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PRESENTATION A MATHEMATICAL MODEL FOR BONE METASTASES CONTROL BY USING TAMOXIFEN

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ABSTRACT. Bone is a common site for metastases (secondary tumor) because of breast and prostate cancer. According to our evaluations the mathematical aspect of the effect of drug in bone metastases has not been studied yet. Hence, this paper suggested a new mathematical model for bone metastases control by using tamoxifen. The proposed model is a system of nonlinear partial differential equations. In this paper our purpose is to present a control model for bone metastases. At end by some numerical simulations, the proposed model is examined by using physician.

Key words and phrases: Mathematical model, Control theory, Bone metastasis, Tamoxifen.

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1. INTRODUCTION

Cancer, one of the most widely spread human health problems, is the uncontrolled growth of abnormal cells in the body. Primary cancers develop metastatic tumors in distant sites and tissues of the body. In this regard, bone is a common site for metastases and up to 70% of breast and prostate cancer patients develop secondary tumors in the bone environment [4].

Physiologically, RANK/RANKL/OPG pathway plays a crucial role in bone remodeling. Receptor activator of nuclear factor κ_B (RANK) is expressed by osteoclast precursors and mature osteoclasts. During remodeling, RANK ligand (RANKL) expressed by cells of the osteoblastic lineage stimulations osteoclast formation and directs osteoclasts towards sites of microdamage. Mature osteoblasts also produce the soluble decoy receptor osteoprotegrin (OPG), which bind to RANKL and hence prevents it from interacting with RANK [4]. Cancer cells produce factors such as the parathyroid hormone-related protein (PTHrP), which induce the production of osteoclast-stimulating RANKL by osteoblasts.

During the last few years, there have been some remarkable studies about the influence of several factors on bone remodeling. As a result, some models have set out to describe bone remodeling and the interaction of various factors. Svetlana V. Komorova and her colleagues constructed a mathematical model of autocrine and paracrine interactions among osteoblasts and osteoclasts that allowed us to calculate cell population dynamics and changes in bone mass at a discrete site of bone remodeling [11]. Also Vincent Lemaire and his colleagues proposed a mathematical model explaining the interactions between osteoblasts and osteoclasts [13]. Another mathematical model was developed by Yanan Wang and his colleagues in 2009. The model incorporates a new understanding about the interaction of PTHrP and other factors with the RANK-RANKL-OPG pathway into bone remodeling, which was able to simulate the anabolic action of bone induced by PTH at the cellular level [20]. A mathematical model was developed for normal bone remodeling and for the dysregulated bone remodeling that occurs in myeloma bone disease by Bruce P Ayati and his colleague. In this model, the interaction of osteoclasts and osteoblasts was modeled as a system of differential equations for these cell populations [1]. Then Garzon-Alvarado simulated metastatic activation in bone marrow in a mathematical model that involves the activation of molecules by bone tissue cells [5]. Ryser and his colleagues in 2012 described osteoprotegerin in bone metastasis in a mathematical model; they demonstrate that at lower expression rates, tumor-derived OPG, enhances the chemotactic RANKL gradient and osteolysis, whereas at higher expression rates OPG broadly inhibits RANKL and decreases osteolysis and tumor burden. They tested this hypothesis using a mathematical model of nonlinear partial differential equations describing the spatial dynamics of OPG, RANKL, PTHrP, osteoclasts, tumor and bone mass [17].

As literature shows, the effect of drugs in bone metastases has not been studied yet using matehmatical models. Thus this research tries to suggest a new mathematical model for the dynamics between tumor cells, OPG, RANKL, PTHrP, osteoclast and chemotherapy drug, as a control theory problem. For this purpose, we intend to study systemic treatment when a special drug that prevent progressing bone metastases is used. These progress are eradicated in a control model. The bases of proposed model here derives from [17], which describes bone metastases completely, with some changes in adding the effect of drug to the equations.

The plan of the paper is as follows: after explaining one metastases growth mechanism in Section 2, we introduce a mathematical model in Section 3 which investigate drug for bone metastases. In Section 4, control model for bone metastasis is defined and finally conclusions are drawn in Section 5.

2. BONE METASTASES GROWTH MECHANISM

A mathematical model uses the language of mathematics to produce a more refined and precise description of the system. In epidemiology, models allow us to translate behavior at various scales, or extrapolate from a known set of conditions to another. In this section we follow [17] to model a single trabecular exposed to bone marrow and pre-existing cancer cells. Hemi-osteonal, trench-like remodeling of trabecular bone reduce the geometry of the problem from three to two spatial dimensions and assuming that the trabecular is locally flat. The model domain becomes a bounded subset of R^2 and it consists 6 state variables:

The local cell density of osteoclast is denoted by $u(x,t)$, where $\mathbf{x}=(x,y)$. The RANKL field is denoted by $\Phi_R(\mathbf{x},t)$, the OPG field by $\Phi_O(\mathbf{x},t)$, PTHrP field is denoted by $\Phi_P(\mathbf{x},t)$, bone density (ρ_B) and tumor density (ρ_T). We introduce the model in several steps, and start with the osteoclast population density (u). The dynamic of the bone metastases model that describe in [17] is:

$$
\begin{aligned}
&\frac{\partial u}{\partial t} = \alpha u^g - \beta u - \xi \frac{\partial}{\partial x}\left(u_a \frac{\partial \Phi_R}{\partial x}\right) + k_1 \frac{\Phi_R}{\lambda + \Phi_R} u_a \\
&\frac{\partial \Phi_R}{\partial t} = \kappa_R \Phi_p \rho_B + \sigma_R \frac{\partial^2 \Phi_R}{\partial x^2} - k_2 \frac{\Phi_R}{\lambda + \Phi_R} u_a - k_3 \Phi_R \Phi_O \\
&\frac{\partial \Phi_O}{\partial t} = \tau_O \rho_T + \sigma_O \frac{\partial^2 \Phi_O}{\partial x^2} - k_O \Phi_O - k_3 \Phi_R \Phi_O \\
&\frac{\partial \Phi_P}{\partial t} = \tau_P \rho_T + \sigma_P \frac{\partial^2 \Phi_P}{\partial x^2} - k_P \Phi_P \\
&\frac{\partial \rho_B}{\partial t} = -k_B u_a \\
&\rho_T = 1 - \rho_B.
\end{aligned}
\tag{2.1}
$$

The total osteoclast population u is split into u_{ss} that is a stable fixed point and a residual u_a, where $u_a(t,x) = u(t,x) - u_{ss}$. Note that $u_a(t,x) \geq 0$ for all $t \geq 0$ [17].

In model (2.1) we see that: $\frac{\partial \rho_B}{\partial t} = -k_B u_a$ and $\rho_T = 1 - \rho_B$; so we can deduce that: $\frac{\partial \rho_T}{\partial t} = k_B u_a$ and model (2.1) convert to:

$$
\begin{aligned}
&\frac{\partial u}{\partial t} = \alpha u^g - \beta u - \xi \frac{\partial}{\partial x}\left(u_a \frac{\partial \Phi_R}{\partial x}\right) + k_1 \frac{\Phi_R}{\lambda + \Phi_R} u_a \\
&\frac{\partial \Phi_R}{\partial t} = \kappa_R \Phi_p (1 - \rho_T) + \sigma_R \frac{\partial^2 \Phi_R}{\partial x^2} - k_2 \frac{\Phi_R}{\lambda + \Phi_R} u_a - k_3 \Phi_R \Phi_O \\
&\frac{\partial \Phi_O}{\partial t} = \tau_O \rho_T + \sigma_O \frac{\partial^2 \Phi_O}{\partial x^2} - k_O \Phi_O - k_3 \Phi_R \Phi_O \\
&\frac{\partial \Phi_P}{\Phi t} = \tau_P \rho_T + \sigma_P \frac{\partial^2 \Phi_P}{\partial x^2} - k_P \Phi_P \\
&\frac{\partial \rho_T}{\partial t} = -k_B u_a
\end{aligned}
\tag{2.2}
$$

The parameters of the model are described in [17].

3. INVESTIGATION OF DRUG FOR BONE METASTASE

There are two main types of bone metastases treatment; local and systemic treatments. Depending on the extension and location of the cancer, one or both types of treatment may be used. Systemic treatments can affect the whole body. In many cases, especially if the cancer has spread to many bones, systemic treatments are used because they can reach cancer cells that

Variable	Description
u	Density of osteoclasts
u_a	Density of active osteoclasts
Φ_R	RANKL concentration
Φ_O	OPG concentration
Φ_P	PTHrP concentration
ρ_B	Bone density
ρ_T	Tumor density

Table 2.1: Variables in model (2.1)

Parameter	value (d is abbreviate day)	Description
α	$9.49mm^{\frac{-1}{2}}d^{-1}$	Production rate of osteoclasts
g	0.5	Autocrine stimulation of osteoclasts
β	$0.2d^{-1}$	Apoptosis rate of osteoclasts
ξ	$1.3\times10^{-3}mm^3pmol^{-1}d^{-1}$	Chemotactic motility of osteoclasts
k_1	$0.3d^{-1}$	RANK RANKL stimulation rate
λ	$13pmolmm^{-1}$	Half saturation of RANK RANKL binding
k_R	$1d^{-1}$	PTHrP mediated production rate of RANKL
σ_R	$0.5\times10^{-2}mm^2d^{-1}$	RANKL diffusivity
k_2	$0.05pmold^{-1}$	RANK RANKL binding rate
k_3	$0.1mmdpmol^{-1}$	RANKL OPG binding rate
τ_O	6	Rate of OPG production by tumor
σ_O	$1.6\times10^{-2}mm^2d^{-1}$	OPG diffusivity
k_O	$10d^{-1}$	OPG degradation rate
τ_P	2	Rate of PTHrP production by tumor
σ_P	$3\times10^{-2}mm^2d^{-1}$	PTHrP diffusivity
k_p	$4d^{-1}$	PTHrP degradation rate
k_B	$3d^{-1}$	Resorption rate of bone by active osteoclasts

Table 2.2: parameters in model (2.1)

have spread throughout the body. Systemic therapies include chemotherapy, hormone therapy, or other medicines that are taken by mouth or injected into the blood. When there are 2 or more metastatic tumors, it's called "metastases" and because we investigate metastases, we consider systemic treatment and introduce a special drug that prevents progressing bone metastases.

There are different kind of drugs that prevents metastases progressing such as Bisphosphonates (zometa) and Tamoxifen. One of the famous and effective drugs that use for bone metastases is tamoxifen [8], which is a hormone drug. Hormones in the body drive the growth of some common cancers; for example, the female hormone estrogen promotes growth breast cancer. One of the main ways to treat cancers is to stop certain hormones from affecting the cancer cells. The main ways of doing this are lowering hormone levels and blocking the hormone's action at the cancer cell. One way which is used more often to lower hormone levels, is to give drugs to keep the hormones from being made. In this regard, tamoxifen is one of the best drugs that block the effects of estrogen on breast cancer. Indeed high-dose of tamoxifen is used as a treatment for bone metastasis; it decreases bone reabsorption [19]. In this part we want to study the effect of this drug on dynamic system of metastases growing. For this purpose it requires to have a glance to cell cycle.

Cell replication occurs in a series of phases, called the cell cycle. The cell cycle phase are: G_0 (nothing is happening), G_1 (a growth phase), S (synthesis, the replication of DNA occurs), G_2 (another growth phase) and $\mathbf{m}$ (mitosis, the actual division from 1 cell into 2 cells). Some chemotherapy agents are able to kill a tumor cell during any phase of the cycle; these are called cell-cycle nonspecific (CNS). Others are only able to kill tumor cells during a specific phase and are unable to work in the resting phase, called cell-cycle specific (CS)[18]. Tamoxifen is a kind of CNS drug [8]; it means that tamoxifen can kill a tumor cell during any phase of the cycle. Because of this ability, tamoxifen is in the top list of anti-tumor drugs

It is assumed that cell kill rate over a short interval of time, is the exponential of drug concentration $y(t)$ at time. Hence an Exponential kill (EK) model is proposed to predict the state of dose-response curve based on the cell cycle phase specificity of the used drug. EK model generates sigmoidal dose-response curves like those measured empirically. In this regards, the fraction of cells killed by using a CNS drug of concentration $C(t)$, is shown in [6] as:

$$f(v) = M(1 - e^{-C(t)}), \tag{3.1}$$

where M is the response coefficient that $0 \leq M \leq 0.5$ [9, 14, 15].

In bone metastasis model (2.2), in [17], Ryser and his colleague show that:

$$\frac{d\rho_T}{dt} = k_B u_a; \tag{3.2}$$

As tamoxifen is an antiestrogen drug, it directly inhibits tumor growth by blocking ER-mediated stimulation of cell growth [2].

Therefore if we consider the efficiency of tamoxifen in preventing metastasis growing on tumor, according to (2.1) we can present the following relation:

$$\frac{d\rho_T}{dt} = k_B u_a - M(1 - e^{-C})\rho_T. \tag{3.3}$$

According to [9] the amount of drug (tamoxifen) dose for the patient is calculated as follows,

$$\frac{\partial C}{\partial t} = v(t) - dC, \tag{3.4}$$

$v(t)$ is the used drug dose and d is the per capita death rate of the drug and $d = 1$.

As an engineering point of view, since such kind of drug is an output agent of the body system, to prevent the illness in a prescribed manner; thus here drug acts like an input in control a system and one can get some help from control theory to present the problem.

4. CONTROL MODEL FOR BONE METASTASES DRUG THERAPY

A mathematical model uses the language of mathematics to produce a more refined and precise description of the system. In this article we intended to present a control model, because as we know drugs in general prevents illness progressing; in other words drug act as a controller of the body. In this regards using control model to show this process is useful. The main purpose of this process is to control the process of progress bone metastasis by using Tamoxifen. As an introductory step, we had studied the bone metastasis model deeply and introduced a development model for treatment by using optimal control. According to the previous section tamoxifen is in the set of CNS drugs and effects on tumor exponentially, so propose the control model that based on the existed literature and Tamoxifen properties for controlling bone

metastases according to (2.2), (3.3) and (3.4) we suggest is as follows:

$$
\begin{aligned}
&\frac{\partial u}{\partial t} = \alpha u^g - \beta u - \xi \frac{\partial}{\partial x}\left(u_a \frac{\partial \Phi_R}{\partial x}\right) + k_1 \frac{\Phi_R}{\lambda + \Phi_R} u_a;\\
&\frac{\partial \Phi_R}{\partial t} = \kappa_R \Phi_p (1-\rho_T) + \sigma_R \frac{\partial^2 \Phi_R}{\partial x^2} - k_2 \frac{\Phi_R}{\lambda + \Phi_R} u_a - k_3 \Phi_R \Phi_O;\\
&\frac{\partial \Phi_O}{\partial t} = \tau_O \rho_T + \sigma_O \frac{\partial^2 \Phi_O}{\partial x^2} - k_O \Phi_O - k_3 \Phi_R \Phi_O;\\
&\frac{\partial \Phi_P}{\partial t} = \tau_P \rho_T + \sigma_P \frac{\partial^2 \Phi_P}{\partial x^2} - k_P \Phi_P;\\
&\frac{\partial \rho_T}{\partial t} = k_B u_a - M(1 - e^{(-C)})\rho_T;\\
&\frac{\partial C}{\partial t} = v(t) - dC.
\end{aligned}
\tag{4.1}
$$

Where the last equation comes from (3.4).

Now it is time to check the proposed method for using tamoxifen in bone metastases because of breast cancer. According to [19] and physician prescription, the proposed dose of tamoxifen for bone metastases patient is $20mg$ daily; it means that we put (set): $v = 20$, in our control model. For implementation of the model we used finite difference method with periodic boundary conditions and initial conditions as specified above. In discretization time, we consider $dt = 0.1$, in the interval $[0, 75]$ with $t_1, t_2, \cdots, t_{75}$ and for bone length we consider $dx = 0.2$ in the interval $[0, 15]$ with $x_1, x_2, \cdots, x_{15}$. In this manner finite difference method is applied to change the control model (4.1) into an algebraic system of equations. So (4.1) is replaced by;

$$
\begin{aligned}
\frac{u(i,j+1) - u(i,j)}{dt} &= \alpha u(i,j)^g - \beta u(i,j)\\
&\quad -\xi \left[\frac{u(i+1,j) - u(i,j)}{dx} \frac{\Phi_R(i+1,j) - \Phi_R(i,j)}{dx}\right]\\
&\quad + \left(\frac{\Phi_R(i+2,j) - 2\Phi_R(i+1,j) + \Phi_R(i,j)}{dx^2}\right) u(i,j)\\
&\quad + k_1 \frac{\Phi_R(i,j)}{\lambda + \Phi_R(i,j)} u(i,j);
\end{aligned}
$$

$$
\begin{aligned}
\frac{\Phi_R(i,j+1) - \Phi_R(i,j)}{dt} &= \kappa_R \Phi_p(i,j) \rho_B(i,j)\\
&\quad + \sigma_R \frac{\Phi_R(i+2,j) - 2\Phi_R(i+1,j) + \Phi_R(i,j)}{dx^2}\\
&\quad - k_2 \frac{\Phi_R(i,j)}{\lambda + \Phi_R(i,j)} (u(i,j) - u_{ss}) - k_3 \Phi_R(i,j) \Phi_O(i,j);
\end{aligned}
$$

$$
\begin{aligned}
\frac{\Phi_O(i,j+1) - \Phi_O(i,j)}{dt} &= \tau_O \rho_T(i,j)\\
&\quad + \sigma_O \frac{\Phi_O(i+2,j) - 2\Phi_O(i+1,j) + \Phi_O(i,j)}{dx^2} - k_O \Phi_o(i,j)\\
&\quad - k_3 \Phi_R(i,j) \Phi_O(i,j);
\end{aligned}
$$

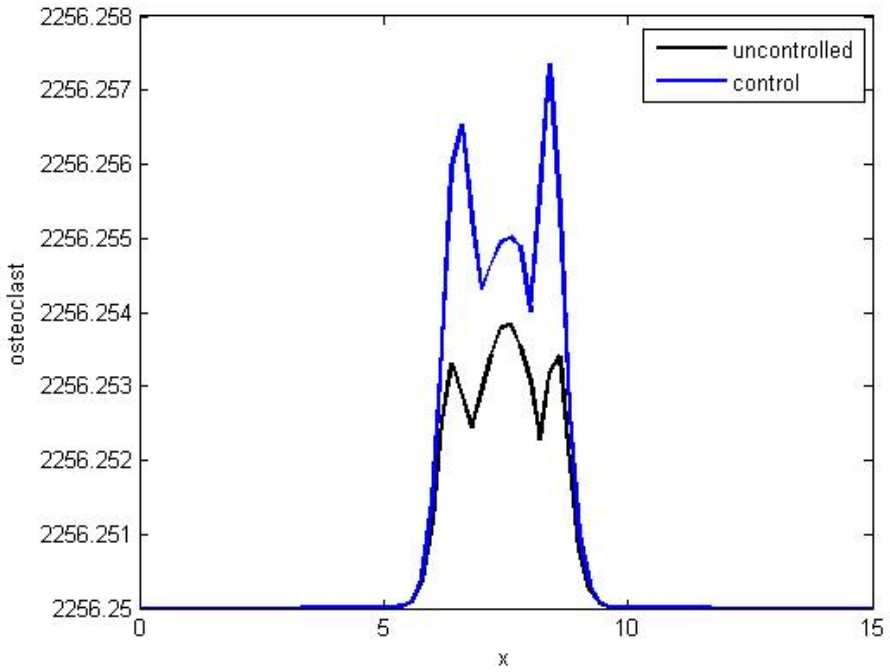

Figure 1: Comparison of osteoclast population density.

$$\begin{aligned}
\frac{\Phi_P(i,j+1)-\Phi_P(i,j)}{dt} &= \tau_P\rho_T(i,j) \\
&\quad +\sigma_P\frac{\Phi_P(i+2,j)-2\Phi_P(i+1,j)+\Phi_P(i,j)}{dx^2} \\
&\quad -k_P\Phi_P(i,j); \\
\frac{\rho_T(i,j+1)-\rho_T(i,j)}{dt} &= k_B(u(i,j)-u_{ss})-M(1-e^{(-C)})\rho_T(i,j), \\
\frac{C(i,j+1)-C(i,j)}{dt} &= v(i,j)-dC(i,j).
\end{aligned}$$

Where for instance $u(i,j)$ is $u(x_i,t_j)$.

In this simulation, the growing of tumor density with and without using drugs base on (4.1) is checked. So at first the uncontrolled system of (2.2) is solved by using finite difference method; it is mentioned that this uncontrolled system was solved in [17] based on clinical observations and the process of bone metastases was studied in 90; where on the first day no tumor had seen. We suppose that our patient has the same conditions modified in [17] and tamoxifen is injected at 15^{th} day of tumor growing. So the initial conditions of control problem (4.1) is the 15^{th} day of illness. The total time that we proposed for using drug is 75 days. In this regard, after solving the uncontrolled system, the set of initial conditions that is used for simulation of this study is: $u(x,0)=2256.25, \Phi_R(x,0)=1.8, \Phi_O(x,0)=0.4, \Phi_P(x,0)=0.15, \rho_T(x,0)=0.5$.

The results in Figures 1-4 show that with starting from the initial conditions and after using tamoxifen with constant dose, tumor burden decrease and osteoclast, RANKL, OPG become near to the case of beginning normal tumor according to [17] that is useful for the patient. In the Figures 1-4, osteoclast density (u), tumor density (ρ_T), RANKL concentration (Φ_R) and OPG concentration (Φ_O) is shown respectively, without drug (uncontrolled) with black and

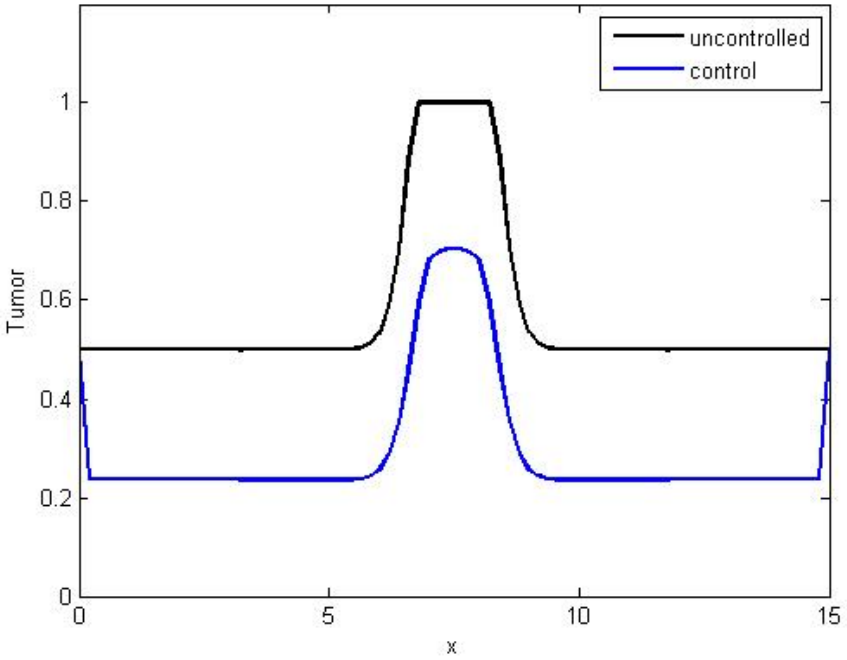

Figure 2: Comparison of tumor density.

with drug (controlled) with blue after applying $20mg$ tamoxifen daily in 75 days. Bone domain is considered $15mm$ long. The y-axis has the following units: osteoclast in cells$/$mm; tumor density is normalized between 0 when there is no tumor per unit length, and 1 when the unit space is fully occupied by the tumor; RANKL in pmol$/$mm; OPG in pmol$/$mm.

Tumor density is shown at 75 days without drug (uncontrolled) and with drug (controlled). The tumor density decreases after using the drug, as shown in the figure. It is necessary to mention that tumor density without using the drug was 1 at final day which is reduced to 0.7046 after using the drug. The obtained figures were confirmed by oncology physicians of Shiraz university.

As is shown in Figure 5, they agree that in 30 days that patient use of the drugs doesn't reduce the tumor and after that tumor density decrease.

5. CONCLUSION AND DISCUSSION

We have extended previous mathematical model by adding drugs to the model by using control theory. For this purpose, we studied on bone metastases and the mathematical models that exist. According to our review the effect of drug in bone metastases has not been studied yet mathematically, so we investigated efficient drugs for bone metastases treatment because of breast cancer. The model is formulated as a system of partial differential equations that describe the relation between osteoclast$/$RANKL$/$OPG$/$PTHrP$/$tumor and drug. One of the famous and effective drugs that is used for bone metastasis is tamoxifen. After choosing drug, we studied the way of adding it to the model. Upon our review, tamoxifen is in the set of CNS drug and its effect to the model exponentially. Also tamoxifen is an antiestrogen drug and directly inhibits tumor growth. We executed our results to the bone metastases model proposed in [17]. In fact, because drug input to the body system, we consider drug as a control variable. We assumed that drug is used at $15th$ days of starting tumor. With this hypothesize we simulated

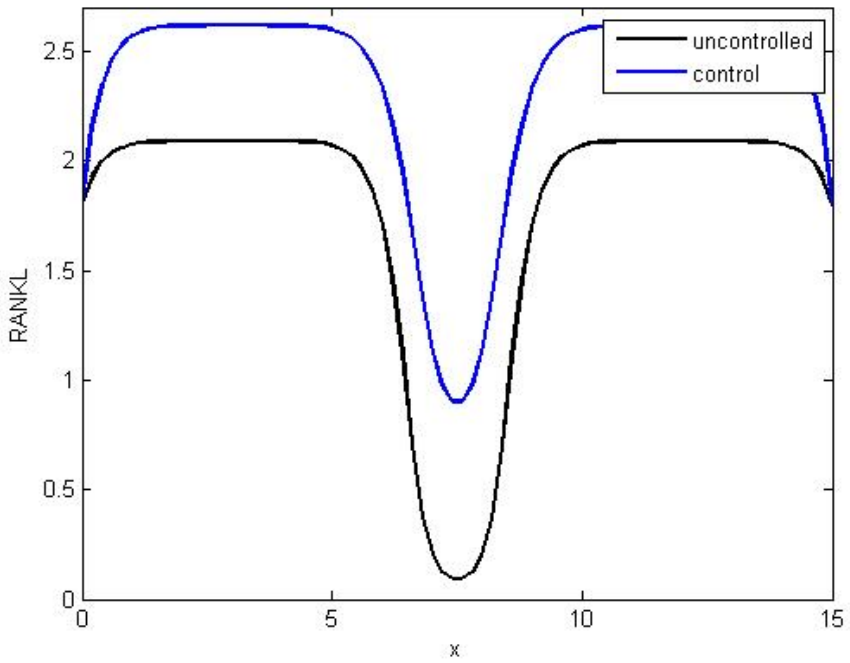

Figure 3: Comparison of RANKL concentration.

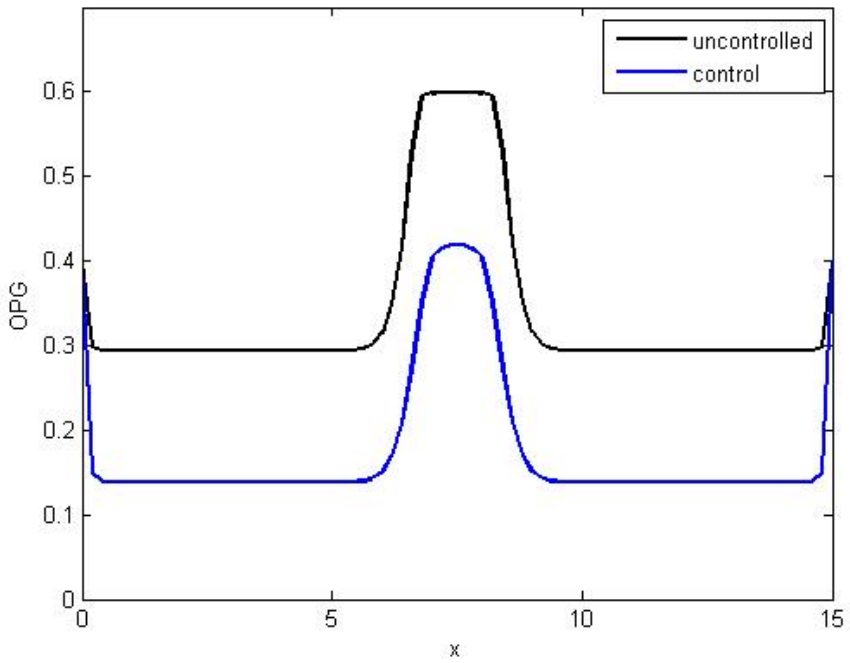

Figure 4: Comparison of OPG concentration.

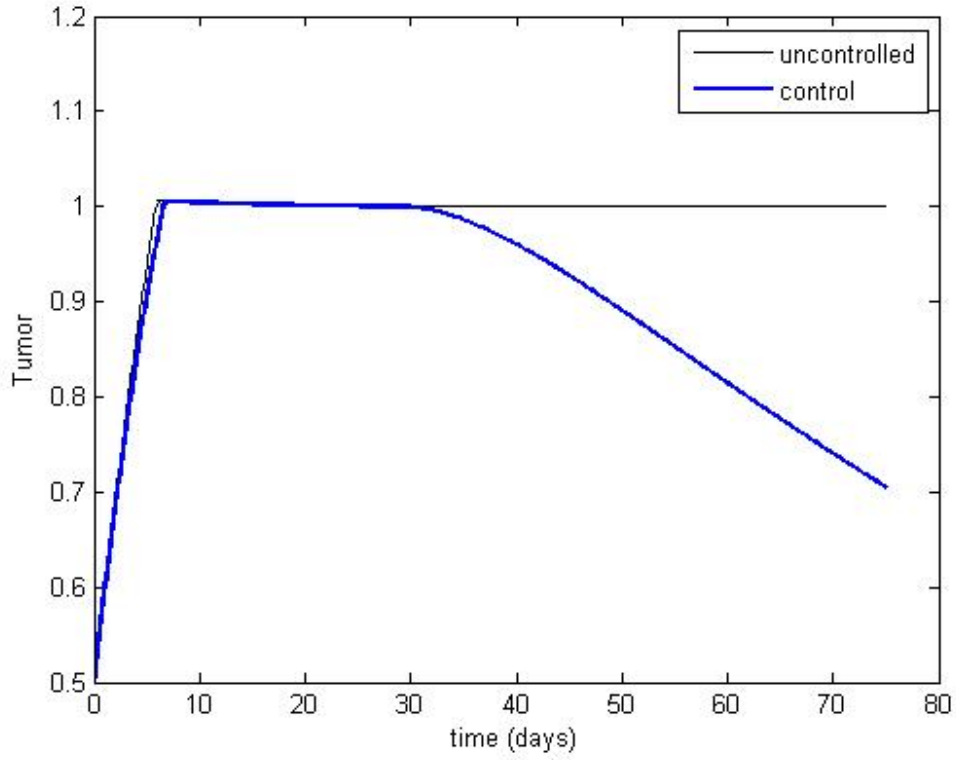

Figure 5: Evolution of tumor density is shown at 75 *days without drug (uncontrolled) and with constant dose* $(v = 20)$.

our model. The equations of the model were solved by using finite difference method. Our simulations show that the treatments play an important role to kill the tumor cells. At the start, prior to using the drug, tumor size is 1, but after using tamoxifen at high doses and adding to the model exponentially, we see that tumor size becomes smaller. We have shown that by using high doses of tamoxifen in breast cancer patient, we can approach RANKL, OPG and osteoclast to the case that tumor beginning. As a future work, this technique could be applied and combine chemotherapy and radiotherapy. Moreover we can evaluate the control model with using objective function and also we can investigate another drug that is used for bone metastases.

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