Stability and 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 application of parathyroid hormone supplementary treatments, is analyzed in terms of the boundedness, asymptotic stability, permanence, and oscillatory behavior. Conditions under which different dynamic behavior may be expected are shown to be sensitive to the period and amplitude of the hormone supplements so that the variation of these parameters are crucial of the proper management and control of this complex system which is an essential component of the human life.

Key-Words: Bone remodeling, asymptotic stability, permanence, impulsive differential equation models

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

Bone plays an important role in the human body. It provides mechanical integrity and protection. Moreover, 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 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. 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 Equation (1) is the rate of increase of PTH which is inhibited by the osteoclastic cells. The first term on the right of Equation (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 Equation (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].

It has been observed that PTH has a very fast dynamics [3 - 5] so that it equilibrates relatively quickly to the level where $\frac{dP}{dt}=0$, at which point

$$P=\frac{c_1}{d_1(k_1+C)} \tag{4}$$

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 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.

2. Impulsive System

As reported by Prank *et al.* [5, 6] 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.

Letting $x_1 = C$, $x_2 = B$, for convenience, we are then led to the following system, where positive decreasing function $f(x_1)$ is used for the effect of the level of x_1, on x_2.

$$\left.\begin{aligned}\frac{dx_1}{dt}&=\left(\left(\frac{a_3 f(x_1)}{k_2+f^2(x_1)}\right)x_2-b_2\right)x_1 \qquad (5)\\ \frac{dx_2}{dt}&=a_4 f(x_1)-\left(\frac{a_5 f(x_1)}{k_3+f(x_1)}\right)x_2-b_3x_2 \qquad (6)\end{aligned}\right\} \quad t\neq nT$$

$$\Delta x_1(t)=-px_1(t), t=nT, \tag{7}$$

$$\Delta x_2(t) = \mu, t=nT \tag{8}$$

where

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

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 Equation (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 (5)-(6) 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 the (5)-(8) is defined by

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

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 (5) – (8) 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 (5) – (8) 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

$$b_3 > \frac{a_3 M_1}{k_2} \tag{9}$$

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,

$$D^+ v + cv = x_1'(t) + x_2'(t) + cx_1(t) + cx_2(t)$$

$$= \frac{a_3 f(x_1)}{k_2 + f^2(x_1)} x_1 x_2 - b_2 x_1 + a_4 f(x_1) - \left(\frac{a_5 f(x_1)}{k_3 + f(x_1)}\right) x_2 - b_3 x_2 + cx_1 + cx_2$$

$$\leq \frac{a_3 x_1 f(x_1)}{k_2} x_2 - b_2 x_1 + a_4 f(x_1) - b_3 x_2 + cx_1 + cx_2$$

$$\leq \left(\frac{a_3 M_1}{k_2} - b_3 + c\right) x_2 + (-b_2 + c) x_1 + a_4 M_2 \leq a_4 M_2 \equiv b$$

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

When $t = t_k$,

$$v(t_k^+) = x_1(kT^+) + x_2(kT^+)$$

$$= x_1(kT) - px_1 + x_2(kT) + \mu \leq v(kT) + \mu$$

By Lemma 2.2 in the work of Lui *et al.* [7], we obtain that, for

$$v(t) \leq v(0) e^{-ct} + b \int_0^t e^{-\int_s^t c\, d\tau}\, ds + \mu \sum_{0 < t_k < t} e^{-\int_{t_k}^t c\, d\tau}$$

$$\leq v(0) e^{-ct} + \frac{b}{c}\left(1 - e^{-ct}\right) + \mu\left[\frac{e^{-c(t-T)} - e^{-c(t-t_{k+1})}}{1 - e^{cT}}\right]$$

$$< \frac{b}{c} + \frac{\mu e^{cT}}{e^{cT} - 1} \equiv M \quad \text{as } t \to \infty.$$

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.

3. Stability at Vanishing Active Osteoblasts

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

$$\frac{dx_2}{dt} = B - Ax_2, t \neq t_k \tag{10}$$

$$x_2(t_k^+) = x_2(t_k) + \mu, t = t_k \tag{11}$$

$$x_2(0^+) = x_{2_0} \tag{12}$$

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

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

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

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 (5) – (6) has a periodic solution and for every solution $\underset{\sim}{x}(t) = (x_1(t), x_2(t))$ of (5) – (6) we have

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

Now, we let

$$\mathcal{C} \equiv \frac{a_3 f(0)}{k_2 + f^2(0)} \tag{13}$$

and state a result on the asymptotic behavior of the solutions $\underset{\sim}{x}(t)$ of (5) – (6).

Theorem 1. Suppose

$$b_2 < \frac{\mathcal{C}B}{A} \tag{14}$$

$$\ln\frac{1}{1-p} > \frac{\mathcal{C}\mu}{A} \tag{15}$$

The solution $(0,\tilde{x}_2(t))$ of (5) – (6) is locally asymptotically stable if

$$T < T_{\min} \equiv \left(\ln\frac{1}{1-p} - \frac{\mathcal{C}\mu}{A}\right) \Big/ \left(\frac{\mathcal{C}B}{A} - b_2\right) \tag{16}$$

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

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

Integrating, we arrive at

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

Linearization of (7) – (8) 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 (16) holds. The proof is complete.

4. Sustained Oscillation

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

$$\left.\begin{aligned} \frac{dx_1}{dt} &= a_4 f(x_2) - \left(\frac{a_5 f(x_2)}{k_3 + f(x_2)}\right)x_1 - b_3 x_1 \equiv F_1(x_1,x_2) \\ \frac{dx_2}{dt} &= \left(\left(\frac{a_3 f(x_2)}{k_2 + f^2(x_2)}\right)x_1 - b_2\right)x_2 \equiv F_2(x_1,x_2) \end{aligned}\right\} t \neq nT \tag{17, 18}$$

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

Relying on the notations used by Lakmeche and Arino [8], we let

$$\Theta_1(x_1,x_2) = x_1 + \mu$$

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

with

$$\varsigma(t) = (\tilde{x}_2(t),0)^T,$$

$$x_0 = (\tilde{x}_2(\tau_0),0)^T,$$

and $\tau_0 = T_{\min}$.

According to [8],

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

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

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

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

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

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

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

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

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

while

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

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

$$a_4 < \frac{a_5 k_3}{k_3 + f^2(0)} \qquad (19)$$

Thus, $C^* > 0$ and $B^* C^* < 0$, and, by Lakmeche and Arino [8], we are thus able to prove the following result.

Theorem 3. The system (1.1)-1.3) has a positive periodic solution which is supercritical provided (9), (14), (15), (19) hold and $T > T_{min}$.

5. Conclusion

We have investigated the boundedness and permanence of the bone remodeling process under impulsive external interferences. The case where active osteoclastic cells level may entirely vanish has also been investigated. 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.

Figure 1. 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 Figure 2(b) to approach a stable limit cycle as time passes.

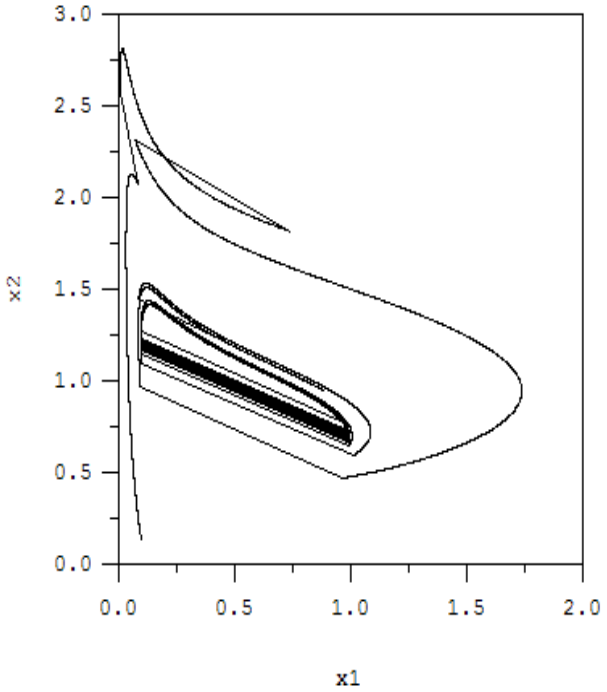

FIGURE 1. Numerical simulation of Equations (5) – (8) showing the solution trajectory approaching the limit cycle as time progresses. Here, $a_1 := 0.05$; $a_3 := 0.0675$; $a_4 := 0.009$; $a_5 := 0.0045$; $b_1 := 0.1$; $b_2 := 0.03$; $b_3 := 0.009$; $k_1 := 0.1$; $k_2 := 0.5$; $k_3 := 0.025$; $p := 0.9$; $x_1(0) = 0.1$, $x_2(0) = 0.135$, $T = 200$, $\mu = 0.5$, $p = 0.9$.

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.* [5], 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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