ORIGINAL ARTICLE

Optimizing the dynamics of bone turnover with genetic algorithm

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Abstract

Control systems and the modeling strategies are not only limited to engineering problems. These approaches can be used in the field of bio-mathematics as well and modern studies have promoted this approach to a great extent. The computational modeling and simulation of bone metastasis is painful yet critical after cancer invades the body. This vicious cycle is complex, and several research centers worldwide are devoted to understanding the dynamics and setting up a treatment strategy for this life-threatening behavior of cancer. Cancerous cells activation and the corresponding process of metastasis is reported to boost during the periodic waves of COVID-19, due to the inflammatory nature of the infection associated with SARS-2 and its variants. The bone cells are comprised of two types of cells responsible for bone formation and resorption. The computational framework of such cells, in spatial form, can help the researchers forecast the bone dynamics in a robust manner where the impact of cancer is incorporated into the computational model as a source of perturbation. A series of computational models are presented to explore the complex behavior of bone metastasis with COVID-19 induced infection. The finite difference algorithm is used to simulate the nonlinear computational model. The results obtained are in close agreement with the experimental findings. The computational results can help explore the vicious cycle's fate and help set up control strategies through drug therapies.

Keywords Drug design · Covid-19 · "Para-thyroid hormone" (parathyroid) · Bone remodeling · Bone metastases · chaos.

Introduction

Bone is a well-structured tissue. Along with preserving its structural integrity, the skeleton must fulfill the body's total calcium needs via extracellular fluid. The bone remodeling process must be retained to maintain appropriate bone and calcium homeostasis functions. "Osteoclasts" are bone-resorbing cells that participate in the process of bone remodeling, while "osteoblasts" are bone-forming cells (Lerner et al. 2019). The process starts with the development of active "Osteoclasts" on a previously dormant bone surface, followed by the excavation of a lacuna. After that, "osteoblasts" replace the resorption cavity and become inactive. Abnormal bone remodeling may result in life-threatening conditions such as osteoporosis. A basic understanding of

"osteoblasts" and "Osteoclasts" and the associated hormones such as parathyroid hormone ("Para-thyroid hormone") and calcitonin (CT) is essential for a complete understanding of bone remodeling.

In bone, the "Para-thyroid hormone"-related protein ("Para-thyroid hormone"rP) receptor (PPR) is expressed by "osteoblast" cells. "Para-thyroid hormone" has a number of effects on these bone-forming cells, including modulating cell proliferation and death rates and modifying the expression patterns of several transcription factors, cytokines, and bone matrix factors. These effects may result in an increase in bone formation. On the other hand, "Para-thyroid hormone" stimulates osteoclastic cells to enhance bone resorption activity, which is regarded as the primary mechanism by which "Para-thyroid hormone" releases calcium from bone. "Osteoclasts" do not produce the PPR but react to the hormone through osteoclastogenic factors released by "Parathyroid hormone"-stimulated "osteoblasts", such as RANK-ligand. "Para-thyroid hormone" is critical in the continual process of bone remodeling since it influences both "osteoblasts" (directly) and "Osteoclasts" (indirectly) (indirectly). Intermittent "Para-thyroid hormone" administration leads

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to net bone growth, while continuous "Para-thyroid hormone" administration (infusion) results in net bone resorption (Kroll 2000). The processes regulating "Para-thyroid hormone"'s anabolic and catabolic effects on bone are complicated and not completely understood. In major clinical research, daily "Para-thyroid hormone" (1–34) administration to bone remodeling disorder patients was demonstrated to dramatically lower the incidence of bone fracture, which is consistent with intermittent "Para-thyroid hormone"'s anabolic action on bone. As a result, the peptide is being utilized to treat this prevalent condition (Tian et al. 1993).

Calcitonin, a 32-aa peptide hormone secreted by thyroid parafollicular cells in response to increased serum calcium, induces a rapid decrease in blood calcium levels, mostly by controlling bone resorption. When calcitonin binds to its receptors on "Osteoclasts", an immediate chain reaction starts, resulting in the removal of a ruffled border, cell retraction, and suppression of cell motility and bone resorption. Calcitonin has been demonstrated to lower the quantity of calcium in the blood pharmaco-logically, but its physiological impact is uncertain. Previous studies revealed that patients with high endogenous calcitonin levels (e.g., those with medullary thyroid carcinoma) or undetectable circulating calcitonin did not influence bone mineral density or calcium metabolism (e.g., those who had undergone thyroidectomy) (Hurley et al. 1987; Wüster et al. 1992). Calcitonin has been hypothesized to have no physiological function in mammals owing to its fluctuating serum levels with no clinical effects. This theory is not widely accepted, and the current consensus is that calcitonin plays a critical role in maintaining the skeleton under calcium stress. Additional research indicates that calcitonin may inhibit bone formation rather than accomplish its pharmacological goal of lowering bone resorption (Davey and Findlay 2013; Naot et al. 2019). These results are consistent with findings from experiments with genetically modified animals.

Tumors may metastasize to other organs, with bone being a common site of metastasis. A hypothesis known as the Paget's-"seed &-soil" hypothesis, the tumour infected cells proliferate by interacting with secondary site cells (Liu et al. 2017). By interfering the regular system, tumor cells interact with cells of bone marrow, to enhance the growth rates. The pelvis, axial skeleton, and bones with abundant bone marrow are often used as metastatic sites for cancer. Bone resorption is characteristic of osteolytic bone metastases, while unstructured bone growth is characteristic of osteoblastic bone metastases. There is resorption and formation of bone, but they are out of balance. Breast and prostate cancers spread/metastasize to the bones. There are different types of cancers, these are divided into two branches, based on their linkage with bone metastasis, the osteolytic cancers for example the breast cancer and the osteobastic cancer, such as the prostate cancer.

Metastatic cells promote bone resorption through two types of mechanisms, one of which depends on RANKL and the other is independent of RANKL. Transforming growth factor-β is released from the bone matrix during resorption, triggering the production of "Para-thyroid hormone"rP by metastatic cells. "Para-thyroid hormone"rP binds to "Para-thyroid hormone" receptors on osteoblastic cells, boosting the release of RANKL and subsequent activation of "Osteoclasts", hence accelerating bone resorption (Guise and Chirgwin 2003). Osteoclast activity in the bone, in turn, produces Transforming growth factor-β, producing a vicious cycle.

Bone metastases are treated with systemic and anti-resorptive therapy for the original malignancy. These medicines inhibit a variety of bone resorption mechanisms and are often used in anti-resorptive therapy. The bone matrix generates/releases the Bisphosphonates, while the bone resorbs and are incorporated into the bone matrix. The synthesis of bisphosphonates, which induce osteoclast death, facilitates apoptosis and inhibits bone resorption. Denosumab is another completely human monoclonal antibody that specifically recognizes and binds to RANKL, hence increasing the OPG/RANKL ratio. Both chemotherapy and hormone treatment stratigies are the topics of debate for the cancer treatment studies these days.

Metastasis may disturb the normal bone remodeling process by increasing bone metabolism. A complete bone metastasis process is decribed in Fig. 1. According to preclinical studies, increasing osteoclast-mediated bone resorption is a critical first step in establishing bone metastases. Numerous disorders, including skeletal malignancies (e.g., bone metastases or multiple myeloma), estrogen deficiency, and the use of glucocorticoids, T-cell activation (as in rheumatoid arthritis), may disrupt the OPG-RANKL-RANK signal transduction pathway, resulting in increased osteoclast formation and bone loss.

SARS-2 is one of the few deadly viruses that have caused severe number of deaths during the time frame of few months. Over the past few years, the virus has emerged in the form of different variants, with different physio-chemical properties, and different cycle duration. These properties vary in some cases, such as variable number of deaths were reported from different parts of the world, under different environmental factors. Similarly, different types of cytokines are reported to be activated during different data based and numerical studies.

Cancer is another leading disease, that has influenced the economy worldwide due to its hallmarks. During this research, an important aspect of the triggering of cancer-bone-metastasis during and after the onset of SARS-2 infection, due to the activation of dormant cancer cells is studied in detail. In the literature, limited information is available to explore this complex phenomena since several key players are involved in the dynamics

Fig. 1 Schematic
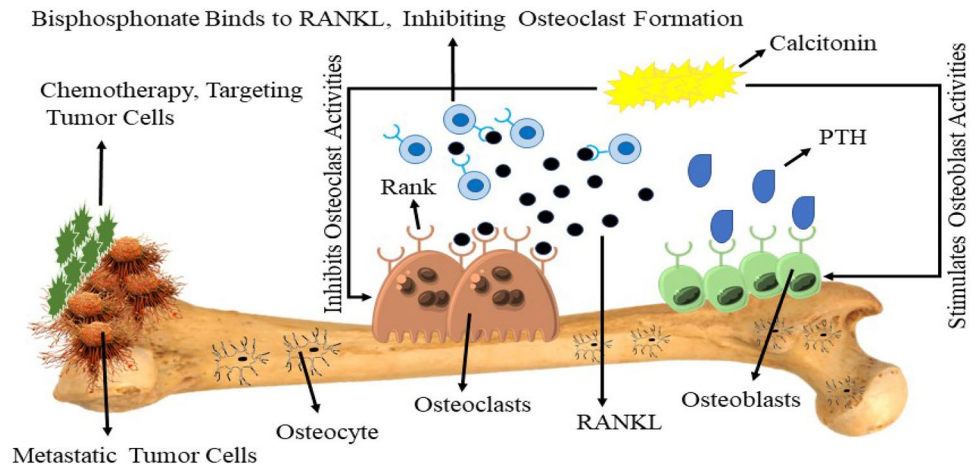
of these diseases i.e. key players of cancer (proteins, ligands, receptors and cytokines), bone metastasis and bone micro-environment, SARS-2 virus, the associated cytokines and the corresponding cytokines storm and the associated viral and bacterial infections. A general overview is that the number of cases of cancer-bone-metastasis increased during the period of COVID-19, and thus there was a strong correlation between the number of such cases and their COVID-19 history (Francescangeli et al. 2020; Bora and Patel 2021).

In the field of computational biology, the clinical data sets can be analyzed for the optimization of the mathematical model parameters, of the specific problem. Exploration and Exploitation are the fundamental components of a meta heuristic algorithm, that can be used for the parameter(s) optimization. A good balance of these aspects is essential to handle the real life problems effectively. In this paper, Swarm intelligence algorithms, a class of meta heuristics algorithms will be used to summarize the medical data sets. Medical data sets often include large feature sets with numerous features that are correlated with each other, hence it is critical to minimize the feature set. Metastatic bone remodeling is a critical process and data based studies, if optimized carefully, can provide useful insight for forecasting and treatment intervention.

During this research, step by step mathematical models are provided to understand the cell-cell and the cell-protein interactions. The nonlinear dynamics of these interactions are purturbed during the course of COVID-19 infection, as discussed above. These mathematical models, when solved numerically using the smart programming tools, provided state of the art results. In the next section, the mathematical models are discussed in detail. Next, the numerical results are provided and noteworthy conclusions are drawn.

Mathematical formulation

In the past, bone remodeling processes were theoretically and computationally simulated. Biochemical interactions between cancer cells and the bone cells and the microenvironment were analyzed and simulated using ordinary differential equations (ODEs). Researchers. (Komarova et al. 2003) presented a model for bone remodeling. In this model, the interaction between "Osteoclasts" and "osteoblasts" was specified by an S-system (Savageau 1988) in which the exponents implicitly reflect biological autocrine (A-C) and paracrine (P-C) components. The interaction of bone-forming "osteoblasts" and bone-decomposing "Osteoclasts" over time is responsible for the temporal evolution of the bone mass. Depending on the initial conditions, the model may mimic a single remodeling cycle or periodic behavior in nature (and there is an indirect relation with the other infections such as SARS-2). This is accomplished by modifying the (P-C) and A-C signaling parameters in response to a variation from the steady-state under the initial conditions. However, this behavior is of limited effectiveness since there is no proof that bone remodeling constantly happens at a specific site.

Ayati et al. (2010) extended Komarova's model (Komarova et al. 2003) to account for multiple myeloma's impact on bone dynamics. In accordance with the Gompertz law, tumor growth affects A-C and (P-C) parameters, altering the periodic remodeling cycle and resulting in a loss of bone mass. However, since this model analyzes myeloma formation in isolation from the bone marrow microenvironment, it is unable to account for myeloma growth's reliance on the bone remodeling system. Although therapy is suggested as a series of step functions that control tumor development and "osteoblast"apoptosis and are able to remove the tumor and restoring bone mass,

it does not take pharmaco-kinetics and pharmaco-dynamics into consideration. Researchers (Komarova 2005) applies the single remodeling cycle behavior evaluated in Komarova's model (Komarova et al. 2003) to explore the anabolic and catabolic effects of external "Para-thyroid hormone" administration on bone remodeling in order to assess the catabolic and anabolic effects of "Para-thyroid hormone" on bone formation. Using the model developed by Researchers. Komarova et al. (2003), Ryser et al. (2009) explicitly integrate concentrations of the OPG and RANKLS and their effects on the system, as well as the spatial growth of a single BMU. Ryser et al. (2010) estimated the parameters of this model and conducted a sensitivity analysis. Furthermore, Ryser et al. developed Ryser et al. (2012) the model by taking into account the impact of the bone disorders, on bone remodeling and investigating the uncertain role of OPG in the system.

Zero-dimensional bone model

The model shown in Komarova (2005) simulates the remodeling of bone in a single discrete site. The model uses ordinary differential equations to explain the populations of bone cells contained in a bone marrow unit (BMU). The bone cells are "Osteoclasts" (responsible for the breakdown of existing bone) and "osteoblasts" (responsible for forming new bone). The model's variables at each instant of time t are the number of "Osteoclasts" $X_1(t)$ and the number of "osteoblasts" $X_2(t)$. The model's equations are

$$\frac{dX_1}{dt} = \alpha_1 X_1^{\gamma_{11}} X_2^{\gamma_{21}} - \alpha_2 X_1, \tag{1}$$

$$\frac{dX_2}{dt} = \alpha_3 X_1^{\gamma_{12}} X_2^{\gamma_{22}} - \alpha_4 X_2, \tag{2}$$

where $\alpha_i (i = 1, 2, 3, 4.)$ are positive parameters. The parameters γ_{ij} represent the combined efficacy of A-C and (P-C) processes. Different measures, such as the number of effectors generated by each donor cell and the receptivity of the target cells, are used to assess this efficiency. The fluctuation in bone mass is subjected to the third equation of the model (Komarova 2005). In steady-state contexts, it was assumed that "Osteoclasts" and "osteoblasts" were composed of less differentiated cells that could not resorb or produce bone but were releasing A-C and (P-C) signaling. Increases in cell counts beyond steady-state levels were associated with precursor cell proliferation and differentiation into mature cells that can function the resorbtion or forming of bone. The third equation of the model, where $X_3(t)$ denotes bone mass, is given by

$$\frac{dX_3}{dt} = -\alpha_5 \max[0, X_1 - \bar{X}_1] + \alpha_6 \max[0, X_2 - \bar{X}_2], \tag{3}$$

where α_5 and α_6 are positive parameters. Consequently, depending on the values of these parameters, the normal bone mass would vary at a frequency observed by experimental procedures with an amplitude equivalent to that of osteoclast and "osteoblast" populations. The model has two steady states given by

$$\bar{X}_1 = \left(\frac{\alpha_2}{\alpha_1}\right)^{\frac{1-\gamma_{22}}{\Gamma}} \left(\frac{\alpha_4}{\alpha_3}\right)^{\frac{\gamma_{21}}{\Gamma}},$$

$$\bar{X}_2 = \left(\frac{\alpha_2}{\alpha_1}\right)^{\frac{\gamma_{12}}{\Gamma}} \left(\frac{\alpha_4}{\alpha_3}\right)^{\frac{1-\gamma_{11}}{\Gamma}},$$

where

$$\Gamma = \gamma_{12}\gamma_{21} - (1 - \gamma_{11})(1 - \gamma_{22}).$$

The model has periodic solution if

$$\Gamma_1 = \alpha_2(\gamma_{11} - 1) + \alpha_2(\gamma_{22} - 1) = 0.$$

While Γ_1 greater than 0 results in unstable oscillations that diverge from the nontrivial steady states, Γ_1 less than 0 results in damped oscillations that converge to steady states.

Zero-dimensional bone metastasis model

Ayati et al. (2010) investigated how tumor development affects bone remodeling and how the tumor influences A-C and (P-C) signaling in the osteoclast and "osteoblast" cell populations. The Ayati's model is given by

$$\frac{dX_1}{dt} = \alpha_1 X_1^{\gamma_{11} + K_{11}\left(\frac{X_4}{K_T}\right)} X_2^{\gamma_{21}} - \alpha_2 X_1, \tag{4}$$

$$\frac{dX_2}{dt} = \alpha_3 X_1^{\gamma_{12}} X_2^{\gamma_{22} + K_{22}\left(\frac{X_4}{K_T}\right)} - \alpha_4 X_2, \tag{5}$$

$$\frac{dX_3}{dt} = -\alpha_5 \max[0, X_1 - \bar{X}_1] + \alpha_6 \max[0, X_2 - \bar{X}_2], \tag{6}$$

$$\frac{dX_4}{dt} = \alpha_7 X_4 \log\left(\frac{K_T}{X_4}\right), \tag{7}$$

where α_7 is growth rate of tumor and K_T is maximum carrying capacity of tumor cells.

Zero-dimensional hybrid bone model with dynamics of "Para-thyroid hormone" and CT

The two main hormones that control bone resorption and growth are "Para-thyroid hormone" and CT. In response to insufficient calcium levels in the blood, the parathyroid glands release "Para-thyroid hormone". It increases the total calcium concentration in the blood via a number of direct and indirect actions on the bone, kidney, and intestinal system. Due to the absence of "Para-thyroid hormone" receptors on "Osteoclasts", "Para-thyroid hormone" promotes bone resorption by activating "osteoblasts". The growth and activity of "osteoblasts" are stimulated and inhibited by the dual-action hormone "Para-thyroid hormone". "Para-thyroid hormone" suppresses the "osteoblasts'" "Para-thyroid hormone" receptors, preventing the differentiation of mesenchymal stem cells into pre"osteoblasts" and hence the synthesis of mature "osteoblasts". The synthesis of CT by parafollicular thyroid cells, which inhibits bone resorption, serves to counteract the stimulation of bone resorption by "Para-thyroid hormone". CT accomplishes this by affecting "Osteoclasts", which reduces blood calcium levels. Due to the influential roles of "Para-thyroid hormone" and CT in the bone metastasis cycle, we decided to update Ayati's model (Ayati et al. 2010) by adding the dynamics of "Para-thyroid hormone" and CT. The novel proposed model is given by

$$\frac{dX_1}{dt} = \alpha_1 X_1^{\gamma_{11} + K_{11}\left(\frac{X_4}{K_T}\right)} X_2^{\gamma_{21}} + \beta_1\left(\frac{X_5}{\beta_2 + X_5^2}\right)$$
$$\left(\frac{1}{\beta_3 + X_6}\right) X_1 X_2 - \alpha_2 X_1, \tag{8}$$

$$\frac{dX_2}{dt} = \alpha_3 X_1^{\gamma_{12}} X_2^{\gamma_{22} + K_{22}\left(\frac{X_4}{K_T}\right)} + \beta_4\left(\frac{X_5}{\beta_5 + X_5}\right)$$
$$- \beta_6\left(\frac{X_2 X_5}{\beta_7 + X_5}\right) - \alpha_4 X_2, \tag{9}$$

$$\frac{dX_3}{dt} = -\alpha_5 \max[0, X_1 - \bar{X}_1] + \alpha_6 \max[0, X_2 - \bar{X}_2], \tag{10}$$

$$\frac{dX_4}{dt} = \alpha_7 X_4 \log\left(\frac{K_T}{X_4}\right) \tag{11}$$

$$\frac{dX_5}{dt} = \alpha_8\left(\frac{1}{\alpha_9 + X_1}\right) - \alpha_{10} X_5, \tag{12}$$

$$\frac{dX_6}{dt} = \alpha_{11}\left(\frac{X_1}{\alpha_{12} + X_5}\right) - \alpha_{13} X_6, \tag{13}$$

where $\beta_m (m = 1, 2, 3, \ldots, 7)$ and $\alpha_n (n = 8, 9, 10, \ldots, 13)$ are positive parameters. The blood concentration of "Para-thyroid hormone" is modeled in Eq. 18. The term $\alpha_8\left(\frac{1}{\alpha_9 + X_1}\right)$ shows the production of "Para-thyroid hormone" from the parathyroid glands, which is slowed down by elevated calcium levels and active "Osteoclasts" (Goltzman 2018), while $\alpha_{10} X_5$ is the natural degradation of "Para-thyroid hormone". Similarly, the blood concentration of CT is modeled in Eq. 19. According to Kübler et al. (1987), the production of CT from the thyroid gland is stimulated by an increase in the number of active "Osteoclasts", while an increase in the amount of parathyroid hormone ("Para-thyroid hormone") decreases the secretion of CT. This process is modeled by the term $\alpha_{11}\left(\frac{X_1}{\alpha_{12} + X_5}\right)$ and natural degradation of CT is modeled by $\alpha_{13} X_6$. The term $\beta_1\left(\frac{X_5}{\beta_2 + X_5^2}\right)\left(\frac{1}{\beta_3 + X_6}\right) X_1 X_2$ in Eq. 14 simulates the boosting effects of "Para-thyroid hormone" and the inhibiting effect of CT on active osteoclast production, which requires cell-to-cell interaction between "Osteoclasts" and "osteoblasts", as reported in Kroll (2000). The terms $\beta_4\left(\frac{X_5}{\beta_5 + X_5}\right)$ and $\beta_6\left(\frac{X_2 X_5}{\beta_7 + X_5}\right)$ in Eq. 15 are used to model "Para-thyroid hormone"'s stimulating and inhibitory effects on the production and differentiation of active "osteoblasts", respectively, as reported in Kroll (2000).

One-dimensional hybrid bone model with dynamics of "Para-thyroid hormone" and CT

We extended the concept of bone mass to include an implicit spatial dimension, such as the trabecular mass under a site on the bone surface. Therefore, we developed a diffusion model in a spatial domain, D, to integrate more aspects of spatial variability.

$$\frac{\partial}{\partial t} X_1(t, x) = \sigma_1 \frac{\partial^2}{\partial x^2} X_1(t, x) + \alpha_1 X_1^{\gamma_{11} + K_{11}\left(\frac{X_4}{K_T}\right)}$$
$$X_2^{\gamma_{21}} + \beta_1\left(\frac{X_5}{\beta_2 + X_5^2}\right)\left(\frac{1}{\beta_3 + X_6}\right) X_1 X_2 - \alpha_2 X_1, \tag{14}$$

$$\frac{\partial}{\partial t} X_2(t, x) = \sigma_2 \frac{\partial^2}{\partial x^2} X_2(t, x) + \alpha_3 X_1^{\gamma_{12}} X_2^{\gamma_{22} + K_{22}\left(\frac{X_4}{K_T}\right)}$$
$$+ \beta_4\left(\frac{X_5}{\beta_5 + X_5}\right) - \beta_6\left(\frac{X_2 X_5}{\beta_7 + X_5}\right) - \alpha_4 X_2, \tag{15}$$

$$\frac{\partial}{\partial t} X_3(t, x) = \sigma_3 \frac{\partial^2}{\partial x^2} X_3(t, x)$$
$$- \alpha_5 \max[0, X_1 - \bar{X}_1] + \alpha_6 \max[0, X_2 - \bar{X}_2], \tag{16}$$

$$\frac{\partial}{\partial t}X_4(t,x) = \sigma_4 \frac{\partial^2}{\partial x^2}X_4(t,x) + \alpha_7 X_4 \log\left(\frac{K_T}{X_4}\right) \qquad (17)$$

$$\frac{\partial}{\partial t}X_5(t,x) = \sigma_5 \frac{\partial^2}{\partial x^2}X_5(t,x) + \alpha_8\left(\frac{1}{\alpha_9 + X_1}\right) - \alpha_{10}X_5, \qquad (18)$$

$$\frac{\partial}{\partial t}X_6(t,x) = \sigma_6 \frac{\partial^2}{\partial x^2}X_6(t,x) + \alpha_{11}\left(\frac{X_1}{\alpha_{12} + X_5}\right) - \alpha_{13}X_6, \qquad (19)$$

where $\sigma_k \frac{\partial^2}{\partial x^2}X_k(t,x)$ $(k = 1,2,3,\ldots,6)$ are diffusion terms with diffusion parameters σ_k. The dependent variables $X_k(t,x)$ $(k = 1,2,3,\ldots,6)$ represent density of "Osteoclasts", "osteoblasts", bone mass, tumor cells, "Para-thyroid hormone", and CT, respectively, at time t with respect to spatial variable x. The initial and boundary conditions of above model are given by

$$X_1(0,x) = X_1^0, \frac{\partial}{\partial x}X_1(t,0) = 0, \frac{\partial}{\partial x}X_1(t,1) = 0,$$

$$X_2(0,x) = X_2^0, \frac{\partial}{\partial x}X_2(t,0) = 0, \frac{\partial}{\partial x}X_2(t,1) = 0,$$

$$X_1(0,x) = X_3^0, \frac{\partial}{\partial x}X_3(t,0) = 0, \frac{\partial}{\partial x}X_3(t,1) = 0,$$

$$X_1(0,x) = X_4^0, \frac{\partial}{\partial x}X_4(t,0) = 0, \frac{\partial}{\partial x}X_4(t,1) = 0,$$

$$X_1(0,x) = X_5^0, \frac{\partial}{\partial x}X_5(t,0) = 0, \frac{\partial}{\partial x}X_5(t,1) = 0,$$

$$X_1(0,x) = X_6^0, \frac{\partial}{\partial x}X_6(t,0) = 0, \frac{\partial}{\partial x}X_6(t,1) = 0.$$

Treatment model

The effects of bisphosphonates, $d_1(t)$, intermittent "Para-thyroid hormone" input, $I_1(t)$ and anticancer treatment, $d_3(t)$, are incorporated into the treatment model and operate on the relevant pathways. The updated model with treatment terms is given by

$$\frac{\partial}{\partial t}X_1(t,x) = \sigma_1 \frac{\partial^2}{\partial x^2}X_1(t,x) + \alpha_1 X_1^{\gamma_{11}+K_{11}\left(\frac{X_4}{K_T}\right)}$$

$$X_2^{\gamma_{21}} + \beta_1\left(\frac{X_5}{\beta_2 + X_5^2}\right)\left(\frac{1}{\beta_3 + X_6}\right) \qquad (20)$$

$$X_1 X_2 - (\alpha_2 + \alpha_{d_1}d_1(t))X_1,$$

$$\frac{\partial}{\partial t}X_4(t,x) = \sigma_4 \frac{\partial^2}{\partial x^2}X_4(t,x) + \alpha_7 X_4 \log\left(\frac{K_T}{X_4}\right) - \alpha_{d_2}d_2(t)X_4 \qquad (21)$$

$$\frac{\partial}{\partial t}X_5(t,x) = \sigma_5 \frac{\partial^2}{\partial x^2}X_5(t,x) + \alpha_8\left(\frac{1}{\alpha_9 + X_1}\right) - \alpha_{10}X_5 + I_1(t). \qquad (22)$$

Osteoclasts produce and absorb bisphosphonates when they resorb bone, inhibiting bone resorption and increasing the cell death. In the treatment model, bisphosphonates are exclusively considered to increase osteoclast apoptosis by adding the term $\alpha_{d_1}d_1(t)$ to α_2. Cancer cells are targeted explicitly by anti-cancer treatment, which then works to induce apoptosis in those cells. In treating bone metastases, it is feasible to use a combination or single-agent chemotherapy. In analyzing the impact of anti-cancer treatment $d_2(2)$ on the tumor's mortality, the term $\alpha_{d_2}d_2(t)X_4$ is included in the equation of tumor growth. Constants α_{d_1} and α_{d_2} represent maximum effect of bisphosphonates and anti-cancer therapy. Paradoxically, continuous administration of the "Para-thyroid hormone" results in net bone resorption, whereas intermittent administration results in net bone formation (Kroll 2000). Intermittent administration of "Para-thyroid hormone" is incorporated into the dynamics of "Para-thyroid hormone" by adding the term $I_1(t)$.

Results

The bone metastasis model proposed in Section 3 is simulated using a finite difference scheme in MATLAB. In order to achieve high accuracy, we use the Crank-Nicholson method, which is based on the average value of the forward-difference and backward-difference methods. The forward and backward-difference approximations for the time derivatives are given by

$$\frac{\partial}{\partial t}X_k(t,x) = \frac{X_k(t+\delta t,x) - X_k(t,x)}{\delta t},$$

$$\frac{\partial}{\partial t}X_k(t,x) = \frac{X_k(t,x) - X_k(t-\delta t,x)}{\delta t},$$

where $k = 1,2,3,\ldots,6$. Similarly, centered difference approximation is used to approximate second spatial derivatives

$$\frac{\partial^2}{\partial x^2}X_k(t,x) = \frac{X_k(t,x+\delta x) - 2X_k(t,x) - X_k(t,x-\delta x)}{\delta x^2}.$$

The values of parameters used in MATLAB simulations are listed in Tables 1, 2.

This article presents a novel dynamic model of spatially heterogeneous bone metastasis. This model considers the interaction between "Osteoclasts" (responsible for bone resorption), "osteoblasts" (responsible for bone formation), "Para-thyroid hormone", and CT subject to treat bone metastases. The computational framework consists of a system of nonlinear partial differential equations for osteoclast-osteoblast interactions driven by A-C-(P-C) signaling, it is feasible to analyze the spatial disparities associated with the growth of tumors and the bone density of the afflicted

regions. We model the production of "Para-thyroid hormone" (through parathyroid glands) and CT (parafollicular cells of the thyroid gland) and their effects on "osteoblasts" and "Osteoclasts". "Para-thyroid hormone" is often used to treat osteoporosis since studies demonstrate that it stimulates bone formation. It has been well known that the method of "Para-thyroid hormone" administration may substantially influence its effects. It is considered to promote bone growth and density when administered intermittently. However, when continuously administered, it has the opposite catabolic effects. Our proposed model deals with intermittent administration of "Para-thyroid hormone" that eventually stimulates bone formation. The pharmaco-dynamics of a drug, bisphosphonates d(t) (to promote apoptosis of "Osteoclasts") and paclitaxel d(t) (for anti-cancer therapy), with its plasma concentration, is represented by a Hill function as

$$
\begin{aligned}
&\text{PD:} \begin{cases} d(t) &= \frac{C_p}{C_{50}+C_p}, \\ C_p &= \frac{P_2}{V}, \end{cases} \\
&\text{PK:} \begin{cases} \frac{dP_1}{dt} &= -k_a P_1; \quad P_1(0) = \text{Dose}, \\ \frac{dP_2}{dt} &= \Omega k_a P_1 - k_e P_2; \quad P_2(0) = 0, \end{cases}
\end{aligned}
\tag{23}
$$

where C_p is the drug's concentration in the plasma, and C_{50} is the concentration that achieves 50% of the maximum effect. The intravenous administration of bisphosphonates (zoledronic acid) and chemotherapy (paclitaxel) is based on a one-compartment pharmaco-kinetic (PK) model with first-order absorption k_a and elimination k_e.

Figure 2 shows the dynamics of intermittent administration of "Para-thyroid hormone". The dose is administrated every 3 days (72 hours) with initial injection value of 40.

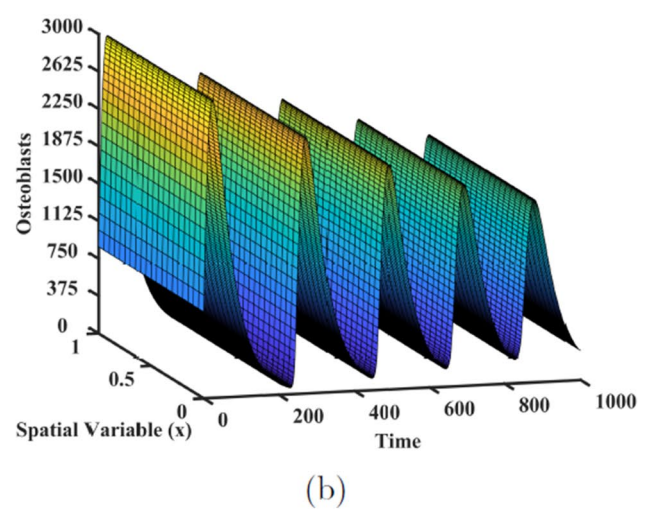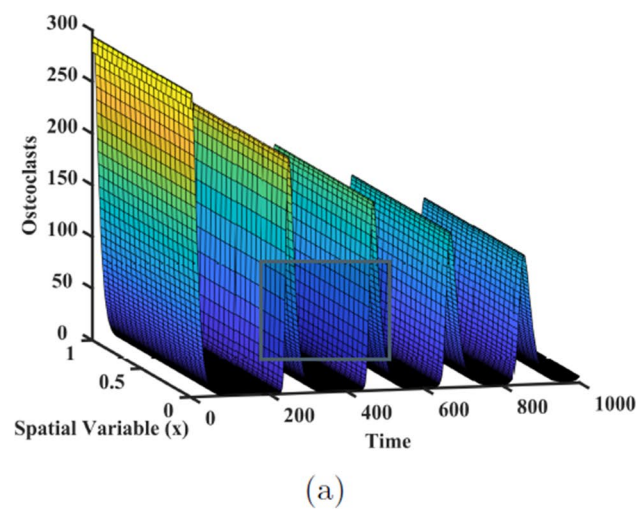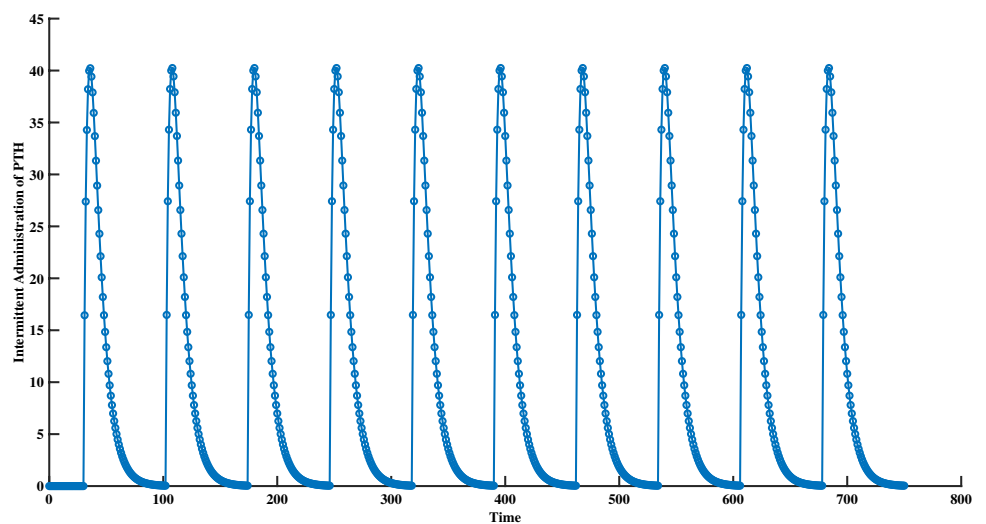**Fig. 2** Intermittent administration of "Para-thyroid hormone" after COVID-19

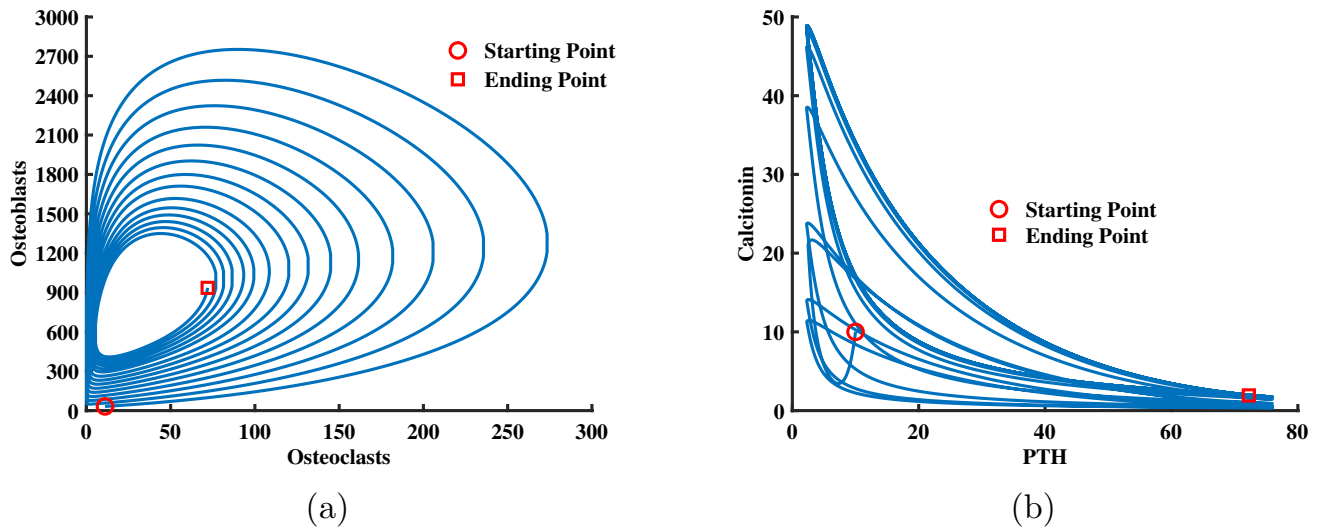**Fig. 3** Densities of osteoclast and "osteoblast" cells

Fig. 4 Phase-plane analysis of "Osteoclasts" vs "osteoblasts" and "Para-thyroid hormone" vs CT

The "Para-thyroid hormone" reaches a high value immediately after injection and then declines in value according to a conventional exponential decay curve. The densities of "Osteoclasts" and "osteoblasts" populations are shown in Fig. 3a, b, respectively. The oscillations in osteoclast and "osteoblast" populations are driven by intermittent "Para-thyroid hormone" treatment. The parameters for net A-C and (P-C) regulation, as well as "osteoblast" and osteoclast clearance rates, determine the period of oscillations. Limit cycle behavior is reflected in the oscillations of "Osteoclasts" and "osteoblasts" (Fig. 4a). Following a change in the number of "Osteoclasts" and "osteoblasts", these cells rapidly return to their oscillatory state and cycle back to the initial attractor, a hallmark of limit cycle behavior. Furthermore, since the

model was built with dissipative and nonlinear properties, the resulting oscillations would be expected to exhibit limit cycle behavior. Phase-plane analysis of "Para-thyroid hormone" and CT dynamics also shows limit cycle behavior that reflects stable oscillations in the trajectories of these hormones. Figure 5 shows the effects of "Para-thyroid hormone" and CT on the population of "Osteoclasts" and "osteoblasts". These 3D plots reflect stable cycles of bone remodeling along "Para-thyroid hormone" and CT.

The bone remodeling cycle is directly and indirectly impacted by cancer cells. Figure 6 depicts the effect of metastasis on bone mass. Due to the prevalence of "Osteoclasts" in the body over "osteoblasts", the presence of metastasis will reduce bone mass. Intermittent
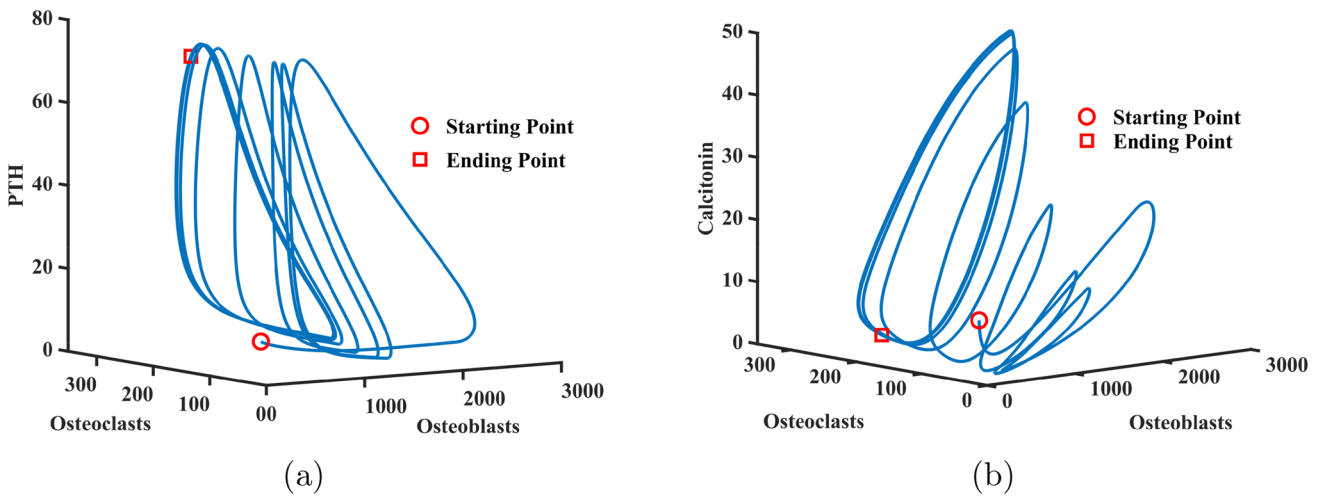

Fig. 5 3D phase portraits of "Osteoclasts" and "osteoblasts" along "Para-thyroid hormone" and CT
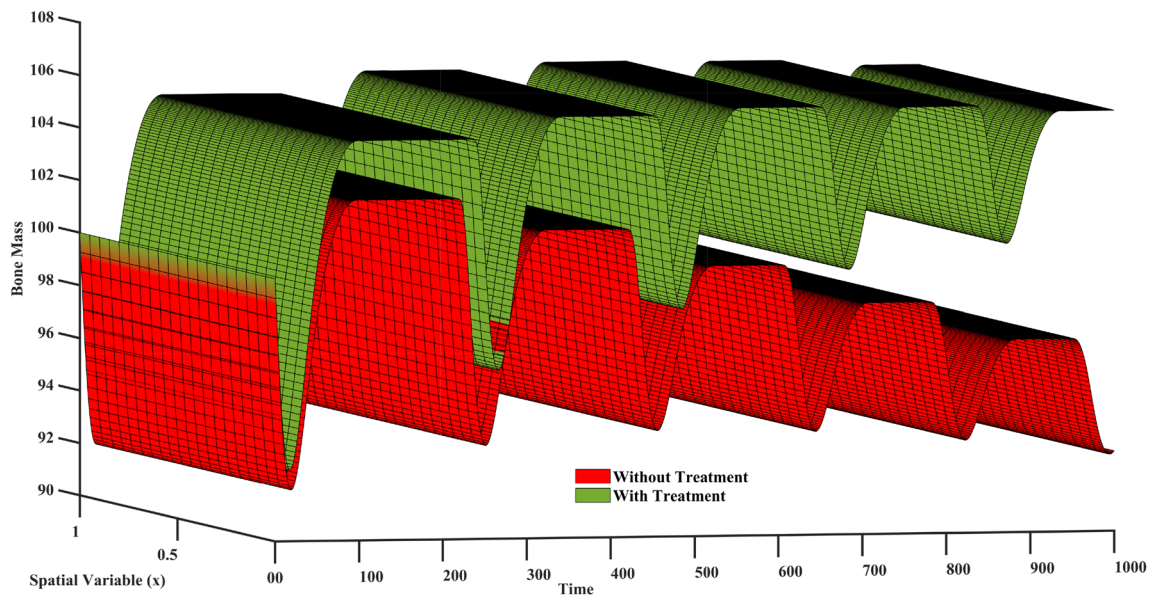
Fig. 6 Bone mass with treatment and without treatment

"Para-thyroid hormone" therapy substantially affects bone mass dynamics in the presence of a malignancy. To investigate the effect of anti-resorptive medication, the model was simulated with the maximum bisphosphonate effect. With chemotherapy, tumor growth may be reduced to near-zero levels, and the normal remodeling cycle can be restored. However, if anti-resorptive medications are not used, the bone mass will decrease due to growing bone resorption and will not be recovered as long as cancer cells exist. In addition, if the remodeling cycle is disrupted, bone resorption may contribute to the formation of tumors. This model does not account for the normal bone physiology processes that repair bone and increase bone mass if bone metastases are completely cleared, which is not common in cancer patients with metastases. Anti-resorptive treatment is not used alone to eliminate cancer cells, but it may at least delay their proliferation and partially restore bone density. With the combination of anticancer therapies, intermittent "Para-thyroid hormone", and bisphosphonates, the size of the tumor reduces and bone mass increases, resulting in a decrease in bone loss. Our investigation led us to conclude that intermittent "Para-thyroid hormone" administration enhanced bone apposition, which is consistent with Kuo et al.'s findings that intermittent administration of "Para-thyroid hormone" enhances osteogenesis (Kuo et al. 2017). However, in any case, the tumor is seldom entirely eradicated, which might lead to its regrowth and it is most likely to increase the tumor size when treatment is stopped.

Discussion

During the COVID-19 infection, the human body undergoes several changes due to the direct and indirect influence of the virus on the immune system, endocrine system and the hormones. The SARS-COV-2 virus invades the parathyroid gland tissues or they cause the chronic-respiratory-alkalosis, thus varying the levels of Parathyroid hormones, that play important role in (a) normal bone cycles as well as (b) cancer initiated bone metastasis. In this article, we examined the impact of CT, "Para-thyroid hormone", and its intermittent delivery on the dynamics of bone remodeling and the role that these factors play in initiating remodeling cycles to better understand bone remodeling in the presence of bone metastases. In addition, the PK/PD analysis of the therapies, which fall mainly under the categories of anticancer therapy and antiresorptive therapy, is used. The model is composed of system of partial differential equations and finite difference scheme is used to simulate the model. The numerical findings demonstrate that the model can exhibit periodic behavior similar to the clinically observed serum calcitonin level (Muse et al. 1986). It is also shown that "Para-thyroid hormone" enhances bone mass and bone formation, which is closely related to clinical studies (Silva et al. 2011).

Table 1 Values and description of parameters used in model

Parameter	Description	Value	Reference
α_1	"Osteoclasts" activation rate	3	Ayati et al. (2010), Coelho et al. (2016), Komarova et al. (2003)
α_2	"Osteoclasts" removal rate	0.2	Ayati et al. (2010), Coelho et al. (2016), Komarova et al. (2003)
α_3	"osteoblasts" activation rate	4	Ayati et al. (2010), Coelho et al. (2016), Komarova et al. (2003)
α_4	"osteoblasts" removal rate	0.02	Ayati et al. (2010), Coelho et al. (2016), Komarova et al. (2003)
α_5	Bone resorption rate	0.0748	Ayati et al. (2010), Coelho et al. (2016), Komarova et al. (2003)
α_6	Bone formation rate	0.0006395	Ayati et al. (2010), Coelho et al. (2016), Komarova et al. (2003)
α_7	Bone metastases growth rate	0.02	Ayati et al. (2010), Coelho et al. (2016)
α_8	Grouth rate of "Para-thyroid hormone" through parathyroid gland	0.2	Chaiya (2017)
α_9	Coefficient of hill function	0.5	Chaiya (2017)
α_{10}	"Para-thyroid hormone" apoptosis rate	0.07	Chaiya (2017)
α_{11}	Grouth rate of CT through parafollicular cells of the thyroid gland	0.3	Chaiya (2017)
α_{12}	Coefficient of hill function	0.5	Chaiya (2017)
α_{13}	CT apoptosis rate	0.5	Chaiya (2017)
α_{d_1}	Maximum effect of bisphosphonates	1.2	Coelho et al. (2016)
α_{d_2}	Maximum effect of anti-cancer therapy	0.017	Coelho et al. (2016)
β_1	Activation rate of "Osteoclasts" through "Para-thyroid hormone"	0.01	Chaiya (2017)
β_2	Coefficient of hill function	10	Chaiya (2017)
β_3	Coefficient of hill function	10	Chaiya (2017)
β_4	Activation rate of "osteoblasts" through "Para-thyroid hormone"	0.02	Chaiya (2017)
β_5	Coefficient of hill function	10	Chaiya (2017)
β_6	Apoptosis rate of "osteoblasts" through "Para-thyroid hormone"	0.4	Chaiya (2017)
β_7	Coefficient of hill function	10	Chaiya (2017)
γ_{11}	"Osteoclasts" A-C regulator	1.15	Ayati et al. (2010), Coelho et al. (2016), Komarova et al. (2003)
γ_{12}	"Osteoclasts"-derived "osteoblasts" paracrine regulator	1.02	Ayati et al. (2010), Coelho et al. (2016), Komarova et al. (2003)
γ_{21}	"osteoblasts"-derived "Osteoclasts" paracrine regulator	-0.5	Ayati et al. (2010), Coelho et al. (2016), Komarova et al. (2003)
γ_{22}	"osteoblasts" A-C regulator	0.2	Ayati et al. (2010), Coelho et al. (2016), Komarova et al. (2003)
K_{11}	Effect of tumor in "Osteoclasts" A-C regulator	0.005	Ayati et al. (2010), Coelho et al. (2016)
K_{22}	Effect of tumor in "osteoblasts" A-C regulator	-0.2	Ayati et al. (2010), Coelho et al. (2016)
K_T	Maximum size of bone metastases	100	Ayati et al. (2010), Coelho et al. (2016)
σ_k	Diffusion coefficients	1×10^{-4}	Ayati et al. (2010)

Conclusions

Models may be expanded to incorporate a range of physiological factors. For instance, it is known that the action of other hormones produced by breast cancer cells, such as estrogen, alters the dynamics of bone remodeling. This is particularly true for women who have had breast cancer therapy. In addition, drug resistance can be included in the model to determine the doses and administration intervals that optimize the therapeutic effect while minimizing the risk of systemic toxicity. It is anticipated that computer simulations of this critical physiological process may aid in

Table 2 Initial values of variables used in model

Parameter	Description	Value	Reference
X_1^0	Intial Value of "Osteoclasts"	11	Ayati et al. (2010), Komarova et al. (2003)
X_2^0	Intial Value of "osteoblasts"	230	Ayati et al. (2010), Komarova et al. (2003)
X_3^0	Intial Value of bone mass	100	Ayati et al. (2010), Komarova et al. (2003)
X_4^0	Intial Value of bone metastasis	1	Ayati et al. (2010), Komarova et al. (2003)
X_5^0	Intial Value of "Para-thyroid hormone"	10	Ayati et al. (2010), Komarova et al. (2003)
X_6^0	Intial Value of CT	10	Ayati et al. (2010), Komarova et al. (2003)

creating therapeutic regimens for patients with metastatic bone disease, as well as in clinical decision-making about treatment alternatives for these patients.

Declarations

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