Optimizing the dynamics of bone turnover with genetic algorithm

Muhammad Idrees1 · Ayesha Sohail2

Received: 27 August 2022 / Accepted: 6 November 2022 / Published online: 21 November 2022
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2022

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 “Para-thyroid 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...
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 pharmacologically, 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 tumor 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 osteoblastic 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. Deno-sumab is another completely human monoclonal antibody that specifically recognizes and binds to RANKL, hence increasing the OPG/RANKL ratio. Both chemotherapy and hormone treatment strategies 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 described 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.
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 perturbed 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

\[
\frac{dX_1}{dt} = \alpha_1 X_1^{\gamma_1} X_2^{\gamma_2} - \alpha_2 X_1, \tag{1}
\]

\[
\frac{dX_2}{dt} = \alpha_3 X_1^{\gamma_3} X_2^{\gamma_4} - \alpha_4 X_2, \tag{2}
\]

where \( \alpha_i \) (\( i = 1, 2, 3, 4, \)) are positive parameters. The parameters \( \gamma_i \) 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 resorption 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 \( \alpha_5 \) and \( \alpha_6 \) 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

\[
\bar{X}_1 = \left( \frac{\alpha_2}{\alpha_1} \right)^{\frac{\gamma_2}{\gamma_1}} \left( \frac{\alpha_4}{\alpha_3} \right)^{\frac{\gamma_4}{\gamma_3}},
\]

\[
\bar{X}_2 = \left( \frac{\alpha_2}{\alpha_1} \right)^{\frac{\gamma_2}{\gamma_1}} \left( \frac{\alpha_4}{\alpha_3} \right)^{\frac{\gamma_4}{\gamma_3}},
\]

where

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

The model has periodic solution if

\[
\Gamma_1 = \alpha_2(\gamma_{11} - 1) + \alpha_3(\gamma_{22} - 1) = 0.
\]

While \( \Gamma_1 \) greater than 0 results in unstable oscillations that diverge from the nontrivial steady states, \( \Gamma_1 \) 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

\[
\frac{dX_1}{dt} = \alpha_1 X_1^{\gamma_{11}} X_2^{\gamma_{12}} - \alpha_2 X_1, \tag{4}
\]

\[
\frac{dX_2}{dt} = \alpha_3 X_1^{\gamma_{21}} X_2^{\gamma_{22}} - \alpha_4 X_2, \tag{5}
\]

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

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

where \( \alpha_7 \) 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

\[
\begin{align*}
\frac{dX_1}{dt} &= a_1 x_1 + K_{11} \left( \frac{x_1}{x_2} \right) X_2 + b_1 \left( \frac{x_5}{x_6} + x_5^2 \right) X_2^2 + \alpha_1 X_1 \left( X_1 \right) X_2 - \alpha_2 X_1, \\
\frac{dX_2}{dt} &= a_2 x_1 + K_{22} \left( \frac{x_1}{x_2} \right) X_2 + b_2 \left( \frac{x_5}{x_6} + x_5^2 \right) X_2^2 + \alpha_2 X_2, \\
\frac{dX_3}{dt} &= -a_3 \max(0, X_1 - X_3) + a_6 \max(0, X_2 - X_3), \\
\frac{dX_4}{dt} &= a_7 \log \left( \frac{X_7}{X_4} \right), \\
\frac{dX_5}{dt} &= a_8 \left( \frac{1}{a_9 + x_1} \right) - \alpha_{10} X_5, \\
\frac{dX_6}{dt} &= a_1 \left( \frac{x_1}{a_{12} + x_5} \right) - \alpha_{13} X_6.
\end{align*}
\]

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 \( \alpha_{11} \left( \frac{x_1}{a_{12} + x_5} \right) \) 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 \( \alpha_{11} \left( \frac{x_1}{a_{12} + x_5} \right) \) and natural degradation of CT is modeled by \( \alpha_{12} X_6 \). The term \( \beta_{1} \left( \frac{x_1}{\beta_1 + x_1} \right) \) 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 \( \beta_{3} \left( \frac{x_3}{\beta_3 + x_3} \right) \) and \( \beta_{4} \left( \frac{x_4}{\beta_4 + x_4} \right) \) 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.

\[
\begin{align*}
\frac{\partial}{\partial t} X_1(t, x) &= \sigma_1 \frac{\partial^2}{\partial x^2} X_1(t, x) + a_1 X_1 \left( \frac{x_1}{x_2} \right) X_2 + b_1 \left( \frac{x_5}{x_6} + x_5^2 \right) X_2^2 + \alpha_1 X_1, \\
\frac{\partial}{\partial t} X_2(t, x) &= \sigma_2 \frac{\partial^2}{\partial x^2} X_2(t, x) + a_2 X_1 + K_{22} \left( \frac{x_1}{x_2} \right) X_2 + b_2 \left( \frac{x_5}{x_6} + x_5^2 \right) X_2^2 + \alpha_2 X_2, \\
\frac{\partial}{\partial t} X_3(t, x) &= \sigma_3 \frac{\partial^2}{\partial x^2} X_3(t, x) + a_3 \left( \frac{x_1}{a_{12} + x_5} \right) - \alpha_{10} X_5, \\
\frac{\partial}{\partial t} X_4(t, x) &= \sigma_4 \frac{\partial^2}{\partial x^2} X_4(t, x) + b_4 \left( \frac{x_5}{\beta_1 + X_5} \right) - \alpha_{13} X_6.
\end{align*}
\]
\[
\frac{\partial}{\partial t} X_4(t, x) = \sigma_4 \frac{\partial^2}{\partial x^2} X_4(t, x) + \alpha_4 X_4 \log \left( \frac{K_T}{X_4} \right) \tag{17}
\]

\[
\frac{\partial}{\partial t} X_5(t, x) = \sigma_5 \frac{\partial^2}{\partial x^2} X_5(t, x) + \alpha_9 \left( \frac{1}{a_9 + X_1} \right) - \alpha_{10} X_5. \tag{18}
\]

\[
\frac{\partial}{\partial t} X_6(t, x) = \sigma_6 \frac{\partial^2}{\partial x^2} X_6(t, x) + \alpha_{11} \left( \frac{X_1}{a_{12} + X_5} \right) - \alpha_{13} X_6. \tag{19}
\]

where \( \sigma_k \frac{\partial}{\partial x} X_k(t, x) \) \((k = 1, 2, 3, \ldots, 6)\) are diffusion terms with diffusion parameters \( \sigma_k \). 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

\[
X_1(0, x) = X_0^1, \quad \frac{\partial}{\partial x} X_1(t, 0) = 0, \quad \frac{\partial}{\partial x} X_1(t, 1) = 0, \]

\[
X_2(0, x) = X_0^2, \quad \frac{\partial}{\partial x} X_2(t, 0) = 0, \quad \frac{\partial}{\partial x} X_2(t, 1) = 0, \]

\[
X_3(0, x) = X_0^3, \quad \frac{\partial}{\partial x} X_3(t, 0) = 0, \quad \frac{\partial}{\partial x} X_3(t, 1) = 0, \]

\[
X_4(0, x) = X_0^4, \quad \frac{\partial}{\partial x} X_4(t, 0) = 0, \quad \frac{\partial}{\partial x} X_4(t, 1) = 0, \]

\[
X_5(0, x) = X_0^5, \quad \frac{\partial}{\partial x} X_5(t, 0) = 0, \quad \frac{\partial}{\partial x} X_5(t, 1) = 0, \]

\[
X_6(0, x) = X_0^6, \quad \frac{\partial}{\partial x} X_6(t, 0) = 0, \quad \frac{\partial}{\partial x} X_6(t, 1) = 0. \]

### 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

\[
\frac{\partial}{\partial t} X_1(t, x) = \sigma_1 \frac{\partial^2}{\partial x^2} X_1(t, x) + \alpha_1 X_1^{\tau_1 + \kappa_1} \left( \frac{x}{\tau_1} \right)
+ \beta_1 \left( \frac{X_5}{\beta_2 + X_5} \right) \left( \frac{1}{\beta_2 + X_6} \right) X_1 X_2 - (\alpha_2 + \alpha_d) d_1(t) X_1, \tag{20}
\]

\[
\frac{\partial}{\partial t} X_4(t, x) = \sigma_4 \frac{\partial^2}{\partial x^2} X_4(t, x) + \alpha_4 X_4 \log \left( \frac{K_T}{X_4} \right) - \alpha_{d_2} d_2(t) X_4. \tag{21}
\]

\[
\frac{\partial}{\partial t} X_5(t, x) = \sigma_5 \frac{\partial^2}{\partial x^2} X_5(t, x) + \alpha_9 \left( \frac{1}{a_9 + X_1} \right) - \alpha_{10} X_5 + I_1(t), \tag{22}
\]

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 \( \alpha_d d_1(t) \) to \( \alpha_2 \). 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 \( d_2(t) \) on the tumor’s mortality, the term \( \alpha_d d_2(t) X_4 \) is included in the equation of tumor growth. Constants \( \alpha_d \) and \( \alpha_d \) 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

\[
\frac{\partial}{\partial t} X_k(t, x) = \frac{X_k(t + \delta t, x) - X_k(t, x)}{\delta t}, \quad \frac{\partial}{\partial t} X_k(t, x) = \frac{X_k(t, x) - X_k(t - \delta t, x)}{\delta t},
\]

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 bones.
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

\[
\text{PD: } \left\{ \begin{array}{l}
d(t) = \frac{C_p}{C_{50} + C_p}, \\
C_p = \frac{P_2}{V},
\end{array} \right.
\]

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.

\[
\text{PK: } \left\{ \begin{array}{l}
\frac{dP_2}{dt} = -k_e P_1; \\
\frac{dP_1}{dt} = \Omega k_a P_1 - k_e P_2; \\
P_2(0) = 0,
\end{array} \right.
\]

where \( P_1 \) and \( P_2 \) are the densities of osteoclast and “osteoblast” cells, respectively.

Fig. 2 Intermittent administration of “Para-thyroid hormone” after COVID-19

Fig. 3 Densities of osteoclast and “osteoblast” cells
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. 4** Phase-plane analysis of “Osteoclasts” vs “osteoblasts” and “Para-thyroid hormone” vs CT

**Fig. 5** 3D phase portraits of “Osteoclasts” and “osteoblasts” along “Para-thyroid hormone” and CT
“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).
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
creating therapeutic regimens for patients with metastatic bone disease, as well as in clinical decision-making about treatment alternatives for these patients.

Data availability The authors have cited the sources of data within the manuscript.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

References

Ayati BP, Edwards CM, Webb G, Wikswo JP (2010) A mathematical model of bone remodeling dynamics for normal bone cell populations and myeloma bone disease. Biol Direct 5:1–17
Bora VR, Patel BM (2021) The deadly duo of covid-19 and cancer! Front Mol Biosci 8:643004
Chaiya I, Rattanakul C (2017) An impulsive mathematical model of bone formation and resorption: effects of parathyroid hormone, calcitonin and impulsive estrogen supplement. Adv Differ Equ 1:1–20
Coelho RM, Lemos JM, Alho I, Valerio D, Ferreira AR, Costa L, Vinga S (2016) Dynamic modeling of bone metastasis, microenvironment and therapy: integrating parathyroid hormone (PTH) effect, anti-resorptive and anti-cancer therapy. J Theor Biol 391:1–12
Davey RA, Findlay DM (2013) Calcitonin: physiology or fantasy? J Bone Miner Res 28(5):973–979
Francescangeli F, De Angelis ML, Zeuner A (2020) Covid-19: a potential driver of immune-mediated breast cancer recurrence? Breast Cancer Res 22(1):1–3
Goltzmann D (2018) Physiology of parathyroid hormone. Endocrinol Metab Clin 47(4):743–758
Guise TA, Chirgwin JM (2003) Transforming growth factor-beta in osteolytic breast cancer bone metastases. Clin Orthop Relat Res 1976–2007(415):S32–S38
Hurley DL, Tiegens RD, Wahrner HW, Heath HH III (1987) Axial and appendicular bone mineral density in patients with long-term deficiency or excess of calcitomin. N Engl J Med 317(9):537–541
Komarova SV (2005) Mathematical model of paracrine interactions between osteoclasts and osteoblasts predicts anabolic action of parathyroid hormone on bone. Endocrinol 146(8):3589–3595
Kumar SV, Smith RJ, Dixon SJ, Sims SM, Wahl LM (2003) Mathematical model predicts a critical role for osteoclast autocrine regulation in the control of bone remodeling. Bone 33(2):206–215
Kroll MH (2000) Parathyroid hormone temporal effects on bone formation and resorption. Bull Math Biol 62(1):163–188
Kübner N, Krause U, Wagner P, Beyer J, Rothmund M (1987) The effect of high parathyroid hormone concentration on calcitonin in patients with primary hyperparathyroidism2. Exp Clin Endocrinol Diabet 90(06):324–330
Kuo S-W, Rimando MG, Liu Y-S, Lee OK (2017) Intermittent administration of parathyroid hormone 1–34 enhances osteogenesis of human mesenchymal stem cells by regulating protein kinase c0. Int J Mol Sci 18(10):2221
Lerner UH, Kindstedt E, Landberg P (2019) The critical interplay between bone resorbing and bone forming cells. J Clin Periodontol 46:33–51
Liu Q, Zhang H, Jiang X, Qian C, Liu Z, Luo D (2017) Factors involved in cancer metastasis: a better understanding to “seed and soil” hypothesis. Mol Cancer 16(1):1–19
Muse KN, Manolagas SC, Deftos LJ, Alexander N, Yen SS (1986) Calcium-regulating hormones across the menstrual cycle. J Clin Endocrinol Metab 62(6):1313–1316
Naot D, Musson DS, Cornish J (2019) The activity of peptides of the calcitonin family in bone. Physiol Rev 99(1):781–805
Ryser MD, Komarova SV, Nigam N (2010) The cellular dynamics of bone remodeling: a mathematical model. SIAM J Appl Math 70(6):1899–1921
Ryser MD, Nigam N, Komarova SV (2009) Mathematical modeling of spatio-temporal dynamics of a single bone multicellular unit. J Bone Miner Res 24(5):860–870
Ryser MD, Qu Y, Komarova SV (2012) Osteoprotegerin in bone metastases: mathematical solution to the puzzle
Savageau MA (1988) Introduction to s-systems and the underlying power-law formalism. Math Comput Model 11:546–551
Silva B, Costa A, Cusano N, Kousteni S, Bilezikian J (2011) Catabolic and anabolic actions of parathyroid hormone on the skeleton. J Endocrinol Invest 34(10):801–810
Tian J, Smogorzewski M, Kedes L, Massry SG (1993) Parathyroid hormone-parathyroid hormone related protein receptor messenger RNA is present in many tissues besides the kidney. Am J Nephrol 13(3):210–213
Wüster C, Raue F, Meyer C, Bergmann M, Ziegler R (1992) Long-term treatment alternatives for these patients.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.