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MATHEMATICAL OPTIMIZATION OF BREAST CANCER TREATMENTS: ANALYZING CONTROL STRATEGIES FOR HORMONE THERAPY, KETOGENIC DIET AND IMMUNOTHERAPY

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Abstract. The most prevalent cancer in women, breast cancer continues to be a major public health concern. Our knowledge of how cancer cells interact with the immune system has improved thanks to clinical procedures and theoretical models, but more work is still required, particularly in order to investigate the genetic and molecular aspects using mathematical analysis. In this work, we create a mathematical model of the dynamics of breast cancer that includes immunotherapy, hormonetherapy, and the ketogenic diet. In order to maximize the efficacy of these treatments, this paper presents an optimal control framework that builds on previous foundational research. In order to optimize the three primary treatment controls hormonal therapy, ketogenic diet, and immunotherapy we closely analyze a comprehensive mathematical model that the author developed. By optimizing these controls, we investigate the most effective ways to control the progression of breast cancer using sophisticated mathematical tools. We also present comprehensive numerical simulations to validate and visualize our theoretical results, providing useful information for implementing these ideal treatment approaches. This study builds on earlier research to produce fresh findings that support more precise and efficient treatment of breast cancer.

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1. INTRODUCTION

Breast cancer is one of the critical health issues affecting the female gender all over the world. The cancer mainly originates from the manner in which genes that control or facilitate cell growth mutate in the ducts or lobules of the breast cells to cause a malignant tumor, which may further invade the rest of the body if not detected and managed earlier. It is said to be one of the most complex kinds of cancers, with variations in its growth rates and how it affects the body. Generally, it becomes common with increasing age in women; however, it may develop anytime after puberty according to the National Breast Cancer Foundation team (NBCF) [1]. Understanding the dynamics how it unfolds and interrelates with the normal processes in the human body is important in efforts to improve diagnostic and treatment methods.

ER-positive breast cancer is the type of breast cancer that has estrogen receptors on the surface of cancer cells. Receptors are proteins that accept certain molecules, called hormones like estrogen, which in this case goads on cancer growth. These same receptors bound to proteins can also be seen in normal cells of the breast, but in the case of ER-positive breast cancer, the receptors will enhance the growth of tumors when estrogen is bound to them. If these receptors are found on the surface of breast cancer cells, the cancer is often called hormone receptor-positive or hormone-positive breast cancer. This type of cancer is typically treated with hormone therapy in order to block or lower the effects of estrogen[2].

Cancer has turned into a severe health issue in Morocco, data for the year 2022 show that breast cancer is the most prevalent cancer in Moroccan women, representing about 38.8% of all cancer cases among females, with 12,756 cases reported out of a cumulative total of 32,872 cancer cases. Therefore, breast cancer becomes one of the significant public health burdens, being nearly 40% of the female cancer diagnoses, which are remarkably higher than those of other cancers, like cervix uteri at 8%, and colorectum at 7.8% [3]

With year 2024 in view, this information outlines the relevance and urgency of research into treatments against breast cancer and points out that this type of cancer continues to be the most

prevalent among women in Morocco. The high prevalence underlines the need for improved therapeutic approaches able to include new methods such as immunotherapy in dealing with this growing public health problem.

According to the World Health Organization (WHO) [5], the number of new cancer cases worldwide will sharply rise from 20 million in 2022 to 35.3 million by 2050. The organization also urges all preventive measures to be taken, such as quitting smoking, drinking less alcohol, sticking to a healthy diet, frequent exercise, and vaccination against primary diseases, besides regular screening for its early detection to reduce mortality rates. These include lung, breast, colon, prostate, and stomach cancers, which are among the deadliest and most common forms of cancer worldwide.

The landscape of breast cancer treatment has drastically changed over the last few decades, with improvement in multiple therapeutic modalities. One such advancement is hormone therapy including agents such as tamoxifen and aromatase inhibitors that target estrogen signaling pathways promoting the growth of the tumor and reduced, consequently, recurrence rates and increased survival. Aromatase inhibitors discovery as well as selective estrogen receptors modulators enlarged the possibility of treatment, above all in post-menopausal women. Parallel to this, immunotherapy has been developing as a most hopeful approach for the treatment of several malignancies, breast cancer included. Several kinds of immunotherapy, such as checkpoint inhibitors and chimeric antigen receptor T-cell therapy, are under study and hold much promise in improving the body's immune response against cancer cells. These therapies zero in on that innate property of the immune system to kill cancer cells, giving new hope to patients with either advanced or resistant forms of the disease[6].

Another pioneering field of research at present is the ketogenic diet that high intake of fat is associated with a low intake of carbohydrates. Hence, this dietary pattern thus changes the metabolism from glucose to ketones in the body and could deprive the cancer cells of their main energy supply and inhibit such cell growth . Thus, initial studies reveal that ketogenic diets may exhibit synergism with conventional therapies, probably altering the metabolic environment of the tumor, which would ultimately help manage the patient better [7].

Despite all of these advances, optimization of treatment strategies has been elusive. Indeed, much of a traditional approach to the optimization of therapy involves a trial-and-error method that is relatively inefficient and thus leaves many patients receiving suboptimal outcomes. One such tool that has time and again been used with very great potential for helping to understand the dynamics of disease and treatment effects is mathematical modeling. In our previous paper [8], we presented a detailed mathematical model to study the dynamics of normal cells, tumor cells and immune cells in the presence of estrogen and various treatments. In this model, the interactions among those constituents of interest were taken into consideration, which may provide a basic framework for probing the effects of treatments and searching for possible improvements.

The current paper is built upon this by introducing an optimal control framework to further develop/refine treatment strategies against estrogen receptor-Positive (ER+) breast cancer. In this paper, we will be concerned with the extension of the previous model presented in [8] by the introduction of three new key control variables related to hormone therapy, ketogenic diet and immunotherapy. We will use advanced mathematical techniques to find the optimal control strategy for the maximization of the efficacy of treatment while keeping the side effects at a minimum.

Our scheme is based on the detailed analysis of a nonlinear system of ordinary differential equations (ODEs), including the effects of the three controls. We will use this model to explore different kinds of treatment and identify the most efficient way to handle disease development in order to find out which of these strategies is more effective in managing disease progression. To confirm our theoretical results, we will perform a series of numerical simulations that will give practical insights into how to apply these strategies and their consequences for the patients.

2. Model Formulation

In this section, we formulate a related optimal control problem for the model in [8], involving ketogenic diet, anti-cancer drugs and immunotherapy dose, as control interventions to be used with a view of optimizing treatment of breast cancer. Here, we would want to minimize the size of a tumor, which denotes the degree of diseases in the body. Therefore, we will use as many anti-cancer drugs as possible. Nevertheless, we have also minimized the systemic cost

depending on the quantities of anti-cancer drugs, considering that high drug concentrations are harmful and could bring about some lethal side effects. In addition, our third control is the dose of immunotherapy. It enhances the immune system, hence its activity of killing cancer cells. In this regard, immunotherapy can have a very important role in fighting breast cancer by turning on and sustaining the body's natural defenses against tumor cells. That is, it improves outcomes by hitting some key pathways and mechanisms that breast cancer cells use to evade immune detection. This intervention tries to harness the power of the immune system and is thus of key importance in our fight against breast cancer.

In order to find the optimal control rates according to time $u_1(t)$, $u_2(t)$ and $u_3(t)$, we consider the following nonlinear system:

$$
\left\{
\begin{array}{l}
\dfrac{dN}{dt} = N(a_1 - b_1 N) - \dfrac{d_1 TN}{1+\varepsilon T} - l_1 NE(1-u_1(t)), \\
\dfrac{dT}{dt} = Ta_2(1-u_2(t)) - b_2 T^2 - g_1 IT - m_d T + l_1 NE(1-u_1(t)), \\
\dfrac{dI}{dt} = s + \dfrac{rIT}{o+T} - g_2 IT - mI - \dfrac{l_3 IE}{g+E}(1-u_1(t)) + \dfrac{p_M IM}{J_M + M}, \\
\dfrac{dE}{dt} = p(1-u_1(t)) - \theta E, \\
\dfrac{dM}{dt} = u_3(t) - n_M M + \dfrac{\chi MI}{\xi + I}.
\end{array}
\right. \tag{2.1}
$$

We now explain the model parameters and describe the terms biologically for a better understanding of the interactions presented in each equation.

2.1. Modeling normal cells. The dynamics of normal cells N are described by:

$$\frac{dN}{dt} = N((a_1 - b_1 N) - \frac{d_1 TN}{1+\varepsilon T} - l_1 NE(1-u_1(t)).$$

Here, a_1 represents the logistic growth rate of normal cells, b_1 is their natural death rate, $\dfrac{d_1 TN}{1+\varepsilon T}$ models the infection rate with d_1 as the inhibition rate and ε as the saturation effect, and $l_1 NE(1-u_1(t))$ accounts for the reduction in normal cells due to estrogen, modulated by the hormone therapy control $u_1(t)$.

2.2. Modeling tumor cells. Tumor cell dynamics are given by:

$$\frac{dT}{dt} = Ta_2(1-u_2(t)) - b_2 T^2 - g_1 IT - m_d T + l_1 NE(1-u_1(t)).$$

In this equation, a_2 is the growth rate of tumor cells, influenced by the ketogenic diet control $u_2(t)$. The term b_2T^2 reflects the quadratic death rate of tumor cells, g_1IT models tumor cell removal by the immune response, m_d denotes tumor cell death due to nutrient starvation, and $l_1NE(1-u_1(t))$ describes the transformation of normal cells into tumor cells under the influence of estrogen and hormone therapy $u_1(t)$.

2.3. Modeling lymphocytes. The dynamics of immune cells I are represented by:

$$\frac{dI}{dt} = s + \frac{rIT}{o+T} - g_2IT - mI - \frac{l_3IE}{g+E}(1-u_1(t)) + \frac{p_MIM}{j_M+I}.$$

Here, s is the constant source rate of immune cells, $\frac{rIT}{o+T}$ reflects the nonlinear growth of immune cells stimulated by tumor presence with r as the immune response rate and o as the immune threshold, g_2IT models immune cell inactivation, m denotes natural death rate of immune cells, $\frac{l_3IE}{g+E}(1-u_1(t))$ accounts for suppression of immune cells by estrogen, and $\frac{p_MIM}{j_M+I}$ represents activation of immune cells by immunotherapy.

2.4. Modeling estrogen. Estrogen dynamics are described by:

$$\frac{dE}{dt} = p(1-u_1(t)) - \theta E.$$

In this equation, p represents the production rate of estrogen, θ is the decay rate, and $u_1(t)$ modulates the production rate reflecting the impact of hormone therapy on estrogen levels.

2.5. Modeling immunotherapy. The dynamics of immunotherapy M are modeled by:

$$\frac{dM}{dt} = u_3(t) - n_MM + \frac{\chi_MIM}{\xi+I}.$$

Here, $u_3(t)$ represents the control intervention for immunotherapy administration (the amount of IL-2 injected per day per litre of body volume (in IU/l per day) [13]), n_M denotes the turnover rate of the drug, and $\frac{\chi_MIM}{\xi+I}$ models the production of immunotherapy influenced by activated immune cells with x_M as the production rate and ξ as a saturation constant.

3. THE OPTIMAL CONTROL

All control interventions were optimized in a way to ensure the most effective treatment approach with minimized harm for treating breast cancer. To this end, we consider the following objectif functional:

$$J(u) = \int_0^{T_f} A_1 T(t) + A_2 E(t) + \frac{1}{2} A_3 u_1^2(t) + \frac{1}{2} A_4 u_2^2(t) + \frac{1}{2} A_5 u_3^2(t) dt, \tag{3.1}$$

where the functions u_1, u_2, and u_3 represent the ketogenic diet, anti-cancer drugs, and immunotherapy dose, respectively. A_i is a positive weight parameter associated with the control u_i with $i \in \{1,2,3\}$ and T_f is the period of control. The goal is to find a set of optimal controls (u_1^*, u_2^*, u_3^*) such that:

$$J(u_1^*, u_2^*, u_3^*) = \min_{(u_1,u_2,u_3)\in U} J(u_1, u_2, u_3),$$

where U is the control set defined by:

$$U = \left\{ (u_1, u_2, u_3) \mid u_i \text{ is measurable}, 0 \leq u_i(t) \leq u_{i\max} \leq 1, i = 1,2,3, \forall t \in [0, T_f] \right\}.$$

3.1. Existence of an Optimal Control.

The initial outcome concerns the existence of an optimal control, as stated in the following theorem.

Theorem 3.1. *There exists an optimal control $u^* = (u_1^*, u_2^*, u_3^*)$ such that:*

$$J(u^*) = \min\{J(u) \mid u = (u_1, u_2, u_3) \in U\}.$$

Proof. The control set U is non-empty, convex, and closed by definition. The right-hand side functions of the state equations are continuous and bounded above by the sum of the bounded controls and state variables, with a linear dependence on $u_i(t)$ through coefficients that depend on time and state. The integrand of $J(u_i)$ is convex with respect to U, which satisfies the necessary convexity conditions for optimality. Additionally, the integrand is bounded below by a function of the form $-c_2 + c_1 u_i^2$ where $c_1 > 0$, ensuring the boundedness of the objective functional. These conditions, together with the compactness of the control system, guarantee the existence of an optimal control. □

We will now examine some of the possible strategies for treating breast cancer using hormonal therapy, a ketogenic diet, and immunotherapy. In the Sequential Therapy Approach, hormonal therapy is applied first and the ketogenic diet afterwards. The Adaptive Therapy Approach combines hormonal therapy and immunotherapy and adjusts the dosage of each modulating with the patient's response. This third strategy, called Integrative Metabolic and Immune Modulation, applies the ketogenic diet along with immunotherapy. Personalized Combination Therapy: tailoring all three treatments to the individual; Cyclic Treatment Regimen: cycling through the therapies, balancing side effects; Optimized Combination Therapy: adjusting treatments in real-time to patient feedback. All have the intention of maximizing effectiveness while reducing side effects to the lowest degree possible.

3.2. Optimality System.

Now, we can apply Pontryagin's minimum principle to determine an optimal solution [17]. This principle changes problems (2.1) and (3.1) into the following pointwise minimization of the Hamiltonian H with respect to u, such that:

$$\begin{aligned}
H = {} & A_1T + A_2E + \frac{1}{2}A_3u_1(t)^2 + \frac{1}{2}A_4u_2(t)^2 + \frac{1}{2}A_5u_3(t)^2 \\
& + \theta_1(t)\left[N(a_1 - b_1N) - \frac{d_1TN}{1+\varepsilon T} - l_1NE(1-u_1(t))\right] \\
& + \theta_2(t)\left[T(a_2(1-u_2(t)) - b_2T) - g_1IT - m_dT + l_1NE(1-u_1(t))\right] \\
& + \theta_3(t)\left[s + \frac{rIT}{o+T} - g_2IT - mI - \frac{l_3IE}{g+E}(1-u_1(t)) + \frac{P_MIM}{j_M+M}\right] \\
& + \theta_4\left[p(1-u_1(t)) - \theta E\right] + \theta_5\left[u_3(t) - n_MM + \frac{\chi MI}{\xi+I}\right],
\end{aligned}$$

where, θ_1, θ_2, θ_3, θ_4 and θ_5 are the adjoint variables. We then determine these adjoint variables by applying the necessary conditions to the Hamiltonian H. Using Pontryagin's Maximum Principle [17], we derived a minimized Hamiltonian that reduces the objective function or cost functional. we were able to characterize the optimal control set u_1^*, u_2^*, and u_3^* as presented in the following result.

Theorem 3.2. *(Characterization of the Optimal Control) Given an optimal control u_1^*, u_2^*, and u_3^* and solutions to the corresponding state system that minimize the functional $J(u)$, there exist*

adjoint variables θ_i *for* $i = 1,2,3,4$ *satisfying:*

$$\begin{aligned}
\frac{d\theta_1}{dt} &= -\theta_1\left(a_1 - 2b_1N^*\right) + \frac{d_1T^*}{1+\varepsilon T^*}\theta_1 + l_1E^*(1-u_1^*(t))\theta_1 - l_1E^*(1-u_1^*(t))\theta_2,\\
\frac{d\theta_2}{dt} &= -A_1 + \frac{\theta_1 d_1 N^*}{(1+\varepsilon T^*)^2} - \theta_2\left(a_2(1-u_2^*(t)) - 2b_2T^* - g_1I^* - m_d\right) - \frac{\theta_3 rI^*}{o+T^*},\\
\frac{d\theta_3}{dt} &= \theta_2 g_1 T^* - \theta_3\left(\frac{rT^*}{o+T^*} - g_2T^* - m - \frac{l_3E^*}{g+E^*}(1-u_1^*(t)) + \frac{P_{M^*}M^*}{j_{M^*}+M^*}\right) - \theta_5\frac{\chi M^*\xi}{(\xi+I^*)^2},\\
\frac{d\theta_4}{dt} &= -A_2 + l_1N^*(1-u_1^*(t))(\theta_1-\theta_2) - \theta_3\left(\frac{l_3I^*g}{(g+E^*)^2}(1-u_1^*(t))\right) + \theta_4\theta,\\
\frac{d\theta_5}{dt} &= -\theta_3\frac{P_MI^*j_{M^*}}{(j_{M^*}+M^*)^2} + \theta_5\left(n_{M^*} - \frac{\chi I^*}{\xi+I^*}\right).
\end{aligned}$$

where $\theta_i\left(T_f\right) = 0$ *for* $i = 1,2,3,4,5$. *Moreover, the optimal control can be represented by:*

$$u_1^* = \min\left\{\max\left\{0, \frac{1}{A_3}\left(\theta_2 l_1 N^*E^* - \theta_1 l_1 N^*E^* - \theta_3\frac{l_3I^*E^*}{g+E^*} + \theta_4 p\right)\right\}, 1\right\}, \tag{3.2}$$

$$u_2^* = \min\left\{\max\left\{0, \frac{\theta_2 a_2 T^*}{A_4}\right\}, 1\right\}, \tag{3.3}$$

$$u_3^* = \min\left\{\max\left\{0, -\frac{\theta_5}{A_5}\right\}, 1\right\}. \tag{3.4}$$

Proof. By Pontryagin's maximum principle, there exist adjoint variables θ_1, θ_2, θ_3, θ_4 and θ_5 which satisfy the following equations:

$$\begin{aligned}
\frac{d\theta_1}{dt} &= -\frac{\partial H}{\partial N}, \quad \theta_1(T_f) = 0;\\
\frac{d\theta_2}{dt} &= -\frac{\partial H}{\partial T}, \quad \theta_2(T_f) = 0;\\
\frac{d\theta_3}{dt} &= -\frac{\partial H}{\partial I}, \quad \theta_3(T_f) = 0;\\
\frac{d\theta_4}{dt} &= -\frac{\partial H}{\partial E}, \quad \theta_4(T_f) = 0;\\
\frac{d\theta_5}{dt} &= -\frac{\partial H}{\partial M}, \quad \theta_5(T_f) = 0.
\end{aligned}$$

where H is the Hamiltonian and defined as:

$$H(N,T,M,E,M,u_1,u_2,u_3,\theta) = L(N,T,M,E,M,u_1,u_2,u_3) + \theta_1\dot{N} + \theta_2\dot{T} + \theta_3\dot{I} + \theta_4\dot{E} + \theta_5\dot{M}$$

The optimal control u^* is obtained by solving the equations:

$$\frac{\partial H}{\partial u_1} = 0 \text{ at } u_1 = u_1^*, \quad \frac{\partial H}{\partial u_2} = 0 \text{ at } u_2 = u_2^*, \quad \text{and} \quad \frac{\partial H}{\partial u_3} = 0 \text{ at } u_3 = u_3^*.$$

Hence, we obtain

$$u_1^* = \frac{1}{A_3}\left(\theta_2 l_1 N^* E^* - \theta_1 l_1 N^* E^* - \theta_3 \frac{l_3 I^* E^*}{g+E^*} + \theta_4 p\right), \tag{3.5}$$

$$u_2^* = \frac{\theta_2 a_2 T^*}{A_4}, \tag{3.6}$$

$$u_3^* = -\frac{\theta_5}{A_5}. \tag{3.7}$$

□

4. Numerical Simulation and Analysis

The discretized system using the Euler's method is given by:

$$\begin{aligned}
\frac{N_{i+1}-N_i}{h} &= N_i(a_1 - b_1 N_i) - \frac{d_1 T_i N_i}{1+\varepsilon T_i} - l_1 N_i E_i\left(1-u_1^i\right),\\
\frac{T_{i+1}-T_i}{h} &= T_i a_2\left(1-u_2^i\right) - b_2 T_i^2 - g_1 I_i T_i - m_d T_i + l_1 N_i E_i\left(1-u_1^i\right),\\
\frac{I_{i+1}-I_i}{h} &= s + \frac{r I_i T_i}{o+T_i} - g_2 I_i T_i - m I_i - \frac{l_3 I_i E_i}{g+E_i}\left(1-u_1^i\right) + \frac{p_{M_i} I_i M_i}{J_{M_i}+M_i},\\
\frac{E_{i+1}-E_i}{h} &= p\left(1-u_1^i\right) - \theta E_i,\\
\frac{M_{i+1}-M_i}{h} &= u_3^i - n_{M_i} M_i + \frac{\chi_M I_i}{\xi + I_i}.
\end{aligned}$$

where:

- N_i, T_i, I_i, E_i, M_i are the variables at time step t_i,
- $N_{i+1}, T_{i+1}, I_{i+1}, E_{i+1}, M_{i+1}$ are the variables at the next time step t_{i+1},
- h is the time step size.

The adjoint system approximated by the first-order backward difference method is given by:

$$\begin{aligned}
\frac{\theta_1^{n-i}-\theta_1^{n-i-1}}{h} &= -\theta_1^{n-i}(a_1 - 2b_1 N_{i+1}) + \frac{d_1 T_{i+1}}{1+\varepsilon T_{i+1}}\theta_1^{n-i} + l_1 E_{i+1}(1-u_1^i(t))\theta_1^{n-i} - l_1 E_{i+1}(1-u_1^i(t))\theta_2^{n-i},\\
\frac{\theta_2^{n-i}-\theta_2^{n-i-1}}{h} &= -A_1 + \theta_1^{n-i}\frac{d_1 N_{i+1}}{(1+\varepsilon T_{i+1})^2} - \theta_2^{n-i}\left(a_2(1-u_2^i(t)) - 2b_2 T_{i+1} - g_1 I_{i+1} - m_d\right) - \theta_3^{n-i}\frac{r I_{i+1}}{o+T_{i+1}},\\
\frac{\theta_3^{n-i}-\theta_3^{n-i-1}}{h} &= \theta_2^{n-i} g_1 T_{i+1} - \theta_3^{n-i}\left(\frac{r T_{i+1}}{o+T_{i+1}} - g_2 T_{i+1} - m - \frac{l_3 E_{i+1}}{g+E_{i+1}}(1-u_1^i(t)) + \frac{P_M M_{i+1}}{j_M + M_{i+1}}\right) -\\
&\qquad \theta_5^{n-i}\frac{\chi M_{i+1}\xi}{(\xi + I_{i+1})^2},\\
\frac{\theta_4^{n-i}-\theta_4^{n-i-1}}{h} &= -A_2 + l_1 N_{i+1}(1-u_1^i(t))(\theta_1^{n-i} - \theta_2^{n-i}) - \theta_3^{n-i}\frac{l_3 I_{i+1} g}{(g+E_{i+1})^2}(1-u_1^i(t)) + \theta_4^{n-i}\theta,
\end{aligned}$$

$$\frac{\theta_5^{n-i}-\theta_5^{n-i-1}}{h}=-\theta_3^{n-i}\frac{P_M I_{i+1}}{(j_M+M_{i+1})^2}+\theta_5^{n-i}\left(n_M-\frac{\chi I_{i+1}}{\xi+I_{i+1}}\right).$$

The algorithm outlining the approximation method for determining the optimal control is as follows: *Algorithm*

Step 1 : $N(0)=N_0, T(0)=T_0, I(0)=I_0, E(0)=E_0, M(0)=M_0, \theta_1(t_f)=0, \theta_1(t_f)=0, \theta_2(t_f)=0, \theta_3(t_f)=0, \theta_4(t_f)=0, \theta_5(t_f)=0, u_1(0)=0, u_2(0)=0, u_3(0)=0.$

step 2: for $i=0,...,n-1$, do:

$$N_{i+1}=N_i+h\left(N_i(a_1-b_1N_i)-\frac{d_1T_iN_i}{1+\varepsilon T_i}-l_1N_iE_i\left(1-u_1^i\right)\right),$$

$$T_{i+1}=T_i+h\left(T_ia_2\left(1-u_2^i\right)-b_2T_i^2-g_1I_iT_i-m_dT_i+l_1N_iE_i\left(1-u_1^i\right)\right),$$

$$I_{i+1}=I_i+h\left(s+\frac{rI_iT_i}{o+T_i}-g_2I_iT_i-mI_i-\frac{l_3I_iE_i}{g+E_i}\left(1-u_1^i\right)+\frac{pM_iI_iM_i}{J_M+M_i}\right),$$

$$E_{i+1}=E_i+h\left(p\left(1-u_1^i\right)-\theta E_i\right),$$

$$M_{i+1}=M_i+h\left(u_3^i-n_MM_i+\frac{\chi M_iI_i}{\xi+I_i}\right),$$

$$\theta_1^{n-i-1}=\theta_1^{n-i}+h\left[-\theta_1^{n-i}(a_1-2b_1N_{i+1})+\frac{d_1T_{i+1}}{1+\varepsilon T_{i+1}}\theta_1^{n-i}+l_1E_{i+1}(1-u_1^i(t))\theta_1^{n-i}-l_1E_{i+1}(1-u_1^i(t))\theta_2^{n-i}\right],$$

$$\theta_2^{n-i-1}=\theta_2^{n-i}+h\left[-A_1+\theta_1^{n-i}\frac{d_1N_{i+1}}{(1+\varepsilon T_{i+1})^2}-\theta_2^{n-i}\left(a_2(1-u_2^i(t))-2b_2T_{i+1}-g_1I_{i+1}-m_d\right)-\theta_3^{n-i}\frac{rI_{i+1}}{o+T_{i+1}}\right],$$

$$\theta_3^{n-i-1}=\theta_3^{n-i}+h\left[\theta_2^{n-i}g_1T_{i+1}-\theta_3^{n-i}\left(\frac{rT_{i+1}}{o+T_{i+1}}-g_2T_{i+1}-m-\frac{l_3E_{i+1}}{g+E_{i+1}}(1-u_1^i(t))+\frac{P_{M_{i+1}}M_{i+1}}{j_{M_{i+1}}+M_{i+1}}\right)\right.$$
$$\left.-\theta_5^{n-i}\frac{\chi M_{i+1}\xi}{(\xi+I_{i+1})^2}\right],$$

$$\theta_4^{n-i-1}=\theta_4^{n-i}+h\left[-A_2+l_1N_{i+1}(1-u_1^i(t))(\theta_1^{n-i}-\theta_2^{n-i})-\theta_3^{n-i}\frac{l_3I_{i+1}g}{(g+E_{i+1})^2}(1-u_1^i(t))+\theta_4^{n-i}\theta\right],$$

$$\theta_5^{n-i-1}=\theta_5^{n-i}+h\left[-\theta_3^{n-i}\frac{P_{M_{i+1}}I_{i+1}}{(j_{M_{i+1}}+M_{i+1})^2}+\theta_5^{n-i}\left(n_{M_{i+1}}-\frac{\chi I_{i+1}}{\xi+I_{i+1}}\right)\right],$$

$$Q_{i+1}=\frac{1}{A_3}\left(\theta_2^{n-i-1}l_1N_{i+1}E_{i+1}-\theta_1^{n-i-1}l_1N_{i+1}E_{i+1}-\theta_3^{n-i-1}\frac{l_3I_{i+1}E_{i+1}}{g+E_{i+1}}+\theta_4^{n-i-1}p\right),$$

$$R_{i+1}=\frac{\theta_2^{n-i-1}a_2T_{i+1}}{A_4},$$

$$S_{i+1}=-\frac{\theta_5^{n-i-1}}{A_5},$$

$$u_1^{i+1}=\min\left\{\max\left\{0,Q_{i+1}\right\},1\right\},$$

$$u_2^{i+1}=\min\left\{\max\left\{0,R_{i+1}\right\},1\right\},$$

$$u_3^{i+1}=\min\left\{\max\left\{0,S_{i+1}\right\},1\right\}.$$

end for

Step 3: For $i = 1, \ldots, n$, write:

$$N^*(t_i) = N_i, \quad T^*(t_i) = T_i, \quad I^*(t_i) = I_i, \quad E^*(t_i) = E_i, \quad M^*(t_i) = M_i, \quad u_1^*(t_i) = u_1^i, \quad u_2^*(t_i) = u_2^i, \quad u_3^*(t_i) = u_3^i.$$

end for

Parameter	**Description**	**Rate**
a_1	Logistic growth rate of normal cells	0.7
b_1	Natural death rate of normal cells	0.00002
d_1	Inhibition rate of normal cells due to DNA damage	6×10^{-9}
ε	Saturation effect constant in the infection rate of normal cells	0.1
l_1	Rate at which excess estrogen leads to DNA mutation and reduction of normal cells	0.068
a_2	Limited growth rate of tumor cells	1.028
b_2	Death rate of tumor cells due to starvation of nutrients (influenced by ketogenic diet)	0.001
g_1	Coefficient representing the removal of tumor cells due to the immune response	3×10^{-10}
m_d	Natural death rate of tumor cells	2.0
s	Constant source rate of immune response	130
r	Immune response rate representing the activation of immune cells by tumor cells	0.20
o	Immune threshold rate	3×10^5
g_2	Interaction coefficient representing the inactivation of immune cells by tumor cells	1×10^{-7}
m	Natural death rate of immune cells	0.29
l_3	Suppression rate of immune cells due to excess estrogen	0.002
g	Estrogen threshold rate	0.1
p	Source rate of estrogen	$1.3 \times 10^{1.5}$

θ	Decay rate of estrogen after being washed out from the body	0.97
n_M	Turnover rate of immunotherapy drug per day per litre of body volume	0.117427
χ	Production rate of immunotherapy from activated immune cells (CD8+ T)	0.07874
ξ	Saturation constant in the Michaelis–Menten interaction term for immunotherapy production	2503.6
j_M	Production rate of immunotherapy from activated immune cells (CD8+ T)	2.5036×10^5
p_M	Production rate of immunotherapy from activated immune cells (CD8+ T)	0.0668
$u_1(t)$	Control intervention representing hormone therapy	Control function over time
$u_2(t)$	Control intervention representing the ketogenic diet	Control function over time
$u_3(t)$	Control intervention representing the amount of IL-2 (immunotherapy drug)	Control function over time

In this section, we present and discuss the results obtained through the numerical simulation of the proposed optimal control model. The dynamics of the system's key variables namely, natural cells (N), tumor cells (T), immune cells (I), and estrogen levels (E) are analyzed both with and without the application of the control interventions. The controls considered include hormone therapy, ketogenic diet, and immunotherapy, aiming to minimize tumor burden while managing systemic effects.

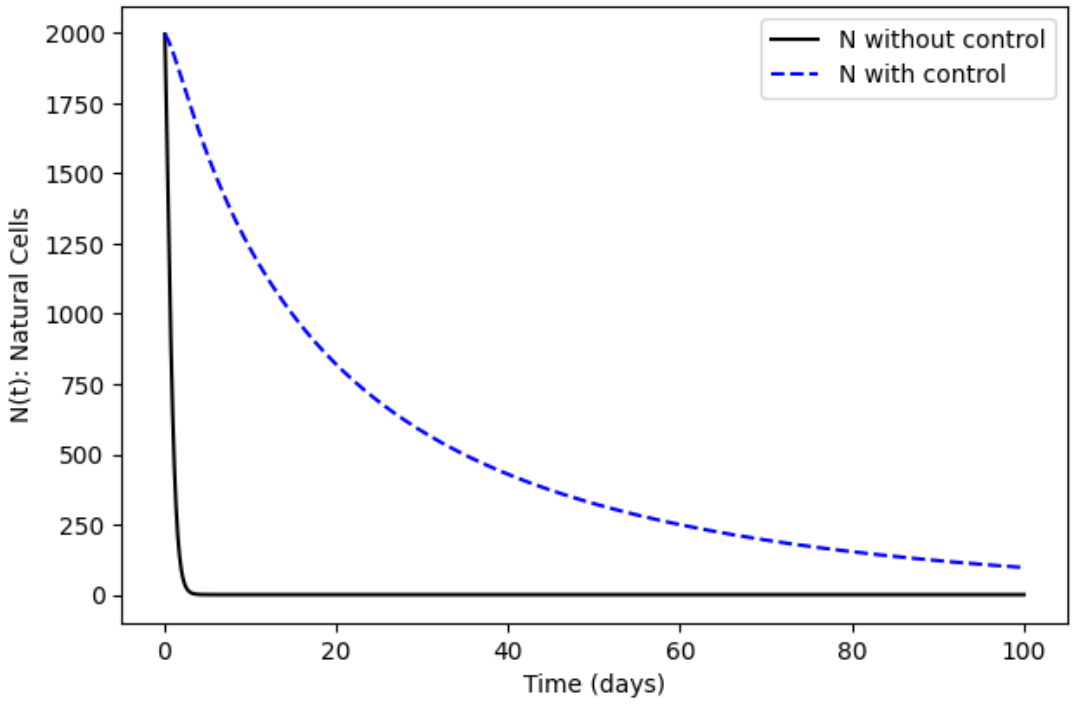

FIGURE 1. Natural Cell Population Dynamics with and without Treatment

$N(t)$ in figure(1) displays distinct dynamics under controlled and uncontrolled scenarios. Without the application of control strategies, the natural cells rapidly decline to very low levels within a few days, due to the overwhelming effects of tumor burden and excess estrogen. However, when control interventions are implemented namely hormone therapy, ketogenic diet, and immunotherapy the natural cells experience a slower, more gradual reduction, stabilizing at a significantly higher level compared to the uncontrolled case. This improvement highlights the protective role of the therapeutic strategies, particularly hormone therapy in reducing estrogen induced damage, and demonstrates that the integrated treatment plan not only targets tumor eradication but also contributes to the preservation of normal tissue integrity.

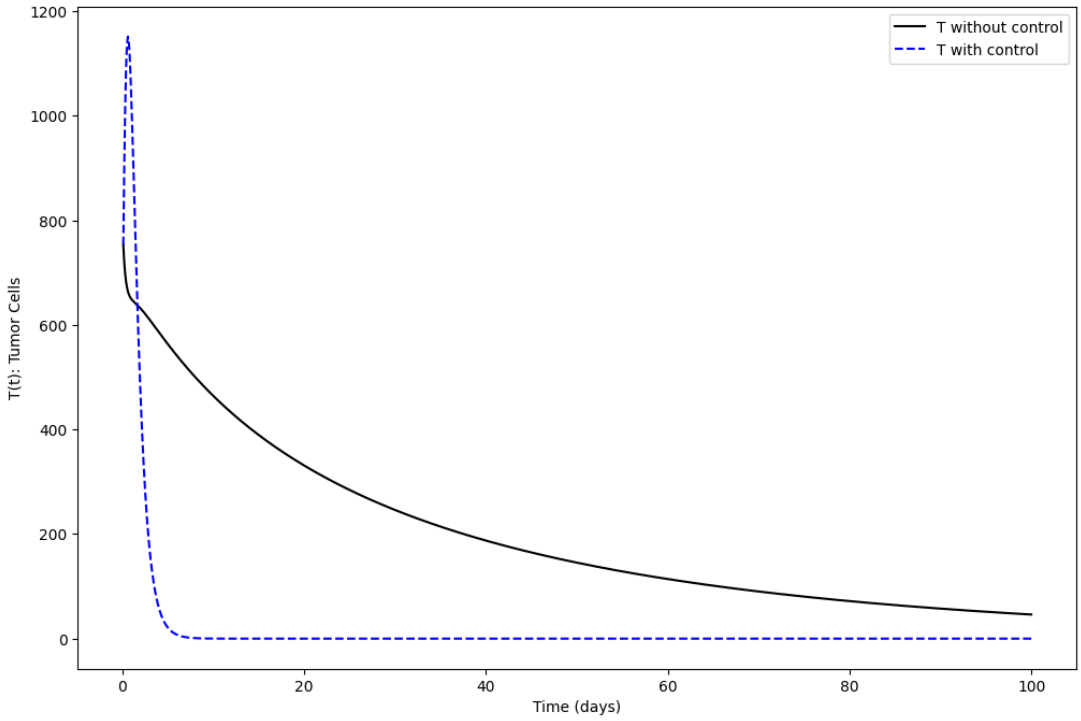

FIGURE 2. Tumor Cell Population Dynamics with and without Treatment

The tumor cells $T(t)$ exhibit a markedly different behavior in figure(2). In the absence of control interventions, the tumor cell population shows a slow but steady decline over time, reflecting the natural immune response and resource competition within the system. Upon implementing the control strategies, the tumor burden is dramatically reduced to almost negligible levels within a few days. The controls, specifically the ketogenic diet depriving the tumor of glucose and immunotherapy enhancing immune response, coupled with estrogen suppression through hormone therapy, synergistically contribute to the rapid eradication of the tumor population. This result demonstrates the effectiveness of the combined control approach in achieving the primary objective of minimizing tumor growth and suggests a promising potential for therapeutic application.

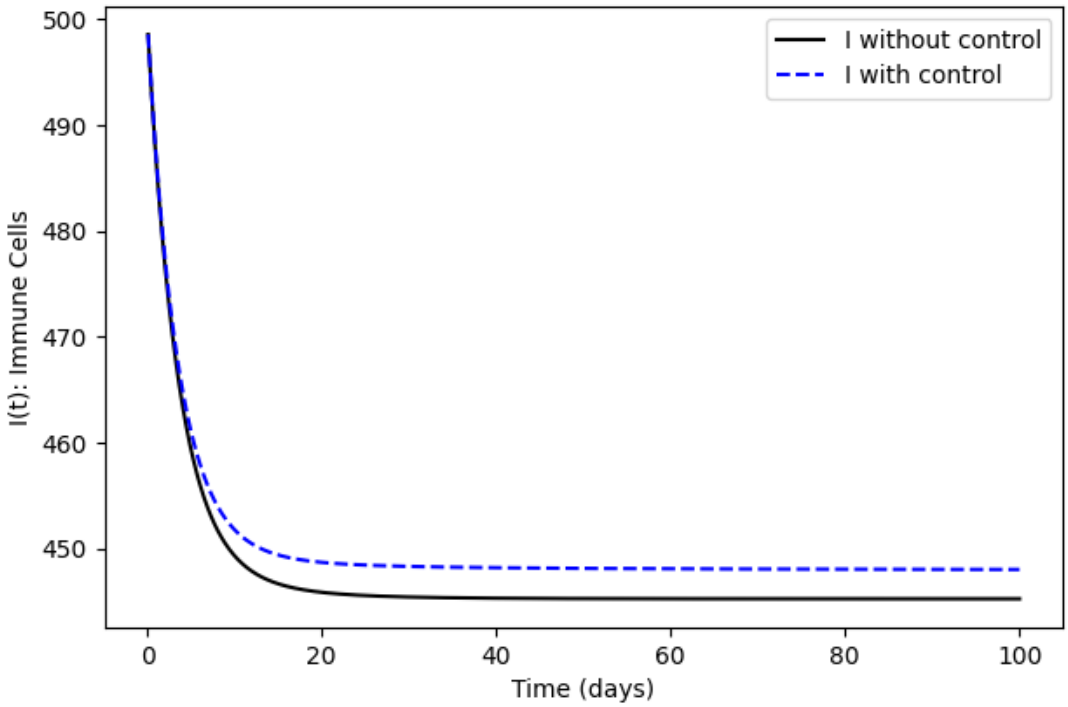

FIGURE 3. Immune Cell Population Dynamics with and without Treatment

In figure (3), $I(t)$ is critically influenced by the introduction of control measures. In the absence of treatment, the immune response initially exhibits a rapid decline, followed by stabilization at a lower baseline. This reflects the immunosuppressive effects exerted by the tumor and estrogen. With the application of optimal controls, immune cells decline at a slower rate and stabilize at a higher plateau compared to the uncontrolled scenario. Notably, immunotherapy contributes to sustaining a more robust immune presence, enhancing the overall defense against tumor progression. These results confirm that integrating immunotherapy within the treatment plan significantly reinforces immune system activity, aligning with therapeutic goals of immunomodulation in breast cancer management.

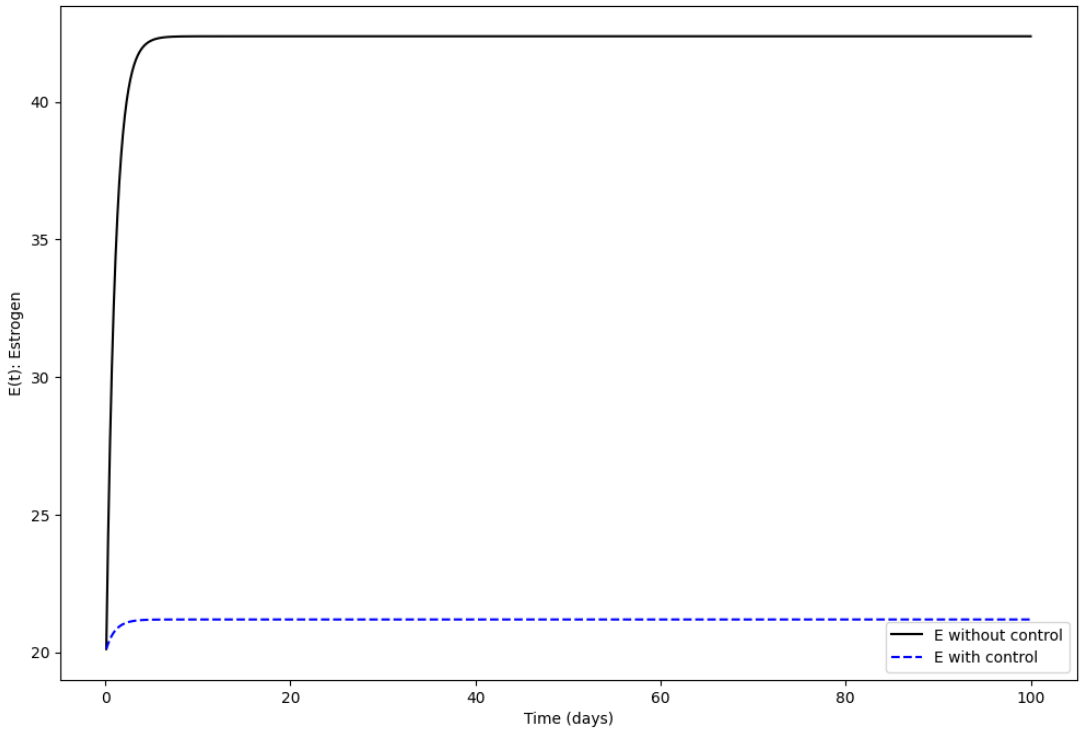

FIGURE 4. Estrogen Level Over Time

The behavior of estrogen $E(t)$ is particularly significant given the estrogen dependence of ER^+ breast cancer. Without control, estrogen levels increase rapidly and stabilize at a high concentration, providing a continuous stimulus for tumor growth. The application of hormone therapy markedly suppresses estrogen levels, maintaining them at a low and stable value throughout the simulation period. This effective suppression directly impacts tumor dynamics by cutting off the hormonal growth signal essential for tumor proliferation. The results align with the therapeutic goals of hormone therapy, illustrating its pivotal role in managing ER^+ breast cancer progression within the model framework.

5. CONCLUSION

In this study, we developed and analyzed a comprehensive mathematical model incorporating hormone therapy, ketogenic diet, and immunotherapy as control interventions against ER^+ breast cancer. Our optimal control framework, grounded in rigorous theoretical analysis and

numerical simulation, demonstrated the significant benefits of coordinated therapeutic strategies. The tumor cell population was markedly reduced with the introduction of controls, while estrogen levels were effectively suppressed, depriving cancer cells of their primary growth signal. Furthermore, the treatment preserved a greater number of natural cells and strengthened the immune system's response, confirming the synergistic potential of combining metabolic, hormonal, and immunological interventions. Collectively, these findings validate the proposed optimal control approach as a promising strategy for enhancing breast cancer treatment outcomes, minimizing systemic toxicity, and offering a holistic management framework for patients.

6. Further research

Future work could extend the current model by incorporating spatial heterogeneity through partial differential equations to reflect the tumor micro environment's complexity more realistically. Additionally, integrating patient specific parameters derived from clinical data would enable the development of personalized treatment strategies. Investigating resistance mechanisms to hormone therapy and immunotherapy within the model could further refine predictive capabilities and optimize long-term treatment planning. Finally, exploring the impact of treatment scheduling and dose variation, including the use of adaptive control strategies, may enhance the practical applicability of the model and contribute to more effective, patient-tailored therapeutic regimens.

Conflict of Interests

The authors declare that there is no conflict of interests.

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