

Stability Analysis of an Impulsive Differential Equation Model for Bone Metabolism under Estrogen Treatment during COVID-19 Infection

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Abstract: - COVID-19-associated inflammation, immobilization, and altered endocrine signaling can disrupt bone remodeling. We formulate a reduced impulsive differential-equation model for the interactions among parathyroid hormone, active osteoclasts, and active osteoblasts under periodic estrogen intervention. After a quasi-steady reduction of the fast parathyroid-hormone variable, we establish positivity and dissipativity, derive the unique osteoclast-free periodic solution, and obtain its exact transverse Floquet multiplier, which is shown to be exact for the unreduced three-dimensional model as well. Sufficient conditions for global attraction and uniform persistence are proved, and a simple-eigenvalue bifurcation of positive periodic solutions is characterized through the Poincaré map. Analytical sensitivity and constrained pulse-design formulas are confirmed by numerical calculations.

Key-Words: - Impulsive mathematical model, bone, COVID-19-associated effects, parathyroid hormone, estrogen treatment, persistence, sensitivity analysis

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1 Introduction

Population aging is a major global health concern. The number of people aged 60 years or older is projected to reach 1.4 billion by 2030 and 2.1 billion by 2050 [1]. Osteoporosis is characterized by reduced bone mass and an increased risk of fracture, and it commonly results from a sustained imbalance between bone resorption and bone formation [2]. Osteoclasts resorb mineralized bone, whereas osteoblasts form new bone. Their coordinated activity maintains skeletal strength, mineral homeostasis, and the repair of microdamage [3], [4].

Bone remodeling is regulated by several endocrine and local mediators, including parathyroid hormone (PTH), calcitonin, and estrogen. Estrogen suppresses osteoclast differentiation and activity and supports osteoblast survival and function [5], [6]. These biological interactions have motivated ordinary, delayed, and impulsive differential-equation models of bone turnover and hormone supplementation [7], [8], [9], [10].

COVID-19 may affect bone health through inflammation, immobilization, altered endocrine

signaling, and the renin–angiotensin system [11], [12], [13], [14]. A continuous model for COVID-19-associated bone remodeling was developed and its oscillatory dynamics were analyzed by geometric singular perturbation [15]. In 2021, impulsive estrogen supplementation in a model with a different hormonal structure was studied in [10]. The present study uses the biological mechanisms introduced in [15] but addresses a different mathematical question: how periodic estrogen pulses change extinction, coexistence, and bifurcation thresholds in the COVID-19-associated model.

This work is distinct from the analyses in [10] and [15] in several respects. We derive an exact transverse Floquet exponent for the osteoclast-free periodic state and establish a sufficient condition for its global attraction. A hybrid logarithmic Lyapunov function provides a verifiable dissipativity criterion which, combined with an average-Lyapunov argument, yields uniform persistence. We formulate the Poincaré map explicitly, verify a simple-eigenvalue bifurcation, numerically continue the bifurcating branch beyond its locally proved regime, and derive

analytical pulse sensitivities together with a constrained design formula. All reported thresholds are checked numerically. We also show that the transverse multiplier and the critical pulse interval obtained after the quasi-steady reduction are exact for the unreduced three-dimensional system, so the reported thresholds are not artifacts of that reduction.

2 A Modified Mathematical Model

We extend the differential-equation model proposed in [15] to include both COVID-19-associated alterations in bone-cell dynamics and the normalized effects of periodic estrogen intervention. Here, $X(t)$ denotes normalized PTH concentration above baseline, $Y(t)$ the normalized active-osteoclast population, and $Z(t)$ the normalized active-osteoblast population. Between interventions, the continuous model is

$$\left. \begin{aligned} \frac{dX}{dt} &= \frac{a_1}{k_1 + Y} - b_1 X, \\ \frac{dY}{dt} &= \left(\frac{a_2 + a_3 X}{k_2 + X^2} + \frac{a_4 Y}{k_3 + Y} \right) YZ - b_2 Y, \\ \frac{dZ}{dt} &= a_5 X - \frac{a_6 XZ}{k_4 + X} - (a_7 + b_3)Z, \end{aligned} \right\} \quad (1)$$

for $t \neq nT$. At $t = nT$, $n = 0, 1, 2, \dots$, the pulse map represents the net modeled effect of an estrogen intervention: it reduces the active-osteoclast state by the fraction α and increases the active-osteoblast state by β . Equation (2) is a phenomenological state-jump assumption motivated qualitatively by estrogen-related bone biology [5], [6], [16]. Accordingly, α and β are normalized model controls rather than clinically calibrated doses:

$$\left. \begin{aligned} Y(nT^+) &= (1 - \alpha)Y(nT^-), \\ Z(nT^+) &= Z(nT^-) + \beta, \end{aligned} \right\} \quad (2)$$

where $0 < \alpha < 1$ and $\beta > 0$. The parameter $T > 0$ is the interval between successive pulses. All model parameters are positive, and the state variables and parameters are normalized as in [15]. The quantities α and β are dimensionless state jumps.

Following the time-scale separation used in [15], PTH is assumed to equilibrate rapidly relative to the bone-cell populations. Setting $\frac{dX}{dt} = 0$ gives the quasi-steady relation below.

$$X = f(Y) = \frac{a_1}{b_1(k_1 + Y)}. \quad (3)$$

Substitution of (3) into (1) yields the reduced impulsive system

$$\left. \begin{aligned} \frac{dY}{dt} &= Y[r(Y)Z - b_2] \\ \frac{dZ}{dt} &= a_5 f(Y) - q(Y)Z \end{aligned} \right\} t \neq nT, \quad (4)$$

$$\left. \begin{aligned} Y(nT^+) &= (1 - \alpha)Y(nT^-), \\ Z(nT^+) &= Z(nT^-) + \beta, \end{aligned} \right\}$$

where

$$\left. \begin{aligned} r(Y) &= \frac{a_2 + a_3 f(Y)}{k_2 + f^2(Y)} + \frac{a_4 Y}{k_3 + Y}, \\ q(Y) &= \frac{a_6 f(Y)}{k_4 + f(Y)} + a_7 + b_3. \end{aligned} \right\} \quad (5)$$

The saturating term $\frac{a_4 Y}{k_3 + Y}$ represents the COVID-19-associated enhancement of osteoclast reproduction inherited from [15], with k_3 its half-saturation constant. The coefficient a_7 contributes to COVID-19-associated osteoblast loss. The quantities α , β , and T are the normalized impulsive-treatment controls.

3 Positivity of Solutions and the Osteoclast-Free Periodic Solution

We write $S(t) = (Y(t), Z(t))$ and take $S(0^+) \in \mathbb{R}_+^2$. Between impulses, the vector field in (4) is locally Lipschitz on $\mathbb{R}_+^2$. In what follows, we define $f_0 = f(0) = \frac{a_1}{b_1 k_1}$, $A = a_5 f_0$, $D_0 = a_7 + b_3$, $G_\infty = \frac{a_2}{k_2} + a_4$, $M_Z = \frac{A}{D_0} + \frac{\beta}{1 - \exp(-D_0 T)}$ and $R_u = \frac{a_2}{k_2} + \frac{a_3 f_0}{k_2} + a_4$ which is used in the proof of Lemma 2. Existence, uniqueness, and forward continuation of solutions of (4) on each inter-pulse interval, together with the jump map, follow from the general theory of impulsive differential equations [17].

Lemma 1. If $S(0^+) \geq 0$, then $S(t) \geq 0$ for every $t \geq 0$. If $S(0^+) > 0$, then $S(t) > 0$ for every $t \geq 0$.

Proof. The set $Y = 0$ is invariant for (4) because the right-hand side of the first equation carries the factor Y , and on $Z = 0$ the second equation gives $\frac{dZ}{dt} = a_5 f(Y) > 0$. Hence, no solution can leave $\mathbb{R}_+^2$ between consecutive pulses. The jump map sends (Y, Z) to $((1 - \alpha)Y, Z + \beta)$ with $0 < \alpha < 1$ and $\beta > 0$, so it maps $\mathbb{R}_+^2$ into itself and the open positive quadrant into itself. Both assertions follow by induction over the pulse intervals.

Lemma 2. For every solution $(Y(t), Z(t))$ of (4) with $Y(0^+) \geq 0$, $Z(0^+) \geq 0$:

(i) $Z(t)$ is uniformly ultimately bounded, with no restriction on the parameters; indeed

$$\limsup_{t \rightarrow \infty} Z(t) \leq M_Z, \quad (6)$$

(ii) if, in addition,

$$\left(\frac{a_2}{k_2} + a_4\right) \frac{\beta}{1 - e^{-D_0 T}} < b_2, \quad (7)$$

then $Y(t)$ is uniformly ultimately bounded. Consequently, there exists $M > 0$ such that $Y(t) \leq M$ and $Z(t) \leq M$ for all sufficiently large t .

Proof. If $Y(0^+) = 0$, then $Y(t) \equiv 0$, and only the estimate for Z is required. Assume henceforth that $Y(0^+) > 0$, so $Y(t) > 0$.

Step 1:

Since $f(Y) \leq f_0$ and the term $-\frac{a_6 f(Y)Z}{k_4 + f(Y)}$ is non-positive,

$$\dot{Z} \leq A - D_0 Z, \quad t \neq nT,$$

with $Z(nT^+) = Z(nT^-) + \beta$. The scalar comparison equation has a globally attracting T -periodic solution whose maximum is M_Z . Therefore, for every $\varepsilon_1 > 0$, there is $t_1 > 0$ such that

$$Z(t) \leq M_Z + \varepsilon_1 \quad (t \geq t_1).$$

Thus, $\limsup_{t \rightarrow \infty} Z(t) \leq M_Z$. This proves part (i).

Step 2:

Condition (7), together with $1 - \exp(-D_0 T) < D_0 T$, implies

$$\frac{G_\infty}{D_0} < \frac{b_2 T}{\beta}.$$

Choose c such that $\frac{G_\infty}{D_0} < c < \frac{b_2 T}{\beta}$, and define the hybrid Lyapunov function

$$V(t) = \ln Y(t) + cZ(t).$$

Between impulses,

$$\dot{V} = [r(Y) - cq(Y)]Z + ca_5 f(Y) - b_2.$$

Because $r(Y) \rightarrow G_\infty$, $q(Y) \rightarrow D_0$, and $f(Y) \rightarrow 0$ as $Y \rightarrow \infty$, there exist $R > 0$ and $\varepsilon > 0$ such that, whenever $Y \geq R$,

$$r(Y) - cq(Y) \leq 0, \quad ca_5 f(Y) \leq \varepsilon.$$

Choose ε sufficiently small that

$$\mu = b_2 T - c\beta - \ln(1 - \alpha) - \varepsilon T > 0.$$

At an impulse,

$$V(nT^+) - V(nT^-) = \ln(1 - \alpha) + c\beta.$$

Consequently, if $Y(t) \geq R$ throughout an inter-pulse interval, then the total change of V over that interval is at most $-\mu < 0$. After Z has entered the bound $Z \leq M_Z + 1$, any excursion of Y into $Y \geq R$ begins with

$$V \leq \ln R + c(M_Z + 1).$$

Moreover, once $Z(t) \leq M_Z + 1$ holds, the right-hand side of the expression for $\dot{V}$ is bounded above by the constant $K = R_u(M_Z + 1) + ca_5 f_0$, so V increases by at most $KT + c\beta$ on any single inter-pulse interval. Hence, V cannot grow without bound: every complete inter-pulse interval spent in $\{Y \geq R\}$ decreases V by at least μ , while an interval on which Y drops below R leaves V no larger than $\ln R + c(M_Z + 1) + KT + c\beta$.

Since $Z(t) \geq 0$, we have $\ln Y(t) \leq V(t)$, so $Y(t)$ is uniformly ultimately bounded. Together with part (i), this proves the lemma.

On the invariant boundary $Y = 0$, the second equation of (4) becomes

$$\dot{Z} = A - DZ, \quad Z(nT^+) = Z(nT^-) + \beta. \quad (8)$$

Here, $D = \frac{a_6 f_0}{k_4 + f_0} + a_7 + b_3$, with f_0 and A defined above.

Lemma 3. Equation (8) has the unique positive T -periodic solution

$$\tilde{Z}(t) = \frac{A}{D} + \frac{\beta e^{-D(t-nT)}}{1 - e^{-DT}}, \quad (9)$$

$nT < t \leq (n+1)T^-$, where the superscript minus denotes the left limit immediately before the next pulse. At each impulse time, the periodic solution is assigned its post-pulse (right-limit) value and the endpoint in (9) is interpreted as the pre-pulse left limit. Every solution of (8) converges exponentially to $\tilde{Z}(t)$. Thus, $E_0(t) = (0, \tilde{Z}(t))$ is the unique osteoclast-free periodic solution of (4).

Proof. Variation of constants on one inter-pulse interval gives

$$Z((n+1)T^-) = \frac{A}{D} + [Z(nT^+) - A/D]e^{-DT}.$$

Combining this relation with the jump condition produces an affine contraction with ratio e^{-DT} . Its unique fixed point is $\frac{A}{D} + \frac{\beta}{(1-e^{-DT})}$, which gives (9) and exponential convergence.

4 Threshold Dynamics and Global Stability

Let

$$J = r(0) = \frac{a_2 + a_3 f_0}{k_2 + f_0^2}. \quad (10)$$

Linearization of (4) about $E_0(t)$ gives a triangular variational system. The two Floquet multipliers are

$$\rho(T) = (1 - \alpha) \exp \left[\frac{J\beta}{D} + \left(\frac{AJ}{D} - b_2 \right) T \right], \quad (11)$$

$$\rho_Z(T) = e^{-DT}.$$

The identity $\int_0^T \tilde{Z}(t) dt = \frac{AT}{D} + \frac{\beta}{D}$ has been used in (11).

Theorem 1. The osteoclast-free periodic solution $E_0(t)$ is locally asymptotically stable if $\rho(T) < 1$ and unstable if $\rho(T) > 1$.

Proof. Because $0 < e^{-DT} < 1$, the stability is then determined entirely by $\rho(T)$. The conclusion follows from Floquet theory for impulsive systems [18]. If $\rho(T) = 1$ the linearization is inconclusive; this

borderline case is precisely the bifurcation point analyzed in Theorem 4.

We introduce the exact invasion exponent

$$\Lambda(T) \equiv \ln \rho(T) = \ln(1 - \alpha) + \frac{J\beta}{D} + \left(\frac{AJ}{D} - b_2 \right) T. \quad (12)$$

Let $s = \frac{AJ}{D} - b_2$. If $s \neq 0$ and the value below is positive, the critical pulse interval is

$$T_c = \frac{\ln[1/(1 - \alpha)] - J\beta/D}{AJ/D - b_2}. \quad (13)$$

Since $f(Y) \leq f_0$,

$$r(Y) \leq \frac{a_2}{k_2} + \frac{a_3 f_0}{k_2} + a_4 \equiv R_u. \quad (14)$$

With $\delta = a_7 + b_3 = D_0$, define

$$\Gamma \equiv \ln(1 - \alpha) + R_u \left(\frac{AT}{\delta} + \frac{\beta}{\delta} \right) - b_2 T. \quad (15)$$

Theorem 2. If $\Gamma < 0$, then every solution of (4) with $Y(0^+) > 0$ and $Z(0^+) \geq 0$ satisfies

$$Y(t) \rightarrow 0, \quad Z(t) - \tilde{Z}(t) \rightarrow 0 \quad \text{as } t \rightarrow \infty. \quad (16)$$

Therefore, $E_0(t)$ is globally asymptotically stable in the positive state space.

Proof. From (4) and (14), for every sufficiently large n ,

$$\ln \frac{Y((n+1)T^+)}{Y(nT^+)} \leq \Gamma + o(1). \quad (17)$$

If $\Gamma < 0$, the right-hand side is eventually bounded above by a negative constant. Hence, the post-pulse sequence $Y(nT^+)$ decays geometrically. Boundedness of Z and the differential equation for Y then imply $Y(t) \rightarrow 0$ throughout every inter-pulse interval.

Let $e(t) = Z(t) - \tilde{Z}(t)$. The jumps cancel, so $e(nT^+) = e(nT^-)$.

Between pulses,

$$\dot{e} = -q(Y)e + a_5[f(Y) - f_0] + [D - q(Y)]\tilde{Z}(t). \quad (18)$$

Because $q(Y) \geq \delta > 0$, $Y(t) \rightarrow 0$, and f and q are continuous, the forcing terms in (18) converge to zero. Variation of constants gives $e(t) \rightarrow 0$ which completes the proof.

The hypothesis $\Gamma < 0$ of Theorem 2 is strictly stronger than the local condition $\rho(T) < 1$ of Theorem 1. Subtracting (12) from (15) gives $\Gamma - \Lambda(T) = (AT + \beta)(\frac{R_u}{\delta} - \frac{J}{D}) \geq 0$, because $R_u \geq J$ by (14) and $\delta = D_0 \leq D$. Hence, $\Gamma < 0$ implies $\Lambda(T) < 0$, that is, $\rho(T) < 1$, so $E_0(t)$ is also locally asymptotically stable by Theorem 1, and the global attraction proved above indeed upgrades to global asymptotic stability. The inequality is illustrated by the first parameter set in Table 3 (Appendix), for which $\Gamma = -1.746802$ exceeds $\Lambda = -2.608888$.

Here, we note that the multiplier (11) and the critical interval (13) are exact for the unreduced three-dimensional system (1)–(2), and not only for the reduced system (4). Indeed, on the invariant set $Y = 0$ the first equation of (1) becomes

$$\frac{dX}{dt} = \frac{a_1}{k_1} - b_1 X$$

whose unique periodic solution is the constant $X \equiv f_0$. Since X is unaffected by the impulses (2), the osteoclast-free periodic solution of (1)–(2) is exactly $(f_0, 0, \tilde{Z}(t))$ with the same $\tilde{Z}(t)$ as in (9). Moreover, the right-hand side of the second equation of (1) carries the factor Y , so its partial derivatives with respect to X and Z vanish at $Y = 0$. The variational system about $(f_0, 0, \tilde{Z}(t))$ is therefore block triangular. Its transverse multiplier is exactly $\rho(T)$ as given in (11), while the two remaining multipliers are $e^{-b_1 T} < 1$ and $e^{-D T} < 1$. Consequently, the thresholds $\rho(T) = 1$ and $T = T_c$ are properties of the full model and are not artifacts of the quasi-steady-state reduction.

5 Permanence and Bifurcation of Positive Periodic Solutions

System (4) is called permanent if there exist constants $0 < m < M < \infty$ such that every positive solution satisfies

$$m \leq Y(t), Z(t) \leq M \quad (19)$$

for all sufficiently large t .

Theorem 3. Assume the condition (7) and $\Lambda(T) > 0$. Then, system (4) is permanent in the sense of (19).

Proof. The pulse-to-pulse Poincaré map is continuous and point dissipative by Lemma 2. Furthermore, $q(Y) \leq D$ for $Y \geq 0$, and after each pulse $Z(nT^+) \geq \beta$. Hence, $Z(t) \geq \beta e^{-DT}$ after the first pulse. It remains to establish a positive lower bound for Y .

On the boundary $Y = 0$, the only compact invariant set is E_0 . For positive Y near the boundary, the one-period change in $\ln Y$ converges uniformly to $\Lambda(T) > 0$. Thus, E_0 is an isolated uniform repeller for the interior. More explicitly, Lemmas 1 and 2 supply interior forward invariance and a compact absorbing set. Continuity follows from the locally Lipschitz inter-pulse flow and the continuous jump map. The maximal invariant subset of the boundary is this single fixed point, and its stable set contains no interior point because of the positive uniform logarithmic growth rate. Hence, the hypotheses of the uniform-persistence theorem for point-dissipative maps [19] are satisfied, and the theorem gives a constant $m_Y > 0$ such that $Y(t) \geq m_Y$ for all sufficiently large t . Combining this

lower bound with the lower bound for Z and the absorbing set from Lemma 2 proves permanence.

We now formulate the bifurcation directly through the Poincaré map, which makes the required derivatives unambiguous; a related formulation for impulsive systems is given in [20]. Let $P_T: \mathbb{R}_+^2 \rightarrow \mathbb{R}_+^2$ map a state immediately after one pulse to the state immediately after the next pulse. Its boundary fixed point is

$$x_0(T) = \left(0, \frac{A}{D} + \frac{\beta}{1 - e^{-DT}}\right). \quad (20)$$

Because the set $Y = 0$ is invariant under P_T , we have $P_Y(0, Z) = 0$ for every Z , so the partial derivative of P_Y with respect to Z vanishes at x_0 and $D_x P_T(x_0)$ is lower triangular with diagonal entries $\rho(T)$ and e^{-DT} . In particular, the multiplier 1 attained at $T = T_c$ is algebraically simple, since $e^{-DT_c} \neq 1$, and the corresponding right eigenvector may be normalized by $v_Y = 1$.

At $T = T_c$, $D_x P_{T_c}(x_0)$ has the simple multiplier 1 and the second multiplier $e^{-DT_c} < 1$. Let v and w be corresponding right and left eigenvectors, normalized by $w^T v = 1$, and define

$$\begin{aligned} a &= \frac{1}{2} w^T D_x^2 P_{T_c}(x_0)[v, v], \\ b &= \left. \frac{d\rho}{dT} \right|_{T=T_c} = \frac{AJ}{D} - b_2. \end{aligned} \quad (21)$$

Theorem 4. Suppose $T_c > 0$, $a \neq 0$, and $b \neq 0$. Then, a unique local branch of non-boundary fixed points of P_T bifurcates from $(x_0(T_c), T_c)$. With the center coordinate normalized by $v_Y = 1$, its osteoclast component satisfies

$$Y^*(T) = -\frac{b}{a}(T - T_c) + o(|T - T_c|). \quad (22)$$

The branch is biologically positive on the side for which the leading term in (22) is positive.

Proof. Translate the boundary branch to the origin by writing $x = x_0(T) + u$. Lyapunov–Schmidt reduction of $P_T(x) - x = 0$ gives the scalar equation $u_Y[b(T - T_c) + au_Y + o(|T - T_c| + |u_Y|)] = 0$.

The simple-eigenvalue and transversality assumptions permit application of the Crandall–Rabinowitz theorem [21], which gives (22).

The Crandall–Rabinowitz theorem guarantees only the local branch described by (22). Continuation beyond that neighborhood is examined numerically in Section 7.

6 Sensitivity Analysis and Constrained Design

Because the stability multiplier is explicit, its logarithmic sensitivities are also explicit:

$$\frac{\partial \ln \rho}{\partial \alpha} = -\frac{1}{1 - \alpha}, \quad \frac{\partial \ln \rho}{\partial \beta} = \frac{J}{D}, \quad \frac{\partial \ln \rho}{\partial T} = \frac{AJ}{D} - b_2. \quad (23)$$

Thus, a larger fractional reduction α always decreases the invasion multiplier, whereas a larger osteoblast increment β increases it in this model because osteoblasts appear in the osteoclast growth term. The effect of increasing the pulse interval depends on the sign of $\frac{AJ}{D} - b_2$.

The dependence of stability on the underlying physiological parameters is quantified by the normalized sensitivity index of the invasion multiplier,

$$S_p = \frac{\partial \ln \rho}{\partial \ln p} = \frac{p}{\rho} \frac{\partial \rho}{\partial p} = p \frac{\partial \Lambda}{\partial p},$$

which measures the fractional change in ρ caused by a fractional change in a parameter p . For physiological parameters that enter through $f_0 = \frac{a_1}{b_1 k_1}$, $A = a_5 f_0$,

$D = \frac{a_6 f_0}{k_4 + f_0} + a_7 + b_3$, and $J = r(0)$, the chain rule gives

$$\begin{aligned} S_p &= p \left(\frac{\partial \Lambda}{\partial J} \frac{\partial J}{\partial p} + \frac{\partial \Lambda}{\partial A} \frac{\partial A}{\partial p} + \frac{\partial \Lambda}{\partial D} \frac{\partial D}{\partial p} \right), \\ \frac{\partial \Lambda}{\partial J} &= \frac{\beta + AT}{D}, \quad \frac{\partial \Lambda}{\partial A} = \frac{JT}{D}, \\ \frac{\partial \Lambda}{\partial D} &= -\frac{J(\beta + AT)}{D^2}. \end{aligned}$$

The controls α , β and T and the osteoclast removal rate b_2 enter Λ directly rather than through f_0 , A , D and J ; for these, differentiation of (12) gives $S_\alpha = -\alpha/(1 - \alpha)$, $S_\beta = J\beta/D$, $S_T = (AJ/D - b_2)T$ and $S_{b_2} = -b_2 T$.

Two parameters are exceptional: the maximal osteoclast-recruitment rate a_4 and the half-saturation constant k_3 enter $r(Y)$ only through the term $\frac{a_4 Y}{k_3 + Y}$, which vanishes at $Y = 0$. Hence, a_4 and k_3 do not appear in $J = r(0)$ and satisfy $S_{a_4} = S_{k_3} = 0$.

For a prescribed contraction target $0 < \rho_* \leq 1$ and fixed (β, T) , the smallest pulse reduction that satisfies $\rho(T) \leq \rho_*$ is, with $s = \frac{AJ}{D} - b_2$,

$$\alpha_{\min}(T; \beta, \rho_*) = \max \left\{ 0, 1 - \rho_* \exp \left(-\frac{J\beta}{D} - sT \right) \right\}. \quad (24)$$

If $s = \frac{AJ}{D} - b_2 > 0$ and α cannot exceed $\alpha_{\max}$, the longest feasible pulse interval and therefore the interval that minimizes pulse frequency is

$$T_{\text{opt}} = \frac{\ln \rho_* - \ln(1 - \alpha_{\max}) - J\beta/D}{s}. \quad (25)$$

This expression applies when its right-hand side is positive.

Equations (23)–(25) also provide a robustness margin. If $\Lambda = -m < 0$ and uncertainty changes the exponent by at most $\eta < m$, then stability is retained.

7 Numerical Verification

Every closed-form quantity in this section follows from the two parameter sets of Table 1 (Appendix) by direct substitution; the periodic states, the coefficient a of (21) and the continuation shown in Figure 3 (Appendix) are obtained by numerical integration of (4). The two sets share the same PTH block, so $f_0 = 2.355072$ and $D = 1.025081$ in both cases. The derived constants and the three threshold quantities are collected in Table 3 (Appendix); the two cases are discussed in turn below.

Case 1: global attraction. For the first parameter set, $\Gamma = -1.746802 < 0$, so Theorem 2 applies, and the osteoclast-free periodic solution attracts every positive solution. Condition (7) also holds, its left-hand side being $0.017729 < b_2 = 0.50$, and the invasion multiplier is $\rho = 0.073616 < 1$. Figure 1 (Appendix) shows the decay of $Y(t)$ from a large initial value and the convergence of $Z(t)$ to the periodic state (9).

Case 2: permanence. For the second parameter set, the left-hand side of condition (7) is $0.229871 < b_2 = 0.31$, while $\Lambda = 1.866246 > 0$ and hence $\rho = 6.463988 > 1$, so the osteoclast-free state is invaded. Theorem 3 therefore predicts permanence. Iteration of P_T converges to the positive post-pulse fixed point $(Y^*, Z^*) = (0.0239386, 1.5288785)$.

The computed fixed point satisfies

$$\|P_T(Y^*, Z^*) - (Y^*, Z^*)\|_\infty < 4 \times 10^{-12}.$$

Over the limiting cycle, $0.0239386 \leq Y(t) \leq 0.1994885$ and $0.6088785 \leq Z(t) \leq 1.5288785$, as shown in Figure 2 (Appendix).

For the same continuous parameters and pulse amplitudes as the persistence case, (13) gives

$$T_c = 4.912046.$$

Centered variational differentiation of P_T at $(x_0(T_c), T_c)$, with convergence checked under step refinement, gives $a = -16.59538$ and $b = 0.366797$,

$$-\frac{b}{a} = 0.0221024.$$

The numerically differentiated value of b agrees with the closed-form expression $b = \frac{AJ}{D} - b_2$ of (21) to six significant digits, which validates the variational computation. Only a is genuinely numerical.

Hence, Theorem 4 predicts a positive branch for $T > T_c$ with slope 0.0221024. Figure 3 (Appendix) confirms this slope in a neighborhood of T_c and continues the branch numerically to $T = 15$, where it has saturated near $Y^* = 0.0258$. Formula (22) is therefore a local statement and should not be extrapolated. Figure 3 (Appendix) displays the analytical stability and contraction boundaries from (24). The logarithmic sensitivities (23) at the persistence parameter set are $\partial \ln \rho / \partial \alpha = -8.333333$, $\partial \ln \rho / \partial \beta = 0.346239$ and $\partial \ln \rho / \partial T = 0.366797$. These are raw derivatives with respect to the controls. The corresponding normalized indices reported in Table 2 (Appendix) are $S_\alpha = -7.333$, $S_\beta = 0.319$ and $S_T = 3.668$.

As an illustrative constrained calculation, take $\rho_* = 0.90$, $\alpha_{\max} = 0.95$, and $\beta = 0.92$. Equation (25) yields $T_{\text{opt}} = 7.011594$. This is a normalized mathematical design value, not a clinical prescription.

The normalized parameter sensitivities of ρ are listed in Table 2 (Appendix). For the persistence set, the ordering begins with $|S_\alpha| > |S_{a_3}| \approx |S_{a_5}|$ and continues as $|S_{a_7}| > |S_T| > |S_{b_2}|$. The pulse fraction α is the most influential control ($S_\alpha = -7.333$). The coefficient a_3 directly strengthens the PTH-dependent contribution to osteoclast growth, whereas a_5 controls PTH-driven osteoblast production and affects osteoclast invasion indirectly through the boundary osteoblast state. The removal coefficients a_7 , b_2 , and b_3 and the PTH-mediated inhibition coefficient a_6 are stabilizing. Consistent with the analytical result, $S_{a_4} = S_{k_3} = 0$. The different magnitudes for the global attraction set arise from that parameter set and pulse regimen. They should not be attributed solely to the fact that ρ is small.

8 Discussion

The exact exponent (12) separates the roles of the three pulse controls. The direct osteoclast reduction contributes $\ln(1 - \alpha)$, the osteoblast increment contributes $\frac{J\beta}{D}$, and the inter-pulse dynamics contribute $(AJ/D - b_2)T$. This decomposition is more informative than a list of sufficient inequalities because it remains valid even when the signs of the numerator and denominator in (13) change.

The parameter sensitivity analysis in Table 2 (Appendix) complements this decomposition. The coefficient a_3 directly promotes osteoclast invasion, whereas a_5 acts indirectly by increasing the osteoblast boundary state that appears in the osteoclast growth term. The pulse fraction α remains the most influential stabilizing control in the persistence example. This

ranking identifies priorities for parameter estimation, but it is local to the specified normalized parameter set and should be reassessed after calibration to patient data.

One structural consequence of (10) deserves emphasis. The COVID-19-associated recruitment term $\frac{a_4 Y}{k_3 + Y}$ vanishes at $Y = 0$, so a_4 and k_3 enter neither J nor, consequently, $\rho(T)$, $\Lambda(T)$ and T_c . The invasion threshold is therefore entirely insensitive to this mechanism, and COVID-19 acts on the threshold only through the osteoblast-loss coefficient a_7 , whose normalized sensitivity $S_{a_7} = -3.733$ is among the largest in Table 2 (Appendix). The parameters a_4 and k_3 do act on the sufficient condition (15) through R_u , on the boundedness condition (7) through G_∞ , and on the amplitude of the bifurcating positive branch. This separation of roles is a property of the model rather than a limitation of the analysis, and it should be taken into account when the recruitment term is calibrated against data.

The global condition (15) is deliberately stronger than local stability: it bounds the nonlinear osteoclast growth term over the entire positive state space and therefore guarantees convergence from arbitrary positive initial data.

The permanence theorem combines the hybrid Lyapunov estimate of Lemma 2 with the transverse invasion exponent. The bifurcation analysis uses derivatives of a clearly defined Poincaré map. We report the simple-eigenvalue coefficients and a fixed-point residual below 4×10^{-12} so that the branch direction and the numerical periodic state can be checked independently.

The model has several limitations. Its parameters are normalized rather than estimated from patient data, and α and β are state-jump controls rather than pharmacokinetic dose variables. COVID-19 is represented only through effective deterministic coefficients. Environmental noise, adherence variability, physiological delays, and uncertainty in the time-scale separation may shift the thresholds. These mechanisms should be introduced only when supported by data. Otherwise, they add complexity without identifiable parameters. We note in particular that distributed delays or stochastic forcing would replace the Floquet framework used here by a theory of impulsive functional or random differential equations, in which the exact multiplier (11) is no longer available; that extension is therefore left to separate work.

9 Conclusion

An impulsive model of bone remodeling under periodic estrogen intervention during COVID-19-associated disruption has been analyzed within a consistent threshold framework. The osteoclast-free periodic solution is governed locally by the exact multiplier (11), which, together with the critical interval (13), is exact for the unreduced three-dimensional model as well, so the reported thresholds are not artifacts of the quasi-steady reduction. A separate comparison-Lyapunov condition establishes global attraction, while dissipativity together with a positive invasion exponent establishes permanence. The Poincaré-map formulation yields a locally proved simple-eigenvalue bifurcation, while numerical continuation traces positive periodic states beyond the local regime. Closed-form sensitivities and a constrained design boundary quantify how the normalized controls α , β , and T affect stability. Clinical interpretation will require pharmacokinetic calibration and validation against longitudinal hormonal and bone-cell data.

Declaration of Generative AI and AI-assisted technologies in the writing process:

During the preparation of this work the authors used ChatGPT in order to edit language and improve readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Contribution of Individual Authors to the Creation of a Scientific Article (Ghostwriting Policy)

Supassorn Aekthong contributed to analytical derivations, numerical calculations, and preparation of the initial draft. Chontita Rattanakul contributed to conceptualization, model formulation, methodology, supervision, validation, and critical revision of the manuscript. Both authors reviewed and approved the final version.

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Conflict of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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APPENDIX

Table 1. Parameter sets used for numerical verification

Parameter	Global-attraction case	Persistence/ bifurcation case
a_1	0.13	0.13
a_2	0.06	0.06
a_3	0.20	0.94
a_4	0.10	0.18
a_5	0.10	0.83
a_6	0.28	0.28
a_7	0.54	0.54
b_1	0.69	0.69
b_2	0.50	0.31
b_3	0.25	0.25
k_1	0.08	0.08
k_2	0.86	0.86
k_3	0.69	0.69
k_4	0.45	0.45
α	0.50	0.88
β	0.10	0.92
T	4.00	10.00
$Y(0^+)$	0.80	0.057
$Z(0^+)$	0.20	0.083

Source: created by the authors.

Table 2. Normalized sensitivity indices $S_p = \frac{\partial \ln \rho}{\partial \ln p}$ of the invasion multiplier ρ for the two parameter sets defined in Table 1.

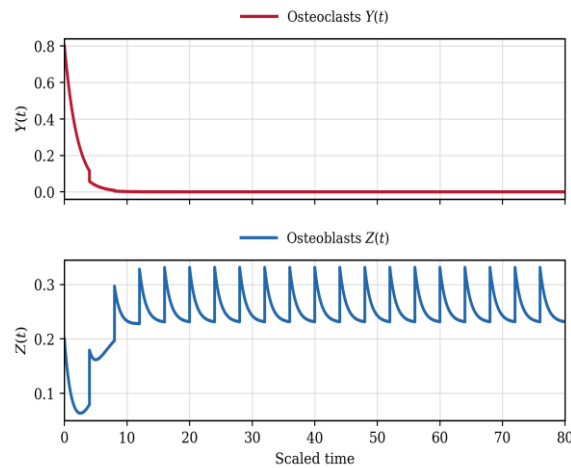
Parameter	$S_p(\text{global-attraction set})$	$S_p(\text{persistence set})$
a_1	0.002	1.136
a_2	0.010	0.187
a_3	0.075	6.900
a_4	0.000	0.000
a_5	0.076	6.768
a_6	-0.019	-1.625
a_7	-0.044	-3.733
b_1	-0.002	-1.136
b_2	-2.000	-3.100
b_3	-0.021	-1.728
k_1	-0.002	-1.136
k_2	-0.011	-0.951
k_3	0.000	0.000
k_4	0.003	0.261
α	-1.000	-7.333
β	0.008	0.319
T	-1.924	3.668

Source: created by the authors.

Table 3. Derived constants and threshold quantities for the two parameter sets of Table 1, computed from the definitions in Section 3 and equations (10)–(15)

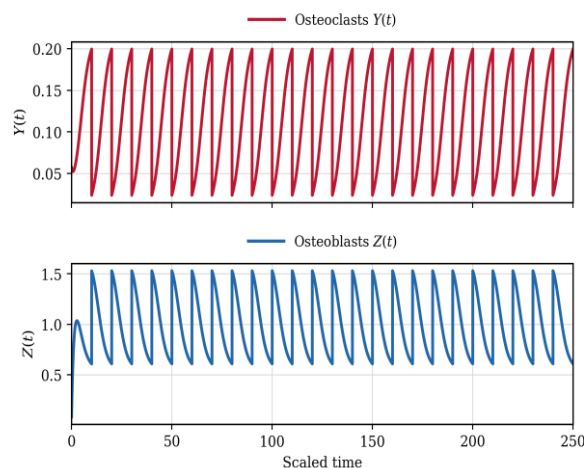
Quantity	Global-attraction case	Persistence case
f_0	2.355072	2.355072
A	0.235507	1.954710
D	1.025081	1.025081
J	0.082889	0.354923
R_u	0.717459	2.823916
G_∞	0.169767	0.249767
Γ	−1.746802	67.940982
Λ	−2.608888	1.866246
ρ	0.073616	6.463988

Source: created by the authors.



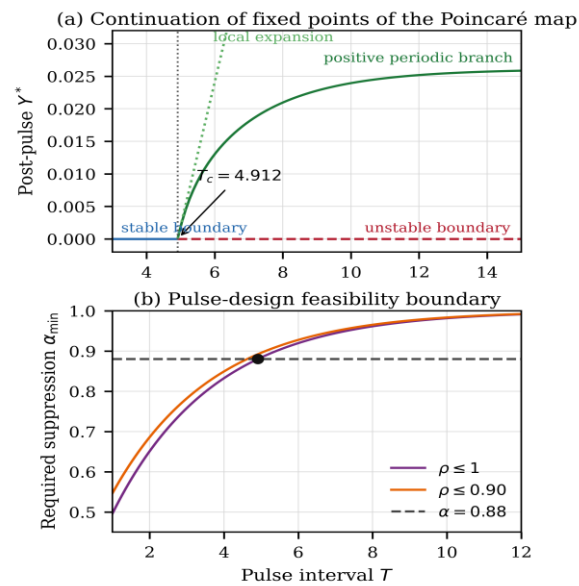
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Fig. 1: Global convergence to the osteoclast-free periodic state predicted by Theorem 2 for the first parameter set in Table 1



Source: created by the authors.

Fig. 2: Persistent positive periodic response predicted by Theorem 3 for the second parameter set in Table 1



Source: created by the authors.

Fig. 3: (a) Numerical continuation of the boundary and positive fixed points of the Poincaré map; the vertical line marks $T_c = 4.912046$. (b) Minimum pulse reduction required for $\rho \leq 1$ and $\rho \leq 0.90$ when $\beta = 0.92$. The black point corresponds to $\alpha = 0.88$ and $T = T_c$.