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Analytic approach to explore dynamical osteoporotic bone turnover

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Abstract

Background: The dynamics of the osteoporotic bone turnover is studied in this paper with the aid of stability analysis of the associated mathematical model. Osteoporosis, which is a common bone disorder, is studied in this papper in detail with an emphasis on the relative threshold values. We examine the expository signaling among the bone cells named osteoclast and osteoblast. Main functioning of osteoblasts is bone formation, whereas osteoclasts are bone removal cells.

Methods: Mathematical framework for osteoporotic bone turnover comprising of the communication between osteoclasts and osteoblasts has been presented to exhibit the conditions for stability in bone turnover.

Results: The percentage ratios of the population of osteoblasts/osteoclasts have been determined via numerical simulations. The remedial upshots of targeting osteoporotic cells participating in such process are examined.

Conclusions: From our analysis we have conclude that the role of external agents in treating the diseased bone can be better interpreted with the aid of a theoretical model.

Keywords: Bone remodeling; Osteoporosis; Stability analysis; Numerical simulations

1 Introduction

The bone formation and resorption is a continuous process and is known that collagen strands and lifeless bone minerals cover about 60–70 percent of the area of a bone at a local site, whereas the remaining proportion carries water. An infant body contains 270 bones, whereas an adult skeleton is made of 260 bones, which happens due to the continuous process of bone resorption and formation. There are two forms of bones, called cortical and trabecular (also known as cancellous). A cortical bone is an external layer of bone, which is hard and thick, whereas a spongy and soft structure lying inside the bone is called a trabecular bone. The main functioning of the bone includes the support to body and provides the base to marrow. There are numerous kinds of bone cells, but mainly two cells, named osteoclast (C) and osteoblast (B), take part in the functioning and maintenance of a bone. The main activity of osteoclast includes the resorption of mineralized tissues, whereas osteoblasts are bone-forming cells. Osteocytes are bone cells lying at the deep rooted area of a bone.

A bone guarantees redesigning for the duration of whole life in spatially and transiently discrete destinations in an organized procedure including resorption, trailed by formation

of a new bone [19]. Bone remodeling is accountable for development and mechanically instigated adaptation of bone and entails the processes of bone formation and resorption, however, globally correlated, takes place separately at anatomical different sites. Such a tightly correlated event needs harmonized activities of multicellular components to confirm that bone removal and making take place successively at the identical anatomical place to preserve the bone volume.

The two cells mainly responsible for bone remodeling process are osteoclasts (C) and osteoblasts (B). The key role of both kinds of cells is quite opposite; osteoclasts are bone-resorbing cells, whereas osteoblasts function as bone-forming cells. Osteoclasts are lethally differentiated myeloid multinucleated osteoclast precursors, which are exclusively transformed to eradicate mineralized bone milieu. Precursors of osteoclasts flow in the blood, and bone marrow and adult osteoclasts are produced from synthesis of the precursors. Such an evolution takes place after the signaling through receptor activators of NF-$\kappa\beta$ and its ligand. During bone resorption, osteoclasts append to the bone and develop tight seals with the underlying bone matrix in roughly circular extensions of their cytoplasm, and within these sealed zones, they form ruffled border membranes. By this sealing and secretory means the bone matrix is concurrently degraded, and bone minerals are dissolved while protecting neighboring cells from the harmful effects of HCl. Osteoblasts are mononucleated cellular units derived from osteoblast precursors. They are responsible for manufacturing of the major proteins of bone and type 1 collagen like osteocalcin and osteopontin, which compile the organic milieu of bone. These cells are also accountable for the mineralization of bone and fabricate enzyme alkaline phosphates. Recent investigations exhibit the role of osteoblasts as an imperative component in governing osteoclastogenesis. Another type of bone cells namely osteocytes, a latent state of osteoblasts, also participate in bone maintenance and mineralization. Many therapies of different bone disorders affect through osteocytes.

Various growth factors give paracrine coupling amongst C and B and additionally autocrine cycles for positive and negative input control of every cell kind. Among the most essential components, there are the proresorptive cytokine receptor activator of nuclear factor β ligand (RANKL) and its decoy receptor osteoprotegerin (OPG), which are communicated by B and corresponding control of C [17, 24]. Complex formation of OPG and RANK with RANKL give anabolic and catabolic effects on bones, respectively. Several other elements like transforming growth factor-β (TGF-β) and parathyroid hormone (PTH) also incorporate in such phenomena.

Multiple and dispensable activities of TGF-β family incorporate monitoring of various characteristics and outcomes of cell functions, including growth, prolifiration, and dispersal, in all organisms of the human body. TGF-β plays a vital role in administrating the perpetuation of bone metabolic homeostasis [18]. TGF-β is discharged and enacted by resorbing osteoclasts and gives an anabolic effect on a bone by directly influencing the osteoblasts [3, 7]. Although TGF-β directly takes part in the emergence of osteoclasts during the latent state of osteoblasts, it hinders bone removal by diminishing the expression of RANKL on osteoblasts [23].

PTH employs typical actions on bone metabolism by triggering its receptor on target cells. Its main functioning includes calcium regulation. PTH has dual effects on bone turnover process. Constant exposure to PTH gives a negative feedback, whereas a sporadic contact to low quantity of PTH is coupled with positive effects. A number of studies

have been conducted to investigate the effect of PTH drug in dysregulated bone remodeling and showed anabolic effects on bones.

Sclerostin, encrypted by SOST gene, is an extravasated glycoprotein expressed by osteocytes [4, 28, 29]. It is a C-terminal cysteine knot-like (CTCK) domain and has resemblance to the DAN family of bone morphogenetic protein (BMP) antagonists. Animal™ models have been found potentially valuable for investigating sclerostin for the reason that they have high conservancy over vertebrates (the percentages of the sequences of amino acids measured in the mouse and rate are 88 and 89, respectively, which are quite similar to human sequences) [4]. Binding of sclerostin to its coreceptors expressed on the surface of osteoblasts constrains the Wntβ-catenin signaling [14] and, consequently, suppresses differentiation, production, and undertakings of osteoblastic cells [2]. Experimental study on SOST knockout mice showed high levels of bone mass phenotype [15], whereas the results were rather contrasting, i.e., a low-mass phenotype was observed in a transgenic mice with an overexpression of SOST gene [12]. Therefore, osteoblast movement is self-synchronized by a negative feedback setup.

Poroelasticity is the study based on the relation among deformation and fluid flow in a fluid drenched malleable medium [6]. The main activities of bone fluid include the transportation of nutrients to cells engrossed in medium and moving waste of cells away. It also provides minerals to bone tissue for relocation. A mechanosensory system of bone and bone fluid are strongly interconnected. A mechanical stress plays a vital role in supplying the bone fluid. A mechanical strain supports the bone deformation process, which in turn produces the fluid flow [20, 30]. Bone cells also get affected through such a mechanism of mechanical strain; it helps in maintaining the bone remodeling process. Many bone diseases like osteoporosis have been examined by applying a continuous mechanical stress; such a stress gave anabolic effects on bone formation, whereas catabolic affects bone resorption [8]. A disparity among RANKL/OPG signaling equipoise gives rise to several bone pathological processes, mostly associated with ageing, called osteopenia, and with more extremity, osteoporosis. Osteoporosis is a bone-related disorder regarded as skeletal infirmity with low bone mineral density (BMD), which subsequently causes recurrent microharms and impulsive cracks; it is a persistent syndrome demanding long-term cure. Middle-aged women and elderly people are the prime targets of osteoporosis, and currently its influence is intensely rising socially and economically; WHO has declared it as the second foremost healthcare issue. In a regular bone remodeling process, RANKL/OPG is prudently balanced; the rise in RANKL plays a vital part in supporting resorption via osteoclast development, activities, and persistence. As the human body gets older, the density of the osteons expands, and the cortical sponginess and architectural damages of bone also rise due to the execution of a large number of remodeling cycles. This scenario initiates a vicious cycle where microharms occur often, consequently weakening bone configuration and increasing proportion of impulsive fractures [31]. Furthermore, latest analyses on bone remodeling propose that plasma levels OPG and RANKL are contrariwise linked to BMD and take part in the growth of osteoporosis in postmenopausal women [9].

Recently, many researchers have developed several mathematical models of bone remodeling to study the deep dynamics of intracellular and intercellular mechanisms of bone. Some of the models allow just the estimation of cell population dynamics and alteration in bone density; the first attempt in this regard was by Komarova et al. [11], whereas

some of them deal with several bone diseases including the tight coupling between bone cells and their potential therapies based on their efficacy, first introduced by Lemaire et al. [13]. Komarova et al. [11] model depicts that the dynamical behavior of bone remodeling strictly depends on the regulation of bone resorbing cells by autocrine factors, and the osteoclast–osteoblast communication produces a complex nonlinear structure, which cannot be figured out from the analysis of each cell class alone. Many researchers extended the model of Komarova et al. afterward. Ayati et al. [1] developed a model to study myeloma bone disorder and demonstrated how therapeutic strategies might be examined through such computational systems. Chen-Charpentier and Diakite [5] introduced delays in the model of Komarova et al. [11] and checked the stability and bifurcation. Ryser et al. [25] developed a mathematical model based on partial differential equations with time delays to simulate the dynamics of bone multicellular units. Their system illustrates the RANKL/OPG signaling pathway along with osteoclast–osteoblast communication. Lemaire et al. [13] proposed a mathematical framework comprising of cellular control and biochemical feedbacks systems responsible for the modulation of bone remodeling. Their model also incorporates simulation of the growth of several metabolic disorders such as osteoporosis, estrogen dearth, or vitamin D deficiency and determines possible treatments based on their effectiveness. Since RANK/RANKL/OPG signaling pathway is a main signaling cascade synchronizing bone turnover, practical insinuation of particular RANKL/OPG expression profiles on bone density were profoundly investigated by Pivonka et al. [21]. They developed a model comprising of the dynamics of bone cellular units, based on the work of Lemaire et al. [13] integrating the RANK/RANKL/OPG pathway along with the modulating effect of TGF-Î^2 on bone cells. Pivonka et al. [22] for the first time introduced a PK model of drug denosumab along with a PD model of bone remodeling and analyzed the effect of denosumab on osteoporosis through this PK/PD model.

2 Mathematical models

2.1 Osteoporotic model

Here we describe a simplified version of Liò's model [16] to depict the temporal variations in osteoclasts (C) and osteoblasts (B) cell concentrations during an osteoporotic bone turnover. We make the following assumptions by taking into account the dysregulated bone remodeling process defined in the previous section.

1. The number of osteoclasts (osteoblasts) includes the populations of osteoclasts (osteoblasts) precursors and osteoclasts (osteoblasts).
2. The death rate of bone resorbing and bone-forming cells is proportional to the present populations of that particular cell.
3. As the ageing factor (a_{ageing}) plays a crucial role in the development of osteoporosis and weakens the bones by destroying the bone cells, this effect has been included in bone removal and forming bone cells.
4. No external effects have been included in the population system.

Based on these assumptions, the following model gives a more general view of temporal changes in both bone cells concentrations:

$$\begin{aligned} \frac{dC}{dt} &= a_1 g_1(C,B) - a_{\text{ageing}} b_1 C, \\ \frac{dB}{dt} &= a_2 g_2(C,B) - a_{\text{ageing}} b_2 B, \end{aligned} \tag{1}$$

Table 1 Parametric values

Parameter values		
Parameter	Description	Value
a_1	*C*-differentiation rate	3/day
a_2	*B*-differentiation rate	4/day
b_1	*C*-apoptosis rate	0.2/day
b_2	*B*-apoptosis rate	0.02/day
δ_1	paracrine effect of *C* onto *B*	0
δ_2	paracrine effect of *B* onto *C*	1
s_1	bone removal rate	0.0748/day
s_2	bone formation rate	0.0006395/day
a_{ageing}	ageing factor	2
δ_{OL}	RANKL effect	0.1
C	steady level of *C*	(Control, Osteoporosis) = (1.16, 1.78)
B	steady level of *B*	(Control, Osteoporosis) = (231.72, 177.91)
C_0	initial value of *C*	(Control, Osteoporosis) = (11.16, 11.78)
B_0	initial value of *B*	(Control, Osteoporosis) = (231.72, 177.91)
Y_0	initial value of *Y*	(Control, Osteoporosis) = (1, 1)
d_1	proportionality constant	0.00005/day

where C and B represent the populations of bone resorbing and bone forming cells, respectively, a_i; $i = 1, 2$ are the proliferation rates of osteoclasts and osteoblasts precursors, respectively, and b_i; $i = 1, 2$ are the apoptosis rates of C and B, respectively. The function $g_i(C, B)$; $i = 1, 2$ illustrates the communication between C and B depending on the autocrine and paracrine factors involved in the growth rate of both cells.

Now considering the function $g_i(C, B)$; $i = 1, 2$ in a power law approximation form provided in [16], our system (1) takes the following form:

$$\begin{aligned} \frac{dC}{dt} &= a_1 C^{\delta_{11}} B^{\delta_{21}+\delta_{OL}} - a_{\text{ageing}} b_1 C, \\ \frac{dB}{dt} &= a_2 C^{\delta_{12}} B^{\delta_{22}} - a_{\text{ageing}} b_2 B. \end{aligned} \tag{2}$$

The parametric values are listed in Table 1.

In system (2), δ_{ij}; $i, j = 1, 2$ represents the net effect of several growth factors participating in bone turnover process and producing autoregulations in osteoclasts and osteoblasts or effecting one cell type through the other. We supposed that the quantity of these growth factors depend on the donor cells population at any instant. The brief description of δ_{ij}; $i, j = 1, 2$ is as follows:

δ_{11}, net effect of osteoclasts autocrine factors,

δ_{21}, osteoblasts-released paracrine factors influencing osteoclasts,

δ_{12}, osteoclasts-released paracrine factors influencing osteoblasts,

δ_{22}, net effect of osteoblasts autocrine factors.

Due to an imbalance in bone turnover practice in an osteoporotic bone, a disruption in OPG-RANKL complex formation occurs, which influences the paracrine effect produced by osteoblasts on osteoclasts. To incorporate this aspect, a supplementary factor (δ_{OL}) has been added in the model. A change in bone density (Y) occurs as the C and B concentrations exceed their steady-state level; this aspect is described by the equation

$$\frac{dY}{dt} = -s_1 \max(C - \bar{C}, 0) + s_2 \max(B - \bar{B}, 0). \tag{3}$$

In (3), the steady-state values of C and B are represented, and s_i; $i = 1, 2$ are the normalized activities of bone resorption and formation, respectively.

A numerical evidence of system (2) along with Eq. (3) is provided in [16]. In this paper, a theoretical analysis of this system has been conducted to provide the evidence of the existence of a periodic solution. We modify system (2) by making the following assumptions:

- $C^{\delta_{11}} \propto C$ and $B^{\delta_{22}} \propto B$
- $\delta_1 = \delta_{21}$ and $\delta_2 = \delta_{12}$, where δ_i, $i = 1, 2$, represent the paracrine effects produced by RANK-RANKL-OPG signalling pathway and other factors including PTH and TGF-β. In addition, the effect of δ_1 is catabolic as it represses the concentration of osteoclasts, whereas δ_2 stimulates the production of osteoblasts and so produces an anabolic effect on osteoblasts population.

So, based on these assumptions, system (2) takes the following form:

$$\begin{aligned} \frac{dC}{dt} &= a_1 C B^{\delta_1+\delta_{OL}} - a_{\text{ageing}} b_1 C, \\ \frac{dB}{dt} &= a_2 C^{\delta_2} B - a_{\text{ageing}} b_2 B. \end{aligned} \tag{4}$$

2.2 Theoretical investigation of the model

The theoretical investigation helps to understand the model dynamics [10, 26, 27]. The schematic (Fig. 1) depicts the role of osteoclast precursors, active osteoclasts, osteoblasts, and RANK-RANKL-OPG signaling pathway during the osteoporosis. We will study the qualitative aspects of system (4) only, as Eq. (3) is decoupled from the system. Let (C_0, B_0) be the initial condition of the system. Then a unique solution of (4) exists if $\delta_1 + \delta_{OL}, \delta_2 \geq 0$ and $C_0, B_0 > 0$. It is easy to see that (4) can be written as

$$\begin{aligned} \frac{dC}{C} &= \left(a_1 B^{\delta_1+\delta_{OL}} - a_{\text{ageing}} b_1\right) dt, \\ \frac{dB}{B} &= \left(a_2 C^{\delta_2} - a_{\text{ageing}} b_2\right) dt, \end{aligned} \tag{5}$$

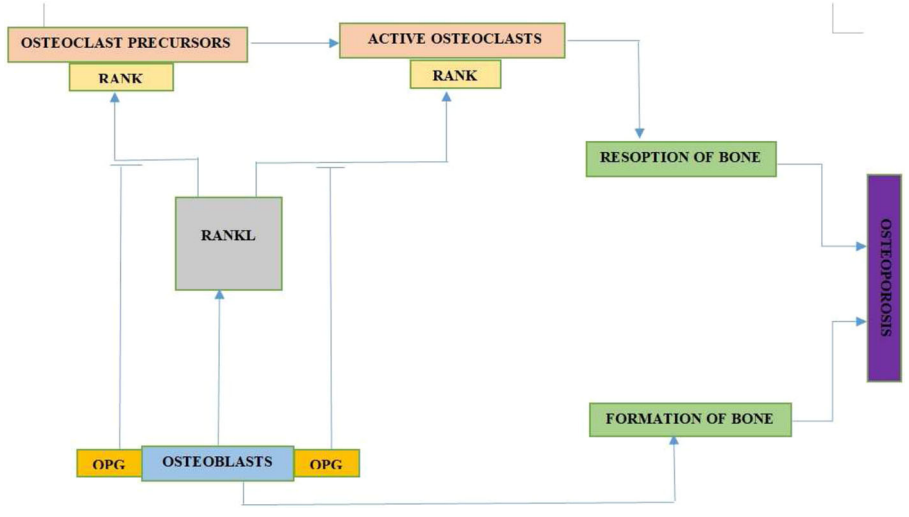

Figure 1 Graphical depiction of osteoporotic model

which gives the following solution:

$$\begin{aligned} C &= C_0 e^{\int_{t_0}^{t} a_1 B^{\delta_1+\delta_{OL}} - a_{\text{ageing}} b_1 \, dx}, \\ B &= B_0 e^{\int_{t_0}^{t} a_2 C^{\delta_2} - a_{\text{ageing}} b_2 \, dx}. \end{aligned} \tag{6}$$

By setting $\frac{dC}{dt} = \frac{dB}{dt} = 0$, following steady states have been obtained: $(0,0)$ if $\delta_1 + \delta_{OL}, \delta_2 \geq 0$ and

$$(C,B) = \left(\left(\frac{b_2 a_{\text{ageing}}}{a_2} \right)^{\frac{1}{\delta_2}}, \left(\frac{b_1 a_{\text{ageing}}}{a_1} \right)^{\frac{1}{\delta_1+\delta_{OL}}} \right), \tag{7}$$

which always exists. The jacobian of (4) around the steady state (C,B) is

$$J(C,B) = \begin{pmatrix} a_1 B^{\delta_1+\delta_{OL}} - b_1 a_{\text{ageing}} & (\delta_1 + \delta_{OL}) B^{\delta_1+\delta_{OL}-1} (a_1 C) \\ a_2 \delta_2 C^{\delta_2 - 1} B & a_2 C^{\delta_2} - b_2 a_{\text{ageing}} \end{pmatrix}. \tag{8}$$

The eigen values evaluated at the equilibrium poin (C,B) have a vanishing real part only if $(\delta_1 + \delta_{OL})\delta_2 \leq 0$, which a gives a unique positive periodic solution of (4). In the next theorem, the oscillatory behaviour of the nonlinear system (4) is shown.

Theorem 1 *A unique positive oscillatory solution of nonlinear system* (4) *exists subjected to positive initial conditions and the property* $(\delta_1 + \delta_{OL})\delta_2 \leq 0$.

Proof System (4) implies

$$\frac{a_1 B^{\delta_1+\delta_{OL}} - a_{\text{ageing}} b_1}{B} \, dB = \frac{a_2 C^{\delta_2} - a_{\text{ageing}} b_2}{C} \, dC,$$

which after integration yields

$$B^{-b_1 a_{\text{ageing}}} e^{\frac{a_1 B^{\delta_1+\delta_{OL}}}{\delta_1+\delta_{OL}}} = K C^{-b_2 a_{\text{ageing}}} e^{\frac{a_2 C^{\delta_2}}{\delta_2}},$$

where C represents the constant of integration. We define a new variable z as follows:

$$z = B^{-b_1 a_{\text{ageing}}} e^{\frac{a_1 B^{\delta_1+\delta_{OL}}}{\delta_1+\delta_{OL}}}.$$

Also, we have

$$z = K C^{-b_2 a_{\text{ageing}}} e^{\frac{a_2 C^{\delta_2}}{\delta_2}},$$

where K is the constant of integration. To investigate the behaviour of $z(C,B)$, we consider the condition $(\delta_1 + \delta_{OL})\delta_2 \leq 0$. In particular, let $\delta_1 + \delta_{OL} < 0$. This implies that, as $B \to 0$ and $B \to \infty$, we have $z \to 0$, whereas as $C \to 0$ and $C \to \infty$, we have $z \to \infty$. Now we determine the first-order derivative of z w.r.t. C:

$$\frac{dz}{dC} = K e^{\frac{a_2}{\delta_2} C^{\delta_2}} C^{-b_2 a_{\text{ageing}} - 1} \left(-b_2 a_{\text{ageing}} + a_2 C^{\delta_2} \right).$$

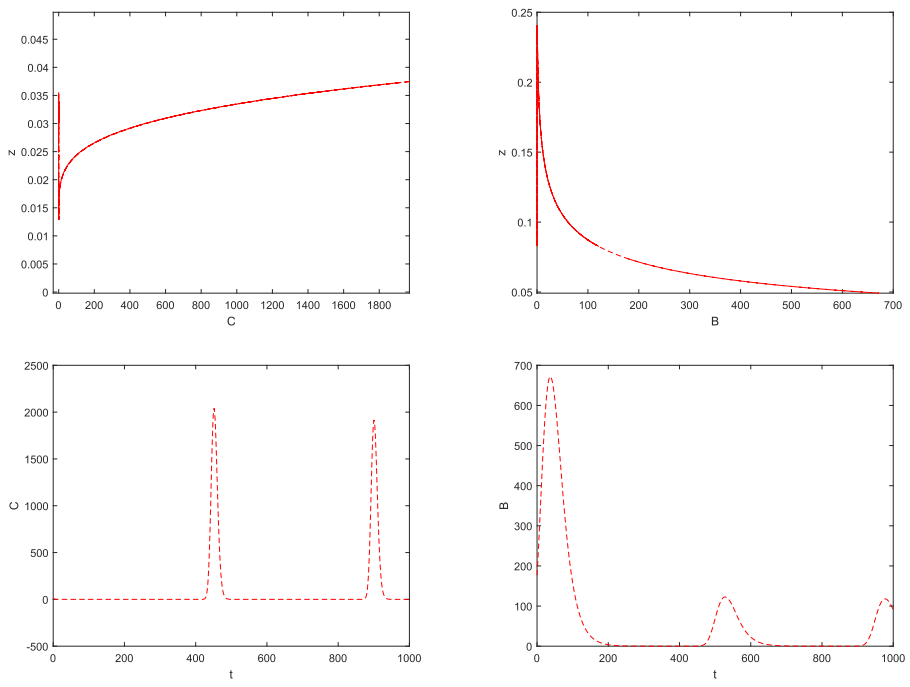

Figure 2 Change in z relative to change in osteoclast and osteoblast density

A similar argument is obtained for $\frac{dz}{dB}$. It is clear that $\frac{dz}{dC} = \frac{dz}{dB} = 0$ at the equilibrium point (C, B) is given in (7). The behavior of the function z is depicted in Fig. 2. It is easy to see that, as $z \to 0$, B exists, but C vanishes. As B increases, it intersects just one value of C. A further increment in the value of B gives intersection with two values of C. We have a similar scenario for C over B. It gives a closed curve in CB-phase plane where $B = B(C)$. Hence the solution of (4) is oscillatory and positive. □

2.3 External agents influencing the osteoporotic bone turnover

In (5), system (4) has been modified by including an external effect, produced by osteocytes, as a consequence of a mechanical strain applied. Such an effect has been depicted in the form of a function $\gamma(t)$ that counts the RANKL produced by osteocytes along with its regulation by Sclerostin inhibition. So system (4) takes the following form:

$$\begin{aligned} \frac{dC}{dt} &= B^{\delta_{21}+\delta_{OL}}\left(a_1 C + d_1 \frac{\gamma(t)}{C}\right) - a_{\text{ageing}} b_1 C, \\ \frac{dB}{dt} &= a_2 C^{\delta_{12}} B - a_{\text{ageing}} b_2 B; \end{aligned} \tag{9}$$

where d_1 represents the proportionality constant. At present, no precise functional form of $\gamma(t)$ is constructed, so we assume a consistent input of osteoclasts and investigate the stability of the following system:

$$\begin{aligned} \frac{dC}{dt} &= B^{\delta_{21}+\delta_{OL}}\left(a_1 C + \frac{d_1}{C}\right) - a_{\text{ageing}} b_1 C, \\ \frac{dB}{dt} &= a_2 C^{\delta_{12}} B - a_{\text{ageing}} b_2 B. \end{aligned} \tag{10}$$

2.3.1 Stability analysis of the model

Assume (C_0, B_0) to be the initial conditions of system (6); $C_0, B_0 \geq 0$, for $(\delta_1 + \delta_{OL})\delta_2 < 0$, the system has a unique positive solution. The first equation of system (6) takes the following form:

$$\frac{dC}{dt} = C\left(a_1 B^{\delta_1+\delta_{OL}} - a_{\text{ageing}} b_1 + d_1 \frac{B^{\delta_1}}{C^2}\right) \Rightarrow \frac{dC}{dt} > C\left(a_1 B^{\delta_1+\delta_{OL}} - a_{\text{ageing}} b_1\right),$$

which gives

$$C > C_0 e^{\left(\int_{t_0}^{t} a_1 B^{\delta_1+\delta_{OL}} - a_{\text{ageing}} b_1 dx\right)}.$$

The second equation of system (6) implies

$$B = B_0 e^{\left(\int_{t_0}^{t} a_2 C^{\delta_2} - a_{\text{ageing}} b_2 dx\right)}.$$

The following unique steady state has been obtained by setting $\frac{dC}{dt} = \frac{dB}{dt} = 0$.

$$(C, B) = \left(\left(\frac{b_2}{a_2}\right)^{\frac{1}{\delta_2}}, \left(\frac{b_1 C^2}{a_1 C^2 + d_1}\right)^{\frac{1}{\delta_1+\delta_{OL}}}\right).$$

The jacobian matrix of (6) is computed as follows:

$$J(C, B) = \begin{pmatrix} a_1 B^{\delta_1+\delta_{OL}} - b_1 a_{\text{ageing}} - d_1 \frac{B^{\delta_1+\delta_{OL}}}{C^2} & (\delta_1 + \delta_{OL}) B^{\delta_1+\delta_{OL}-1}(a_1 C + \frac{d_1}{C}) \\ a_2 \delta_2 C^{\delta_2-1} B & a_2 C^{\delta_2} - b_2 \end{pmatrix}. \tag{11}$$

$\text{tr}(J(C, B) = 0)$ and $\text{Det}(J(C, B) > 0)$ at the nontrivial steady-state value (C, B); $(\delta_1 + \delta_{OL})\delta_2 \leq 0$. So, dynamically, we have a probable fulcrum for the system. Dulac's criterian has been implemented to show the nonexistence of the oscillatory solutions for system (6).

Theorem *The nonlinear system* (6) *with the initial condition* (C_0, B_0), *provided that* $C, B > 0$ *and* $(\delta_1 + \delta_{OL})\delta_2 \geq 0$, *exhibits a positive solution, which shows affinity toward the stable equilibrium solution* (C, B).

Proof We consider the domain $\Gamma = R^+ \times R^+$, a simply connected region of the 2D-plane, and the function $f(C, B) = \frac{1}{CB}$ is continuously differentiable on Γ. Assume that $h(C, B) = B^{\delta_1+\delta_{OL}}(a_1 C + \frac{d_1}{C}) - a_{\text{ageing}} b_1 C$ and $k(C, B) = a_2 C^{\delta_2} B - a_{\text{ageing}} b_2 B$, it is easy to see that the functions $h(C, B)$ and $k(C, B)$ are equal to the right-hand side of system (6). Then

$$f(C, B)h(C, B) = \frac{(a_1 B^{\delta_1+\delta_{OL}-1} - a_{\text{ageing}} b_1)}{B} + d_1 \frac{B^{\delta_1+\delta_{OL}-1}}{C_1^2}.$$

$$f(C, B)k(C, B) = \left(\frac{a_2 C^{\delta_2} - a_{\text{ageing}} b_2}{C}\right).$$

As

$$\frac{\partial(fh)}{\partial C} + \frac{\partial(fk)}{\partial B} = -2d_1 \frac{B^{\delta_1+\delta_{OL}} - 1}{C^3}$$

is not equal to zero and does not switch sign in the region Γ, this implies the nonexistence of closed orbits in Γ. □

3 Numerical simulations

The inspiration behind this scheme is that we can now solve the normalized boundary value problem, although nonlinear, quite easily, using both analytic and numerical schemes. The most widely employed numerical method for the boundary value problems is the collocation method. The advantage of this method is that it reduces the nth-order differential equation(s) into n first-order differential equations, thus reducing the computational cost on a large domain with small step size and a range of parameters. We have simplified the three systems using the generalized collocation method (GCM). Collocation methods are basically implicit Runge–Kutta quadrature techniques.

Figures 2, 3 and 4 presents the total bone mass and change in osteoblast relative to change in osteoclast for osteoporotic bone model (Eq. (2)) and for a model where the external agents (Eq. (6)) were taken into account. From Fig. 4 it is evident that the external agents influence the osteoclast and osteoblast activity and hence the osteoporotic bone mass. The external agent was incorporated into the model when the total bone mass was 6% lower than the actual bone mass (steady state) due to osteoporosis. From our numerical

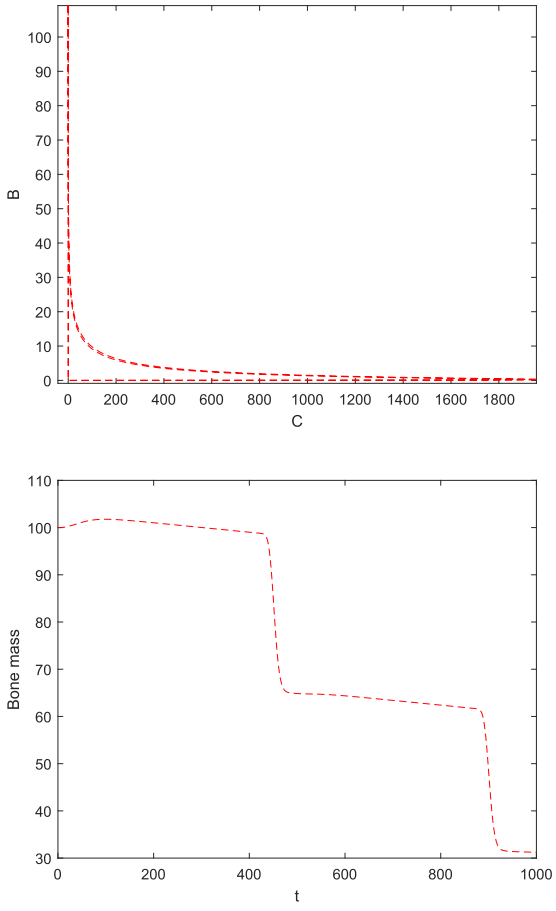

Figure 3 Phase space portrait and total bone mass

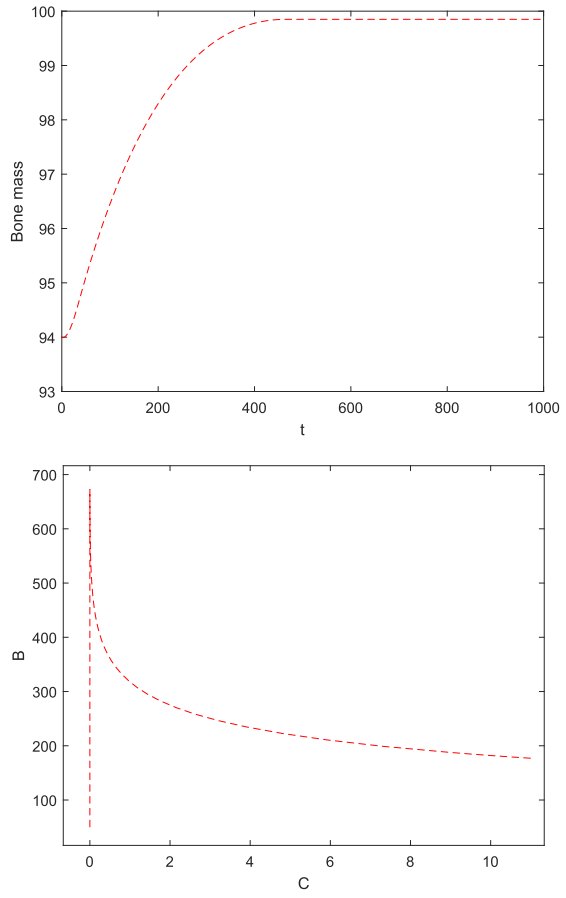

Figure 4 Application of external agents and corresponding phase space portrait and total bone mass

results (as shown from the inclination in total bone mass) we can depict that the external agent can be prescribed as an efficient therapeutic agent.

3.1 Conclusions and future work

In this paper, complex dynamics of bone diseases are studied with the aid of numerical experiments. The stability analysis is of great significance in the field of computational biology. It helps to validate the parametric values, the correct selection of thresholds values, which are useful during diseases diagnosis and therapeutics. In this paper, we have considered these factors with the aid of an extended model, where the external agent and its role as a therapeutic strategy are examined. In our future work, we aim to extend this study by interfacing it with clinical trials.

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Availability of data and materials
This paper contains no any studies with human participants or animals performed by any of the authors. All the data related to the current study were provided along with this paper.

Competing interests
The authors declare that there is no conflict of interests.

Authors' contributions
SJ conceived the paper and prepared materials and methods. MY did the analytic analysis. YB did numerical computations. AS did results and discussion. AbS did the literature review. All authors equally contributed in the final version of the manuscript. All authors read and approved the final manuscript.

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