Mathematical Modeling of Bone Formation and Resorption: Effects of Parathyroid Hormone and Vitamin D

Chontita Rattanakul, Sahattaya Rattanamongkonkul and Saowaros Srisuk

***Abstract*—**A mathematical model is proposed here in order to investigate the effects of parathyroid hormone and vitamin D on bone formation and resorption processes. Singular perturbation technique is then applied to analyze the model. The conditions on the system parameters for which a limit cycle exists are then derived. Numerical investigation is also carried out to support our theoretical prediction. The result shows that the model can exhibits a periodic solution corresponding to the pulsatile secretion of parathyroid hormone observed in the clinical evidence.

***Keywords*—**bone formation, bone resorption, limit cycle, mathematical model, parathyroid hormone, vitamin D.

I. Introduction

BONE is a highly organized tissue. The primary functions of bone are to provide support and protection as well as to provide the environment for hemopoiesis [1]. In addition, bone is the major calcium reservoir of the body since over 99% of total body calcium is stored in the skeleton [1]. To maintain its structural integrity, a great deal of new cells must be produced continuously. The two types of bone cells, osteoblasts and osteoclasts are responsible for bone formation and bone resorption, respectively [1]. The purposes of bone formation and resorption processes are to regulate calcium homeostasis, to repair micro-damaged bones (from everyday stress) and also to shape and sculpture the skeleton during growth [2]-[4]. There are several factors that effect bone formation and resorption such as parathyroid hormone (PTH), vitamin D, calcitonin, estrogen, and interleukin-6 (IL-6). In this paper, we will concentrate on the effects of PTH and vitamin D on the number of active osteoclasts and the number of active osteoblasts.

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II. Model Formulation

We now proceed to propose a nonlinear mathematical model to describe bone formation and resorption processes based on the effects of PTH and vitamin D as follows. Let us denote the concentration of PTH above the basal level at time t by $X(t)$, the serum level of vitamin D at time t by $Y(t)$, the number of active osteoclasts at time t by $Z(t)$, and the number of active osteoblasts at time t by $W(t)$. 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.

PTH secreted from the parathyroid gland plays an important role in maintaining the extracellular Ca^{2+} concentration within the very narrow range usually observed in vivo [5]. Since the level of serum calcium varies directly with the number of active osteoclasts, therefore the more active osteoclasts means the more calcium released into blood. PTH is released in response with rapidity as well as exquisite sensitivity to low extracellular concentrations of free calcium. When the calcium concentration decreases, there is a steep increase in secretion of PTH [5]. On the other hand, vitamin D has a negative feedback on PTH synthesis, hence the increase in the level of vitamin D leads to the decrease in the level of PTH [6]. In addition, low levels of PTH are secreted even when blood calcium levels are high [5]. The equation for the rate of PTH secretion above the basal level is then assumed to take the form

$$\frac{dX}{dt} = \frac{a_1}{(k_1 + Y)(k_2 + Z)} - b_1 X \tag{1}$$

where a_1, b_1, k_1 and k_2 are positive constants.

Vitamin D maintains the blood calcium in the normal range by enhancing the efficiency of intestinal calcium absorption and by increasing the mobilization of stem cells to become osteoclasts that, in turn, mobilize calcium stores from bone [7]-[10]. On the other hand, PTH increases the synthesis of

calcitonin, the active form of vitamin D [6], [11]. Therefore, the equation for the rate of change in serum level of vitamin D is then assumed to have the form

$$\frac{dY}{dt} = \frac{a_2 + a_3 X}{k_3 + Z} - b_2 Y \tag{2}$$

where a_2, a_3, k_3 and b_2 are positive constants.

Osteoclasts are bone resorbing cells originated from hemopoietic stem cells of the monocyte/macrophage lineage [12]. The differentiation and activation of osteoclasts are regulated by osteoblasts [13], [14] requiring several factors such as osteoclast differentiation factor (ODF) which was found to be identical to receptor activator NF-kB ligand (RANKL) [13], [15], [16]. Vitamin D interacts with its VDR in osteoblast resulting in the expression of RANKL which recognized by its corresponding receptor RANK on the preosteoclast. The interaction of RANKL and RANK results in signal transduction inducing the preosteoclast to be come a mature osteoclast [17]-[19]. Therefore, the dynamics of the active osteoclastic population can be described by the following equation

$$\frac{dZ}{dt} = \left(\frac{a_4 + a_5 X}{k_4 + X^2} \right) YZW - b_3 Z \tag{3}$$

where a_4, a_5, b_3 and k_4 are positive constants.

Osteoblasts are bone forming cells derived from the mesenchymal stem cells. The proliferation and differentiation of osteoblasts involve many factors such as FGF, IGF-I, TGF-beta [1]. PTH has both stimulating effect and inhibiting effects on osteoblasts proliferation and differentiation [13]. On the other hand, vitamin D has been found to stimulate the reproduction of active osteoblastic cells [20]. The dynamics of the osteoblastic population can be described by the following equation

$$\frac{dW}{dt} = \left(\frac{a_6 - a_7 W}{k_5 + X} \right) X + \frac{a_8 YW}{k_6 + Y} - b_4 W \tag{4}$$

where a_6, a_7, a_8, b_4, k_5 and k_6 are positive constants.

III. MODEL ANALYSIS

We assume that PTH has the very fast dynamics, Vitamin D has the fast dynamics. The osteoclastic population possesses the slow dynamics and the osteoblastic population has the slowest dynamics. Consequently, we scale the dynamics of the three components and parameters of the system in term of small positive parameters $0 < \varepsilon < 1$, $0 < \delta < 1$ and $0 < \eta < 1$ as follows.

Letting $x = X, y = Y, z = Z, w = W, c_1 = a_1, c_2 = \frac{a_2}{\varepsilon}, c_3 = \frac{a_3}{\varepsilon}$, $c_4 = \frac{a_4}{\varepsilon\delta}, c_5 = \frac{a_5}{\varepsilon\delta}, d_1 = b_1, d_2 = \frac{b_2}{\varepsilon}, d_3 = \frac{b_3}{\varepsilon\delta}$, we are led to the following model equations:

$$\frac{dx}{dt} = \frac{c_1}{(k_1 + y)(k_2 + z)} - d_1 x \equiv f(x, y, z, w) \tag{5}$$

$$\frac{dy}{dt} = \varepsilon \left(\frac{c_2 + c_3 x}{k_3 + z} - d_2 y \right) \equiv \varepsilon g(x, y, z, w) \tag{6}$$

$$\frac{dz}{dt} = \varepsilon\delta \left(\left(\frac{c_4 + c_5 x}{k_4 + x^2} \right) yzw - d_3 z \right) \equiv \varepsilon\delta h(x, y, z, w) \tag{7}$$

$$\frac{dw}{dt} = \varepsilon\delta\eta \left(\left(\frac{c_6 - c_7 w}{k_5 + x} \right) x + \frac{c_8 yw}{k_6 + y} - d_4 w \right) \equiv \varepsilon\delta\eta k(x, y, z, w) \tag{8}$$

The shapes and relative positions of the manifolds $\{f = 0\}$, $\{g = 0\}$, $\{h = 0\}$ and $\{k = 0\}$ determine the shapes, directions and speeds of the solution trajectories. We now analyze each of the equilibrium manifolds in detail.

The manifold $\{f = 0\}$

This manifold is given by the equation

$$x = \frac{c_1}{d_1 (k_1 + y)(k_2 + z)} \equiv A(y, z) \tag{9}$$

which is a decreasing function of *y* and *z*. It intersects the *x*-axis on the (x, y) – plane at the point where

$$x = \frac{c_1}{d_1 k_1 k_2} \equiv x_1 \tag{10}$$

The manifold $\{g = 0\}$

This manifold is given by the equation

$$y = \frac{1}{d_2} \left(\frac{c_2 + c_3 x}{k_3 + z} \right) \equiv B(x, z) \tag{11}$$

which is an increasing function of *y* and a decreasing function of *z*. It intersects the *y*-axis on the (x, y) – plane at the point where

$$y = \frac{c_2}{d_2 k_3} \equiv y_1 \tag{12}$$

Moreover, the manifold $\{f = 0\}$ intersects the manifold $\{g = 0\}$ along the curve

$$x = \frac{c_1}{d_1 (k_1 + B(x, z))(k_2 + z)} \tag{13}$$

which intersects the (x, y) – plane at the point where $z = 0$

$$x = \frac{\left\{ \begin{array}{l} -d_1 k_2 (d_2 k_1 k_3 + c_2) + \\ \sqrt{\left[d_1 k_2 (d_2 k_1 k_3 + c_2) \right]^2 + 4 c_1 c_3 d_1 d_2 k_2 k_3} \end{array} \right\}}{2 c_3 d_1 k_2} \equiv x_2 \tag{14}$$

and

$$y = \frac{c_2 + c_3 x_3}{d_2 k_3} \equiv y_2 \tag{15}$$

The manifold $\{h = 0\}$

This manifold consists of two submanifold which are the trivial manifold $z = 0$ and the nontrivial manifold

$$y=\frac{d_3}{w}\left(\frac{k_4+x^2}{c_4+c_5x}\right)\equiv C(x,w) \tag{16}$$

The nontrivial manifold is independent of the variable *z* and thus this submanifold is parallel to the *z*-axis. It attains the relative minimum at the point where

$$x=\frac{-c_4\pm\sqrt{c_4^2+c_5^2k_4}}{c_5}\equiv x_m \tag{17}$$

and

$$y=\frac{d_3}{w}\left(\frac{k_4+x_m^2}{c_4+c_5x_m}\right)\equiv y_m(w) \tag{18}$$

On the other hand, the nontrivial manifold intersects the *y*-axis on the (*x*,*y*)-plane at the point where

$$y=\frac{d_3k_4}{c_4w}\equiv y_3(w) \tag{19}$$

Moreover, the manifold $\{f=0\}$ intersects the nontrivial manifold $\{h=0\}$ along the curve

$$x=\frac{c_1}{d_1\left(k_1+C(x,w)\right)\left(k_2+z\right)} \tag{20}$$

which has a relative minimum point $L\left(x_m,y_m(w),z_m(w)\right)$ where

$$z_m(w)=\frac{c_1}{d_1\left(k_1+y_m\right)x_m}-k_2 \tag{21}$$

Also, the curve $\{f=h=0\}$ intersects the (*x*,*y*)-plane at the point where $z=0$, $x=x_3(w)$, $x_3(w)$ is a root of

$$\begin{aligned}&\left(d_1d_3k_2\right)x^3+\left(c_5d_1k_1k_2w\right)x^2\\&+\left(d_1k_2\left(c_4k_1w+d_3k_4\right)-c_1c_5w\right)x-c_1c_4w=0\end{aligned} \tag{22}$$

and

$$y=\frac{d_3}{w}\left(\frac{k_4+x_2^2(w)}{c_4+c_5x_2(w)}\right)\equiv y_4(w) \tag{23}$$

Note that $x_3(w)$ is only one positive root of (19) if

$$d_1k_2\left(c_4k_1w+d_3k_4\right)<c_1c_5w \tag{24}$$

The manifold $\{k=0\}$

This manifold is given by the equation

$$w=\frac{c_6x\left(k_6+y\right)}{c_7x\left(k_6+y\right)-c_8y\left(k_5+x\right)+d_4\left(k_5+x\right)\left(k_6+y\right)}\equiv D(x,y) \tag{25}$$

which is independent of the variable *z*.

Theorem 1 Suppose inequality (24) holds. If ε,δ and η are sufficiently small and

$$x_m<x_2<x_3(w) \tag{26}$$

and

$$y_4(w)<y_2<y_3(w) \tag{27}$$

where all the parametric values are given as above, then a limit cycle exists for the system of (5)-(8). The limit cycle can be constructed by concatenation of catastrophic various transitions occurring at three different speeds.

The proof of the theorem is based on geometric singular perturbation method [21], [22]. This method is a useful tool in the analysis of the different types of flows that clear separation in time scales: the fast flow, the intermediate flow, and the slow flow.

Under the conditions in Theorem 1, without loss of generality we start from point *I* and we assume that the position of *I* is as in Fig. 1 with $\{f\neq 0\}$. A fast transition will tend to point *J* on the manifold $\{f=0\}$. Here, $\{g<0\}$ and a transition at intermediate speed will be made in the direction of decreasing *y* until point *K* on the curve $\{f=h=0\}$ is reached. An intermediate transition then follows along this curve to some point *L* where the stability of submanifold will be lost. A jump to point *M* on the other stable part of $\{f=h=0\}$ followed by an intermediate transition in the direction of increasing *y* until the point *N* is reached since $\{g>0\}$ here. Once the point *N* is reached the stability of submanifold will be lost. A jump to point *O* on the other stable part of $\{f=h=0\}$ followed by an intermediate transition in the direction of decreasing *y* since $\{g<0\}$ here. Consequently, an intermediate transition will bring the system back to the point *L*, followed by flows along the same path repeatedly, resulting in the closed orbit *LMNOL*. Thus, limit cycle in the system for ε,δ and η are sufficiently small exists.

IV. NUMERICAL SIMULATION

A computer simulation of the system (5)-(8) with parametric values chosen to satisfy the condition in Theorem 1 is presented in Fig. 2. The solution trajectory, shown in Fig. 2a project onto the (x,y)-plane, tends to a limit cycle as theoretically predicted. The corresponding time courses of the concentration of PTH above the basal level, the level of serum vitamin D, the number of active osteoclasts and the number of active osteoblasts are as shown in Fig. 2b, 2c, 2d and 2e, respectively.

V. CONCLUSION

In this paper, the effects of PTH and vitamin D on bone formation and resorption have been investigated mathematically. The conditions on the system parameters for which a periodic solution exists are derived. A result of computer simulation of the model also shows that our model can exhibit a periodic behavior corresponding to the clinical observations in the pulsatile secretion of PTH, and the serum level of vitamin D [23]-[25].

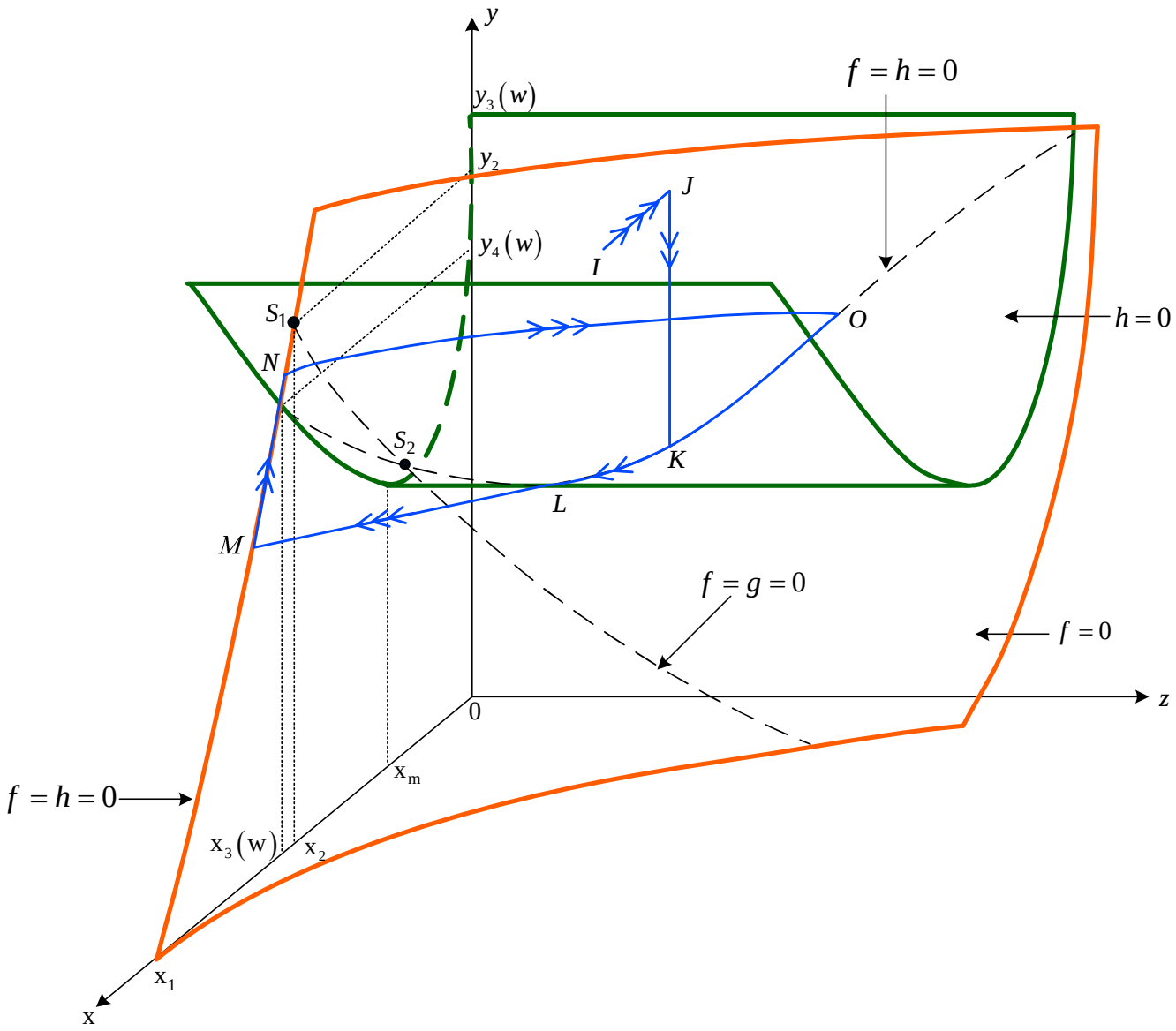

Fig. 1 The three equilibrium manifolds $\{f=0\},\{g=0\}$ and $\{h=0\}$ in the (x,y,z) – space in the case of limit cycle exists. Segments of the trajectories with one, two, and three arrows represent slow, intermediate, and fast transitions, respectively.

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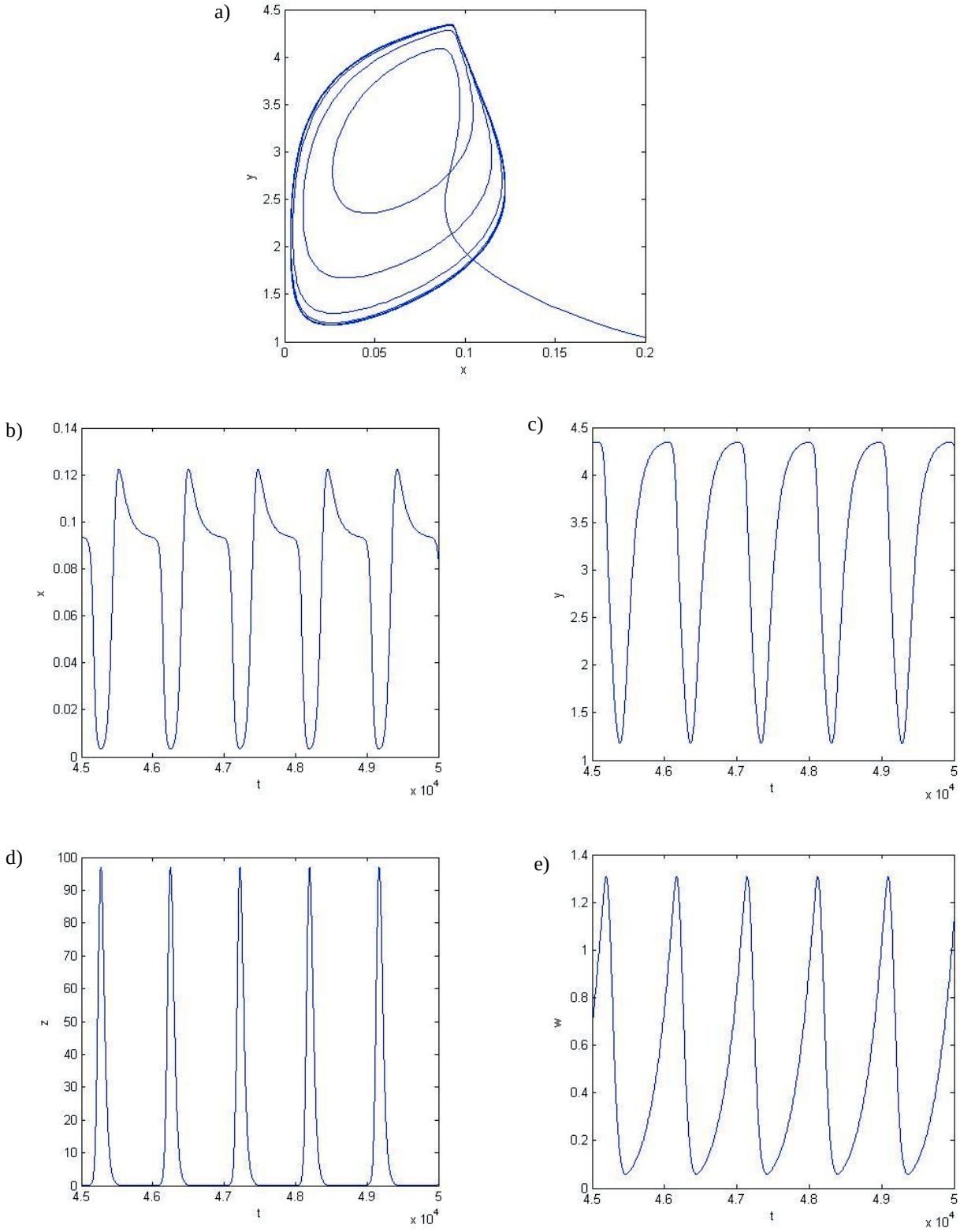

Fig. 2 A computer simulation of the model systems (5)-(8) with $c_1 = 0.1, c_2 = 0.8, c_3 = 0.8, c_4 = 0.5, c_5 = 0.1, c_6 = 0.1, c_7 = 0.1, c_8 = 0.95$, $k_1 = 1$, $k_2 = 2$, $k_3 = 5$, $k_4 = 3$, $k_5 = 1$, $k_6 = 5$, $d_1 = 0.1$, $d_2 = 0.04$, $d_3 = 0.3$, $d_4 = 0.4$, $\varepsilon = 0.2$, $\delta = 0.5$, $\eta = 0.9$, $x(0) = 0.5$, $y(0) = 0.2$, $z(0) = 1$ and $w(0) = 5$. (a) The solution trajectory projected onto the (x,y)-plane. (b) The corresponding time courses of the concentration of PTH above the basal level (x). (c) The corresponding time courses of the level of serum vitamin D (y), (d) number of active osteoclastic cells (z), and (e) number of active osteoblastic cells (w).

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