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# An impulsive mathematical model of bone formation and resorption: effects of parathyroid hormone, calcitonin and impulsive estrogen supplement

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## Abstract

In this paper, we propose an impulsive mathematical model of bone formation and resorption accounting for the number of active osteoclastic cells, bone resorbing cells, and the number of active osteoblastic cells, bone forming cells, based on the effects of parathyroid hormone and calcitonin with impulsive estrogen supplement. The model is then analyzed theoretically in terms of its stability, permanence and oscillatory behavior. The conditions on the model parameters, for which the desirable behaviors of the solution of the system can be expected, are derived. Numerical simulations are also carried out in order to support our theoretical predictions. The results indicate that the frequency and dosage of the estrogen supplements are important since the behavior of the solution of the system depends on the frequency and dosage of the estrogen supplements.

**Keywords:** bone remodeling process; calcitonin; parathyroid hormone; estrogen; impulsive treatment; mathematical model

## 1 Introduction

Bone is a highly organized tissue. Apart from attending to its own structural integrity, the skeleton must also respond to systemic needs for adequate amounts of calcium in the extracellular fluid. In order to maintain normal functions of bone and calcium homeostasis, bone remodeling process is needed to be taken into account. In bone remodeling process, osteoclasts act as bone resorbing cells, while osteoblasts act as bone forming cells. The process begins with the appearance of active osteoclasts on a previously inactive surface of bone, after which a lacuna will be excavated. Subsequently, osteoblasts then refill the resorption cavity and become inactive osteoblasts [1–3]. Serious health conditions such as osteoporosis may occur when the bone remodeling process is imbalanced (e.g. there is excessively deep resorption space produced by osteoclasts, or the replenishment of the resorption space by the activation of osteoblasts is incomplete). For a better understanding of bone remodeling process, the basic knowledge about osteoblasts, osteoclasts and the involving hormones such as parathyroid hormone (PTH) and calcitonin (CT) is necessary.

Osteoblasts derived from mesenchymal cells are responsible for bone formation. The stromal stem cells proliferate preosteoblast precursors, and then preosteoblasts precur-

sors proliferate preosteoblasts. After that, preosteoblasts differentiate into osteoblasts, and then osteoblasts become osteocytes or resting osteoblasts [4]. Note that the differentiation and activation of osteoclasts require direct physical contact with osteoblasts that produce at least two indispensable cytokines [1]. On the other hand, osteoclasts derived from the hemopoietic cells are responsible for bone resorption. The hemopoietic stem cells proliferate preosteoclast precursor cells, and then preosteoclasts precursors differentiate into preosteoclasts. After that, preosteoclasts differentiate into osteoclasts [4].

PTH and CT are principal hormones involved in bone formation and resorption. PTH is secreted from the parathyroid glands in response to the low calcium level in blood. It increases calcium concentration in blood by various direct and indirect actions on bone, kidney and intestine [1]. On bone, PTH enhances bone resorption by stimulating the activation of osteoclasts indirectly through osteoblasts since osteoclasts do not possess PTH receptors while osteoblast precursors possess them. Moreover, PTH has both stimulating and inhibiting effects on the differentiation and activation of osteoblasts [1]. PTH stimulates the differentiation of mesenchymal stem cells to preosteoblasts, but it inhibits the differentiation of osteoblasts in mature cells through the process of down-regulation of PTH receptors on osteoblasts [5–7]. In contrast to PTH, CT produced by the parafollicular cells of the thyroid gland inhibits bone resorption by acting on osteoclasts resulting in the decrease of calcium level in blood [1, 2].

As discussed above, an excessively deep resorption space produced by osteoclasts or an incomplete replenishment of the resorption space by the activation of osteoblasts can result in bone remodeling imbalance. If remodeling imbalance exists after the completion of a remodeling cycle, the degree of bone loss will be exacerbated and that leads to osteoporosis [8]. Osteoporosis is a bone metabolic disease which is characterized by low bone mass, the structural deterioration of bone and an increased risk of fracture. It occurs most frequently in postmenopausal women [3]. An increase in the activation frequency of new bone remodeling units and an increase in remodeling imbalance, especially resulting from the increase of osteoclastic formation, are observed when estrogen is deficient [8–12]. In osteoporosis patients, estrogen replacement therapy has been widely used to prevent menopausal bone loss and reduce the risk of fracture [8–12]. Kanatani *et al.* [10] and Riggs *et al.* [12] reported that the presence of estrogen results in the decrease of bone resorption by inhibiting the activity of osteoclasts. The works of Prestwood *et al.* [9] and Albright *et al.* [11] indicated the decrease in the values of biochemical markers of bone turnover due to the short-term estrogen treatment. However, there are some serious risks and side effects from the estrogen replacement therapy such as breast cancer and heart disease [8, 13]. High doses of estrogen results in weight loss in rats, and an increase in tumor formation was observed in aging rats with long-term treatment of estrogen [14]. Hence, the appropriate dose and duration of estrogen treatment are necessary and need to be investigated in details.

Mathematical models of bone remodeling process were proposed and analyzed theoretically and numerically [15–20]. However, the model that incorporates the effects of PTH, CT and the impulsive treatments of estrogen has not been proposed and analyzed yet. In the next section, we will develop a system of impulsive differential equations to study the effects of PTH, CT and the impulsive estrogen replacement therapy on bone remodeling process.

## 2 Model development

In bone remodeling process, estrogen is responsible for many osteoclast suppressing activities both directly and indirectly. Estrogen limits the size of preosteoclast and osteoclast populations, and it also limits the production of osteoclasts by restraining the production and secretion of cytokine that stimulate a stimulator of osteoclast development [21–30]. Moreover, in the presence of estrogen, osteoblastic stromal cells synthesize more anti-osteoclast OPG than osteoclast-stimulating receptor activator RANKL. Since OPG is a soluble decoy RANK-like receptor that binds to and covers up RANKL molecules sticking out of the surfaces of osteoblastic stromal cells, then the more OPG means the less RANKL available on the osteoblastic stromal cells’ surfaces for binding to their real RANK receptors, and that reduces the RANK signals needed to drive differentiation of the osteoclast progenitors into mature osteoclasts. Hence, the increase in the level of estrogen results in the decrease in the number of osteoclasts [21–30]. On the other hand, it has been reported that estrogen also has stimulating effects on osteoblasts as well by attenuating PTH-induced inhibition of osteoblast proliferation [31, 32]. Estrogen also directly modulates differentiation of bipotential stromal cells into the osteoblast and adipocyte lineages, causing a lineage shift toward the osteoblast, which leads to direct stimulation of bone formation [33]. We then propose an impulsive model to investigate the effects of PTH, CT and impulsive estrogen treatments on bone remodeling process as follows:

$$\left. \begin{aligned} \frac{dx}{dt} &= \frac{a_1}{k_1 + z} - b_1x & (1a) \\ \frac{dy}{dt} &= \frac{a_2z}{k_2 + x} - b_2y & (1b) \\ \frac{dz}{dt} &= \frac{a_3xz w}{(k_3 + x^2)(k_4 + y)} - b_3z & (1c) \\ \frac{dw}{dt} &= \frac{a_4x}{k_5 + x} - \frac{a_5xw}{k_6 + x} - b_4w & (1d) \end{aligned} \right\} t \neq nT$$

with

$$\left. \begin{aligned} \Delta z(t) &= -\rho z(t) \\ \Delta w(t) &= \mu \end{aligned} \right\} t = nT,$$

(1e)  
(1f)

where  $x(t)$  denotes the concentration of PTH above the basal level in blood at time  $t$ ,  $y(t)$  denotes the concentration of CT above the basal level in blood at time  $t$ ,  $z(t)$  denotes the number of active osteoclasts at time  $t$ ,  $w(t)$  denotes the number of active osteoblasts at time  $t$  and all parameters in the model are positive constant.  $\Delta z(t) = z(t^+) - z(t)$ ,  $\Delta w(t) = w(t^+) - w(t)$ ,  $T$  represents the period of impulsive treatment of estrogen,  $n \in Z_+$ ,  $Z_+ = \{1, 2, 3, \dots\}$ ,  $\rho$  represents the inhibiting effect of estrogen supplement on osteoclasts,  $0 < \rho < 1$ , and  $\mu$  represents the stimulating effect of estrogen supplement on osteoblasts,  $\mu > 0$ .

Here, the rate of change of PTH concentration in blood is represented by (1a). The first term on the right-hand side accounts for the secretion rate of PTH from the parathyroid glands which is inhibited by the increase in the calcium levels indicated by the increase in the number of active osteoclasts [1].

The rate of change of CT concentration in blood is represented by (1b). The elevation of calcium levels indicated by the increase in the number of active osteoclasts stimulates

the secretion of CT from the thyroid gland, whereas the increase in the level of PTH suppresses the secretion of CT as reported in [34]. Hence, the secretion rate of CT is then assumed to be represented by the first term on the right-hand side of (1b).

The rate of change of the number of active osteoclasts is represented by (1c). The first term on the right-hand side accounts for the stimulating effect of PTH and the inhibiting effect of CT on the reproduction of active osteoclasts which requires the cell to cell interaction of osteoclasts and osteoblasts as indicated in [20].

The rate of change of the number of active osteoblasts is represented by (1d). The first and the second terms on the right-hand side account for the stimulating effect and the inhibiting effect of PTH on the reproduction and differentiation of active osteoblasts as mentioned in [20], respectively.

The last terms of (1a)-(1d) account for the removal rates of PTH, CT, active osteoclasts and active osteoblasts, respectively.

The inhibition effect of estrogen treatment on the number of active osteoclasts is represented by (1e), while the stimulating effect of estrogen treatment on the number of active osteoblasts is represented by (1f).

As it has been observed clinically in [1, 35, 36], the dynamics of PTH and CT are very fast compared to the changes in the number of active osteoclasts and active osteoblasts. We then assume in what follows that PTH and CT equilibrate quickly to the level at which  $\frac{dx}{dt} = 0$  and  $\frac{dy}{dt} = 0$ , respectively. That is,

$$x = \frac{a_1}{b_1(k_1 + z)} \equiv f_1(z) \tag{2}$$

and

$$y = \frac{a_2}{b_2} \left( \frac{z}{k_2 + f_1(z)} \right) = \frac{a_2 b_1 z (k_1 + z)}{b_2 [a_1 + b_1 k_2 (k_1 + z)]} \equiv f_2(z). \tag{3}$$

Hence, system (1a)-(1f) can be reduced to the system of (4a)-(4d) as follows:

$$\left. \begin{aligned} \frac{dz}{dt} &= \frac{a_3 f_1(z) z w}{(k_3 + f_1^2(z))(k_4 + f_2(z))} - b_3 z \end{aligned} \right\} t \neq nT \tag{4a}$$

$$\left. \begin{aligned} \frac{dw}{dt} &= \frac{a_4 f_1(z)}{k_5 + f_1(z)} - \frac{a_5 f_1(z) w}{k_6 + f_1(z)} - b_4 w \end{aligned} \right\} \tag{4b}$$

with

$$\Delta z(t) = -\rho z(t) \tag{4c}$$

$$\Delta w(t) = \mu \tag{4d}$$

### 3 Preliminaries

Let

$$V : R_+ \times R_+^2 \rightarrow R_+,$$

where  $R_+ = [0, \infty)$ ,  $R_+^2 = \{S \in R^2 : S = (z, w), z \geq 0, w \geq 0\}$ . The map defined by the right-hand side of (4a)-(4b) is denoted by  $F = (F_1, F_2)$ .

**Definition 1** The function  $V$  defined in (4a) is said to belong to class  $V_0$  if

- (a)  $V$  is continuous in  $(nT, (n + 1)T] \times R_+^2 \rightarrow R_+$  and for each  $S \in R_+^2, n \in Z_+$ ,  
 $\lim_{(t,Y) \rightarrow (nT^+, S)} V(t, Y) = V(nT^+, S)$  exists, and
- (b)  $V$  is locally Lipschitzian in  $S$ .

**Definition 2** Suppose  $V \in V_0$ . For  $(t, S) \in (nT, (n + 1)T] \times R_+^2$ , the upper right derivative of  $V(t, S)$  with respect to (4a)-(4d) is defined by

$$D^+ V(t, S) = \limsup_{h \rightarrow 0^+} \frac{1}{h} [V(t + h, S + hF(t, S)) - V(t, S)],$$

where  $F = (F_1, F_2)$ .

In what follows, we assume that the solution of (4a)-(4d),  $S(t) = (z(t), w(t))$ , is a piecewise continuous function. That is,  $S(t) : R_+ \rightarrow R_+^2$ ,  $S(t)$  is continuous on  $(nT, (n + 1)T]$ ,  $n \in Z_+$  and  $\lim_{t \rightarrow nT^+} S(t) = S(nT^+)$  exists. Then the global existence and uniqueness of solution to (4a)-(4d) is guaranteed by the smoothness properties of  $F$  (see [37] for more details).

Since  $\frac{dz}{dt} = 0$  whenever  $z(t) = 0, t \neq nT, \frac{dw}{dt} > 0$  whenever  $w(t) = 0, t \neq nT$  and  $z(nT^+) = (1 - \rho)z(nT), 0 < \rho < 1, w(nT^+) = w(nT) + \mu, \mu > 0$ , we have the following lemma.

**Lemma 1** Suppose  $S(t) = (z(t), w(t))$  is a solution of (4a)-(4d) with  $S(0^+) \geq 0$ . Then  $S(t) \geq 0$  for all  $t \geq 0$ .

**Lemma 2** There exists a constant  $M > 0$  such that, for sufficiently large  $t$ ,  $z(t) \leq M$  and  $w(t) \leq M$  provided that

$$b_4 > \frac{a_1 a_3}{b_1 k_3 k_4}, \tag{5}$$

where  $(z(t), w(t))$  is a solution of (4a)-(4d).

*Proof* We let  $v(t) = z(t) + w(t)$ ,  $M_1 = \sup z f_1(z) = \frac{a_1}{b_1}$  and  $M_2 = \sup f_1(z) = \frac{a_1}{b_1 k_1}$ .

For  $t \neq nT$ , we choose a positive constant  $c$  for which

$$c = \min \left\{ b_3, b_4 - \frac{a_3 M_1}{k_3 k_4} \right\}.$$

Then

$$\begin{aligned} D^+ v + cv &= \frac{dz}{dt} + \frac{dw}{dt} + cz + cw \\ &= \frac{a_3 f_1(z) zw}{(k_3 + f_1^2(z))(k_4 + f_2(z))} - b_3 z + \frac{a_4 f_1(z)}{k_5 + f_1(z)} - \frac{a_5 f_1(z) w}{k_6 + f_1(z)} - b_4 w \\ &\quad + cz + cw \\ &\leq (c - b_3)z + \left( \frac{a_3 M_1}{k_3 k_4} - b_4 + c \right) w + \frac{a_4 M_2}{k_5} \\ &\leq \frac{a_4 M_2}{k_5} \equiv M_0. \end{aligned}$$

Hence  $D^+ v \leq -cv + M_0$ .

For  $t = nT$ ,

$$\begin{aligned} v(nT^+) &= z(nT^+) + w(nT^+) \\ &= (1 - \rho)z(nT) + w(nT) + \mu \\ &= z(nT) + w(nT) + \mu - \rho z(nT) \\ &\leq v(nT) + \mu. \end{aligned}$$

Therefore, Lemma 2.2 of Liu *et al.* [38] implies that, for  $t \in (nT, (n + 1)T]$ ,

$$\begin{aligned} v(t) &\leq v(0)e^{-ct} + \int_0^t M_0 e^{-c(t-s)} ds + \sum_{0 < t_n < t} \mu e^{-c(t-t_n)} \\ &\leq v(0)e^{-ct} + M_0 \left( \frac{1}{c} - \frac{e^{-ct}}{c} \right) + \mu \left( \frac{e^{-c(t-T)} - e^{-c(t-t_{n+1})}}{1 - e^{cT}} \right) \\ &< \frac{M_0}{c} + \mu \left( \frac{e^{cT}}{e^{cT} - 1} \right) \equiv M \quad \text{as } t \rightarrow \infty. \end{aligned}$$

Thus,  $v(t)$  is uniformly ultimately bounded, and hence there exists a constant  $M > 0$  such that  $z(t) \leq M$  and  $w(t) \leq M$  for sufficiently large  $t$ . □

#### 4 Stability when there is no active osteoclast

Now, let us consider the reduced impulsive system (4a)-(4d) when there is no active osteoclast ( $z = 0$ ):

$$\frac{dw}{dt} = A - Bw, \quad t \neq nT, \tag{6}$$

$$w(nT^+) = w(nT) + \mu, \quad t = nT, \tag{7}$$

$$w(0^+) = w_0, \tag{8}$$

where  $A \equiv \frac{a_1 a_4}{b_1 k_1 k_5 + a_1}$  and  $B \equiv \frac{a_1 a_5}{b_1 k_1 k_6 + a_1} + b_4$ . Note that  $A > 0$  and  $B > 0$ . We can see that

$$\tilde{w}(t) = \frac{\mu e^{-B(t-nT)}}{1 - e^{-BT}} + \frac{A}{B}, \quad t \in (nT, (n + 1)T] \tag{9}$$

is a periodic solution of (6)-(8) with  $\tilde{w}(0^+) = \frac{\mu}{1 - e^{-BT}} + \frac{A}{B} > 0$ .

Hence, the positive solution of (6)-(8) is

$$w(t) = \left( w_0 - \frac{A}{B} - \frac{\mu}{1 - e^{-BT}} \right) e^{-Bt} + \tilde{w}(t), \quad t \in (nT, (n + 1)T].$$

This leads to the following result.

**Lemma 3** *System (6)-(8) has a positive periodic solution  $\tilde{w}(t)$ , and for every solution  $w(t)$  of (6)-(8), we have  $w(t) \rightarrow \tilde{w}(t)$  as  $t \rightarrow \infty$ .*

Therefore, system (4a)-(4d) has a periodic solution at the vanishing level of active osteoclasts

$$(0, \tilde{w}(t)) = \left( 0, \frac{\mu e^{-B(t-nT)}}{1 - e^{-BT}} + \frac{A}{B} \right)$$

for  $t \in (nT, (n + 1)T]$  and  $\tilde{w}(nT^+) = \tilde{w}(0^+) = \frac{\mu}{1 - e^{-BT}} + \frac{A}{B}, n \in \mathbb{Z}_+$ .

**Theorem 1** *The solution  $(0, \tilde{w}(t))$  of (4a)-(4d) is locally asymptotically stable provided that*

$$0 < T < T_{\max}, \tag{10}$$

$$b_3 < \frac{AD}{B}, \tag{11}$$

$$\frac{D\mu}{B} < \ln\left(\frac{1}{1 - \rho}\right), \tag{12}$$

where  $T_{\max} \equiv \frac{1}{(\frac{AD}{B} - b_3)} [\ln(\frac{1}{1 - \rho}) - \frac{D\mu}{B}]$  and  $D \equiv \frac{a_1 a_3 b_1 k_1}{k_4 (a_1^2 + b_1^2 k_1^2 k_3)}$ .

*Proof* Consider a small perturbation from the point  $(0, \tilde{w}(t))$

$$z(t) = u_1(t),$$

$$w(t) = \tilde{w}(t) + u_2(t).$$

Then we may write

$$\begin{pmatrix} u_1(t) \\ u_2(t) \end{pmatrix} = \Phi(t) \begin{pmatrix} u_1(0) \\ u_2(0) \end{pmatrix}, \quad 0 < t < T,$$

where  $\Phi(t)$  satisfies

$$\frac{d\Phi(t)}{dt} = \begin{pmatrix} D\tilde{w}(t) - b_3 & 0 \\ * & -B \end{pmatrix} \Phi(t)$$

and  $\Phi(0) = I$ , the identity matrix. Hence, the fundamental solution matrix is

$$\Phi(t) = \begin{pmatrix} \exp \int_0^t (D\tilde{w}(s) - b_3) ds & 0 \\ * & \exp \int_0^t (-B) ds \end{pmatrix}.$$

Since the term  $(*)$  is not required in further analysis, it is not necessary to find the exact expression for  $(*)$ .

Linearization of (4c)-(4d) yields

$$\begin{pmatrix} u_1(nT^+) \\ u_2(nT^+) \end{pmatrix} = \begin{pmatrix} 1 - \rho & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} u_1(nT) \\ u_2(nT) \end{pmatrix}.$$

According to Floquet theory, the solution  $(0, \tilde{w}(t))$  of (4a)-(4d) is locally stable if  $|\lambda_i| < 1$ ,  $i = 1, 2$ , where  $\lambda_i$  is an eigenvalue of

$$M = \begin{pmatrix} 1 - \rho & 0 \\ 0 & 1 \end{pmatrix} \Phi(T).$$

Note that the eigenvalues of  $M$  are

$$\lambda_1 = (1 - \rho) \exp \int_0^T (D\tilde{w}(s) - b_3) ds = (1 - \rho) \exp \left( \frac{D\mu}{B} + \frac{ADT}{B} - b_3T \right),$$

$$\lambda_2 = \exp \int_0^T (-B) ds = \exp(-BT).$$

Since  $0 < \rho < 1, B > 0$  and (10)-(12) hold, then

$$\left( \frac{AD}{B} - b_3 \right) T < \ln \left( \frac{1}{1 - \rho} \right) - \frac{D\mu}{B}.$$

Hence,

$$|\lambda_1| = (1 - \rho) \exp \left( \frac{D\mu}{B} + \frac{ADT}{B} - b_3T \right) < 1$$

and

$$|\lambda_2| = \exp(-BT) < 1.$$

Therefore, Floquet theory implies that the solution  $(0, \tilde{w}(t))$  of (4a)-(4d) is locally stable and the proof is complete. □

### 5 Permanence of the system

**Definition 3** The reduced impulsive system (4a)-(4d) is said to be permanent if there are constants  $m, M > 0$  (independent of the initial values) and a finite time  $t_0$  such that for all solutions with initial values  $z(0^+) > 0$ , and  $w(0^+) > 0$ ,

$$m \leq z(t) \leq M, \tag{13}$$

$$m \leq w(t) \leq M, \tag{14}$$

for all  $t > t_0$ . Note that  $t_0$  may depend on the initial values.

**Theorem 2** *Suppose that*

$$b_3 < \frac{DE}{B}, \tag{15}$$

$$T > T^*. \tag{16}$$

*System (4a)-(4d) is permanent if (5) holds where  $E \equiv a_4b_2k_4(a_1 + b_1k_1k_2)$  and  $T^* \equiv \frac{B}{E} \ln(\frac{1}{1-\rho})$ .*

*Proof* Suppose that  $S(t) = (z(t), w(t))$  is a solution of system (4a)-(4d) with  $z(0^+) > 0$  and  $w(0^+) > 0$ . Since (5) holds, Lemma 2 implies that there is a constant  $M > 0$  such that, for sufficiently large  $t$ ,  $z(t) \leq M$  and  $w(t) \leq M$ .

Since  $\frac{a_4 f_1(z)}{k_5 + f_1(z)} > 0$  and  $(\frac{a_5 f_1(z)}{k_6 + f_1(z)} + b_4)$  is a decreasing function when  $z > 0$ , (4b) implies that

$$\begin{aligned} \frac{dw}{dt} &\geq -Bw, \quad t \neq nT, \\ w(nT^+) &= w(nT) + \mu, \quad t = nT \end{aligned}$$

and then we have

$$w(t) > \tilde{w}(t) - \frac{A}{B} - \varepsilon$$

for some  $\varepsilon > 0$  and for sufficiently large  $t$ .

Hence,

$$w(t) > \frac{\mu e^{-BT}}{1 - e^{-BT}} - \varepsilon \equiv m_1$$

for sufficiently large  $t$ .

Therefore, we only need to show that there exists a constant  $m_2 > 0$  such that  $z(t) > m_2$ .

In order to do so, for some  $m_3 > 0$ , we first let

$$\begin{aligned} \hat{M}_1 &= a_1^2 + b_1^2 k_3 (k_1 + m_3)^2, \\ \hat{M}_2 &= b_2 k_4 (a_1 + b_1 k_2 (k_1 + m_3)) + a_2 b_1 m_3 (k_1 + m_3), \\ \hat{M}_3 &= \frac{a_1 a_3 b_1 b_2 k_1 (a_1 + b_1 k_1 k_2)}{\hat{M}_1 \hat{M}_2}, \\ \hat{M}_4 &= \frac{a_1 a_4}{B(a_1 + b_1 k_5 (k_1 + m_3))}. \end{aligned}$$

Next, we do the two steps as follows.

*Step 1.* We will prove by contradiction that there exists  $t_1$  such that  $z(t_1) \geq m_3$ .

Suppose that  $z(t) < m_3$  for all positive  $t$ . We observe from (4b) and (4d) that

$$\begin{aligned} \frac{dw}{dt} &= \frac{a_4 f_1(z)}{k_5 + f_1(z)} - \frac{a_5 f_1(z)w}{k_6 + f_1(z)} - b_4 w, \quad t \neq nT \\ &\geq \frac{a_1 a_4}{a_1 + b_1 k_5 (k_1 + z)} - Bw \\ &\geq \frac{a_1 a_4}{a_1 + b_1 k_5 (k_1 + m_3)} - Bw, \\ w(t^+) &= w(t) + \mu, \quad t = nT. \end{aligned}$$

Consider the comparison system

$$\frac{dP}{dt} = \frac{a_1 a_4}{a_1 + b_1 k_5 (k_1 + m_3)} - BP, \quad t \neq nT, \tag{17}$$

$$P(t^+) = P(t) + \mu, \quad t = nT, \tag{18}$$

$$P(0^+) = w(0^+). \tag{19}$$

Hence,

$$\tilde{P}(t) \equiv \frac{\mu e^{-B(t-nT)}}{1 - e^{-BT}} + \frac{a_1 a_4}{B(a_1 + b_1 k_5(k_1 + m_3))}, \quad t \in (nT, (n + 1)T] \tag{20}$$

is a periodic solution of (17)-(19) with  $\tilde{P}(0^+) \equiv \frac{\mu}{1 - e^{-BT}} + \frac{A}{B} > 0$ . The positive solution of (17)-(19) is

$$P(t) = \left( P(0^+) - \frac{a_1 a_4}{B(a_1 + b_1 k_5(k_1 + m_3))} - \frac{\mu}{1 - e^{-BT}} \right) e^{-Bt} + \tilde{P}(t) \tag{21}$$

for  $t \in (nT, (n + 1)T]$  and  $P(t) \rightarrow \tilde{P}(t) = \frac{\mu e^{-B(t-nT)}}{1 - e^{-BT}} + \frac{a_1 a_4}{B(a_1 + b_1 k_5(k_1 + m_3))}$  as  $t \rightarrow \infty$ .

The comparison theorem [37] then implies that  $w(t) \geq P(t)$ .

Next, let us consider (4a)

$$\begin{aligned} \frac{dz}{dt} &= \frac{a_3 f_1(z)zw}{(k_3 + f_1^2(z))(k_4 + f_2(z))} - b_3 z \\ &= \frac{a_1 a_3 b_1 b_2 (k_1 + z)(a_1 + b_1 k_2 (k_1 + z))zw}{(a_1^2 + b_1^2 k_3 (k_1 + z)^2)(b_2 k_4 (a_1 + b_1 k_2 (k_1 + z)) + a_2 b_1 z (k_1 + z))} - b_3 z \\ &\geq \left( \frac{a_1 a_3 b_1 b_2 k_1 (a_1 + b_1 k_1 k_2)w}{\hat{M}_1 \hat{M}_2} - b_3 \right) z. \end{aligned}$$

Since  $w(t) \geq P(t)$ , there is  $T_1 > 0$  such that

$$\tilde{P}(t) - \varepsilon_1 < P(t) \leq w(t), \quad t \neq nT, t \geq T_1$$

for a sufficiently small  $\varepsilon_1 > 0$ .

Therefore,

$$\begin{aligned} \frac{dz}{dt} &\geq (\hat{M}_3(\tilde{P}(t) - \varepsilon_1) - b_3)z, \quad t \neq nT, t \geq T_1, \\ z(t^+) &= (1 - \rho)z(t), \quad t = nT, t \geq T_1. \end{aligned}$$

Letting  $N \in \mathbb{Z}_+$  and  $NT \geq T_1$ , and integrating over  $(nT, (n + 1)T], n \geq N$ , then we obtain

$$\begin{aligned} z((n + 1)T) &\geq z(nT)(1 - \rho) \exp\left( \int_{nT}^{(n+1)T} (\hat{M}_3(\tilde{P}(t) - \varepsilon_1) - b_3) dt \right) \\ &= z(nT)(1 - \rho) \exp\left( (\hat{M}_3 \hat{M}_4 - \varepsilon_1 \hat{M}_3 - b_3)T + \frac{\hat{M}_3 \mu}{B} \right) \\ &= z(nT)\eta, \end{aligned}$$

where  $\eta \equiv (1 - \rho) \exp((\hat{M}_3 \hat{M}_4 - \varepsilon_1 \hat{M}_3 - b_3)T + \frac{\hat{M}_3 \mu}{B})$ .

Consider

$$\ln \eta = \ln(1 - \rho) + (\hat{M}_3 \hat{M}_4 - \varepsilon_1 \hat{M}_3 - b_3)T + \frac{\hat{M}_3 \mu}{B}.$$

For sufficiently small  $\varepsilon_1 > 0$ ,

$$\begin{aligned} \ln \eta &\approx \ln(1 - \rho) + (\hat{M}_3 \hat{M}_4 - b_3)T + \frac{\hat{M}_3 \mu}{B} \\ &> \ln(1 - \rho) + (\hat{M}_3 \hat{M}_4 - b_3)T. \end{aligned}$$

Since (15) and (16) hold, we can choose a small  $m_3 > 0$  such that  $\ln \eta > 0$ , and hence

$$\eta \equiv (1 - \rho) \exp\left((\hat{M}_3 \hat{M}_4 - \varepsilon_1 \hat{M}_3 - b_3)T + \frac{\hat{M}_3 \mu}{B}\right) > 1. \tag{22}$$

Then  $z((n+k)T) \geq z(nT)\eta^k \rightarrow \infty$  as  $k \rightarrow \infty$ . It contradicts the boundedness of  $z(t)$ . Hence, there is  $t_1 > 0$  such that  $z(t_1) \geq m_3$ .

*Step 2.* If  $z(t) \geq m_3$  for all  $t > t_1$ , then the proof is complete. Otherwise,  $z(t) < m_3$  for some  $t > t_1$ . Letting  $t^* = \inf_{t > t_1} \{z(t) < m_3\}$ . There are two possible subcases.

Case 1:  $t^* = n_1 T$  for some  $n_1 \in Z_+$ . This means  $z(t) \geq m_3$  for  $t \in (t_1, t^*]$  and, by the continuity of  $z(t)$ , we have  $z(t^*) = m_3$ .

Since there are  $M > 0$  and  $m_1 > 0$  such that  $z(t) < M$ , and  $m_1 < w(t) < M$  for sufficiently large  $t$ , we choose  $M' > 0$  and  $m'_1 > 0$  such that

$$z(t) < M' \quad \text{and} \quad m'_1 < w(t) < M'$$

and

$$m'_1 < \frac{b_3}{\hat{M}_3} \tag{23}$$

such that

$$\left| w(t^{**}) - \frac{a_1 a_4}{B(a_1 + b_1 k_5(k_1 + m_3))} - \frac{\mu}{1 - e^{-BT}} \right| - \mu < M'. \tag{24}$$

Then choose  $n_2, n_3 \in Z_+$  such that

$$n_2 T > \frac{1}{B} \ln\left(\frac{M' + \mu}{\varepsilon_1}\right) \tag{25}$$

and

$$(1 - \rho)^{n_2} \exp((n_2 + 1)\eta_1 T) \eta^{n_3} > 1, \tag{26}$$

where

$$\eta_1 \equiv \hat{M}_3 m'_1 - b_3 < 0.$$

Let  $T' = n_2 T + n_3 T$ . We claim that there is  $t_2 \in (t^*, t^* + T']$  such that  $z(t_2) > m_3$ . Otherwise, considering (21) with  $P(t^{**}) = w(t^{**})$ , we have

$$P(t) = \left( P(t^{**}) - \frac{a_1 a_4}{B(a_1 + b_1 k_5(k_1 + m_3))} - \frac{\mu}{1 - e^{-BT}} \right) e^{-B(t-t^*)} + \tilde{P}(t)$$

for  $t \in (nT, (n + 1)T]$  and  $n_1 \leq n \leq n_1 + n_2 + n_3$ .

For  $n_2T \leq t - t^* \leq T'$ , we have

$$\begin{aligned} |P(t) - \tilde{P}(t)| &= \left| P(t^{*+}) - \frac{a_1 a_4}{B(a_1 + b_1 k_5(k_1 + m_3))} - \frac{\mu}{1 - e^{-BT}} \right| e^{-B(t-t^*)} \\ &= \left| w(t^{*+}) - \frac{a_1 a_4}{B(a_1 + b_1 k_5(k_1 + m_3))} - \frac{\mu}{1 - e^{-BT}} \right| e^{-B(t-t^*)} \\ &< (M' + \mu) e^{-B(t-t^*)} \\ &< (M' + \mu) e^{-Bn_2T} \\ &< \varepsilon_1. \end{aligned}$$

Then

$$\tilde{P}(t) - \varepsilon_1 < P(t) < w(t).$$

As in Step 1, we have

$$\begin{aligned} z(t^* + T') &= z(n_1T + n_2T + n_3T) \\ &\geq z(t^* + n_2T) \eta^{n_3}. \end{aligned}$$

From (4a), we have

$$\begin{aligned} \frac{dz}{dt} &= \frac{a_3 f_1(z)zw}{(k_3 + f_1^2(z))(k_4 + f_2(z))} - b_3z, \quad t \neq nT \\ &\geq (\hat{M}_3 w - b_3)z \\ &\geq (\hat{M}_3 m'_1 - b_3)z \tag{27} \\ &= \eta_1 z, \end{aligned}$$

$$z(t^+) = (1 - \rho)z(t), \quad t = nT.$$

Integrating the above over  $[t^*, t^* + n_2T]$ , we obtain

$$\begin{aligned} z(t^* + n_2T) &\geq z(t^*) (1 - \rho)^{n_2} \exp\left(\int_{n_1T}^{n_1T+n_2T} \eta_1 dt\right) \\ &\geq m_3 (1 - \rho)^{n_2} \exp(n_2 \eta_1 T) \\ &\geq m_3 (1 - \rho)^{n_2} \exp((n_2 + 1) \eta_1 T), \end{aligned}$$

and hence

$$\begin{aligned} z(t^* + T') &\geq z(t^* + n_2T) \eta^{n_3} \\ &\geq m_3 (1 - \rho)^{n_2} \exp((n_2 + 1) \eta_1 T) \eta^{n_3} \\ &> m_3, \end{aligned}$$

which contradicts the definition of  $m_3$ . Hence, there is  $t_2 \in (t^*, t^* + T']$  such that  $z(t_2) > m_3$ .

Now, let  $\tilde{t} = \inf_{t > t^*} \{z(t) > m_3\}$ . Then  $z(t) < m_3$  for  $t \in (t^*, \tilde{t})$ , and by the continuity of  $z(t)$ , we have  $z(\tilde{t}) = m_3$ . We choose  $l \in \mathbb{Z}_+$  such that  $l \leq n_2 + n_3$  and  $t^* + lT \geq \tilde{t}$ , and suppose  $t \in (t^* + (l - 1)T, t^* + lT]$ . From (27), we have

$$\begin{aligned} z(t) &\geq z(t^{*+})(1 - \rho)^{l-1} \exp((l - 1)\eta_1 T) \exp(\eta_1(t - (t^* + (l - 1)T))) \\ &= z(t^*)(1 - \rho)^l \exp((l - 1)\eta_1 T) \exp(\eta_1(t - (t^* + (l - 1)T))) \\ &= m_3(1 - \rho)^l \exp(\eta_1(t - t^*)) \\ &\geq m_3(1 - \rho)^{n_2+n_3} \exp(\eta_1 lT) \\ &\geq m_3(1 - \rho)^{n_2+n_3} \exp((n_2 + n_3)\eta_1 T). \end{aligned}$$

Since  $\eta_1 < 0$  and  $l \leq n_2 + n_3$ , letting

$$\bar{m}_2 = m_3(1 - \rho)^{n_2+n_3} \exp((n_2 + n_3)\eta_1 T),$$

we have  $z(t) \geq \bar{m}_2$  for  $t \in (t^*, \tilde{t})$ . We can continue in the same way by using  $\tilde{t}$  instead of  $t^*$ . Then we shall have  $z(t) \geq \bar{m}_2$  for all  $t$  large enough.

Case 2:  $t^* \neq nT$  for all  $n \in \mathbb{Z}_+$ . This means  $z(t) \geq m_3$  for  $t \in [t_1, t^*)$  and  $z(t^*) = m_3$ . Suppose  $t^* \in (n'_1 T, (n'_1 + 1)T)$  for some  $n'_1 \in \mathbb{Z}_+$ . There are two possible subcases.

Case 2.1:  $z(t) \leq m_3$  for all  $t \in (t^*, (n'_1 + 1)T]$ . We claim that there is  $t'_2 \in [(n'_1 + 1)T, (n'_1 + 1)T + T']$  such that  $z(t'_2) > m_3$ . Otherwise, considering (21) with  $P((n'_1 + 1)T^+) = w((n'_1 + 1)T^+)$ . For  $t \in (nT, (n + 1)T]$ ,  $n'_1 + 1 \leq n \leq n'_1 + 1 + n_2 + n_3$ , we obtain

$$P(t) = \left( P((n'_1 + 1)T^+) - \frac{a_1 a_4}{B(a_1 + b_1 k_5(k_1 + m_3))} - \frac{\mu}{1 - e^{-BT}} \right) e^{-B(t - (n'_1 + 1)T)} + \tilde{P}(t).$$

Similarly to Case 1, for  $n_2 T \leq t - t^*$ , we obtain

$$|P(t) - \tilde{P}(t)| < \varepsilon_1.$$

Then

$$\tilde{P}(t) - \varepsilon_1 < P(t) \leq w(t).$$

Since  $n_2 T \leq (n'_1 + 1 + n_2)T - t^*$ , we have

$$\begin{aligned} z((n'_1 + 1 + n_2)T) &\geq z(t^*)(1 - \rho)^{n_2} \exp(\eta_1((n'_1 + 1 + n_2)T - t^*)) \\ &\geq m_3(1 - \rho)^{n_2} \exp(\eta_1((n'_1 + 1 + n_2)T - n'_1 T)) \\ &\geq m_3(1 - \rho)^{n_2} \exp((n_2 + 1)\eta_1 T). \end{aligned}$$

Then

$$\begin{aligned} z((n'_1 + 1 + n_2 + n_3)T) &\geq z((n'_1 + 1 + n_2)T) \eta^{n_3} \\ &\geq m_3(1 - \rho)^{n_2} \exp((n_2 + 1)\eta_1 T) \eta^{n_3} \\ &> m_3, \end{aligned}$$

which contradicts the definition of  $m_3$ . Hence, there is  $t'_2 \in [(n'_1 + 1)T, (n'_1 + 1)T + T']$  such that  $z(t'_2) > m_3$ .

Now, let  $\bar{t} = \inf_{t > t^*} \{z(t) > m_3\}$ . Then  $z(t) \leq m_3$  for  $t \in [t^*, \bar{t})$ , and  $z(\bar{t}) = m_3$ . We choose  $l' \in \mathbb{Z}_+$  such that  $l' \leq n_2 + n_3 + 1$  and suppose  $t \in (n'_1 T + (l' - 1)T, n'_1 T + l' T]$ . From (27), we have

$$\begin{aligned} z(t) &\geq z((n'_1 T + (l' - 1)T)^+) \exp(\eta_1(t - (n'_1 T + (l' - 1)T))) \\ &= z(n'_1 T + (l' - 1)T)(1 - \rho) \exp(\eta_1(t - (n'_1 T + (l' - 1)T))) \\ &\geq z(t^*)(1 - \rho)^{l'-1} \exp(\eta_1(t - t^*)) \\ &\geq m_3(1 - \rho)^{l'-1} \exp(\eta_1(t - t^*)). \end{aligned}$$

Since  $\eta_1 < 0$  and  $t - t^* \leq l' T$ , hence

$$z(t) \geq m_3(1 - \rho)^{n_2+n_3} \exp((n_2 + n_3 + 1)\eta_1 T).$$

Letting

$$m_2 = m_3(1 - \rho)^{n_2+n_3} \exp((n_2 + n_3 + 1)\eta_1 T),$$

we have  $z(t) \geq m_2$  for  $t \in (t^*, \bar{t})$ . We can continue in the same way by using  $\bar{t}$  instead of  $t^*$ . Then we shall have  $z(t) \geq m_2$  for all  $t$  large enough.

Case 2.2: There is  $t'' \in (t^*, (n'_1 + 1)T]$  such that  $z(t'') > m_3$ . Let  $\underline{t} = \inf_{t > t^*} \{z(t) > m_3\}$ . Hence,  $z(t) < m_3$  for  $t \in [t^*, \underline{t})$ , and  $z(\underline{t}) = m_3$ . For  $t \in [t^*, \underline{t})$ , (27) holds, we have

$$\begin{aligned} z(t) &\geq z(t^*) \exp\left(\int_{t^*}^t \eta_1 dt\right) \\ &= m_3 \exp(\eta_1(t - t^*)) \\ &\geq m_3 \exp(\eta_1 T) \\ &> m_2 \end{aligned}$$

since  $t < n'_1 T + T < t^* + T$ .

For  $t > \underline{t}$ , we can continue in the same way since  $z(\underline{t}) \geq m_3$ . Since  $m_2 < \bar{m}_2 < m_3$ , we have  $z(t) \geq m_2$  for  $t \geq t_1$ . The proof is complete. □

### 6 Existence and stability of positive periodic solution

We now investigate the possibility of bifurcation of positive periodic solution to system (4a)-(4d) near  $(0, \tilde{w}(t))$ . In order to do so, it is more convenient to exchange the state variables and consider the following system instead:

$$\frac{dz}{dt} = \frac{a_4 f_1(w)}{k_5 + f_1(w)} - \frac{a_5 f_1(w)z}{k_6 + f_1(w)} - b_4 z, \quad t \neq nT, \tag{28}$$

$$\frac{dw}{dt} = \frac{a_3 f_1(w)zw}{(k_3 + f_1^2(w))(k_4 + f_2(w))} - b_3 w, \quad t \neq nT \tag{29}$$

with

$$\Delta z(t) = \mu, \quad t = nT, \tag{30}$$

$$\Delta w(t) = -\rho w(t), \quad t = nT. \tag{31}$$

Let

$$F_1(z, w) \equiv \frac{a_4 f_1(w)}{k_5 + f_1(w)} - \frac{a_5 f_1(w)z}{k_6 + f_1(w)} - b_4 z,$$

$$F_2(z, w) \equiv \frac{a_3 f_1(w)zw}{(k_3 + f_1^2(w))(k_4 + f_2(w))} - b_3 w.$$

According to Lakmeche and Arino [39],

$$\Theta_1(z, w) = z + \mu, \quad \Theta_2(z, w) = (1 - \rho)w, \quad \zeta(t) = (\tilde{w}(t), 0)^T,$$

$$S_0 = (\tilde{w}(\tau_0), 0)^T, \quad \tau_0 = T_{\max}$$

and

$$\frac{\partial \Phi_1(\tau_0, S_0)}{\partial \tau} = \frac{\partial \tilde{w}(\tau_0, S_0)}{\partial t} = \frac{-B\mu \exp(-B\tau_0)}{1 - \exp(-B\tau_0)} < 0,$$

$$\frac{\partial \Phi_1(\tau_0, S_0)}{\partial z} = \exp\left(\int_0^{\tau_0} \frac{\partial F_1(\zeta(r))}{\partial z} dr\right) = \exp(-B\tau_0),$$

$$\begin{aligned} \frac{\partial \Phi_1(\tau_0, S_0)}{\partial w} &= \int_0^{\tau_0} \exp\left(\int_v^{\tau_0} \frac{\partial F_1(\zeta(r))}{\partial z} dr\right) \frac{\partial F_1(\zeta(v))}{\partial w} \exp\left(\int_0^v \frac{\partial F_2(\zeta(r))}{\partial w} dr\right) dv \\ &= \int_0^{\tau_0} \exp(-B(\tau_0 - v)) f_1'(0) \left( \frac{a_4 k_5}{(k_5 + f_1(0))^2} - \frac{a_5 k_6 \tilde{w}(v)}{(k_6 + f_1(0))^2} \right) \\ &\quad \times \exp\left(\int_0^v (D\tilde{w}(r) - b_3) dr\right) dv, \end{aligned}$$

$$\frac{\partial \Phi_2(\tau_0, S_0)}{\partial w} = \exp\left(\int_0^{\tau_0} \frac{\partial F_2(\zeta(r))}{\partial w} dr\right) = \exp\left(\int_0^{\tau_0} (D\tilde{w}(r) - b_3) dr\right),$$

$$\begin{aligned} \frac{\partial^2 \Phi_2(\tau_0, S_0)}{\partial z \partial w} &= \int_0^{\tau_0} \exp\left(\int_v^{\tau_0} \frac{\partial F_2(\zeta(r))}{\partial w} dr\right) \frac{\partial^2 F_2(\zeta(v))}{\partial z \partial w} \exp\left(\int_0^v \frac{\partial F_2(\zeta(r))}{\partial w} dr\right) dv \\ &= \frac{D\tau_0}{1 - \rho} > 0, \end{aligned}$$

$$\begin{aligned} \frac{\partial^2 \Phi_2(\tau_0, S_0)}{\partial w^2} &= \int_0^{\tau_0} \exp\left(\int_v^{\tau_0} \frac{\partial F_2(\zeta(r))}{\partial w} dr\right) \frac{\partial^2 F_2(\zeta(v))}{\partial w^2} \exp\left(\int_0^v \frac{\partial F_2(\zeta(r))}{\partial w} dr\right) dv \\ &\quad + \int_0^{\tau_0} \left[ \exp\left(\int_v^{\tau_0} \frac{\partial F_2(\zeta(r))}{\partial w} dr\right) \frac{\partial^2 F_2(\zeta(v))}{\partial z \partial w} \right] \\ &\quad \times \left[ \int_0^v \exp\left(\int_\theta^v \frac{\partial F_1(\zeta(r))}{\partial z} dr\right) \frac{\partial F_1(\zeta(\theta))}{\partial w} \right. \\ &\quad \times \left. \exp\left(\int_0^\theta \frac{\partial F_2(\zeta(r))}{\partial w} dr\right) d\theta \right] dv \\ &= \int_0^{\tau_0} \frac{2a_3 \tilde{w}(v)}{1 - \rho} \left( \frac{k_4 f_1'(0)(k_3 - 2f_1^2(0)) - f_1(0) f_2'(0)(k_3 + f_1^2(0))}{k_4^2 (k_3 + f_1^2(0))^2} \right) dv \end{aligned}$$

$$\begin{aligned}
 & + Df_1'(0) \int_0^{\tau_0} \left[ \exp\left(\int_v^{\tau_0} (D\tilde{w}(r) - b_3) dr\right) \right] \\
 & \times \left[ \int_0^v \left( \frac{a_4 k_5}{(k_5 + f_1(0))^2} - \frac{a_5 k_6 \tilde{w}(\theta)}{(k_6 + f_1(0))^2} \right) \right. \\
 & \left. \times \exp\left(\int_0^\theta (D\tilde{w}(r) - b_3) dr - B(v - \theta)\right) d\theta \right] dv, \\
 \frac{\partial^2 \Phi_2(\tau_0, S_0)}{\partial w \partial \tau} & = \frac{\partial F_2(\zeta(\tau_0))}{\partial w} \exp\left(\int_0^{\tau_0} \frac{\partial F_2(\zeta(r))}{\partial w} dr\right) \\
 & = (D\tilde{w}(\tau_0) - b_3) \exp\left(\int_0^{\tau_0} (D\tilde{w}(r) - b_3) dr\right) \\
 & = \frac{1}{1 - \rho} \left[ \frac{D\mu \exp(-B\tau_0)}{1 - \exp(-B\tau_0)} + \frac{AD}{B} - b_3 \right].
 \end{aligned}$$

Now, we can compute

$$d'_0 = 1 - \left( \frac{\partial \Theta_2}{\partial w} \frac{\partial \Phi_2}{\partial w} \right)_{(\tau_0, S_0)} = 1 - (1 - \rho) \exp\left(\int_0^{\tau_0} (D\tilde{w}(r) - b_3) dr\right),$$

where  $\tau_0$  is the root of  $d'_0 = 0$ . Note that  $d'_0 > 0$  if  $T < T_{\max}$  and  $d'_0 < 0$  if  $T > T_{\max}$ . We can also compute

$$\begin{aligned}
 a'_0 & = 1 - \left( \frac{\partial \Theta_1}{\partial z} \frac{\partial \Phi_1}{\partial z} \right)_{(\tau_0, S_0)} = 1 - \exp(-B\tau_0) > 0, \\
 b'_0 & = - \left( \frac{\partial \Theta_1}{\partial z} \frac{\partial \Phi_1}{\partial w} + \frac{\partial \Theta_1}{\partial w} \frac{\partial \Phi_2}{\partial w} \right)_{(\tau_0, S_0)} \\
 & = - \frac{\partial \Phi_1(\tau_0, S_0)}{\partial w} \\
 & = - \int_0^{\tau_0} \exp(-B(\tau_0 - v)) f_1'(0) \left( \frac{a_4 k_5}{(k_5 + f_1(0))^2} - \frac{a_5 k_6 \tilde{w}(v)}{(k_6 + f_1(0))^2} \right) \\
 & \quad \times \exp\left(\int_0^v (D\tilde{w}(r) - b_3) dr\right) dv, \\
 B^* & = - \left[ \left( \frac{D\mu \exp(-B\tau_0)}{1 - \exp(-B\tau_0)} \right) \left( 1 - \frac{B\tau_0}{1 - \exp(-B\tau_0)} \right) + \frac{AD}{B} - b_3 \right], \\
 C^* & = 2(1 - \rho) \frac{b'_0}{a'_0} \frac{\partial^2 \Phi_2}{\partial z \partial w} - (1 - \rho) \frac{\partial^2 \Phi_2}{\partial w^2}.
 \end{aligned}$$

Note that  $C^* > 0$  and  $B^* < 0$  if

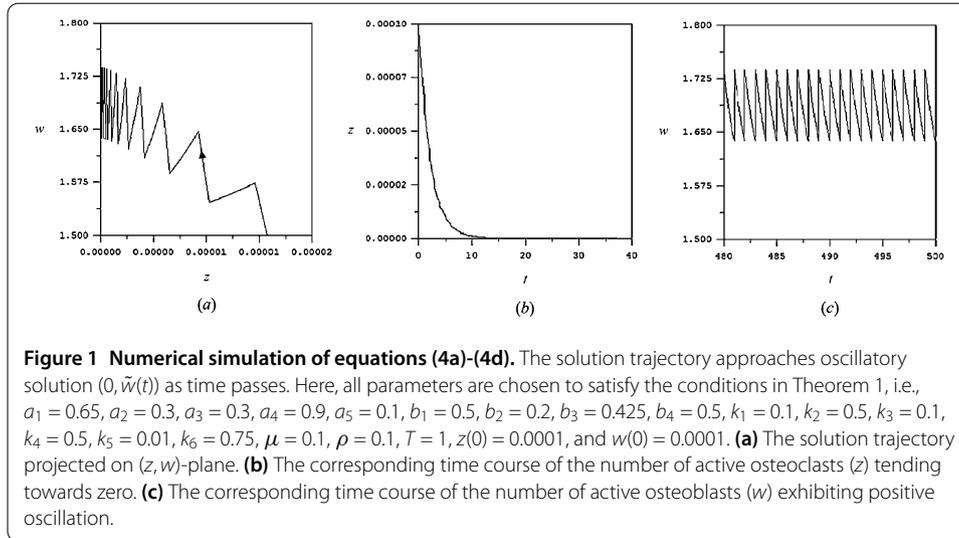
$$k_4 f_1'(0) (k_3 - 2f_1^2(0)) < f_1(0) f_2'(0) (k_3 + f_1^2(0)), \tag{32}$$

$$\frac{a_4 k_5}{(k_5 + f_1(0))^2} > \frac{a_5 k_6}{(k_6 + f_1(0))^2} \left[ \frac{\mu}{1 - \exp(-B\tau_0)} + \frac{A}{B} \right] \tag{33}$$

and

$$\frac{AD}{B} - b_3 - D\mu > 0. \tag{34}$$

Hence, the following result is obtained according to Lakmeche and Arino [39].



**Theorem 3** *System (28)-(31) has a positive periodic solution which is supercritical provided*

$$T > T_{\max} \tag{35}$$

and (5), (11)-(12), (32)-(34) hold.

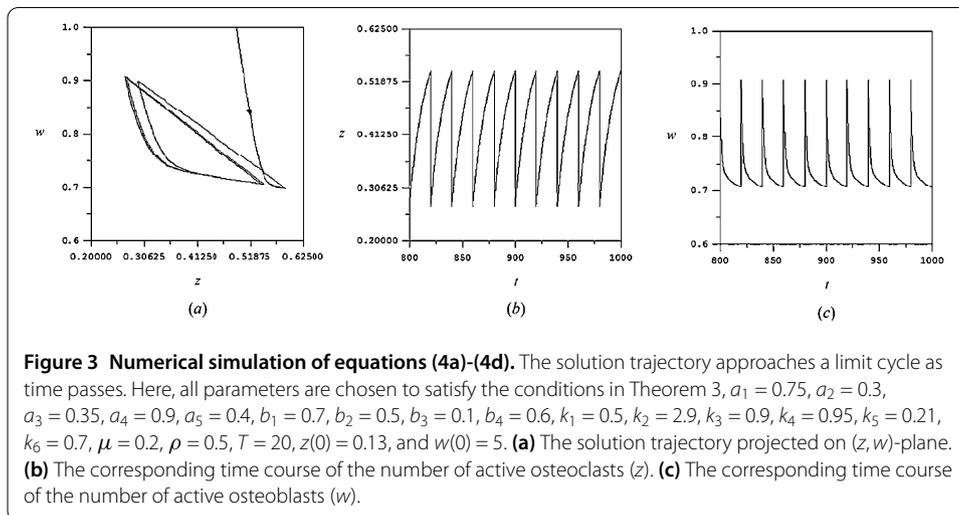
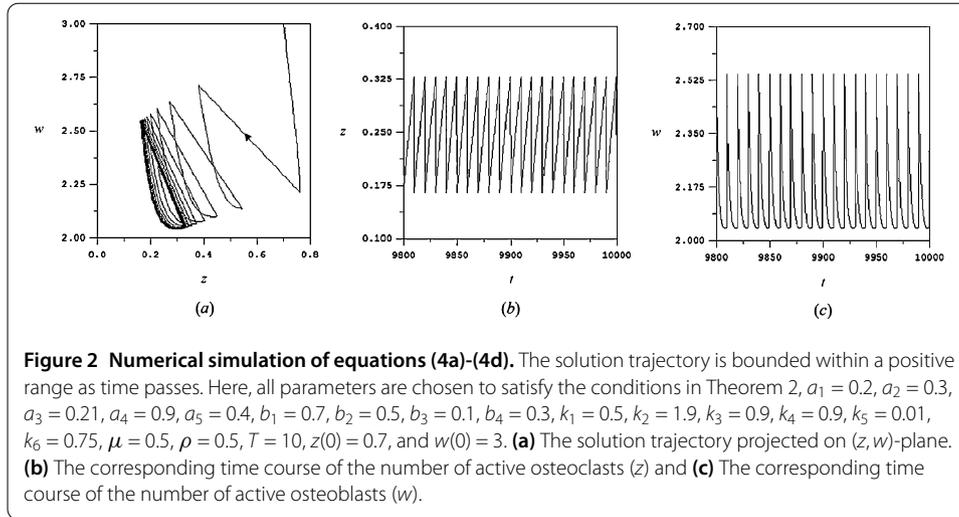
### 7 Numerical simulations

In this section, numerical simulations are carried out in order to support our theoretical predictions.

Firstly, all parameters are chosen to satisfy all conditions in Theorem 1. In Figure 1, we can see that the solution of system (4a)-(4d) converges asymptotically to the oscillatory solution  $(0, \tilde{w}(t))$  as time passes conforming with our theoretical prediction. Figure 2 shows that the solution of system (4a)-(4d) is bounded within a positive range as time passes when all parameters are chosen to satisfy all conditions in Theorem 2. Here, the simulation result also agrees with our theoretical prediction. Finally, the solution trajectory of system (4a)-(4d) shown in Figure 3 exhibits the sustained oscillations as time passes when all parameters are chosen to satisfy all conditions in Theorem 3. A limit cycle occurs as theoretically predicted.

### 8 Conclusion

We have developed an impulsive system of bone remodeling process in order to investigate the effect of estrogen supplements. The model is then analyzed theoretically so that the conditions on the system parameters, for which the desirable behaviors of the solution of the system can be expected, are derived. We can see that the frequency of estrogen treatments  $\frac{1}{T}$ , the dosages of estrogen supplements indicated by  $\mu$  and  $\rho$  play important roles in controlling the number of active osteoclasts and active osteoblasts, the different frequencies and dosages of estrogen supplements might lead to the undesirable behavior of the system. For example, the solution of the system might be unbounded, which means that the number of active osteoclasts, bone resorbing cells, might increase to very high



levels or the number of active osteoblasts, bone forming cells, decreases to very low levels resulting in the net bone resorption instead of bone formation, which is the expected outcome of the estrogen supplements.

Moreover, a condition needed to guarantee the existence of positive oscillation in the number of active osteoblasts and active osteoclasts resembling clinical observation stated in Theorem 3 is  $T > T_{max}$ , where  $T_{max}$  depends on  $\mu$  and  $\rho$ . Hence, if the dosage of estrogen supplement reflected by  $\mu$  and  $\rho$  is fixed, an appropriate frequency of estrogen supplement  $\frac{1}{T}$  can be chosen so that  $T > T_{max}$  as required by Theorem 3 to guarantee the desirable levels of active osteoblasts and active osteoclasts. Therefore, the dosage and the frequency of estrogen supplement are the keys to the effectiveness of estrogen supplement in osteoporosis patients.

**Competing interests**

The authors declare that they have no competing interests.

**Authors' contributions**

The first author analyzed the model theoretically. The second author developed the model and carried out numerical simulations.

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