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Research article

Nonlinear dynamics of estrogen receptor-positive breast cancer integrating experimental data: A novel spatial modeling approach

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Abstract: Oncology research has focused extensively on estrogen hormones and their function in breast cancer proliferation. Mathematical modeling is essential for the analysis and simulation of breast cancers. This research presents a novel approach to examine the therapeutic and inhibitory effects of hormone and estrogen therapies on the onset of breast cancer. Our proposed mathematical model comprises a nonlinear coupled system of partial differential equations, capturing intricate interactions among estrogen, cytotoxic T lymphocytes, dormant cancer cells, and active cancer cells. The model's parameters are meticulously estimated through experimental studies, and we conduct a comprehensive global sensitivity analysis to assess the uncertainty of these parameter values. Remarkably, our findings underscore the pivotal role of hormone therapy in curtailing breast tumor growth by blocking estrogen's influence on cancer cells. Beyond this crucial insight, our proposed model offers an integrated framework to delve into the complexity of tumor progression and immune response under hormone therapy. We employ diverse experimental datasets encompassing gene expression profiles, spatial tumor morphology, and cellular interactions. Integrating multidimensional experimental data with mathematical models enhances our understanding of breast cancer dynamics and paves the way for personalized treatment strategies. Our study advances our comprehension of estrogen receptor-positive breast cancer and exemplifies a transformative approach that merges experimental data with cutting-edge mathematical modeling. This framework promises to illuminate the complexities of cancer progression and therapy, with broad implications for oncology.

Keywords: breast cancer; estrogen; mathematical modeling; hormone therapy; sensitivity analysis

1. Introduction

Breast cancer, the most prevalent disease among women globally, was responsible for over 2.3 million diagnoses and 685,000 fatalities in 2020 [1]. It comprises different kinds that develop in the lobules and ducts of breast tissue [2]. The most common kind is invasive ductal carcinoma, which starts in the ducts and spreads to nearby breast tissue. Other types of breast cancer include inflammatory breast cancer, which is aggressive in nature, and invasive lobular carcinoma, which starts in the lobules [3]. Although the precise etiology of the phenomenon is still unknown, it is widely believed that a combination of genetic and environmental factors influences its manifestation [4]. Risk factors for breast cancer include several characteristics, such as advanced age, familial and personal medical history, breast density and particular genetic abnormalities [5]. Mutations in BRCA1 and BRCA2 genes significantly increase the risk of breast cancer. These genes are responsible for repairing DNA damage, and mutations can impair this function, leading to a higher likelihood of cancer development. A family history of breast cancer, especially in first-degree relatives (mother, sister, daughter), can elevate an individual's risk. Specific genetic mutations passed down through families can be responsible for this predisposition. Prolonged exposure to estrogen, either through early menstruation, late menopause or the use of hormone replacement therapy, can increase the risk of breast cancer. Estrogen can promote cell growth in breast tissue. The symptoms of breast cancer vary depending on the stage of the disease, including manifestations such as the presence of breast tumors, variations in breast form or size, discharge from the nipple and modifications in the skin. The timely identification and intervention of breast cancer afford a considerable likelihood of survival and the attainment of a state of well-being for the majority of women affected by it [6].

Breast cancer is a complex disease that has numerous subtypes, including lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS), inflammatory breast cancer (IBC) and metastatic cancer, each with distinct morphological characteristics, biological behaviors and clinical consequences [7]. LCIS is a precancerous disorder that may develop into invasive cancer, whereas invasive lobular carcinoma spreads beyond breast lobules and may metastasize to other organs [8]. DCIS arises from the breast ducts and remains confined to its original site without invading surrounding tissues [9]. In contrast, IBC, a less common and highly aggressive subtype, is characterized by the infiltration of malignant cells into the skin and lymphatic vessels of the breast [10]. Unlike other forms of breast cancer, IBC often lacks a discernible lump. Consequently, prompt and aggressive treatment is imperative due to its rapid growth and propensity for metastasis. The activation of both innate and adaptive immunity significantly impacts the immune response to breast cancer. In particular, the activation of cytotoxic T lymphocytes (CTLs) and helper T cells plays a critical role in defending against cancer growth [11]. Moreover, antigen-presenting cells play a crucial role in identifying tumors and presenting tumor fragments to T cells. The immune system comprises organs, tissues, cells and molecules that all function together to produce an immune response that protects us from microorganisms, removes toxins and destroys cancer cells [12]. Numerous immunosuppressive chemicals may be found in the microenvironment of tumors with a high burden, which may be responsible for the suppression of the stimulation and activation of immune responses. Tumor-associated macrophages, regulatory T cells and myeloid-derived suppressor cells are significant cells that inhibit the creation of a robust immune response. In addition to increasing the tumor's invasiveness, the production of immunosuppressive cytokines and chemicals, including interleukin-10, transforming growth factor-β and vascular endothelial growth

factor, also makes the environment around the tumor more immunosuppressive [13].

The pathogenesis of breast cancer is profoundly influenced by estrogen, an essential hormone that is imperative for the physiological development and functioning of the female reproductive system [14]. Several physiological functions, including the development of the mammary gland, depend critically on estrogen. However, it is important to note that under certain conditions, estrogen may also play a role in the onset and advancement of breast cancer [15]. This involvement primarily occurs through the interaction of estrogen with estrogen receptors located on the surface of breast cancer cells. Upon binding, estrogen activates a cascade of intracellular signaling pathways that can result in the stimulation of key processes such as cell proliferation, survival and migration [16]. Consequently, these cellular events can lead to the formation of breast tumors and their potential dissemination to distant sites within the body. In the clinical management of estrogen-driven breast cancer, a range of therapeutic interventions are employed to mitigate the oncogenic effects of estrogen. These strategies include the use of fulvestrant, tamoxifen, aromatase inhibitors and selective estrogen receptor modulators, all of which either block the actions of estrogen or reduce its production within the body. These interventions represent essential components of breast cancer treatment and prevention strategies, aiming to disrupt the estrogen-driven pathways responsible for the disease's development and progression.

Mathematical modeling is a powerful tool that can be used to understand the complex interactions between estrogen and breast cancer cells. Mathematical models can predict how breast cancer cells will respond to different treatments and identify new targets for drug development. One of the most important factors in the development of breast cancer is the presence of estrogen receptors on the surface of breast cancer cells. Estrogen receptors are proteins that bind to estrogen and transmit signals that stimulate the proliferation of breast cancer cells [17]. Mathematical models can be used to study the effects of estrogen stimulation on breast cancer cells. These models can help researchers to understand how estrogen promotes the growth of breast cancer cells and identify new ways to block the effects of estrogen. Mathematical models can also be used to predict how breast cancer cells will respond to different treatments. For example, mathematical models can predict how breast cancer cells respond to chemotherapy, radiation therapy, or hormone therapy. This information can be used to develop personalized treatment plans for breast cancer patients.

The use of ordinary differential equations has been employed in the study of tumor development and decay, specifically in scenarios involving two or three cell populations consisting of tumor cells and effector cells [18, 19]. Complex models, including populations of tumor-related cells and cytokines, have been developed in order to investigate specific aspects of tumor biology [20, 21]. Mathematical models focused on the examination of breast cancer development and therapy have introduced innovative perspectives on the dynamics of breast cancer. Jarrett et al. [22] presented a mathematical model to describe the dynamics of HER2-positive breast cancer in the presence of targeted treatment using trastuzumab. According to the proposed mathematical model, the administration of trastuzumab might lead to the stabilization of vasculature and subsequent reduction in tumor development. Wei [23] proposed a theoretical framework for estrogen receptor-positive breast cancer. The numerical simulation results demonstrated that the model had multistability, indicating the presence of three distinct phases in the immunoediting process. The model was subsequently updated to include the incorporation of AZD9496, a novel selective estrogen receptor degrader and palbociclib, a cyclin-dependent kinase 4 and 6 inhibitor [24]. The research posited that using monotherapy with a single medicine may prove futile, but implementing combination treatment might have a synergistic impact. McKenna et al. [25]

developed a mathematical model encompassing triple-negative breast cancer and its treatment with doxorubicin chemotherapy. The model was used to examine the response to therapy.

In 2018, Oke et al. developed a deterministic compartmental model with four dimensions to track the progression of breast cancer. The authors found that excess estrogen in the body affected the formation of tumor cells and they emphasized the advantages of breast cancer alleviation policies that combine anti-cancer medications and ketogenic diet techniques [26]. Mufudza et al. examined the impact of estrogen, as a potential risk factor, on breast cancer dynamics [27]. A deterministic mathematical model was developed that incorporates both the immune response and estrogen, aiming to elucidate the general dynamics of breast cancer. Their results showed that a greater likelihood of breast cancer growth was linked to an overabundance of estrogen. Ouifki and Oke have proposed a novel ordinary differential equation-based mathematical model to describe the dynamics of interactions between dormant and active breast cancer cells, estrogen and p53 [28]. The model was designed to consider the association between estrogen and p53, as well as their respective contributions to the activation of dormant breast cancer cells and the apoptosis of active tumor cells. The authors have presented explicit conditions that may prevent paradoxical cancer recurrence as a result of prolonged hormone deprivation therapy.

A comprehensive review of the literature revealed a lack of studies that incorporate mathematical modeling and hormone therapy in estrogen-positive breast cancer. In this study, a mathematical model using partial differential equations was developed to examine valuable insights into the underlying mechanisms that govern tumor growth and the effects of estrogen on tumor cells. This mathematical model can incorporate various factors, such as the diffusion of estrogen in the breast tissue, the proliferation of tumor cells and the response of these cells to estrogen. The developed model allows researchers to investigate the interactions between estrogen and breast cancer cells and predict different treatments' impact on tumor growth. The model can provide insights into breast cancer development and progression mechanisms by incorporating data from multiple sources, such as clinical trials and laboratory experiments. Furthermore, it may help to elucidate hormone therapy's effects and drive the design of personalized treatment strategies for patients with breast cancer. Overall, the proposed mathematical model represents an important step toward improving our understanding of breast cancer and developing more effective treatments for this disease.

2. Mathematical model

This section aims to develop a mathematical model that provides a framework for analyzing the complicated dynamics underlying estrogen receptor-positive breast cancer. The mathematical model presented herein offers a complete framework for analyzing the complex dynamics underlying estrogen receptor-positive breast cancer. This model is fundamentally based on a carefully designed partial differential equation system that captures the intricate interactions between estrogen, CTLs, dormant cancer cells and active cancer cells within the tumor microenvironment. The progression of breast cancer is significantly influenced by each component of this framework, with estrogen being a crucial factor in cell proliferation and immune responses influencing tumor growth and regression. The objective of this mathematical framework is to elucidate the intricate connections among these elements, providing insights into the effects of hormone treatment and estrogen inhibition on the dynamics of breast tumors. For the reader's convenience, we illustrate the mathematical framework by using a

schematic diagram, as shown in Figure 1.

Let y_1 denote the compartment of dormant cancer cells, and their logistic growth is defined by the term $c_1 y_1 \left(1 - \frac{y_1}{c_2}\right)$, where c_1 is the growth rate and c_2 is the carrying capacity of dormant cancer cells. The concept of "carrying capacity" is often used in the context of ecology to describe the maximum population size that a particular environment can sustainably support. However, when discussing dormant breast cancer cells, the term is applied metaphorically and within the framework of cancer biology to describe a similar concept. Dormant breast cancer cells refer to cancer cells that have entered a quiescent or inactive state within the body. These cells are not actively dividing and forming tumors but they are still present in the body. In this context, carrying capacity refers to the limit or threshold of dormant cancer cells that the body can tolerate without becoming actively proliferative and causing disease progression. The growth rate of the dormant cancer cell population may be regulated negatively by a factor $c_3 y_1 y_4$, where y_4 represents the density of estrogen hormones and c_3 is the probability rate for dormant cancer cell transformation into active cancer cells. The equation of dormant cancer cells is given by

$$\frac{dy_1}{dt} = c_1 y_1 \left(1 - \frac{y_1}{c_2}\right) - c_3 y_1 y_4. \tag{2.1}$$

Cancers of the breast, epidermis and cervix typically give rise to names that reflect the type of tissue in which the DNA is altered. The 145 primary breast cancers that have been found are based on 51 cell lines of malignancy that are divided into two principal strands: one with estrogen receptors, known as the luminal type, and the other without estrogen receptors, which is known as the basal-like type [29]. We use the following equation to describe the dynamics of active breast cancer cells:

$$\frac{dy_2}{dt} = c_3 y_1 y_4 + c_4 y_2 \left(1 - \frac{y_2}{c_5}\right) - c_6 y_2 \left(\frac{y_3}{c_7 + y_3}\right) + c_8 y_4. \tag{2.2}$$

The term $c_3 y_1 y_4$ defines the growth of active cancer cells due to dormant cancer cells with the aid of estrogen. The logistic growth of active breast cancer cells is defined by the term $c_4 y_2 \left(1 - \frac{y_2}{c_5}\right)$, while the term $c_6 y_2 \left(\frac{y_3}{c_7 + y_3}\right)$ represents the degradation of cancer cells due to immune responses. Excessive estrogen-induced DNA mutations will also repopulate active cancer cells by the factor $c_8 y_4$.

There are different types of immune cells that have different roles in breast cancer. In our model, we only consider the dynamics of CTLs and their role in breast cancer. We model the logistic growth of a comprehensive immune response triggered by cancer cells. To characterize immune cells' stimulation by malignant cells, we introduce the term $c_9 y_3 \left(1 - \frac{y_3}{c_{10}}\right)\left(\frac{y_2}{c_{11} + y_2}\right)$. This term shows the logistic growth of immune cells and its activation by cancer cells in the Michaelis-Menten form. The natural degradation of immune cells is denoted by $c_{13} y_3$ and the term $c_{12} y_2 y_3$ describes the deterioration of immune cells after interaction with cancer cells. Overall, the equation of CTLs is given by

$$\frac{dy_3}{dt} = c_9 y_3 \left(1 - \frac{y_3}{c_{10}}\right)\left(\frac{y_2}{c_{11} + y_2}\right) - c_{12} y_2 y_3 - c_{13} y_3. \tag{2.3}$$

Adipocytes are primarily responsible for the production of estrogen. In postmenopausal women with breast cancer, estrogen levels may be higher than the modest quantity. Typically, adipose tissues in the breasts, brain, osteoblasts and numerous other tissues produce estrogen, circulating throughout

the body. The volume of estrogen replicated in the body depends on the amount already present. This study entails the use of c_{14} to model constant estrogen production throughout the body, and natural degradation is represented by $c_{15}y_4$. The equation for estrogen is given by

$$\frac{dy_4}{dt} = c_{14} - c_{15}y_4. \tag{2.4}$$

The schematic diagram of the whole modeling process is given in Figure 1.

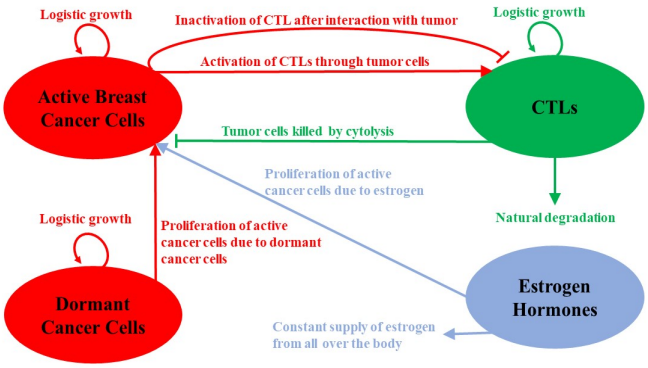


Figure 1. A schematic diagram showing the interaction of dormant cancer cells, active cancer cells, CTLs and estrogen.

2.1. Zero dimensional mathematical model

Combining all of the equations, the proposed zero-dimensional mathematical model is given by

$$\frac{dy_1}{dt} = c_1 y_1\left(1 - \frac{y_1}{c_2}\right) - c_3 y_1 y_4, \tag{2.5}$$

$$\frac{dy_2}{dt} = c_3 y_1 y_4 + c_4 y_2\left(1 - \frac{y_2}{c_5}\right) - c_6 y_2\left(\frac{y_3}{c_7 + y_3}\right) + c_8 y_4, \tag{2.6}$$

$$\frac{dy_3}{dt} = c_9 y_3\left(1 - \frac{y_3}{c_{10}}\right)\left(\frac{y_2}{c_{11} + y_2}\right) - c_{12} y_2 y_3 - c_{13} y_3, \tag{2.7}$$

$$\frac{dy_4}{dt} = c_{14} - c_{15} y_4, \tag{2.8}$$

where $c_1, c_2, ..., c_{15}$ are positive constants. The model equations are non-dimensionalized by using

$$y_1(t) = \frac{Y_1(\tau)}{k_1}, \quad y_2(t) = \frac{Y_2(\tau)}{k_2}, \quad y_3(t) = \frac{Y_3(\tau)}{k_3}, \quad y_4(t) = \frac{Y_4(\tau)}{k_4}, \quad \tau = k_5 t,$$

where $k_5 = k_1 c_6$. The values of k_1, k_2 and k_5 are taken as suggested by [30] while the values of k_3 and k_4 are taken accordingly. After the simplification and replacement of τ by t, the dimensionless model of the system given by (2.5)–(2.8) is as follows:

$$\frac{dY_1}{dt} = \alpha_1 Y_1\left(1 - \frac{Y_1}{\alpha_2}\right) - \alpha_3 Y_1 Y_4, \tag{2.9}$$

$$\frac{dY_2}{dt} = \alpha_4 Y_1 Y_4 + \alpha_5 Y_2\left(1 - \frac{Y_2}{\alpha_6}\right) - \alpha_7 Y_2\left(\frac{Y_3}{\alpha_8 + Y_3}\right) + \alpha_9 Y_4, \tag{2.10}$$

$$\frac{dY_3}{dt} = \alpha_{10} Y_3\left(1 - \frac{Y_3}{\alpha_{11}}\right)\left(\frac{Y_2}{\alpha_{12} + Y_2}\right) - \alpha_{13} Y_2 Y_3 - \alpha_{14} Y_3, \tag{2.11}$$

$$\frac{dY_4}{dt} = \alpha_{15} - \alpha_{16} Y_4, \tag{2.12}$$

where the values of α_i $(i = 1, 2, 3, ..., 16)$ are given by

$$\alpha_1 = \frac{c_1}{k_5}, \quad \alpha_2 = c_2 k_1, \quad \alpha_3 = \frac{c_3}{k_4 k_5}, \quad \alpha_4 = \frac{c_3 k_2}{k_1 k_4 k_5},$$
$$\alpha_5 = \frac{c_4}{k_5}, \quad \alpha_6 = c_5 k_2, \quad \alpha_7 = \frac{c_6}{k_5}, \quad \alpha_8 = c_7 k_3,$$
$$\alpha_9 = \frac{c_8 k_2}{k_4 k_5}, \quad \alpha_{10} = \frac{c_9}{k_5}, \quad \alpha_{11} = c_{10} k_3, \quad \alpha_{12} = c_{11} k_2,$$
$$\alpha_{13} = \frac{c_{12}}{k_2 k_5}, \quad \alpha_{14} = \frac{c_{13}}{k_5}, \quad \alpha_{15} = \frac{c_{14} k_4}{k_5}, \quad \alpha_{16} = \frac{c_{15}}{k_5}.$$

2.2. One dimensional mathematical model

We extended the concept of breast tumors to include an implicit spatial dimension under a site on breast tissue. Therefore, we developed a diffusion model in a spatial domain to integrate more aspects of spatial variability. The proposed one-dimensional mathematical model is given by

$$\frac{\partial Y_1(r,t)}{\partial t} = \sigma_1 \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial Y_1(r,t)}{\partial r}\right) + \alpha_1 Y_1(r,t)\left(1 - \frac{Y_1(r,t)}{\alpha_2}\right) - \alpha_3 Y_1(r,t) Y_4(r,t), \tag{2.13}$$

$$\frac{\partial Y_2(r,t)}{\partial t} = \sigma_2 \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial Y_2(r,t)}{\partial r}\right) + \alpha_3 Y_1(r,t) Y_4(r,t) + \alpha_4 Y_2(r,t)\left(1 - \frac{Y_2(r,t)}{\alpha_5}\right)$$
$$- \alpha_6 Y_2(r,t)\left(\frac{Y_3(r,t)}{\alpha_7 + Y_3(r,t)}\right) + \alpha_8 Y_4(r,t), \tag{2.14}$$

$$\frac{\partial Y_3(r,t)}{\partial t} = \sigma_3 \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial Y_3(r,t)}{\partial r}\right) + \alpha_9 Y_3(r,t)\left(1 - \frac{Y_3(r,t)}{\alpha_{10}}\right)\left(\frac{Y_2}{\alpha_{11} + Y_2}\right)$$
$$- \alpha_{12} Y_2 Y_3 - \alpha_{13} Y_3, \tag{2.15}$$

$$\frac{\partial Y_4(r,t)}{\partial t} = \sigma_4 \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial Y_4(r,t)}{\partial r}\right) + \alpha_{14} - \alpha_{15} Y_4(r,t), \tag{2.16}$$

where $Y_1(r,t)$ is the population of dormant cancer cells in the spatial domain r, $Y_2(r,t)$ is the population of active cancer cells in the spatial domain r, $Y_3(r,t)$ is the number of immune cells in the spatial domain r and $Y_4(r,t)$ is the density of estrogen hormones in the spatial domain r. We consider the radially symmetric case, with the tumor environment being a ball $\{0 \le r < L\}$.

2.3. Drug modeling

Hormone therapy may be classified as the primary treatment for estrogen-positive breast cancer, and it functions by inhibiting estrogen's effects on cancer cells. Hormone therapy includes tamoxifen,

aromatase inhibitors, fulvestrant and ovarian suppression. In this article, we model the effect of fulvestrant on estrogen and active cancer cells. Fulvestrant is a medication used to treat certain types of breast cancer, including hormone receptor-positive metastatic breast cancer. It works by blocking the estrogen receptor, which is a protein that allows estrogen to bind and activate breast cancer cells. By blocking this receptor, fulvestrant can slow or stop the growth of cancer cells. Fulvestrant is administered as an injection into the muscle. The dosage and frequency of injections depend on the individual patient and the stage of their breast cancer. The administration of the fulvestrant drug can be modeled by the equation given by

$$\frac{\partial R}{\partial t} = \sigma_5 \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial R}{\partial r}\right) + f(t) - \alpha_{16} R, \tag{2.17}$$

where $f(t)$ is a function used to describe the intermittent input of fulvestrant injections. The intermittent injections are administered at a fixed dose of 25 mg for several weeks [31]. The effect of hormone therapy is modeled by a term $(1-\epsilon)$ and it is added to the dynamics of active cancer cells and estrogen as follows:

$$\begin{aligned}\frac{\partial Y_2}{\partial t} &= \sigma_2 \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial Y_2}{\partial r}\right) + \alpha_3 Y_1 Y_4 + \alpha_4 Y_2\left(1 - \frac{Y_2}{\alpha_5}\right) - \alpha_6 Y_2\left(\frac{Y_3}{\alpha_7 + Y_3}\right) \\ &\quad + \alpha_8(1-\epsilon)Y_4, \end{aligned} \tag{2.18}$$

$$\frac{\partial Y_4}{\partial t} = \sigma_4 \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial Y_4}{\partial r}\right) + \alpha_{14}(1-\epsilon) - \alpha_{15} Y_4. \tag{2.19}$$

The initial and boundary conditions of the one-dimensional model are given by

$$\begin{cases} Y_1(0,r) = Y_1^0, & \frac{\partial}{\partial r}Y_1(t,0) = 0, & \frac{\partial}{\partial r}Y_1(t,1) = 0, \\ Y_2(0,r) = Y_2^0, & \frac{\partial}{\partial r}Y_2(t,0) = 0, & \frac{\partial}{\partial r}Y_2(t,1) = 0, \\ Y_3(0,r) = Y_3^0, & \frac{\partial}{\partial r}Y_3(t,0) = 0, & \frac{\partial}{\partial r}Y_3(t,1) = 0, \\ Y_4(0,r) = Y_4^0, & \frac{\partial}{\partial r}Y_4(t,0) = 0, & \frac{\partial}{\partial r}Y_4(t,1) = 0. \end{cases} \tag{2.20}$$

3. Numerical methods

3.1. Parameter estimation

We use several experimental breast cancer studies to quantify the parametric values of the proposed model. An experimental study based on three xenograft models of endocrine therapy-resistant breast cancer [31] has been used to estimate the parametric values for the logistic component involved in active cancer cell dynamics. We use the MATLAB GUI program "GRABIT" to extract the data from [31]; we then used this data for parameter estimation. The experimental data provided in [32] were used to estimate the values of the cytolysis term. Similarly, the parameters of immune cell dynamics were estimated by using clinical data obtained from the analysis of tumor cells and T lymphocytes in breast cancer patients [33]. Complete details of the parametric values are given in Table 1.

The parameter estimation technique used in this study is summarized in Figure 2. First, a reasonable guess was made to estimate the values of these parameters. Then, the ordinary differential equation system was solved to obtain the estimated values of the tumor dynamics presented by $\mathrm{Y_{par}}$. We then

constructed an error expression (E_{Par}) as the sum of the squared differences between the calculated values (Y_{par}) and the experimental data (Y_{data}). The regression approach is the preferred way of finding a local minimum via unconstrained nonlinear optimization methods such as the Nelder-Mead algorithm. This technique minimizes the value of a function by evaluating the function directly without using any derivatives. The process is terminated and the parameter values are chosen as the optimum values if the error E_{Par} does not exceed the user-specified tolerance (TOL). If this is not the case, the parameters' values are changed and the process is repeated. The process is repeated continuously until convergence occurs. The formula for the minimized objective function is as follows

$$\mathrm{E_{Par}} = \sum_{i=1}^{N} \left(\mathrm{Y}_{\mathrm{par}}^{(i)} - \mathrm{Y}_{\mathrm{data}}^{(i)} \right)^2, \tag{3.1}$$

where E_{Par} denotes the difference between the value of active cancer cells (Y_{par}) estimated from simulations and the observed data (Y_{data}) over N observations.

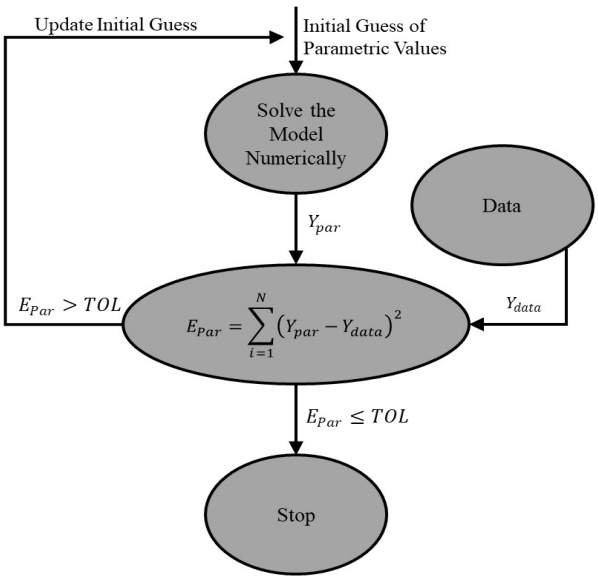


Figure 2. Description of the parameter estimation process.

3.2. Finite-difference scheme

The model given by (2.13)–(2.19) constitutes nonlinearly coupled partial differential equations with initial and boundary conditions given by (2.20). We solve these equations by using the forward-time centred-space (FTCS) finite-difference method. We apply forward difference to the time and central difference for the space variable, i.e.,

$$\begin{cases} \frac{\partial Y}{\partial t} = \frac{Y^{(i,j+1)} - Y^{(i,j)}}{\Delta t}, \\ \frac{\partial Y}{\partial r} = \frac{Y^{(i+1,j)} - Y^{(i-1,j)}}{2(\Delta r)}, \\ \frac{\partial^2 Y}{\partial r^2} = \frac{Y^{(i+1,j)} - 2Y^{(i,j)} + Y^{(i-1,j)}}{(\Delta r)^2}. \end{cases} \tag{3.2}$$

After discretization, we get the following algebraic equations

$$Y_1^{(i,j+1)} = \left[\frac{\sigma_1(\Delta t)}{(\Delta r)^2} + \frac{\sigma_1(\Delta t)}{r_i(\Delta r)}\right] Y_1^{(i+1,j)} + \left[\frac{\sigma_1(\Delta t)}{(\Delta r)^2} + \frac{\sigma_1(\Delta t)}{r_i(\Delta r)}\right] Y_1^{(i-1,j)} + \left[1 + \frac{2\sigma_1(\Delta t}{(\Delta r)^2} + \alpha_1(\Delta t)\left(1 - \frac{Y_1^{(i,j)}}{\alpha_2}\right) - \alpha_3(\Delta t) Y_4^{(i,j)}\right] Y_1^{(i,j)}, \tag{3.3}$$

$$Y_2^{(i,j+1)} = \left[\frac{\sigma_2(\Delta t)}{(\Delta r)^2} + \frac{\sigma_2(\Delta t)}{r_i(\Delta r)}\right] Y_2^{(i+1,j)} + \left[\frac{\sigma_2(\Delta t)}{(\Delta r)^2} + \frac{\sigma_2(\Delta t)}{r_i(\Delta r)}\right] Y_2^{(i-1,j)} + \left[1 + \frac{2\sigma_2(\Delta t}{(\Delta r)^2} + \alpha_4(\Delta t)\left(1 - \frac{Y_2^{(i,j)}}{\alpha_5}\right) - \alpha_6(\Delta t)\left(\frac{Y_3^{(i,j)}}{\alpha_7 + Y_3^{(i,j)}}\right) + \alpha_8(1-\epsilon)(\Delta t)\right] Y_2^{(i,j)} + \alpha_3(\Delta t) Y_1^{(i,j)} Y_4^{(i,j)}, \tag{3.4}$$

$$Y_3^{(i,j+1)} = \left[\frac{\sigma_3(\Delta t)}{(\Delta r)^2} + \frac{\sigma_3(\Delta t)}{r_i(\Delta r)}\right] Y_3^{(i+1,j)} + \left[\frac{\sigma_3(\Delta t)}{(\Delta r)^2} + \frac{\sigma_3(\Delta t)}{r_i(\Delta r)}\right] Y_3^{(i-1,j)} + \left[1 + \frac{2\sigma_3(\Delta t}{(\Delta r)^2} - \alpha_3(\Delta t) + \alpha_9(\Delta t)\left(1 - \frac{Y_3^{(i,j)}}{\alpha_{10}}\right)\left(\frac{Y_2^{(i,j)}}{\alpha_{11} + Y_2^{(i,j)}}\right) - \alpha_{12}(\Delta t) Y_2^{(i,j)}\right] Y_3^{(i,j)}, \tag{3.5}$$

$$Y_4^{(i,j+1)} = \left[\frac{\sigma_4(\Delta t)}{(\Delta r)^2} + \frac{\sigma_4(\Delta t)}{r_i(\Delta r)}\right] Y_4^{(i+1,j)} + \left[\frac{\sigma_4(\Delta t)}{(\Delta r)^2} + \frac{\sigma_4(\Delta t)}{r_i(\Delta r)}\right] Y_4^{(i-1,j)} + \left[1 + \frac{2\sigma_4(\Delta t}{(\Delta r)^2} - \alpha_{14}(1-\epsilon)(\Delta t) - \alpha_{15}(\Delta t)\right] Y_4^{(i,j)}, \tag{3.6}$$

$$R^{(i,j+1)} = \left[\frac{\sigma_5(\Delta t)}{(\Delta r)^2} + \frac{\sigma_5(\Delta t)}{r_i(\Delta r)}\right] R^{(i+1,j)} + \left[\frac{\sigma_5(\Delta t)}{(\Delta r)^2} + \frac{\sigma_5(\Delta t)}{r_i(\Delta r)}\right] R^{(i-1,j)} + \left[1 + \frac{2\sigma_5(\Delta t}{(\Delta r)^2} - \alpha_{16}(\Delta t) + f(t_j)\right] R^{(i,j)}. \tag{3.7}$$

The stability and convergence of the FTCS scheme completely depend on Δt and Δr [34]. The stability condition for FTCS is given by

$$\frac{\sigma \Delta t}{(\Delta r)^2} \leq \frac{1}{2}. \tag{3.8}$$

Thus, we should choose appropriate values of σ, Δt and Δr to satisfy the stability condition of the FTCS scheme.

The finite difference approach is well recognized for its numerical stability and precision, especially in the context of solving partial differential equations that include intricate boundary conditions and irregular geometries. These characteristics distinguish the FTCS scheme from other methods [35, 36] and are critical to accurately characterizing the spatial dynamics of breast cancer growth in the tumor microenvironment, which is characterized by variable features and irregular tumor forms. Our study focuses on modeling breast cancer dynamics in a spatially complex environment, requiring an efficient approach that is capable of addressing multiple challenges. The finite difference method readily extends to higher dimensions, making it suitable for our spatial modeling approach.

3.3. Sensitivity analysis

Global sensitivity analysis is a technique used to analyze the behavior of a mathematical model by considering the impact of varying input parameters simultaneously and uniformly across their full range of possible values [37]. It provides a quantitative measure of how much the model's output changes with variations in the input parameters. This analysis is essential in understanding the behavior of complex models and can help to distinguish key parameters that should be prioritized for further study or optimization. Monte Carlo global sensitivity analysis is a powerful method for assessing input variables' impact on a mathematical model's output. It combines the Monte Carlo method, which involves generating random samples of input values, with global sensitivity analysis, which quantifies the importance of input variables and their interactions with respect to the model output. This approach can provide a comprehensive view of the influence of input variables on the model output, allowing researchers to identify the most critical parameters and prioritize further analysis or optimization. However, it can also be computationally intensive, particularly for models with high-dimensional input spaces.

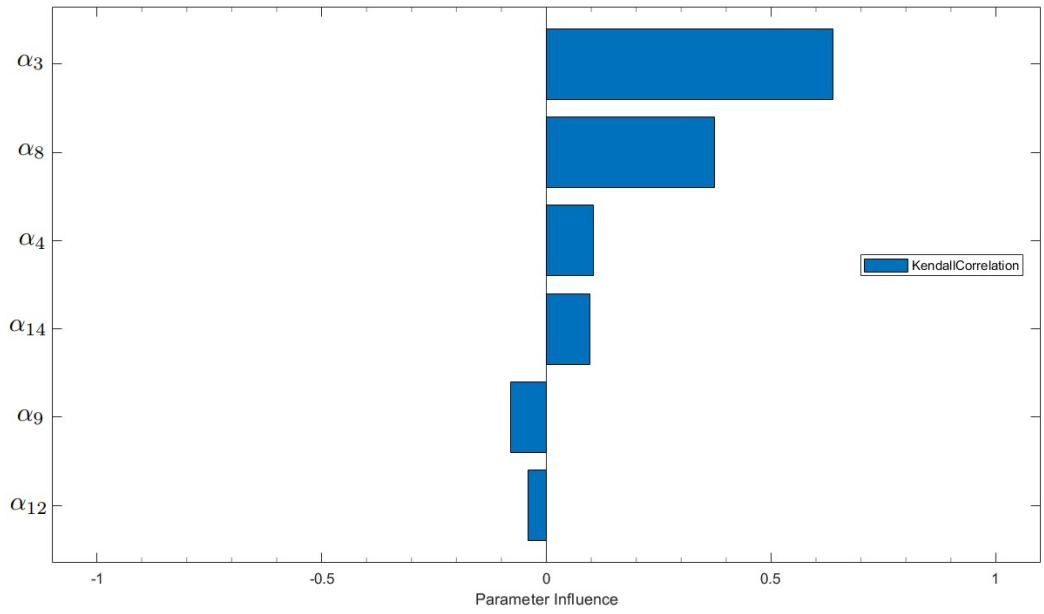
We performed sensitivity analysis before conducting numerical simulations to determine the impact of various parameters on the dynamics of active tumor cells. We evaluated the uncertainty of six parameters, including α_3, α_4, α_8, α_9, α_{12} and α_{14}. A uniform probability distribution was used to generate a sample of 100 values for each parameter. Results from the sensitivity analysis were included in the numerical simulation to monitor parameter values and enhance the performance and reliability of the model.

4. Results and discussion

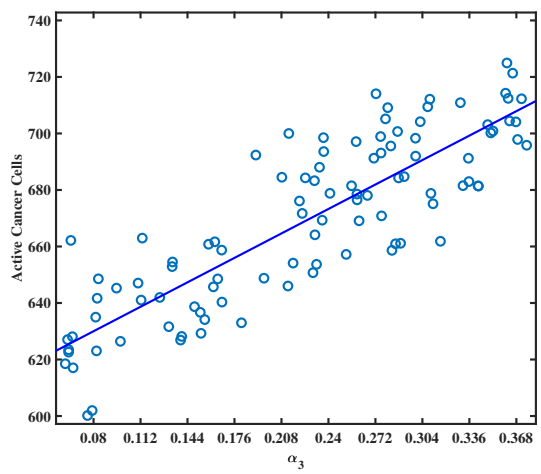
The rank correlation coefficients were computed by using the Kendall correlation technique and displayed by using a tornado plot (see Figure 3a). The tornado plot shows that the population of active cancer cells is very sensitive to the parameters α_3 and α_8. It also shows that four parameters directly impact the population of active cancer cells, while two parameters have an inverse impact. The respective influences of α_3 and α_8 are plotted separately in Figure 3b and 3c. It can be observed that increasing the α_3 and α_8 values increases the population of active cancer cells.

Breast cancer is a complex medical disorder distinguished by aberrant cellular proliferation and division within the tissue of the mammary gland. The carrying capacity of the tissue around it may be reached if breast cancer cells continue to proliferate uncontrolled and advance unabatedly. This, in turn, can result in the development of a tumor and the metastasis of cancerous cells to other parts of the body. The present study deals with the dynamics of active cancer cells and CTLs in the presence of estrogen. Figure 4 shows the dynamics of active cancer cells and CTLs without hormone therapy. Notably, the population of both cellular components approaches the carrying capacity limit in the absence of hormone therapy. Breast cancer cells reaching their carrying capacity may develop into tumors, which can be detected by imaging or a physical exam as a palpable mass or lump. Furthermore, when breast cancer cells proliferate beyond their capability, they may become more invasive and spread to nearby lymph nodes or distant organs via the lymphatic or circulatory systems. This process, commonly referred to as metastasis, poses a formidable obstacle to the treatment of breast cancer and significantly diminishes a patient's chances of survival.

Hormone treatment is a well-recognized therapeutic option for breast cancer that works by either



(a)



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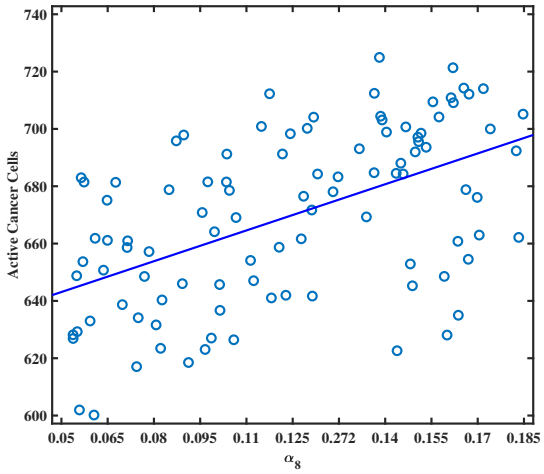


(c)

Figure 3. The results of sensitivity analysis, depicting the influence of different parameters on active cancer cells.

inhibiting estrogen's effects or reducing estrogen levels in the body. Cancer cell proliferation may be successfully inhibited or decreased by using this treatment. In this study, we chose to use the pharmacokinetics and pharmacodynamics of fulvestrant to treat estrogen-positive breast cancer. Fulvestrant, a selective estrogen receptor degrader, stops breast cancer cells from signaling with estrogen. We applied intermittent administration of fulvestrant, which entails administering hormone therapy dosage periodically followed by intervals. This strategy is based on the premise that continuous hormone therapy administration can lead to treatment resistance and a diminishing therapeutic response over time. In our simulations, we applied a fixed dose of 25 mg of fulvestrant administered intermittently over 15 weeks. Figure 5 illustrates the dynamics of active cancer cells and CTLs in response to hormone therapy, depicting cyclic behavior in their population.

Breast cancer cells exhibit cyclic behavior in their activity patterns, with periods of rapid growth followed by periods of slow growth or dormancy. This cyclic behavior is known as the cancer cell cycle, characterized by different phases, including the G0, G1, S, G2 and M phases. The G0 phase is considered dormant, as the cells are not actively dividing, allowing them to evade detection and treatment. The G1 phase is the preparatory phase, where the cells prepare for DNA synthesis. The S phase is the phase where DNA replication occurs. The G2 phase is where the cells prepare for mitosis, and the M phase is where cell division occurs. Breast cancer cells can remain in the G0 phase for extended periods of time, allowing them to evade detection and treatment. However, they can also enter a highly proliferative phase, leading to the rapid growth and spread of the tumor. On the other hand, CTLs, i.e., specialized immune cells that target and eliminate cancer cells, exhibit periodic behavior in their activity patterns. This cyclic behavior is likely due to the influence of the body's internal clock, which regulates various physiological processes. In addition to their circadian rhythm, CTLs exhibit periodic behavior in their activity cycles, with periods of activation followed by rest periods. This allows them to conserve energy and maintain their effectiveness in targeting cancer cells over extended periods of time. The cyclic behavior of breast cancer cells and CTLs was studied by using mathematical modeling and phase plane analysis. Understanding the cyclic behavior of cancer cells and CTLs is essential for the development of effective treatments for breast cancer.

The phase-plane dynamics of active cancer cells and CTLs presented in Figure 6 provide insight into the complex interplay between breast tumor cells and the immune system. CTLs have the ability to recognize and eliminate cancer cells, but tumors can evade detection by reducing antigen expression or by upregulating immune checkpoints. This leads to a dynamic balance between tumor cells and CTLs, with periodic fluctuations in the immune response. In addition, the irregular behavior observed may be influenced by the cell cycle of tumor cells. Breast tumor cells can grow and divide at varying rates, resulting in fluctuations in their numbers over time. These fluctuations can significantly impact the immune response, as CTLs may have more or fewer targets to attack depending on the cell cycle phase of the tumor cells. Therefore, understanding the phase-plane dynamics of breast tumor cells and CTLs is crucial for the development of effective treatments for breast cancer.

Phase plane analysis has been recognized as a valuable tool for examining the dynamics of a system under diverse treatment conditions. Specifically, it has been demonstrated that the system's dynamics rely on the immune response's strength and the cells' proliferation rate. When the immune response is vigorous, and hormone therapy is administered, the trajectories in the phase plane tend to converge to a stable equilibrium point, corresponding to the complete elimination of cancer cells, as presented in Figure 6. However, in the case of a typical immune response, the trajectories tend to spiral towards

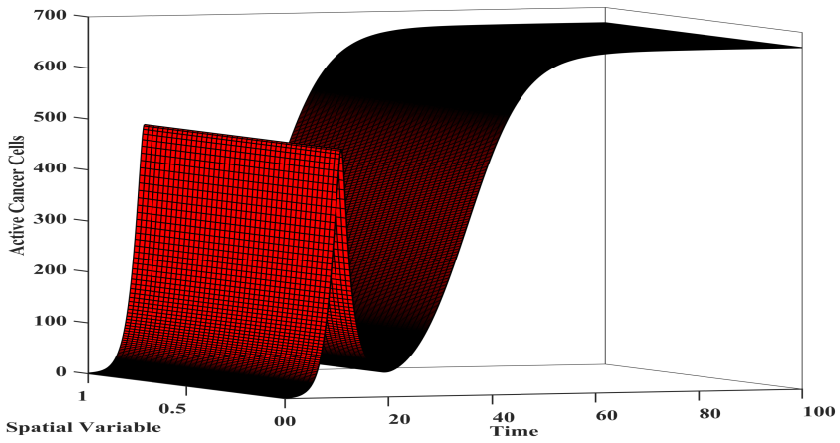
a limited cycle, indicating the system's cyclic behavior and the persistence of cancer cells, as shown in Figure 7a. On the other hand, when the immune response weakens, the trajectories tend to grow exponentially, which results in the cancer cells reaching their maximum carrying capacity, as illustrated in Figure 7b. The proposed mathematical model predicts three distinct states of a breast tumor. With hormone therapy and a robust immune response, a breast tumor can be eradicated entirely or reduced to a minimal size where it poses no harm. According to several studies [38–40], a small tumor never develops into an aggressive type and is termed "cancer without disease." With hormone therapy and a typical immune response, a breast tumor can exist to a limited extent and may grow at the end of treatment. Similarly, when the immune response is below average, breast cancer cells grow quickly despite hormone therapy, reaching their maximum carrying capacity. In our proposed model, the immune response is contingent on the growth rate of CTLs. We have chosen a high value of CTL growth rate for a robust immune response, a median value for an average immune response and a low value for a weakened immune response. All values for the CTL growth were taken from the estimated interval as given in Table 1.

The present study presents a mathematical model that elucidates the intricate dynamics of estrogen hormones and their implications in breast cancer progression. The proposed model considers the effects of hormone therapy on reducing the amount of estrogen in the body or inhibiting its impact on breast cancer cells. The graphical representation of estrogen hormones is depicted in Figure 8. Specifically, Figure 8a demonstrates the progression of estrogen without any treatment, while Figure 8b illustrates estrogen dynamics under hormone therapy's influence. The findings suggest that the hormone therapy intervention leads to a decline in the population of estrogen, signifying its potential therapeutic role in breast cancer treatment. Overall, the proposed mathematical model provides a comprehensive understanding of the underlying mechanisms involved in breast tumor progression and the effects of hormone therapy. Furthermore, this model can serve as a valuable tool for identifying novel therapeutic approaches that may be more efficacious than the current therapies.

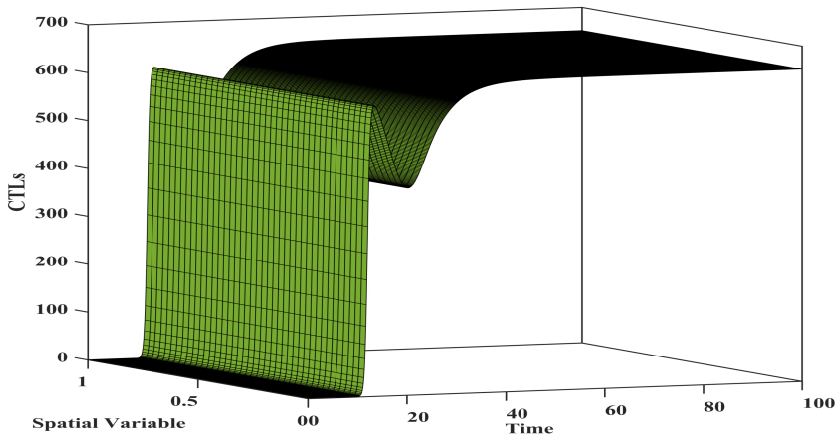
5. Conclusions

Breast cancer is the leading cause of death among women worldwide. Inhibiting or decreasing the estrogen production rate is one potential way to increase survival rates and enhance the quality of life for estrogen receptor-positive breast cancer patients. This paper examines the interaction between estrogen and the cancer-immune response in a deterministic setting. We have reviewed recent articles on the mathematical modeling of estrogen and breast cancer cells. We have developed a partial differential equation model based on breast cancer and estrogen pathology to investigate and predict the response to hormone therapy. The key findings of the proposed mathematical model simulation are given below:

- Estrogen increases the growth of cancer cells.
- An intermittent hormone therapy dose controls breast cancer cells' growth rate.
- At early stages, a robust immune response with intermittent hormone therapy can eliminate a breast tumor or reduce it to a minimal size where it poses no harm.
- With hormone therapy and a typical immune response, a breast tumor can exist to a limited extent and may grow at the end of treatment.
- Sometimes, the immune response is not activated or weakens, and this leads to the breast tumor growing rapidly.

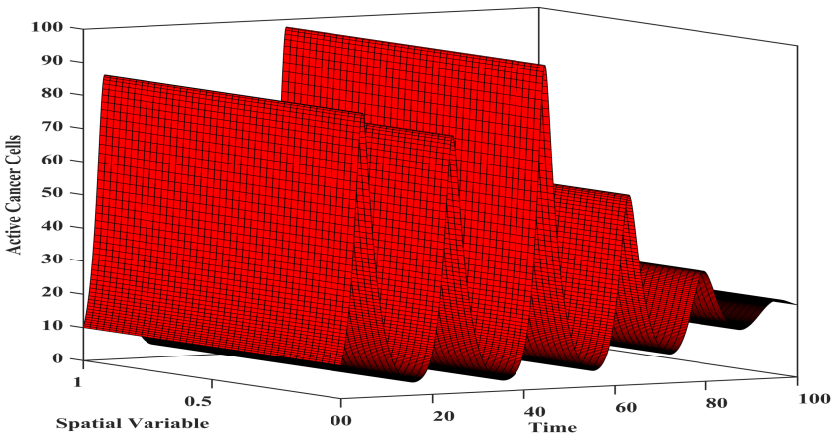


(a)

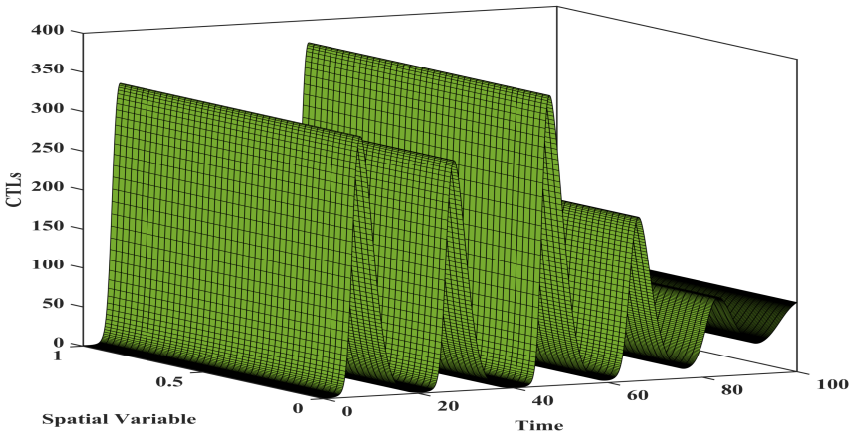


(b)

Figure 4. Populations of active cancer cells and CTLs without hormone therapy.

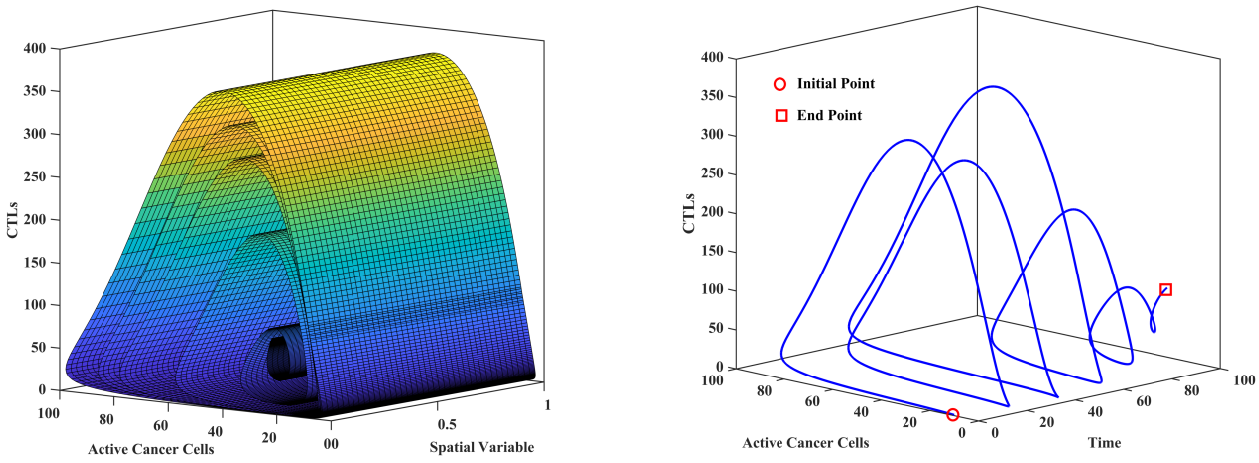


(a)



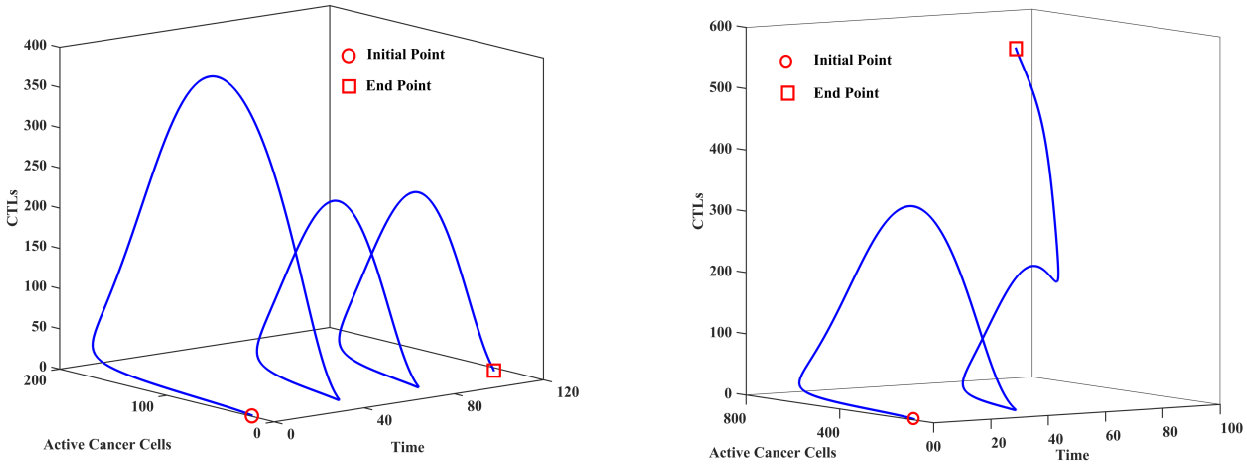
(b)

Figure 5. Populations of active cancer cells and CTLs with effects of hormone therapy.



(a) **(b)**

Figure 6. Phase-plane analysis of active cancer cells and CTLs with hormone therapy and a strong immune response.

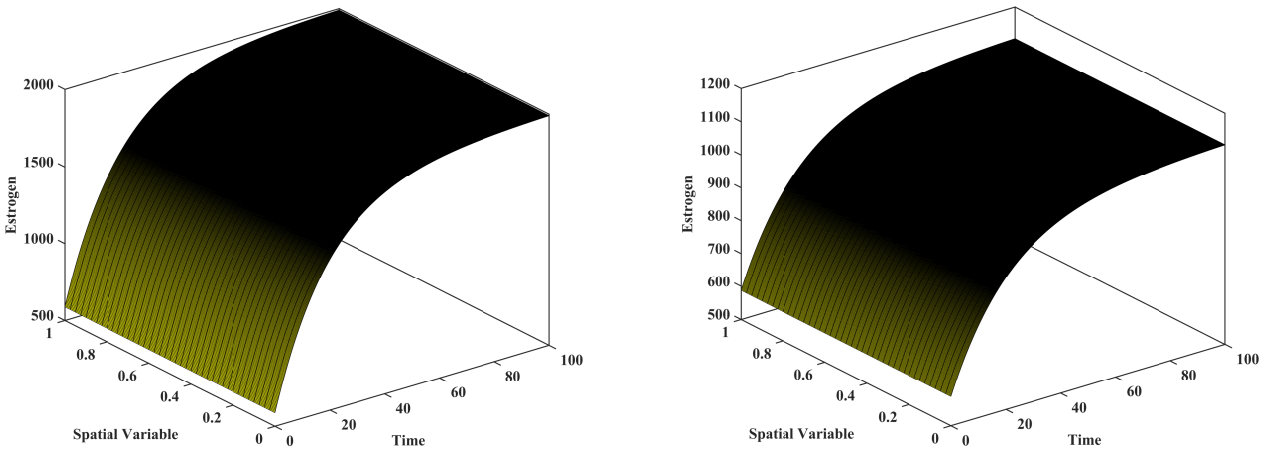


(a) **(b)**

Figure 7. Phase-plane analysis of active cancer cells and CTLs with hormone therapy and a weak immune response.

Table 1. Values and descriptions of parameters used in the model.

Parameter	Description	Value	Reference
α_1	Logistic growth rate of dormant cancer cells	0.5140	Extracted from [41]
α_2	Carrying capacity of dormant cancer cells	10^3	Assumed
α_3	Conversion rate for dormant cancer cells into active cancer cells	0.08 – 0.4	Assumed
α_4	Logistic growth rate of active cancer cells	0.4 – 0.8	Estimated from [31]
α_5	Carrying capacity of active cancer cells	10^3	Extracted from [42]
α_6	Cytolysis rate	1	[11]
α_7	Michaelis constant of Michaelis–Menten kinetics	$1 \times 10^1 - -2 \times 10^2$	Assumed
α_8	Growth of active cancer cells due to estrogen	0.05 – −0.2	Varies
α_9	Logistic growth rate of CTLs	3.7 – 5.8	Estimated from [33]
α_{10}	Carrying capacity of CTLs	10^3	[11]
α_{11}	Michaelis constant of Michaelis–Menten kinetics	$1\times10^1-2\times10^2$	[11]
α_{12}	Inactivation rate of CTLs after interaction with active cancer cells	7.812×10^{-5}	[11]
α_{13}	Natural degradation rate of CTLs	0.8729	[11]
α_{14}	Supply of estrogen	$10^2 - 10^3$	Varies
α_{15}	Natural degradation of estrogen hormones	0.03 – 0.07	Extracted from [43]
σ_1	Diffusion coefficient for dormant cancer cells	1.25×10^{-3}	[44]
σ_2	Diffusion coefficient for active cells	1.25×10^{-3}	[44]
σ_3	Diffusion coefficient for CTLs	1.25×10^{-3}	[44]
σ_4	Diffusion coefficient for estrogen hormones	1.25×10^{-3}	[44]



(a) Without hormone therapy **(b)** With hormone therapy

Figure 8. Population of estrogen with and without hormone therapy.

The developed model only takes the effects of CTLs and ignores the dynamics of other immune responses. An extension of this model would be to include the dynamics of helper T cells and innate immunity responses. Moreover, the proposed model is limited to only the hormone therapy response. However, in the future, we are interested in upgrading the model to include chemotherapy/immunotherapy or a combination of both. Nevertheless, our research provides new opportunities for understanding the molecular mechanisms underlying estrogen and breast cancer cells, and it will help to analyze personalized therapeutic possibilities.

We may investigate the following options for future developments and uses of our approach as part of our continuing research activities. The spatial modeling methodology used in this work incorporates experimental data and mathematical modeling, which enables its use as a tool to investigate the dynamics of various cancer types within their distinct tumor microenvironments. Further research may be directed towards the application of our developed technique to other subtypes of cancer, taking into account the heterogeneity of the tumor microenvironment and the intricacies of the immune response. Building upon our investigation into hormone therapy for breast cancer, we intend to explore the optimization of treatment strategies in other cancer contexts. This could include the development of personalized treatment regimens and the assessment of therapeutic interventions in diverse cancer types. Our methodology can be extended to assess the efficacy of various drugs and treatment combinations in controlling cancer growth. This may be particularly relevant in the context of precision medicine and the development of targeted therapies. Future directions may involve translating our research findings into clinically relevant applications, potentially informing treatment decisions and strategies in oncology.

Use of AI tools declaration

The authors declare that they have not used artificial intelligence tools in the creation of this article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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