A Mathematical Model of Bone Remodeling Process: Effects of Parathyroid Hormone and Calcitonin

Inthira Chaiya, Sahattaya Rattanamongkonkul, and Chontita Rattanakul

***Abstract*—**We develop a nonlinear mathematical model of bone remodeling process based on the effects of parathyroid hormone and calcitonin. The model is then analyzed by using the singular perturbation technique in order to obtain the conditions on the system parameters for which a periodic solution exists. Numerical investigation is also carried out to support our theoretical prediction. The result shows that the model can exhibit a periodic behavior which has been observed in the secretion pattern of calcitonin and parathyroid hormone in normal individuals.

***Keywords*—**bone remodeling process, calcitonin, mathematical model, parathyroid hormone.

I. Introduction

BONE is highly organized tissue. Its primary functions are to provide support and protection, and to provide the environment for hemopoiesis [1]. In adult, approximately 5-10% of the existing bone is replaced every year. Bone remodeling is a dynamic, life-long process in which mature bone tissue is removed from the skeleton by osteoclastic cells and new bone tissue is formed by osteoblastic cells [1]. It is a largely a localized phenomenon that occurs at the level of a basic multicellular unit (BMU), consisting primarily of the action of osteoclasts and osteoblasts [2], [3]. Bone remodeling process consists of three stages: activation of the remodeling site, resorption of bone by osteoclasts, and bone formation by osteoblasts [3]. Bone imbalance can result if the osteoclasts produce an excessively deep resorption space, if the osteoblasts fail to completely refill the resorption space, or if both events occur [4], [5]. If a remodeling imbalance exists after the completion of a remodeling cycle, the degree of bone loss will be exacerbated which leads to osteoporosis [6].

Osteoporosis is now recognized as a major health disorder of bone remodeling, requiring costly medical treatment. It is a bone disease which is characterized by low bone mass, the structural deterioration of bone and an increased risk of fracture [7], [8]. Osteoporosis can affect both men and women of all ages, including children, but it occurs most frequently in the older population, particularly in postmenopausal women [7]. Therefore, an in-depth understanding of bone remodeling process including hormonal action such as parathyroid hormone (PTH), calcitonin (CT), estrogen or interleukin-6 (IL-6) is then required.

Several mathematical models have been proposed to describe bone remodeling process, but none of them concentrate on the effects of CT and PTH. Hence, we will develop a mathematical model to describe bone remodeling process based on the effects of CT and PTH by modifying the model that has been proposed by Rattanakul *et al.* [9].

II. Model Modification

We now modify the nonlinear mathematical model proposed by Rattanakul *et al.* [9] to describe bone remodeling process based on the effects of CT and PTH as follows. Let us denote the level of PTH above the basal level in blood at time t by $X(t)$,the level of CT above the basal level in blood 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.

Since osteoclasts resorb bone and liberate calcium, then the increase in the number of active osteoclastic cells results in the increase in the calcium level in blood. Therefore, the level of calcium in blood varies directly with the number of active osteoclasts. It is widely accepted that parathyroid hormone (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 (bodies of living organisms) [10]. PTH is released in response with rapidity as well as exquisite sensitivity to low extracellular

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concentrations of free calcium. When the calcium concentration decreases, there is a steep increase in secretion of PTH [10]. Therefore, there is an inverse relationship between the concentration of Ca^{2+} and the secretion of PTH, which implies the inverse relationship between the number of active osteoclasts and the secretion of PTH [10], [11]. In addition, low levels of PTH are secreted even when blood calcium levels are high [10]. The equation for the rate of PTH secretion above the basal level is then assumed to take the form

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

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 a_1 and k_1 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 b_1.

Calcitonin (CT) is synthesized by parafollicular C cells of the thyroid gland [12]. The secretion of CT is stimulated by elevated serum calcium level. CT inhibits bone resorption by inhibiting osteoclastic activity resulting in decreasing serum calcium through the interaction of CT and its receptors on the surface of osteoclasts [12]. Therefore, the equation for the rate of calcitonin secretion is then assumed to have the form

$$\frac{dY}{dt} = (a_2 - a_3 Y)YZ - b_2 Y \tag{2}$$

where the first term on the right-hand side of (2) represents the secretion rate of CT from parafollicular cells in the thyroid gland. The last term is the removal rate constant b_2. a_2 and a_3 are positive constants.

Osteoclasts originate from hemopoietic stem cells of the monocyte/macrophage lineage [1]. The differentiation and activation of osteoclasts are regulated principally by osteoblasts through the cell-to-cell interaction with osteoclasts [13], [14]. In addition, 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 them [13]-[15]. However, it has been observed that when the level of PTH increases further, the production of osteoclasts will be decreased [13]. Therefore, the dynamics of the active osteoclastic population can be described by the following equation

$$\frac{dZ}{dt} = \left(\frac{a_4 + a_5 X}{k_2 + X^2} - a_6 Y \right) ZW - b_3 Z \tag{3}$$

where the first term on the right-hand side of (3) represents the stimulating effect of PTH on the reproduction of active osteoclasts and the inhibiting effect of CT on active osteoclasts reproduction 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 b_3. a_4, a_5, a_6 and k_2 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, including PTH [19]. 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

$$\frac{dW}{dt} = \frac{a_7 X}{k_3 + X} - \frac{a_8 XW}{k_4 + X} - b_4 W \tag{4}$$

where the first term on the right-hand side of (4) 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 (4) 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 b_3.

Our model therefore consists of (1)-(4), possessing highly diversified nonlinear characteristics, upon which further analysis and investigation may be carried out in an attempt to explain the mystifying empirical observations previously mentioned.

III. MODEL ANALYSIS

We assume that PTH has the fastest dynamics, CT 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 four components and parameters of the system in term of small positive parameters $0 < \varepsilon << 1$ and $0 < \delta << 1$ as follows. Letting $x = X, y = Y, z = Z, w = W, c_1 = a_1, c_2 = \frac{a_2}{\varepsilon}, c_3 = \frac{a_3}{\varepsilon}$, $c_4 = \frac{a_4}{\varepsilon\delta}, c_5 = \frac{a_5}{\varepsilon\delta}, c_6 = \frac{a_6}{\varepsilon\delta}, c_7 = \frac{a_7}{\varepsilon\delta\eta}, c_8 = \frac{a_8}{\varepsilon\delta\eta}, d_1 = b_1, d_2 = \frac{b_2}{\varepsilon}$, $d_3 = \frac{b_3}{\varepsilon\delta}, d_4 = \frac{b_4}{\varepsilon\delta\eta}$, we are led to the following model equations:

$$\frac{dx}{dt}=\frac{c_1}{k_1+z}-d_1x\equiv f\left(x,y,z,w\right) \tag{5}$$

$$\frac{dy}{dt}=\varepsilon\left(\left(c_2-c_3y\right)yz-d_2y\right)\equiv\varepsilon g\left(x,y,z,w\right) \tag{6}$$

$$\frac{dz}{dt}=\varepsilon\delta\left(\left(\frac{c_4+c_5x}{k_2+x^2}-a_6y\right)zw-d_3z\right)=\varepsilon\delta h\left(x,y,z,w\right) \tag{7}$$

$$\frac{dw}{dt}=\frac{c_7x}{k_3+x}-\frac{c_8xw}{k_4+x}-d_4w \tag{8}$$

The system of (5)-(8), with the small parameters ε, δ and η can then be analyzed by using the geometric singular perturbation method.

The manifold $\left\{f=0\right\}$

This manifold is given by the equation

$$x=\frac{c_1}{d_1\left(k_1+z\right)}\equiv A\left(z\right) \tag{9}$$

We see that this manifold is independent of y and w. Hence, it is parallel to the *y*-axis and *w*-axis. It intersects the *x*-axis at the point where

$$x=\frac{c_1}{d_1k_1}\equiv x_1 \tag{10}$$

Moreover, $A\left(z\right)$ is an decreasing function of z and $A\left(z\right)\to 0$ as $z\to\infty$.

The manifold $\left\{g=0\right\}$

This manifold consists of two submanifolds. One is the trivial manifold $y=0$. The nontrivial one given by the equation

$$y=\frac{c_2z-d_2}{c_3z}\equiv B\left(z\right) \tag{11}$$

This nontrivial manifold is independent of the variable *x* and *w*. Hence, this submanifold is parallel to the x-axis and *w*-axis. It intersects the *z*-axis at the point where

$$z=\frac{d_2}{c_2}\equiv z_1 \tag{12}$$

Moreover, $B\left(z\right)$ is an increasing function of *z* and $B\left(z\right)$ is asymptotic to the line

$$y=\frac{c_2}{c_3}\equiv y_1 \tag{13}$$

as $z\to\infty$.

On the other hand, the manifold $\left\{f=0\right\}$ intersects the manifold $\left\{g=0\right\}$ along the curve

$$\left\{x=\frac{c_1}{d_1\left(k_1+z\right)},y=0\right\}$$

and the curve

$$\left\{x=\frac{c_1}{d_1\left(k_1+z\right)},y=\frac{c_2z-d_2}{c_3z}\right\}$$

The manifold $\left\{h=0\right\}$

This manifold consists of two sub-manifolds. One is the trivial manifold $z=0$ while the other one is the nontrivial manifold

$$y=\frac{1}{c_6}\left(\frac{c_4+c_5x}{k_2+x^2}-\frac{d_3}{w}\right)\equiv C\left(x,w\right) \tag{14}$$

which is independent of *z* and hence, it is parallel to the *z*-axis. $C\left(x,w\right)$ attains its maximum at the points where

$$x=\frac{-c_4+\sqrt{c_4{}^2+c_5{}^2k_2}}{c_5}\equiv x_2 \tag{15}$$

and $$y\left(w\right)=\frac{1}{c_6}\left(\frac{c_4+c_5x_2}{k_2+x_2^2}-\frac{d_3}{w}\right)\equiv y_2\left(w\right) \tag{16}$$

Note that $y_2\left(w\right)>0$ if and only if

$$w>\frac{d_3\left(k_2+x_2^2\right)}{c_4+c_5x_2} \tag{18}$$

For a fixed value of *w*, the nontrivial manifold $y=C\left(x,w\right)$ intersects the *y*-axis at the point where $x=0$ and

$$y=\frac{1}{c_6}\left(\frac{c_4}{k_2}-\frac{d_3}{w}\right)\equiv y_3\left(w\right) \tag{17}$$

Note that $y_3\left(w\right)>0$ if and only if

$$w>\frac{d_3k_2}{c_4} \tag{18}$$

On the other hand, for a fixed value of *w*, the nontrivial manifold $y=C\left(x,w\right)$ intersects the *x*-axis at the point where $y=0$ and

$$x=\frac{c_5w+\sqrt{\left(c_5w\right)^2+4d_3\left(c_4w-d_3k_2\right)}}{2d_3}\equiv x_3\left(w\right) \tag{19}$$

Note that if $y_3\left(w\right)>0$ then $x_3\left(w\right)>0$.

Moreover, $y=C\left(x,w\right)$ is an increasing function of *w* and for a fixed value of x, $y\to\frac{1}{c_6}\left(\frac{c_4+c_5x}{k_2+x^2}\right)$ as $w\to\infty$.

In addition, the manifold $\left\{f=0\right\}$ intersects the manifold $\left\{h=0\right\}$ along the line

$$\left\{x=x_1,z=0\right\}$$

and the curve

$$\left\{x=\frac{c_1}{d_1\left(k_1+z\right)},y=\frac{1}{c_6}\left(\frac{c_4+c_5x}{k_2+x^2}\right)-\frac{d_3}{w}\right\}$$

which attains its relative maximum at the points where

$$x=\frac{-2c_4\pm\sqrt{\left(2c_4^2\right)+4c_5^2k_2}}{2c_5}\equiv x_M>0$$

$$y=\frac{1}{c_6}\left(\frac{c_4+c_5x_M}{k_2+x_M^2}-\frac{d_3}{w}\right)\equiv y_M\left(w\right)$$

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and $z = \frac{1}{d_1}\left(\frac{c_1}{x_M} - d_1 k_1\right) \equiv z_M$

Note that $y_M(w) > 0$ if and only if $w > \frac{d_3\left(k_2 + x_M^2\right)}{c_4 + c_5 x_M}$ and $z_M > 0$ if and only if $x_M < \frac{c_1}{d_1 k_1}$.

Moreover, the manifold $\{f = 0\}$ intersects the manifold $\{g = 0\}$ and the manifold $\{h = 0\}$ at the point where

$$\{x = x_1, y = 0, z = 0\},$$

$$\left\{x = x_{S_1}(w), y = 0, z = z_{S_1}(w)\right\},$$

and $$\left\{x = x_{S_2}(w), y = y_{S_2}(w), z = z_{S_2}(w)\right\}$$

where $x_{S_1}(w) = \frac{c_5 w \pm \sqrt{(c_5 w)^2 + 4d_3(c_4 w - d_3 k_2)}}{2d_3}$,

$$z_{S_1}(w) = \frac{1}{d_1}\left(\frac{c_1}{x_{S_1}} - d_1 k_1\right).$$

$x_{S_2}(w)$ is a positive solution of

$$A_1(w)x^3 + A_2(w)x^2 + A_3(w)x + A_4(w) = 0$$

where

$$A_1(w) = \frac{d_1}{c_1}(c_2 c_6 k_1 w + c_6 d_2 w + c_3 d_3)$$

$$A_2(w) = c_3 - \frac{c_3 c_5 d_1 w}{c_1} - c_2 c_6 w$$

$$A_3(w) = \frac{d_1}{c_1}(c_2 c_6 k_1 k_2 w - c_3 c_4 w + c_3 d_3 k_2 + c_6 d_2 k_2 w + c_3 c_5 w)$$

$$A_4(w) = c_3 c_4 w - c_2 c_6 k_2 w - c_3 d_3 k_2 - c_3 c_4 w$$

and $z_{S_2}(w) = \frac{1}{d_1}\left(\frac{c_1}{x_{S_2}} - d_1 k_1\right)$, $y_{S_2}(w) = \frac{c_2 z_{S_2} - d_2}{c_3 z_{S_2}}$.

The manifold { k = 0 }

This manifold is given by the equation

$$w = \frac{c_7 x^2 + c_7 k_4 x}{(c_8 + d_4)x^2 + (c_8 k_3 + d_4 k_3 + d_4 k_4)x + d_4 k_3 k_4} \equiv \Psi(x) \quad (20)$$

This manifold is independent of y and z. It intersects the *x*-axis at the point where $w = 0$ and $x = 0$ or $x = -k_4$, while it intersects the *w*-axis at the point where $x = 0$ and $w = 0$. Moreover, $w \to \frac{c_7}{c_8 + d_4}$ as $x \to \infty$. On the other hand, $w \to \infty$ as $x \to x_4$ where

$$x_4 \equiv \frac{-(c_8 k_3 + d_4 k_3 + d_4 k_4)}{2(c_8 + d_4)} \pm \frac{\sqrt{(c_8 k_3 + d_4 k_3 + d_4 k_4)^2 - 4d_4 k_3 k_4 (c_8 + d_4)}}{2(c_8 + d_4)} < 0 \quad (21)$$

Theorem 1 If ε, δ and η are sufficiently small, and

$$0 < x_2 < x_1 < x_3(w) \quad (22)$$

$$0 < z_{S_2}(w) < z_M \quad (23)$$

$$y_3(w) > 0 \quad (24)$$

$$x_{S_2}(w) > 0, y_{S_2}(w) > 0, z_{S_2}(w) > 0 \quad (25)$$

where all parametric values are defined as above, then a limit cycle exists for the system of (5)-(8).

The proof of the theorem is based on geometric singular perturbation method [23]-[25]. The limit cycle can consist of various parts. The fast, intermediate, and slow parts are indicated, respectively, by three, two, and one arrows.

Under the conditions in Theorem 1, without loss of generality we start from point *A* and we assume that the position of *A* is as in Fig. 1 with $\{f \neq 0\}$. A fast transition will tend to point *B* 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 *C* on the curve $\{f = h = 0\}$ is reached. An intermediate transition then follows along this curve to some point *D* on the other stable part of $\{f = h = 0\}$ followed by an intermediate transition in the direction of decreasing z until the point *E* is reached since $\{h < 0\}$ here. Once the point *E* is reached the stability of submanifold will be lost. A jump to point *F* on the other stable part of $\{f = h = 0\}$ followed by an intermediate transition in the direction of increasing *z* since $\{h > 0\}$ here. Once the point *G* is reached the stability of submanifold will be lost. A jump to point *H* on the other stable part of $\{f = h = 0\}$. Consequently, an intermediate transition will bring the system back to the point *E*, followed by flows along the same path repeatedly, resulting in the closed orbit *EFGHE*. Thus, limit cycle in the system for ε, δ and η are sufficiently small exists.

IV. NUMERICAL RESULT

A computer simulation of the system (5)-(8) is presented in Fig. 2, with parametric values chosen to satisfy the condition in Theorem 1. The solution trajectory, shown in Fig. 2(a) project onto the (x, y)-plane, tends to a limit cycle as theoretically predicted. The corresponding time courses of the concentration of parathyroid hormone and calcitonin above the basal levels are as shown in Fig. 2(b) and 2(c), respectively.

V. CONCLUSION

We have proposed a mathematical model to study bone remodeling process based on the effects of parathyroid hormone and calcitonin. The conditions on the system parameters for which a periodic solution exists are then derived. Moreover, the numerical result demonstrated that the limit cycle behavior of the system (5)-(8) with parametric values chosen to satisfy Theorem 1 close to the construction

and analysis of our model. In addition, the periodic behaviors which have been observed in the time courses of parathyroid hormone and calcitonin are closely resemble to the pulsatile secretion patterns observed in the clinical data [26].

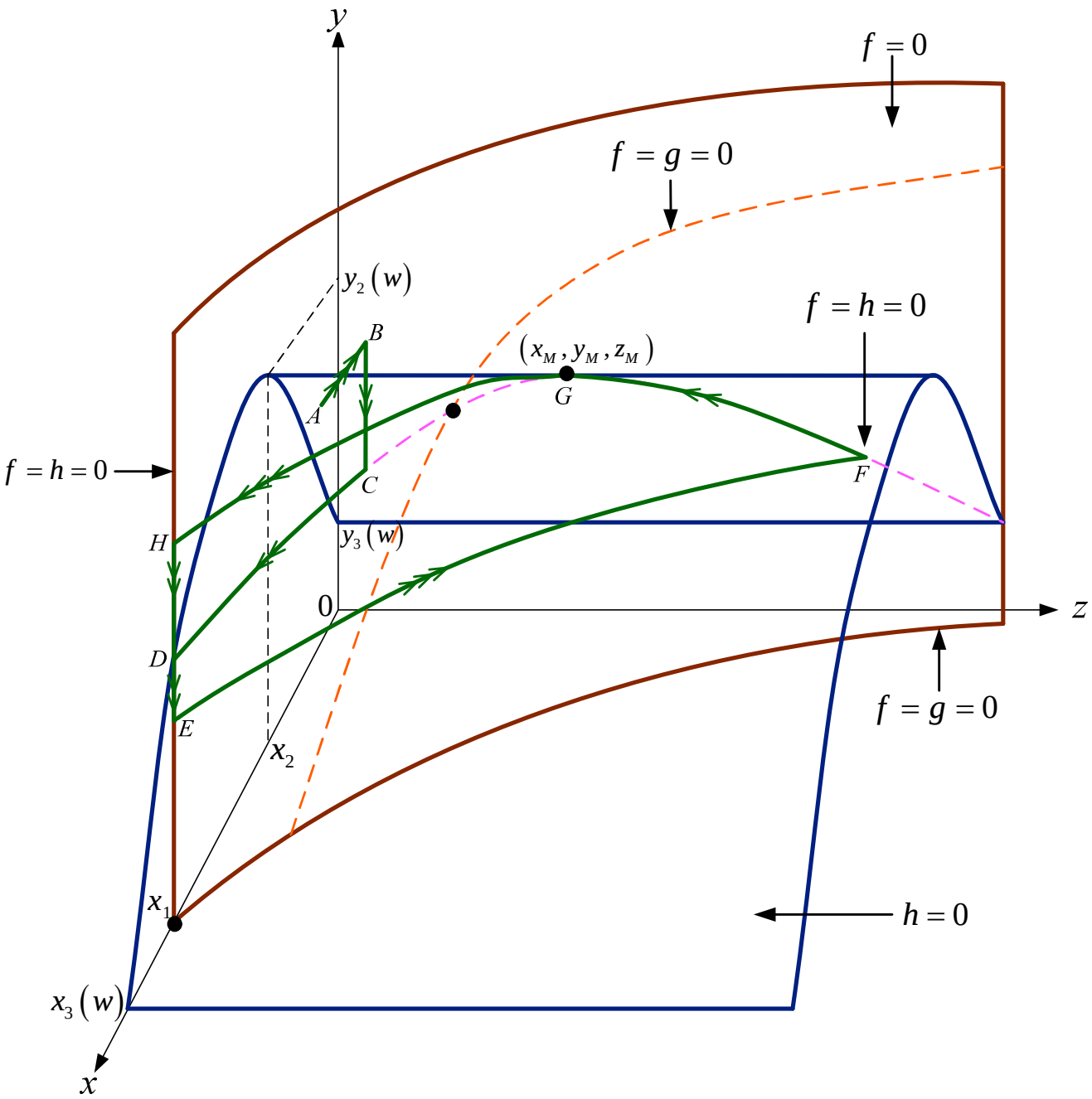

Fig. 1 The three equilibrium manifolds $\{f=0\},\{g=0\}$ and $\{h=0\}$ in the (x,y,z) – space in the case of limit cycle exists. Segments of the trajectories with one, two, and three arrows represent slow, intermediate, and fast transitions, respectively.

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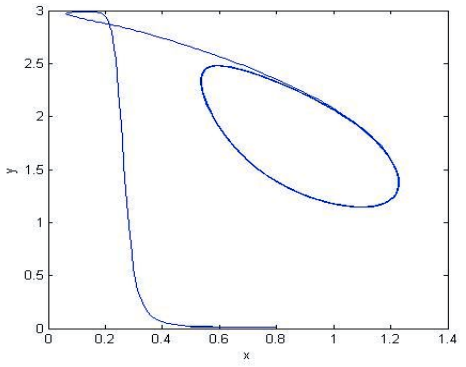
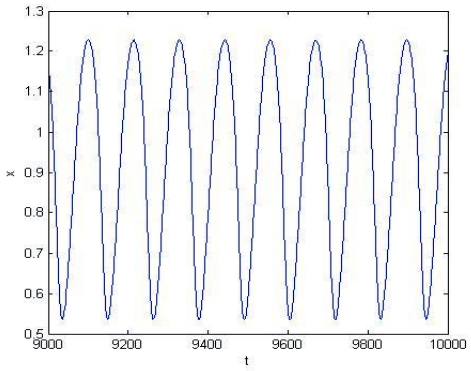
(a)



(b)



(c)

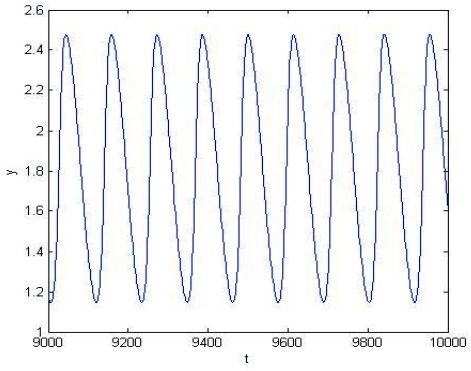


Fig. 2 A computer simulation of the model systems (5)-(8) with $\varepsilon = 0.9$, $\delta = 0.5$, $\eta = 0.3$, $c_1 = 0.3$, $c_2 = 0.3$, $c_3 = 0.1$, $c_4 = 0.4$, $c_5 = 0.9$, $c_6 = 0.3$, $c_7 = 0.5$, $c_8 = 0.2$, $d_1 = 0.5$, $d_2 = 0.03$, $d_3 = 0.25$, $d_4 = 0.2, k_1 = 0.4, k_2 = 0.6, k_3 = 0.5, k_4 = 0.03, x(0) = 0.5, y(0) = 0.01$, $z(0)=0.05$ and $w(0)=3.5$. (a) The solution trajectory projected onto the (x,y)-plane. (b) The corresponding time courses of PTH (x), and (c) CT level (y).

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