Stability, Permanence and Positive Periodicity in a Model of Bone Remodeling under Impulsive PTH Control

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***Abstract*—**In this paper, a mathematical model of bone remodeling process, which incorporates the effect of impulsive hormone supplementary treatments, is investigated both numerically and theoretically. A three dimensional model proposed in our earlier work in 2003 is first extended to incorporate impulsive treatment of estrogen supplement. It is illustrated that it is possible for the treatment to be interrupted with no apparent drop in its desirable effect on maintaining a normal bone mass. When the parathyroid hormone is assumed to have a very fast dynamics, the model in its reduced two dimensional form is then analyzed in terms of the boundedness, asymptotic stability, permanence, and oscillatory behavior. We show that there is a stable periodic solution, at the vanishing level of osteoclastic cells, when the impulsive period is less than some critical value. The conditions for permanence of the system are then given. Finally, it is shown that as the impulsive period increases beyond a certain critical value, the emergence of stable positive periodic solution may be observed under appropriate conditions on the system parameters. Thus, dynamic behavior of the system is sensitive to the period and amplitude of the hormone supplements so that the variation of these parameters are crucial for the proper management and control of this complex system.

***Keywords*—**asymptotic stability, bone remodeling, impulsive differential equation models, permanence.

I. Introduction

MANY systems exhibit impulsive jumps or drops in one or more state variables. For example, predator-prey systems with periodic harvesting, pest management practice where natural enemies are released periodically to control insect pest, cancer growth under pulsatile effects of drug treatments, or physiological control systems such as bone remodeling process impacted by periodic hormone supplement protocols. Such external disturbances can stimulate irregular responses that may become difficult to control. Therefore, the stability and permanence of such systems are of great interest in the clinical point of view.

The skeleton is the hard structural system that not only protects internal organs but also supports body locomotion. Damage to the human skeletal system can lead to serious problems including pain, reduced mobility, morbidity and may culminate into life threatening medical conditions. Bone is under a continuous process of development and renewal called remodelling.

Thus, the skeleton undergoes changes continuously and never attains a permanent state [1]. Loss of bone mass together with progressive architectural alterations in fact continues throughout life, while the rate of alteration increasing with age. The severe loss of bone and the spontaneous fracturing of the remaining bone characterize the condition called osteoporosis [2], a major disorder susceptibility to fracture characterized by low bone mineral density, deterioration of bone tissue, and consequently resulting in bone fragility.

Bone plays an important role in the human body. Apart from providing mechanical integrity and protection, it is the major calcium of the body reservoir since over 99% of the total body calcium is stored in the skeleton. Prevention and reversal of bone loss require an in depth understanding of the remodeling process, namely bone resorption and formation including the action of hormones such as estrogen and parathyroid hormone (PTH).

The Basic Multicellular Unit (BMU) in bone remodeling is a team of cells whose activity results in the local resorption and rebuilding of the bone tissues. It is a generally accepted concept of the Basic Multicellular Unit (BMU) that it is comprised of two cell types; osteoclasts and osteoblasts.

The dynamical system of the bone tissue can be explained by the levels of the osteoclastic cells, which resorp bone, and osteoblastic cells which refill the resorption cavities created by the osteoclastic cells.

Osteoclasts, osteoblasts and their precursors are regulated by a number of systemic factors, including hormones like

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parathyroid hormone, and sex hormones such as estrogens. It was shown that PTH stimulates osteoclasts formation. However, PTH affects osteoclasts only in an indirect way since PTH receptors are located on osteoblasts but are not discovered on the surface of osteoclasts.

In 2003, Rattanakul *et al.* [3] proposed and analyzed a mathematical model of the bone remodeling process consisting of the following nonlinear differential equations.

$$\frac{dP}{dt} = \frac{c_1}{k_1 + C} - d_1 P \tag{1}$$

$$\frac{dC}{dt} = \frac{(c_2 + c_3 P)BC}{k_2 + P^2} - d_2 C \tag{2}$$

$$\frac{dB}{dt} = c_4 P - \frac{c_5 PB}{k_3 + P} - d_3 B \tag{3}$$

where P is the level of the parathyroid hormone above the basal level at time t , C is the density of the active osteoclastic cells at time t , and B is the density of the active osteoblastic cells at time t. The first term on the right of (1) is the rate of increase of PTH which is inhibited by the osteoclastic cells. The first term on the right of (2) is the rate of osteoclastic production which is initially stimulated by PTH at low levels of the hormone, but is eventually inhibited at higher levels of PTH, hence the square term in the denominator of this term. The first term on the right of (3) is the rate of osteoblastic production stimulated by PTH, while the second term here is the rate of osteoblastic cells which saturates at higher level of PTH. The last terms in all these three equations are the respective removal rates of the corresponding state variables. More detail of the derivation of the above model may be found in the work of Rattanakul *et al.* [3].

II. Model Extension for Estrogen Effect

In this work, we shall first illustrate how the nonlinearity of the model by Rattanakul and Lenbury et al. [3] can predict the efficacy of estrogen interrupted treatments which a linear model would not be able to simulate.

Traditionally, estrogen has been used to supplement the reduced hormone production which could lead to osteoporosis [4]. It has been later discovered that prolonged use of estrogen could lead to the development of cancerous tumor [5]. In order to investigate the possibility of interrupted estrogen treatment to reduce the risk of cancer, the model is extended to incorporate estrogen level which is known to help curtail the loss of bone mass [4], by reducing the rate of production of osteoclastic cells. The extended model investigated in [3] consists of the following pulsatile system.

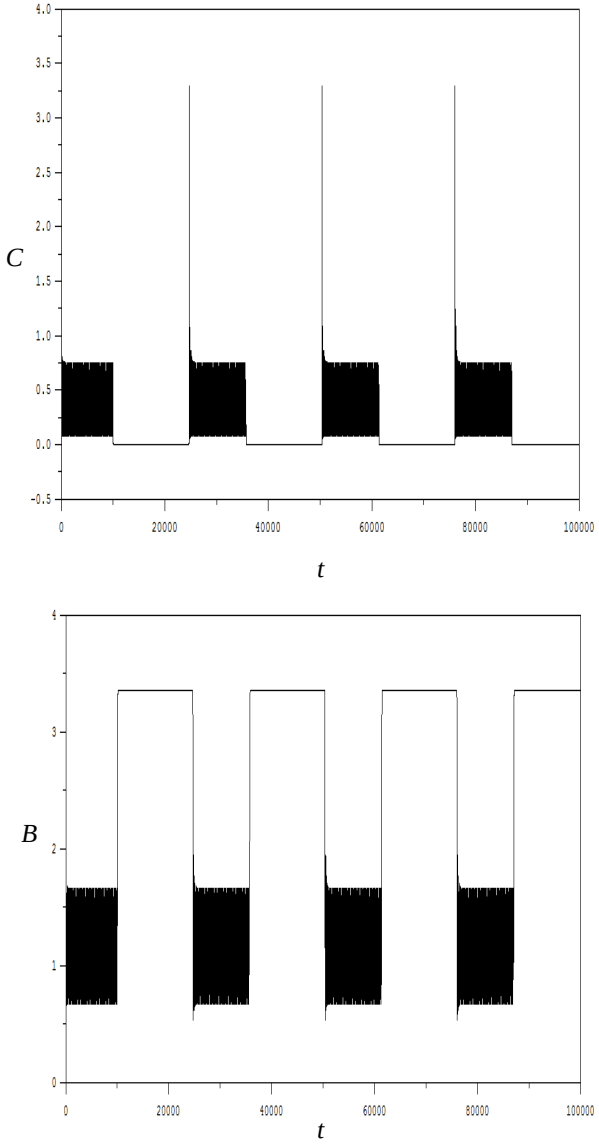


Fig. 1 Computer simulation of (4)-(6) with estrogen applied for 12 days every 28 days.

$$\frac{dP}{dt} = \frac{c_1}{k_1 + C} - d_1 P \tag{4}$$

$$\frac{dC}{dt} = \varepsilon \left[\frac{(c_2 + c_3 P)B}{k_2 + P^2} - d_2 - K_C \right] C \tag{5}$$

$$\frac{dB}{dt} = \varepsilon\delta \left[c_4 P - \frac{c_5 PB}{k_3 + P} - d_3 B \right] \tag{6}$$

Fig. 1 shows a computer simulation of (4)-(6) with

$$K_C = \begin{cases} k_C \text{ if } t \geq 10{,}000 \ \& \ t \bmod 25676 \leq 11004 \\ \text{otherwise} \end{cases}$$

which is the case in where estrogen is applied for 12 days (= 11004 time steps in our simulation) every month (28 days =

25,676 time steps). We see that when estrogen is interrupted after 12 days, the density of osteoclasts increases back up to oscillate at a high level, while the density of osteoblasts drops to a low level signifying a low bone mass.

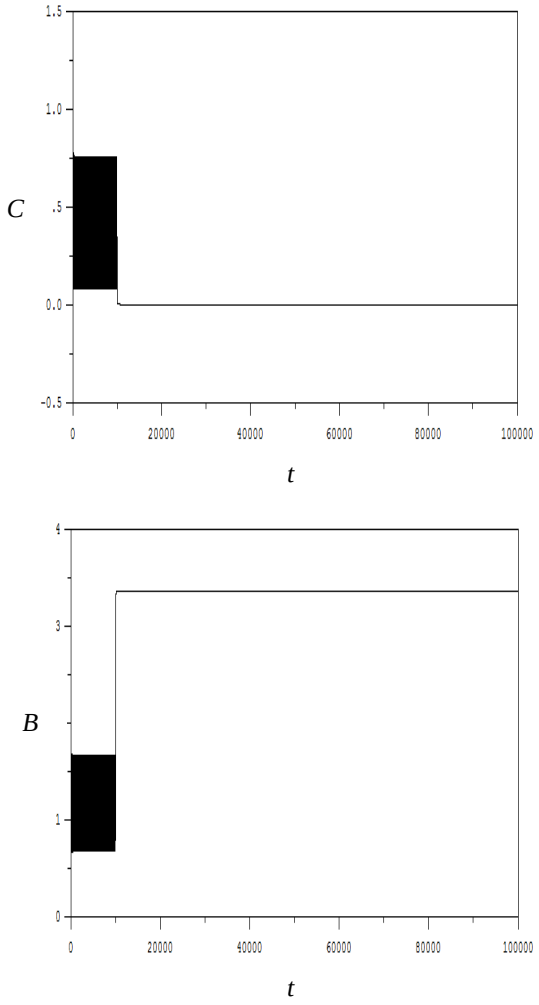


Fig. 2 Computer simulation of (4)-(6) with estrogen applied for 22 days every 28 days.

Figure 2 shows a computer simulation of (4)-(6) with

$$K_C = \begin{cases} k_C \text{ if } t \geq 10{,}000 \ \& \ t \bmod 25{,}676 \leq 20{,}174 \\ \text{otherwise} \end{cases}$$

which is the case in where estrogen is applied for 22 days (=20174 time steps). We see that after estrogent treatment is interrupted at 22 days, the density of osteoclasts remains low, and that of osteoblasts remain high, signifying continued high bone mass.

In both the above simulations, we use $c_1 = 0.1$, $c_2 = 0.2$, $c_3 = 0.6$, $c_4 = 0.1$, $c_5 = 0.05$, $d_1 = 0.2$, $d_2 = 0.3$, $d_3 = 0.1$, $k_1 = 0.1$, $k_2 = 1.5$, $k_3 = 0.1$, $k_c = 0.14$, $\varepsilon = 0.5$, and $\delta = 0.6$. Such numerical experiments clearly illustrate the versatility of nonlinear models in suggesting alternative therapy or drug protocols. The above experiments suggest that interrupted hormone supplements could be adopted, for certain patients, to reduce the risks of side effects. Of course, theoretical analyses are also needed to discover the ranges of physical values that would allow certain required effects to occur in such a complex nonlinear system.

III. Analysis of Impulsive System

In what follows, we take into consideration the clinical observation [6] – [7] that PTH has a very fast dynamics so that it equilibrates relatively quickly to the level where $\frac{dP}{dt} = 0$, at which point

$$P = \frac{c_1}{d_1(k_1 + C)} \tag{7}$$

We may also assume that the zero order stimulation of osteoclastic production in the absence of hormonal or osteoblastic stimulations is neglegible, so that $a_2 = 0$.

We next suggest an impulsive system to model the process subject to periodic PTH supplements and first investigate the bounded property of the model solutions in the next section. Then, the periodic behavior asymptotic stability of the system solutions at vanishing level of active osteoclastic cells density are investigated in Section 3. The conditions are then given in Section 4. under which the state variables remain bounded and non-vanishing and as such the system remains permanent. Supercritical periodic solutions are shown to exist under appropriate conditions on the system parameters. Numerical simulations are given in support of the theoretical predictions in the discussion and conclusion section.

As reported by Prank *et al.* [7], [8] pulsatile hormone secretion is observed in almost every hormonal system. The frequency of episodic hormone release ranges from approximately 10 to 100 pulses in 24 hours. This temporal mode of secretion is an important feature of intercellular information transfer in addition to a dose-response dependent regulation. We thus incorporate the pulsatile hormone stimulus, such as that due periodic PTH supplements. This can result in an abrupt drop in C in proportion to its level at the moment, and an abrupt jump in B in the form of a constant increment.

We now let $x_1 = C$, $x_2 = B$, for convenience. We also denote by $f(x_1)$ the positive decreasing function representing the effect of the level of x_1 on x_2, which is taken to be the function

$$f(x_1) = \frac{c_1}{d_1(k_1 + x_1)}$$

in [3] according to (4). We are then led to the following impulsive model system.

$$\left.\begin{aligned} \frac{dx_1}{dt} &= \left(\left(\frac{a_3 f(x_1)}{k_2 + f^2(x_1)}\right)x_2 - b_2\right)x_1 \qquad (8) \\ \frac{dx_2}{dt} &= a_4 f(x_1) - \left(\frac{a_5 f(x_1)}{k_3 + f(x_1)}\right)x_2 - b_3 x_2 \qquad (9) \end{aligned}\right\} \quad t \neq nT$$

$$\Delta x_1(t) = -px_1(t), t = nT, \quad (10)$$

$$\Delta x_2(t) = \mu, t = nT \quad (11)$$

where

$$\Delta x_1(t) = x_1(t^+) - x_1(t), \Delta x_2(t) = x_2(t^+) - x_2(t)$$

p is the fraction of osteoclasts inhibited by PTH supplements, $0 < p < 1$, and $\mu > 0$ is the increment in osteoblasts due to hormone supplements. The function $f(x_1)$ may be any non-increasing function of x_1. From (4) in our bone model [3] the function is taken to be

$$f(x_1) = \frac{c_1}{d_1(k_1 + x_1)}$$

With $R_+ = [0, \infty), R_+^2 = \left\{ X \in R^2 : X = (x_1, x_2), x_1 \geq 0, x_2 \geq 0 \right\}$ we need the following definition.

Definition 1. We denote by $F = (F_1, F_2)$ the map defined by the right hand side of the system (8)-(9) and let

$$V : R_+ \times R_+^2 \to R_+.$$

Then, V is said to belong to class V_0 if

1. V is continuous in $(nT, (n+1)T] \times R_+^2 \to R_+$ and for each $X \in R_+^2, n \in Z_+$,

$$\lim_{(t,Y) \to (nT^+, X)} V(t, Y) = V(nT^+, X)$$

exists

2. V is locally Lipschitzian in X.

Suppose $V \in V_0$, Then, for $(t, X) \in (nT, (n+1)T] \times R_+^2$, the upper right derivative of $V(t, X)$ with respect to (8)-(11) is defined by

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

We assume that the solution of (5)-(8), denoted by $X(t) = (x_1(t), x_2(t))$ is continuous on $(nT, (n+1)T], n \in Z_+$ and $\lim_{t \to nT^+} X(t) = X(nT^+)$ exists. Then the global existence and uniqueness of solutions to (8)–(11) is guaranteed by the smoothness properties of F. It is straight forward to prove the following result and thus it will be stated without proof.

Lemma 1. Suppose $(x_1(t), x_2(t))$ is a solution of (8) – (11) with $x_i(0^+) \geq 0$. Then $x_i(t) \geq 0$ for all $t \geq 0$.

In what follows, we suppose $x_1 f(x_1)$ is bounded so that

$$M_1 = \sup x_1 f(x_1), M_2 = \sup f(x_1)$$

We then state and prove the following.

Lemma 2. There exists a constant $M > 0$ such that, for t large enough, $x_i \leq M$, $i = 1, 2$, provided

$$b_3 > \frac{a_3 M_1}{k_2} \quad (12)$$

Proof

Defining $v(t) \equiv V(t, x(t)) = x(t) + y(t)$ and when $t \neq t_k$, we choose

$$c = \min \left\{ b_2, b_3 - \frac{a_3 M_1}{k_2} \right\} > 0.$$

Then,

$$\begin{aligned} D^+ v + cv &= x_1'(t) + x_2'(t) + cx_1(t) + cx_2(t) \\ &= \frac{a_3 f(x_1)}{k_2 + f^2(x_1)} x_1 x_2 - b_2 x_1 + a_4 f(x_1) - \left(\frac{a_5 f(x_1)}{k_3 + f(x_1)} \right) x_2 \\ &\quad - b_3 x_2 + cx_1 + cx_2 \\ &\leq \frac{a_3 x_1 f(x_1)}{k_2} x_2 - b_2 x_1 + a_4 f(x_1) - b_3 x_2 + cx_1 + cx_2 \\ &\leq \left(\frac{a_3 M_1}{k_2} - b_3 + c \right) x_2 + (-b_2 + c) x_1 + a_4 M_2 \\ &\leq a_4 M_2 \equiv b \end{aligned}$$

That is, when $t \neq t_k$, $D^+ v(t) \leq -cv + b$.

When $t = t_k$,

$$\begin{aligned} v(t_k^+) &= x_1(kT^+) + x_2(kT^+) \\ &= x_1(kT) - px_1 + x_2(kT) + \mu \leq v(kT) + \mu \end{aligned}$$

By Lemma 2.2 in the work of Lui *et al.* [9], we obtain

$$\begin{aligned} v(t) &\leq v(0) e^{-ct} + b \int_0^t e^{-\int_s^t c d\tau} ds + \mu \sum_{0 < t_k < t} e^{-\int_{t_k}^t c d\tau} \\ &\leq v(0) e^{-ct} + \frac{b}{c} \left(1 - e^{-ct} \right) + \mu \left[\frac{e^{-c(t-T)} - e^{-c(t-t_{k+1})}}{1 - e^{cT}} \right] \\ &< \frac{b}{c} + \frac{\mu e^{cT}}{e^{cT} - 1} \equiv M \quad \text{as } t \to \infty. \end{aligned}$$

So, $v(t)$ is uniformly ultimately bounded. Hence, by the definition of $v(t)$, there exists a constant $M > 0$ such that

$$x_i \leq M, i = 1, 2.$$

for large t.

IV. Stability at Vanishing Active Osteoblasts

Putting $x_1 = 0$, we have a reduced system

$$\frac{dx_2}{dt} = B - Ax_2, t \neq t_k \quad (13)$$

$$x_2(t_k^+) = x_2(t_k) + \mu, t = t_k \quad (14)$$

$$x_2(0^+) = x_{2_0} \quad (15)$$

where

$$A \equiv \frac{a_5 f(0)}{k_3 + f(0)} + b_3, \; B \equiv a_4 f(0).$$

Assuming $A > 0$, a positive periodic solution of (10) – (11) is

$$\tilde{x}_2(t) = \frac{\mu \exp(-A(t - kT))}{1 - \exp(-AT)} + \frac{B}{A}, \quad t \in (kT, (k+1)T)$$

with

$$\tilde{x}_2(0^+) \equiv \frac{\mu}{1 - \exp(-AT)} + \frac{B}{A}.$$

Hence, the positive solution of (10) – (12) is

$$x_2(t)=\left(x_{2_0}-\frac{B}{A}-\frac{\mu}{1-\exp(-AT)}\right)\exp(-At)+\tilde{x}_2(t),$$

for $t\in(kT,(k+1)T)$. Thus, we have the following result.

Lemma 3. System (13) – (14) has a periodic solution and for every solution $\underset{\sim}{x}(t)=(x_1(t),x_2(t))$ of (13) – (14) we have

$$\underset{\sim}{x}(t)\to(0,\tilde{x}_2(t)) \text{ as } t\to\infty$$

Now, we let

$$\mathcal{C}\equiv\frac{a_3 f(0)}{k_2+f^2(0)} \tag{16}$$

and state a result on the asymptotic behavior of the solutions $\underset{\sim}{x}(t)$ of (8) – (9).

Theorem 1. Suppose

$$b_2<\frac{\mathcal{C}B}{A} \tag{17}$$

$$\ln\frac{1}{1-p}>\frac{\mathcal{C}\mu}{A} \tag{18}$$

The solution $(0,\tilde{x}_2(t))$ of (8) – (9) is locally asymptotically stable if

$$T<T_{\min}\equiv\left(\ln\frac{1}{1-p}-\frac{\mathcal{C}\mu}{A}\right)\Big/\left(\frac{\mathcal{C}B}{A}-b_2\right) \tag{19}$$

Proof

Consider a small perturbation from the point $(0,\tilde{x}_2(t))$:

$$x_1=u(t)$$

$$x_2=\tilde{x}_2+v(t)$$

Then, we obtain

$$\begin{pmatrix}u(t)\\v(t)\end{pmatrix}=\Phi(t)\begin{pmatrix}u(t)\\v(t)\end{pmatrix},0<t<T$$

where

$$\frac{d\Phi}{dt}=\begin{pmatrix}-b_2+\mathcal{C}\tilde{x}_2 & 0\\ * & -D-b_3\end{pmatrix}\Phi,$$

and $\Phi(0)=I$.

Integrating, we arrive at

$$\Phi=\begin{pmatrix}\exp\int_0^t(-b_2+\mathcal{C}\tilde{x}_2(s))ds & 0\\ * & \exp\int_0^t(-D-b_3)ds\end{pmatrix}$$

Linearization of (10) – (11) gives

$$\begin{pmatrix}u(t_k^+)\\v(t_k^+)\end{pmatrix}=\begin{pmatrix}1-p & 0\\0 & 1\end{pmatrix}\begin{pmatrix}u(t_k)\\v(t_k)\end{pmatrix}$$

According to the Floquet theory, the stability of $(0,\tilde{x}_2(t))$ depends on the eigenvalues of

$$M_0=\begin{pmatrix}1-p & 0\\0 & 1\end{pmatrix}\Phi(T)$$

which are

$$\lambda_1=e^{-(D+b_3)T}<1$$

$$\lambda_2=(1-p)\exp\int_0^T\left(-b_2+\mathcal{C}\tilde{x}_2(s)\right)ds<1$$

if (19) holds. The proof is complete.

V. PERMANENCE

First, we give a definition of a permanent system.

Definition 1. System (8)-(11) 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 all initial values $x_i(0^+)>0$,

$$m\le x_i(t)\le M,$$

for all $t\ge t_0, i=1,2$.

We are now in the position to prove the following.

Theorem 2. The system (8)-(11) is permanent if (12), (17), (18) hold, and

$$T>T_{\min} \tag{20}$$

Proof

We shall illustrate how this can be proven by considering the case that

$$f(x_1)=\frac{a_1}{b_1(k_1+x_1)}$$

By Lemma 2, there is an M such that $x_i<M$, for t large enough. From (6), we know

$$\frac{dx_2}{dt}\ge -Ax_2, t\ne t_k$$

$$x_2(t_k^+)=x_2(t_k)+\mu, t=t_k$$

and so we have

$$x_2(t)>\tilde{x}_2(t)-\frac{B}{A}-\varepsilon$$

for some t large enough and some $\varepsilon>0$. That is,

$$x_2(t)>\frac{\mu e^{-AT}}{1-e^{-AT}}-\varepsilon\equiv m_2$$

Now, suppose

$$\mathcal{M}_1=k_2b_1^2(k_1+m_3)^2+a_1^2,$$

$$\mathcal{M}_2=\frac{a_1a_3b_1k_1}{\mathcal{M}_1},$$

$$\mathcal{M}_3=\frac{a_1^2a_3a_4k_1}{\mathcal{M}_1A(k_1+m_3)}.$$

for some $m_3>0$. Then, it follows that

$$\mathcal{M}_2<\mathcal{C},$$

$$\mathcal{M}_3<\frac{\mathcal{C}B}{A}$$

Since

$$b_2<\frac{\mathcal{C}B}{A},$$

we can choose m_3 small enough such that

$$b_2<\mathcal{M}_3<\frac{\mathcal{C}B}{A},$$

and

$$T>\frac{1}{\mathcal{M}_3-b_2}\left(\ln\frac{1}{1-p}-\frac{\mathcal{M}_2\mu}{A}\right).$$

Then,

$$(1-p)\exp\left((\mathcal{M}_3-b_2)T+\frac{\mathcal{M}_2\mu}{A}\right)>1$$

Step1. We prove that $\exists t_c$ such that $x_1(t_c) \geq m_3$. By contradiction, if $x_1(t) < m_3$ for all positive t, then we may choose an $\varepsilon_1 > 0$ small enough such that

$$\eta \equiv (1-p)\exp\left((\mathcal{M}_3 - \varepsilon_1 \mathcal{M}_2 - b_2)T + \frac{\mathcal{M}_2 \mu}{A}\right) > 1.$$

We observe, from (9) and (11), that

$$\frac{dx_2}{dt} = a_4 f(x_1) - \frac{a_5 f(x_1) x_2}{k_3 + f(x_1)} - b_3 x_2$$

$$\geq \frac{a_1 a_4}{b_1(k_1 + m_3)} - A x_2, \text{ if } t \neq nT.$$

$$x_2(t^+) = x_2(t) + \mu, \text{ if } t = nT.$$

On the other hand, we compare with the system

$$\frac{dz}{dt} = \frac{a_4 a_1}{b_1(k_1 + m_3)} - Az, \text{ if } t \neq nT \tag{21}$$

$$z(t^+) = z(t) + \mu, \text{ if } t = nT.$$

and

$$z(0) = x_2(0).$$

Then, we see that, by the comparison theorem,

$$x_2(t) \geq z(t)$$

Now, we consider

$$\dot{x}_1 = \left(\frac{a_1 a_3 b_1 (k_1 + x_1)}{k_2 b_1^2 (k_1 + x_1)^2 + a_1^2} x_2 - b_2\right) x_1$$

$$\geq \left(\frac{a_1 a_3 b_1 (k_1 + x_1)}{k_2 b_1^2 (k_1 + m_3)^2 + a_1^2} x_2 - b_2\right) x_1$$

$$\geq \left(\frac{a_1 a_3 b_1 k_1}{\mathcal{M}_1}(\tilde{z}(t) - \varepsilon_1) - b_2\right) x_1$$

where, for $t \in [nT, (n+1)T)$,

$$z(t) = (z(0) - \frac{a_1 a_4}{b_1 A(k_1 + m_3)} - \frac{\mu}{1 - e^{-AT}})e^{-At} + \tilde{z}(t),$$

$$\to \tilde{z}(t) = \frac{\mu e^{-A(t-nT)}}{1 - e^{-AT}} + \frac{a_1 a_4}{b_1 A(k_1 + m_3)}, \text{ as } t \to \infty.$$

Hence, there is a $T_1 > 0$ such that, for $t \geq T_1$,

$$\tilde{z}(t) - \varepsilon_1 < z(t) \leq x_2(t).$$

$$= A(t) x_1$$

for $t \neq nT, t \geq T_1$, and

$$x_1(t^+) = (1-p) x_1(t),$$

for $t = nT, t \geq T_1$. Letting $N \in Z_+$ and $NT \geq T_1$, and integrating over $(nT, (n+1)T], n \geq N$, we obtain

$$x_1((n+1)T) \geq x_1(nT)(1-p)\exp\left(\int_{nT}^{(n+1)T} A(t)dt\right)$$

$$\geq x_1 nT)(1-p)\exp\left((\mathcal{M}_3 - \varepsilon_1 \mathcal{M}_2 - b_2)T + \frac{\mathcal{M}_2 \mu}{A}\right)$$

$$= x_1(nT)\eta$$

Then,

$$x_1((n+k)T) \geq x_1(nT)\eta^k \to \infty \text{ as } k \to \infty$$

which is a contradiction to the boundedness of x_1. Therefore, there is a $t_c > 0$ such that $x_1(t_c) \geq m_3$.

Step 2. If $x_1(t) \geq m_3, \forall t > t_c$, then our job is done. Otherwise, there is a $t' > t_c$ such that

$$x_1(t') < m_3.$$

Then, let $t^* = \inf_{t > t_c}\{t : x_1(t) < m_3\}$. There are two possible cases:

Case 2.1: $t^* = n_1 T$, some $n_1 \in Z_+$.

Case 2.2: $t^* \neq nT, \forall n \in Z_+$.

Case 2.1: $t^* = n_1 T$, some $n_1 \in Z_+$. This means $x_1(t) \geq m_3$ for $t \in [t_1, t^*]$.

Since there are $M > 0$, and $m_2 > 0$ such that $x_1(t) < M$, and $m_2 < x_2(t) < M$ for t large enough, we choose $M' > 0$, and $m_2' > 0$ such that

$$x_1(t) < M', \; m_2' < x_2(t) < M',$$

and

$$m_2' < \frac{b_2 \mathcal{M}_1}{a_1 a_3 b_1 k_1}$$

such that

$$\left| x_2(t^{*+}) - \frac{a_1 a_4}{b_1 A(k_1 + m_3)} - \frac{\mu}{1 - e^{-AT}} \right| - \mu < M'$$

Then, choose $n_2, n_3 \in \mathbb{Z}_+$ such that

$$n_2 T > \frac{1}{A} \ln \frac{M' + \mu}{\varepsilon_1} \tag{22}$$

and

$$(1-p)^{n_2} \exp(n_2 \eta_1 T)\eta^{n_3} > (1-p)^{n_2} \exp((n_2 + 1)\eta_1 T)\eta^{n_3}$$

$$> 1$$

where

$$\eta_1 = \frac{a_1 a_3 b_1 k_1 m_2'}{\mathcal{M}_1} - b_2 < 0.$$

Let $T' = n_2 T + n_3 T$. We claim that there must be a $t_2 \in (t^*, t^* + T']$ such that $x_1(t_2) > m_3$. Otherwise, considering (18) with $z(t^{*+}) = x_2(t^{*+})$, we have

$$z(t) = (z(t^{*+}) - \frac{a_1 a_4}{b_1 A(k_1 + m_3)} - \frac{\mu}{1 - e^{-AT}})e^{-A(t-t^*)} + \tilde{z}(t),$$

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

For $n_2 T \leq t - t^* \leq T'$, we have, since $\eta_1 < 0$ and $l \leq n_2 + n_3$,

$$|z(t) - \tilde{z}(t)| = \left| z(t^{*+}) - \frac{a_1 a_4}{b_1 A(k_1 + m_3)} - \frac{\mu}{1 - e^{-AT}}) \right| e^{-A(t-t^*)}$$

$$= \left| y(t^{*+}) - \frac{a_1 a_4}{b_1 A(k_1 + m_3)} - \frac{\mu}{1 - e^{-AT}}) \right| e^{-A(t-t^*)}$$

$$< (M' + \mu)e^{-A(t-t^*)} \leq (M' + \mu)e^{-An_2 T} < \varepsilon_1$$

by (22). Then,

$$\tilde{z}(t) - \varepsilon_1 < z(t) \leq x_2(t),$$

for $n_2 T + t^* \leq t \leq t^* + T'$. Therefore, as in Step 1., we have

$$x_1(t^* + T') = x_1(n_1 T + n_2 T + n_3 T)$$

$$\geq x_1(n_1T+n_2T)\eta^{n_3}$$
$$= x_1(t^*+n_2T)\eta^{n_3}$$

From (5), for $t \geq 0$, we obtain

$$\dot{x}_1 = \left(\frac{a_1a_3b_1k_1}{M_f}x_2 - b_2\right)x_1$$
$$\geq \left(\frac{a_1a_3b_1k_1}{M_f}m_2' - b_2\right)x_1 = \eta_1 x_1, t \neq nT \quad (23)$$
$$x_1(t^+) = (1-p)x_1(t), t = nT.$$

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

$$x_1(t^*+T') \geq x_1(t^*+n_2T)\eta^{n_3}$$
$$\geq m_3(1-p)^{n_2}\exp(\eta_1 n_2 T)\eta^{n_3} > m_3$$

which contradicts the definition of m_3.

Now, let $\tilde{t} = \inf_{t>t^*}\{x_1(t) > m_3\}$. Then, for $t \in (t^*, \tilde{t}), x_1(t) \leq m_3$, and $x_1(\tilde{t}) = m_3$. 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 (23), we then have

$$x_1(t) \geq x_1(t^{*+})(1-p)^{l-1}\exp((l-1)\eta_1 T)\exp[\eta_1(t-(t^*+(l-1)T))]$$
$$= x_1(t^*)(1-p)^{l}\exp((l-1)\eta_1 T)\exp[\eta_1(t-(t^*+(l-1)T))]$$
$$\geq m_3(1-p)^{l}\exp[\eta_1(t-t^*)]$$
$$\geq m_3(1-p)^{n_2+n_3}\exp(\eta_1 lT),$$
$$\geq m_3(1-p)^{n_2+n_3}\exp(\eta_1(n_2+n_3)T)$$

since $\eta_1 < 0$ and $l \leq n_2+n_3$. Letting

$$m_1' = m_3(1-p)^{n_2+n_3}\exp(\eta_1(n_2+n_3)T),$$

we then have $x_1(t) \geq m_1'$ for $t \in (t^*, \tilde{t})$. We can continue with the same method by using $\tilde{t}$ instead of t^*. Then, we shall have $x_1(t) \geq m_1'$ for $t > t^*$.

Case 2.2: $t^* \neq n\mathrm{T}, \forall n \in Z_+$. Then, $x_1(t) \geq m_3$ for $t \in [t_1, t^*)$. Suppose $t^* \in (n_1'T, (n_1'+1)T]$, $n_1' \in \mathbb{Z}_+$, then $x_1(t^*) = m_3$, and there are two possible subcases.

Case 2.2(a): $x_1(t) \leq m_3$ for all $t \in (t^*, (n_1'+1)T]$. We claim that there is a $t_2' \in ((n_1'+1)T, (n_1'+1)T+T']$ such that $x_1(t_2') > m_3$. Otherwise, let

$$z((n_1'+1)T^+) = x_2((n_1'+1)T^+).$$

Then,

$$z(t) = (z((n_1'+1)T^+) - \frac{a_1a_4}{b_1A(k_1+m_3)} - \frac{\mu}{1-e^{-AT}})e^{-A(t-(n_1'+1)T)} + \tilde{z}(t)$$

for $t \in [nT, (n+1)T)$ and $n_1'+1 < n \leq n_1'+1+n_2+n_3$.

Similarly to Case 2.1, for $n_2T \leq t-t^*$, we obtain

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

Then,

$$\tilde{z}(t) - \varepsilon_1 < z(t) \leq x_2(t).$$

Since $n_2T \leq (n_1'+1+n_2)T - t^*$, we have

$$x_1((n_1'+1+n_2)T) \geq x_1(t^*)(1-p)^{n_2}\exp[\eta_1((n_1'+1+n_2)T - t^*)]$$
$$\geq m_3(1-p)^{n_2}\exp[\eta_1((n_1'+1+n_2)T - n_1'T)]$$
$$\geq m_3(1-p)^{n_2}\exp(\eta_1(n_2+1)T).$$

Then,

$$x_1((n_1'+1+n_2+n_3)T) \geq x_1((n_1'+1+n_2)T)\eta^{n_3}$$
$$\geq m_3(1-p)^{n_2}\exp(\eta_1(n_2+1)T)\eta^{n_3}$$
$$> m_3$$

which is a contradiction.

Now, let $\bar{t} = \inf_{t>t^*}\{x_1(t) > m_3\}$.

Then, for $t \in (t^*, \bar{t})$, $x_1(t) \leq m_3$, and $x_1(\tilde{t}) = m_3$. For $t \in (t^*, \bar{t})$ let $l' \in \mathbb{Z}_+$ 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 (4), we then have

$$x_1(t) \geq x_1(t^*)(1-p)^{l'-1}\exp\left[\int_{t^*}^{t}\eta_1 ds\right]$$
$$= m_3(1-p)^{l'-1}\exp[\eta_1(t-t^*)]$$

since $t < n_1'T + l'T$ and $\eta_1 < 0$. Hence,

$$x_1(t) \geq m_3(1-p)^{n_2+n_3}\exp(\eta_1(n_2+n_3+1)T)$$

Letting

$$m_1 = m_3(1-p)^{n_2+n_3}\exp(\eta_1(n_2+n_3+1)T),$$

we then have $x_1(t) \geq m_1$ for $t \in (t^*, \bar{t})$. For $t > \bar{t}$, the same argument can be continued since $x_1(\bar{t}) \geq m_3$.

Case 2.2(b): There is a $t \in (t^*, (n_1'+1)T)$ such that $x_1(t) > m_3$. Let

$$\underline{t} = \inf_{t>t^*}\{x_1(t) > m_3\}.$$

Hence, $x_1(t) \leq m_3$ for $t \in (t^*, \underline{t})$, and $x_1(\underline{t}) = m_3$. For $t \in (t^*, \underline{t})$, (23) holds and we therefore have

$$x_1(t) \geq x_1(t^*)\exp\left[\int_{t^*}^{t}\eta_1 ds\right] = m_3\exp[\eta_1(t-t^*)]$$
$$\geq m_3\exp\eta_1 T > m_1$$

since $t < n_1'T + T < t^*+T$.

For $t > \underline{t}$, the same argument can be continued since $x_1(\underline{t}) \geq m_3$. Since $m_1 < m_1' < m_3$, we have $x_1(t) \geq m_1$ for $t \geq t_1$. The proof is complete.

VI. Sustained Oscillation

It is now more convenient to exchange the state variables and consider instead the following system.

$$\left.\begin{aligned}\frac{dx_1}{dt} &= a_4 f(x_2) - \left(\frac{a_5 f(x_2)}{k_3 + f(x_2)}\right)x_1 - b_3 x_1 \equiv F_1(x_1, x_2)\\ \frac{dx_2}{dt} &= \left(\left(\frac{a_3 f(x_2)}{k_2 + f^2(x_2)}\right)x_1 - b_2\right)x_2 \equiv F_2(x_1, x_2)\end{aligned}\right\} \quad t \neq nT \quad (24),\ (25)$$

$$\left.\begin{aligned}\Delta x_1 &= \mu\\ \Delta x_2 &= -px_1\end{aligned}\right\} t = k\tau \equiv t_k,$$

Relying on the notations used by Lakmeche and Arino [10], we let

$$\Theta_1(x_1, x_2) = x_1 + \mu,$$
$$\Theta_2(x_1, x_2) = (1-p)x_2,$$

$\varsigma(t) = (\tilde{x}_2(t), 0)^T$, $x_0 = (\tilde{x}_2(\tau_0), 0)^T$, and $\tau_0 = T_{\min}$.

According to [8],

$$\left.\frac{\partial \Phi_1}{\partial \tau}\right|_{\tau_0} = \left.\frac{\partial \tilde{x}_2}{\partial t}\right|_{\tau_0}$$

$$\frac{\partial \Phi_i}{\partial x_i} = \exp \int_0^t \frac{\partial F_i}{\partial x_i}(\varsigma(r))dr, \quad i = 1, 2$$

$$\frac{\partial \Phi_1}{\partial x_2} = \int_0^t e^{\int_u^t \frac{\partial F_1}{\partial x_1}(\varsigma(r))dr} \frac{\partial F_1}{\partial x_2}(\varsigma(u)) e^{\int_0^u \frac{\partial F_2}{\partial x_2}(\varsigma(r))dr} du$$

$$\frac{\partial^2 \Phi_2}{\partial \tau \partial x_2} = \frac{\partial F_2}{\partial x_2} \exp \int_0^t \frac{\partial F_2}{\partial x_2}(\varsigma(r))dr$$

$$\frac{\partial^2 \Phi_2}{\partial x_1 \partial x_2} = \int_0^t e^{\int_u^t \frac{\partial F_2}{\partial x_2}(\varsigma(r))dr} \frac{\partial^2 F_2}{\partial x_1 \partial x_2}(\varsigma(u)) e^{\int_0^u \frac{\partial F_2}{\partial x_2}(\varsigma(r))dr} du$$

and

$$\frac{\partial^2 \Phi_2}{\partial x_2^2} = \int_0^t e^{\int_u^t \frac{\partial F_2}{\partial x_2}(\varsigma(r))dr} \frac{\partial^2 F_2}{\partial x_2^2}(\varsigma(u)) e^{\int_0^u \frac{\partial F_2}{\partial x_2}(\varsigma(r))dr} du$$

for all $0 \le t \le \tau_0$.

Also,

$$a_0' = 1 - \left(\frac{\partial \Theta_1}{\partial x_1} \frac{\partial \Phi_1}{\partial x_1} \right)(\tau_0, x_0),$$

$$b_0' = -\left(\frac{\partial \Theta_1}{\partial x_1} \frac{\partial \Phi_1}{\partial x_2} + \frac{\partial \Theta_1}{\partial x_2} \frac{\partial \Phi_2}{\partial x_2} \right)(\tau_0, x_0),$$

$$d_0' = 1 - \left(\frac{\partial \Theta_2}{\partial x_2} \frac{\partial \Phi_2}{\partial x_2} \right)(\tau_0, x_0) .$$

where τ_0 is the root of $d_0' = 0$. We see that $d_0' > 0$ if $T < T_{min}$, and $d_0' < 0$ if $T > T_{min}$. Also, $a_0' > 0$, $b_0' > 0$, while

$$B^* = -\frac{\partial \Theta_2}{\partial x_2} \left(\frac{\partial^2 \Phi_2}{\partial \tau \partial x_2} + \frac{\partial^2 \Phi_2}{\partial x_1 \partial x_2} \cdot \frac{1}{a_0'} \frac{\partial \Theta_1}{\partial x_1} \cdot \frac{\partial \Phi_1}{\partial \tau} \right)\Bigg|_{(\tau_0, x_0)} < 0$$

$$C^* = -2 \frac{\partial^2 \Theta_2}{\partial x_1 \partial x_2} \left(-\frac{b_0'}{a_0'} \frac{\partial \Phi_1}{\partial x_1} + \frac{\partial \Phi_1}{\partial x_2} \right) \frac{\partial \Phi_2}{\partial x_2}$$

$$+ \frac{\partial \Theta_2}{\partial x_2} \left(2 \frac{b_0'}{a_0'} \frac{\partial^2 \Phi_2}{\partial x_2 \partial x_1} - \frac{\partial^2 \Phi_2}{\partial x_2^2} \right)\Bigg|_{(\tau_0, x_0)}$$

$$> 0$$

provided

$$a_4 < \frac{a_5 k_3}{k_3 + f^2(0)} \tag{26}$$

Thus, $C^* > 0$ and $B^* C^* < 0$, and, by Lakmeche and Arino [10], we are thus able to prove the following result.

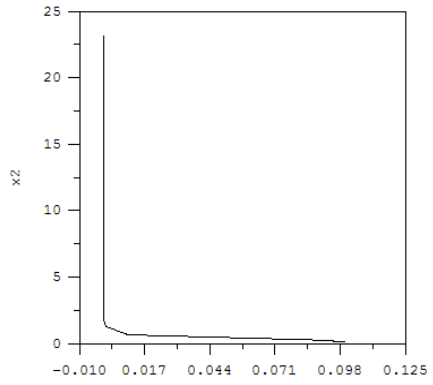
Theorem 3. The system (24)-(25) has a positive periodic solution which is supercritical provided (12), (17), (18), (26) hold and $T > T_{min}$.

VII. Discussion and Conclusion

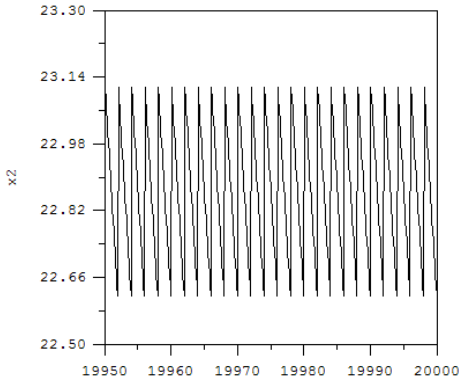
We have investigated the boundedness and permanence of the bone remodeling process under impulsive external interferences. We found that oscillatory behavior in the active osteoblastic cells density can still be observed provided the period and strength of the hormone supplementary impulses satisfy certain control conditions.

Many researchers have proposed several improved and more sophisticated methodologies for the numerical solution of non-linear systems of differential equations (see for example [11]-[14]. For our purpose, we wrote our program using the six point Runge Kutta procedure which satisfactorily integrates our model systems under study.

Fig. 3 shows a computer simulation of (8) – (11) where parameters have been chosen to satisfy these control requirements for the solutions to converge asymptotically to the oscillatory solution $(0, \tilde{x}_2(t))$ as time progresses. Here, the period of PTH supplements is T = 2, while $T_{\min} = 8.005$ so that $T < T_{\min}$ .The solution trajectory in the phase plane is seen in Fig. 3(a), while the corresponding time series of the active osteoblastic cell density is seen in Fig. 3(b) to be periodic even after the osteoclastic cell density has tended to zero.



3a)



3b)

Fig. 3 Numerical simulation of Equations (8) – (11) showing the solution trajectory approaching the limit cycle as time progresses. Here, a_1 := 0.05; a_3 := 0.0675; a_4 := 0.009; a_5 := 0.0045; b_1 := 0.1; b_2 := 0.03; b_3 := 0.009; k_1 := 0.1; k_2 := 0.5; k_3 := 0.025; p := 0.9; $x_1(0) = 0.1$, $x_2(0) = 0.135$, T = 200, μ = 0.5, p = 0.9. (a) The solution trajectory in the phase-plane. (b) The corresponding time series of the level the osteoblastic cells exhibiting positive oscillation.

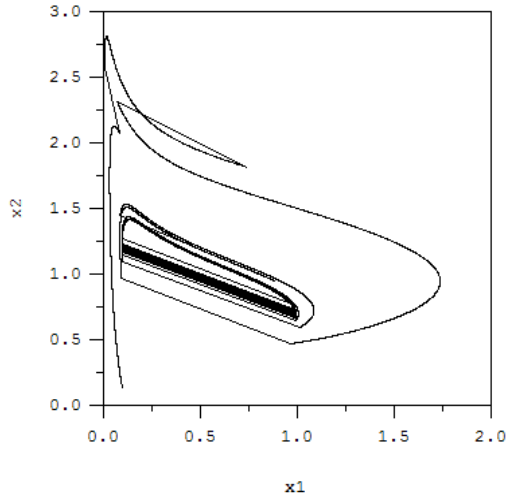
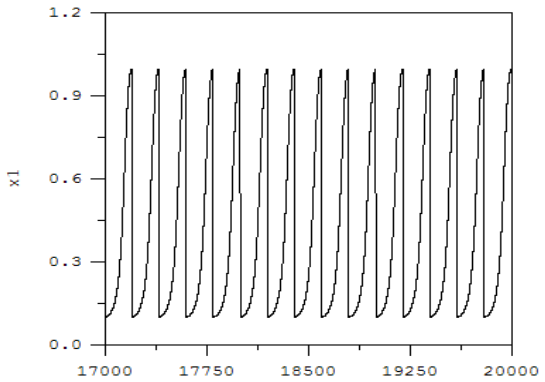


Fig. 4 Computer simulation of the impulsive system (8) – (11) showing the solution trajectory approaching the limit cycle as time progresses. Here, $a_1 := 0.05$; $a_3 := 0.0675$; $a_4 := 0.009$; $a_5 := 0.0045$; $b_1 := 0.1$; $b_2 := 0.03$; $b_3 := 0.009$; $k_1 := 0.1$; $k_2 := 0.5$; $k_3 := 0.025$; $p := 0.9$; $x_1(0) = 0.1$, $x_2(0) = 0.135$, $T = 200$, $\mu = 0.5$, $p = 0.9$.

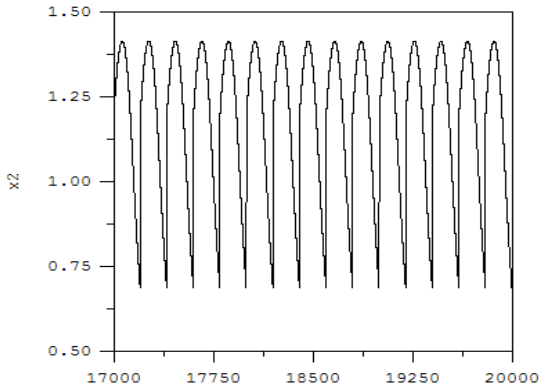
Fig. 4 shows the sustained oscillations in both state variables in the case that the system is permanent, system parameters chosen to satisfy the conditions given in Theorem 3. Here, the period of hormone supplements is $T = 200 > T_{\min} = 8.005$. The solution trajectory is seen in Fig. 4 to approach a stable limit cycle as time passes. The corresponding time series of both state variables in the case of positive sustained oscillations are shown in Fig. 5(a) and 5(b), for the same parameter values as in Fig. 4.

Our analysis suggests a venue for control of the bone resorption and remodelling process by adjustment of the frequency $\frac{1}{T}$ of the treatments or the dosages, reflected by the values of p and μ, in order to obtain the desired outcome. Specifically, our analytical conclusions indicate that we may expect sustained oscillations in the level of osteoblastic cells even at the vanishing level of the active osteoclastic cells at a sufficiently low period of external hormone supplements.

On the other hand, if the period of impulsive supplementary hormone application is kept at a convenient fixed level, then it is possible to adjust the strength of the dose p so that $T_{\min}$, given by (19), renders the inequality (20) true, in which case the system is permanent. Both the active osteoclastic and osteoblastic cells remain positive. Moreover, if (26) also holds then oscillatory behavior resembling clinical data is the outcome.



5a)



5b)

Fig. 5 Computer simulation of the impulsive system (8) – (11) showing the sustained oscillations in the time series of the levels of osteoclastic cells and osteoblastic cells in 5(a) and 5(b), respectively, corresponding to the case seen in Fig. 4.

Thus, we see that it is possible to control the system's dynamic behavior by fine tuning the period T of the impulsive inputs, or the impulse strength p or μ. According to Prank *et al.* [7], recent evidence links osteoporosis, a disease characterized by loss of bone mass and structure, to changes in the dynamics of pulsatile parathyroid (PTH) secretion.

Our investigation is therefore expected to contribute to the better understanding of the different dynamic behavior which could be expected in the system under investigation, as well as assist in the decision making process on the choice of treatment protocols for its management and control.

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