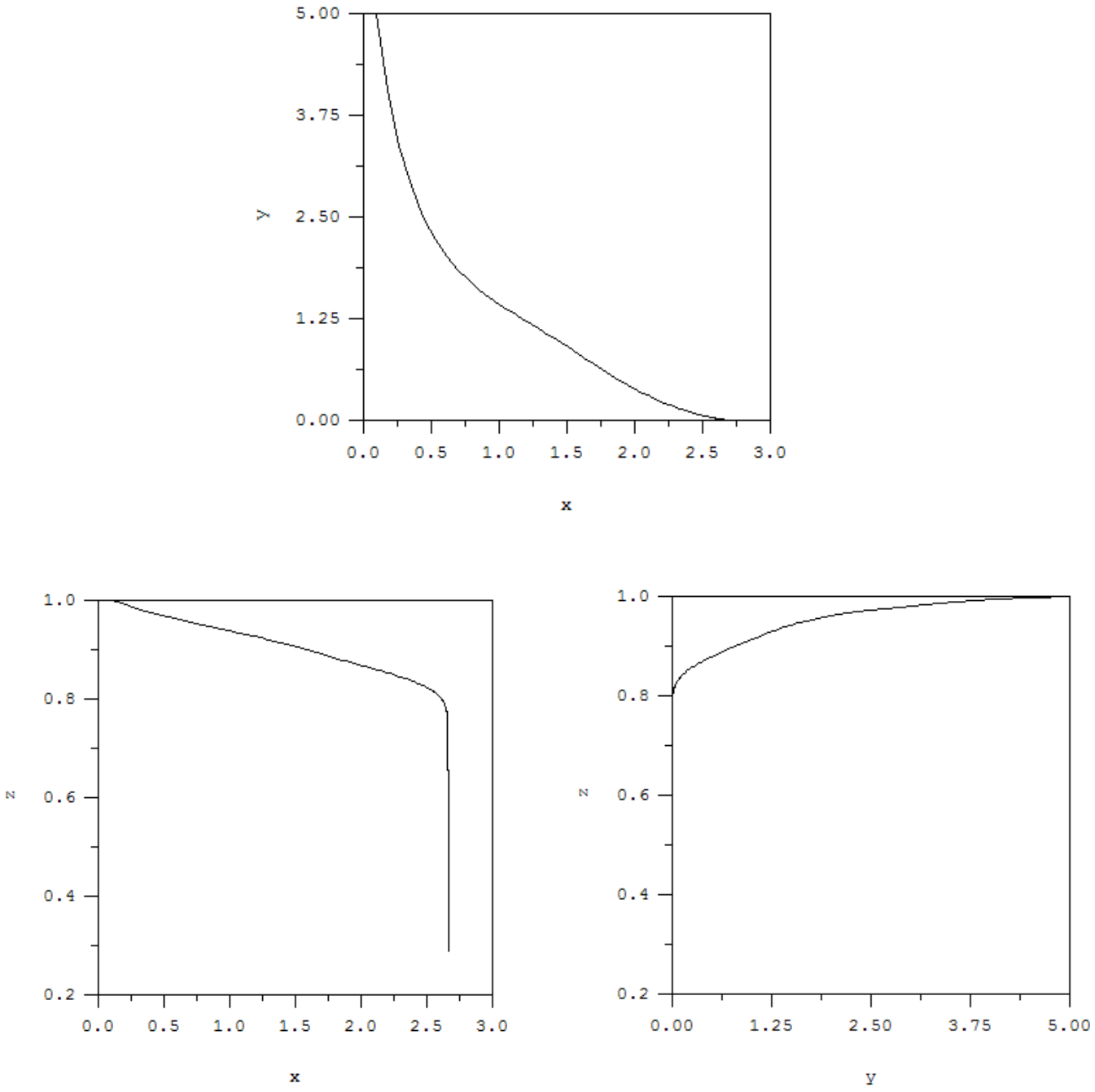

Fig. 5 A computer simulation of the system (4)-(6) with $c_1 = 0.8, c_2 = 0.81, c_3 = 0.001, c_4 = 0.01278, m_1 = 2, m_2 = 2, m_3 = 1,$ $d_1 = 0.15, d_2 = 0.319, d_3 = 0.0128, \tau = 0.05, x(0) = 0.1,$ $y(0) = 5,$ and $z(0) = 1$. The solution trajectory projected onto the (x,y)-plane, (x,z)-plane and (y,z)-plane showing that the solution tends toward a washout steady state.

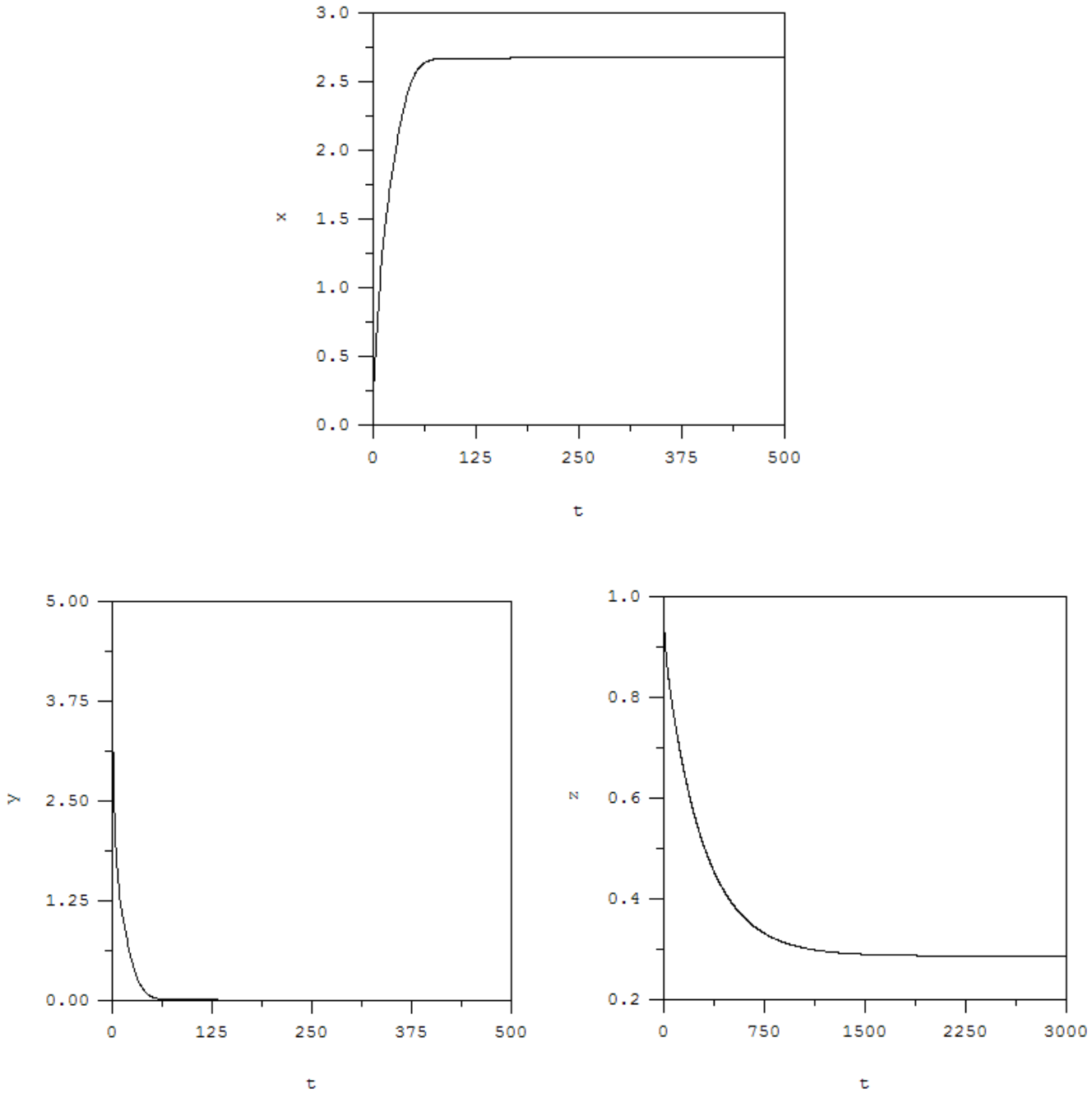

Fig. 6 The corresponding time courses of a) the level of vitamin D (x) in blood, b) the number of active osteoclasts and c) the number of active osteoblasts of the system (4)-(6) with $c_1 = 0.8, c_2 = 0.81, c_3 = 0.001, c_4 = 0.01278, m_1 = 2, m_2 = 2, m_3 = 1, d_1 = 0.15, d_2 = 0.319, d_3 = 0.0128$ $\tau = 0.05, x(0) = 0.1,\ y(0) = 5,$ and $z(0) = 1$ showing that the solution tends toward a washout steady state.

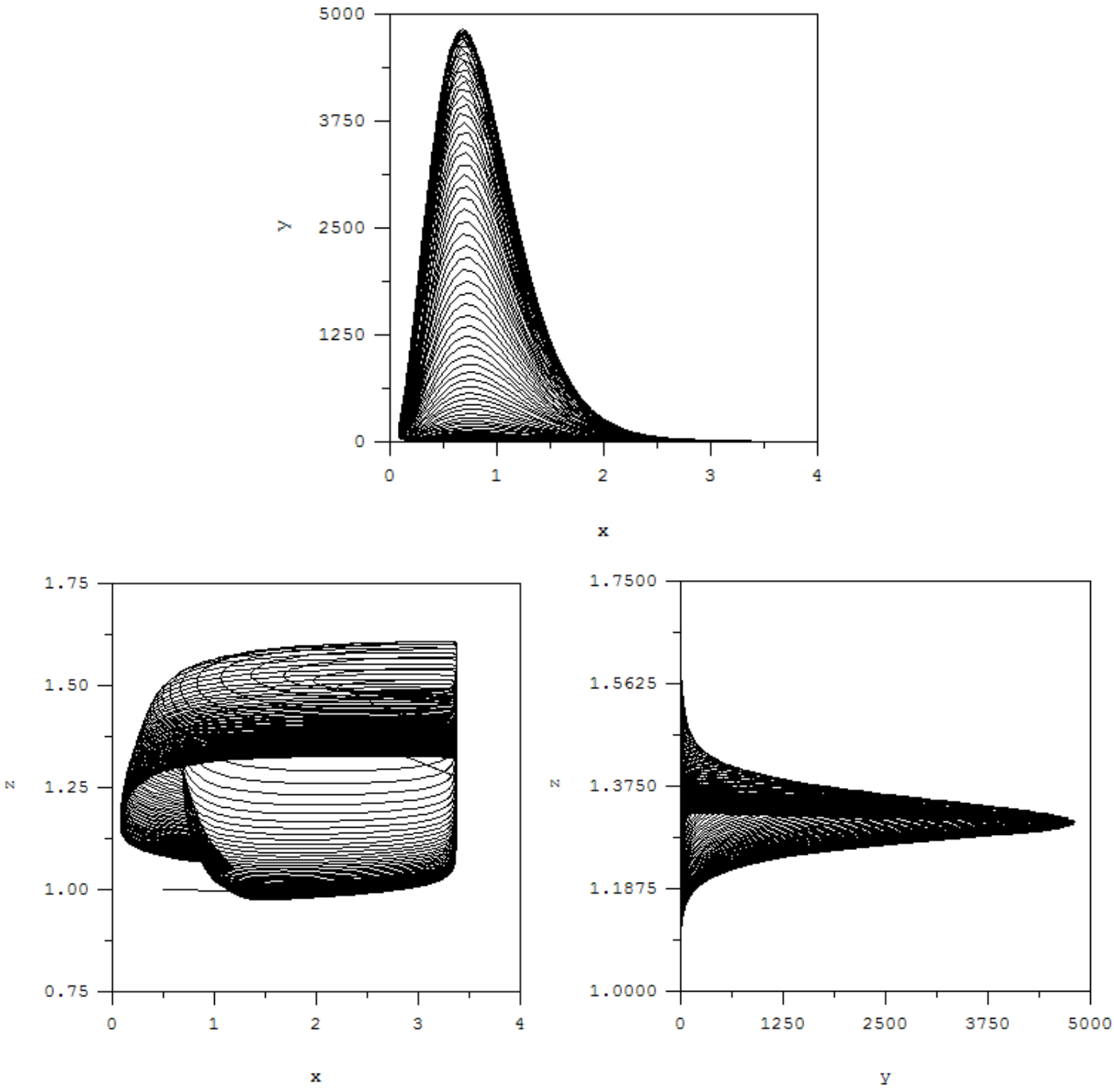

Fig. 7 A computer simulation of the system (4)-(6) with $c_1 = 0.98732, c_2 = 0.991, c_3 = 0.005894, c_4 = 0.014058, m_1 = 2, m_2 = 2, m_3 = 1.2,$ $d_1 = 0.1462, d_2 = 0.3465, d_3 = 0.01386, \tau = 350, x(0) = 0.5,$ $y(0) = 1,$ and $z(0) = 1$. The solution trajectory projected onto the (x,y)-plane, (x,z)-plane and (y,z)-plane showing an irregular pattern exhibited by the model.

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