Int. J. Anal. Appl. (2024), 22:199

International Journal of Analysis and Applications

Fractional-Order Mathematical Modeling of Breast Cancer: Comparing Adaptive Immune Responses and Estrogen Dynamics with Experimental Data

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Abstract. Breast cancer is a significant global health concern that requires innovative approaches to understand its behavior and improve treatment strategies. This paper introduces a new fractional-order mathematical model to explain the complex dynamics of breast cancer progression, including adaptive immune responses and estrogen dynamics. Utilizing Caputo fractional derivatives, our model reveals insights into the impact of fractional-order dynamics on cancer cell populations. Simulation results demonstrate a notable increase in cell populations with higher fractional orders, suggesting heightened aggressiveness, while lower orders correspond to subdued progression. Unlike traditional integer-order models, fractional-order derivatives offer a more nuanced depiction of nonlinear dynamics, crucial for capturing the complexities of cancer progression. Importantly, our findings underscore the potential clinical relevance of fractional-order models in informing personalized treatment strategies, particularly through the modulation of estrogen levels. By integrating treatment considerations, such as hormone therapy, our model holds promise for advancing precision medicine approaches tailored to individual patient characteristics.

1. Introduction

Breast cancer is recognized as the most malignant disease affecting women globally [1]. According to data from the World Health Organization (WHO), the global incidence of breast cancer exceeded 2.3 million cases in 2020 [2]. The incidence of breast cancer varies geographically, with higher rates observed in developed regions [3]. Age is a significant risk factor, and the majority of breast cancer cases occur in women aged 50 and above. However, it is important to note that breast cancer can affect individuals of all ages and awareness of risk factors is vital for early detection. Various risk factors contribute to the development of breast cancer, including genetic mutations

Received: Sep. 7, 2024.

2020 *Mathematics Subject Classification.* 92-10.

Key words and phrases. breast cancer; adaptive immunity; mathematical modeling; sensitivity analysis; numerical simulations.

https://doi.org/10.28924/2291-8639-22-2024-199
ISSN: 2291-8639

(such as BRCA1 and BRCA2), hormonal factors, family history, reproductive factors, and lifestyle choices [4].

Breast cancer is a malignant and widespread tumor that arises from the cell structure of the breast [5]. The disease is complex and diverse, with several subgroups distinguished by unique genetic characteristics and clinical manifestations. This cancer can affect both men and women, although it is much more common in women. Typically, breast cancer originates in the ducts or lobules of the breast and has the potential to metastasize to adjacent tissues as it progresses [6]. Determining the presence or absence of particular receptors, such as human epidermal growth factor receptor 2 (HER2) and hormone receptors, various subtypes of this complex disease exist [7]. Each subtype has unique clinical features and responses to treatment, necessitating personalized approaches to therapy. The triple-negative subtype, which lacks these receptors, presents additional hurdles for developing targeted treatments [8]. Moreover, understanding the tumor microenvironment is crucial for advancing breast cancer treatments. The interactions among cancer cells, immune cells, stromal cells, and extracellular matrix components affect tumor growth, spread, and response to treatment. Grasping these complexities is vital for developing therapies that effectively target cancer cells while sparing healthy tissue.

The link of breast cancer cells to the immune system is essential in controlling the succession of the disease [9]. The immune system has properties to recognize and kill cancer cells. At the same time, cancer cells manage to evade immune recognition and suppression. The breast cancer tumor microenvironment is a dynamic system comprising a network of breast cancer cells, immune cells, stromal cells, and extra-cellular matrix constituents. The interactions between cancer cell types and immune cells, such as T lymphocytes, macrophages, and dendritic cells, are responsible for the complex immune response within this tumor microenvironment. Immune cells penetrate tumors, and their presence brings a better prognosis. Nevertheless, this balance between the pro-tumor and the anti-tumor immune responses is delicate and regulated by cytokines, chemokines, and immunosuppressive molecules produced by cancer and immune cells. In the context of the immune response against breast cancer, cytotoxic T lymphocytes (CTLs) have a very important function on many sides [10]. CTLs, which can recognize and eliminate malignant cells, are essential to the adaptive immune system. The presence of infiltrating CTLs within the tumor microenvironment is associated with a more favorable prognosis in breast cancer patients. These immune cells suppress tumor progression by directly attacking cancer cells and fostering an anti-tumor inflammatory environment. However, breast cancer cells have evolved mechanisms to evade CTL-mediated destruction. These evasion methods consist of reduced antigenicity, defective antigen presentation, and the presence of inhibitory molecules such as programmed death-ligand 1 (PD-L1). As a result, the interaction between cytotoxicity displayed by CTLs and immune escape mechanisms utilized by breast cancer cells in the tumor microenvironment is remarkably intricate [11].

The helper T cells have inhibitory and regulatory roles on other immune cells in a tumor microenvironment [12]. In breast cancer, helper T cell cells play a significant part in the generation of anti-tumor immune response by assisting CTLs in the activation process, which are crucial for identifying and eliminating cancer cells [13]. In addition, helper T cells turn B cells into cells that are evenly active in producing antibodies against antigens from cancer cells. In this context, helper T cell-derived cytokines play a crucial role by modulating the balance between pro-inflammatory and anti-inflammatory responses within the tumor, thus leading to the desired overall immune response. Besides, the hormone estrogen acts as a key development and progression factor in breast cancer [14]. In human breast tissue, estrogen binds to estrogen receptors (ERs) situated on the cell membrane of breast cells. Estrogen- and progesterone-receptor-positive breast cancers, i.e., the receptor-positive subtype, are common types of breast cancer, representing a significant percentage of the total number. The role of estrogen signaling in several domains of breast cancer biology has been observed, including cell growth and proliferation, survival, and the formation of new blood vessels, which supply the cancer with nutrients and energy as they grow [15]. Estrogen production is predominantly regulated by the ovaries in premenopausal women, whereas it is also synthesized in peripheral tissues, including adipose tissue, in postmenopausal women [16]. The risk of developing hormone receptor-positive breast cancer is correlated with increased cumulative exposure to estrogen, which can occur through various means such as hormone replacement therapy, early menarche, or late menopause [17].

Mathematical modeling plays an important role in understanding the complex dynamical relationship between estrogen, the immune system, and breast cancer. Mathematical models in breast cancer research provide a quantitative framework to simulate the complex biological processes underlying tumor growth, progression, and treatment response. Mathematical models contribute to the identification of potential biomarkers and therapeutic targets, facilitating the development of innovative and tailored therapies. By integrating data from diverse sources and accounting for the complexities inherent in breast cancer and immune interactions with estrogen, mathematical modeling serves as a critical tool in advancing our understanding and improving outcomes for individuals affected by breast cancer. Researchers use mathematical models to investigate connections between immune cells, cancer cells, and therapies. Jarrett et al. used mathematical and experimental models to study trastuzumab's effect on HER2-overexpressed BC in mice [18]. Moreover, a mathematical model was developed to investigate how MCF-7 BC cells interact with immune cells [19]. Multiple studies have shown a correlation between immune cells and prognosis in breast tumors. Macrophage density correlates with the prognosis of BC. Helper T-cells and cytotoxic T-cells are more strongly linked to better prognosis in ER-negative tumors than in ER-positive tumors, and CD8+ T lymphocytes lower the risk of death from numerous subtypes of BC. Advanced breast tumors have also been shown to include more regulatory T-cells and a lower T-helper to regulatory T-cell ratio. These findings indicate that networks of interactions between immune cells and their relative abundance are essential to the genesis and spread of BC.

The use of mathematical modeling is a valuable technique for gaining a comprehensive understanding of the complex interactions occurring inside the tumor microenvironment [20]. As a result, researchers have investigated several aspects of the interplay between tumors and the immune system. In [21], a model including delays was presented to investigate the dynamics of tumor-immune interactions and the regulation of malignant tumor development. In [20], qualitative analyses were performed to investigate the interactions between tumors and cytokines within the context of treatment circumstances. Furthermore, the study conducted by [22] introduced a novel mathematical model aimed at tackling the issue of immune surveillance in the context of tumor development. The research conducted in [23] focused on the optimization of cancer self-remission and the stability analysis of physiologically feasible equilibrium states. Additionally, the study investigated the use of chaos theory and optimum control techniques in cancer models with uncertain parameters [24]. It is expected that immunotherapies will have a significant impact on the suppression of tumor cell growth. Kuznetsov et al. [25] explored the nonlinear dynamics of immunogenic tumors, representing a fundamental contribution to this particular research area. Kirschner and Panetta [26] provided a mathematical exposition on the relationships between tumor cells, immune cells, and IL-2, elucidating the occurrence of oscillations in tumor development within both short-term and long-term scenarios.

The application of fractional-order theoretical models on the immune system's dynamics with breast cancer allows us to obtain a holistic view and better understanding of these complex biological processes. Most real-world mathematical models use integer-order derivatives and integrals, which may not adequately capture the complexity of natural process dynamics. Incorporating non-integer order derivatives into fractional-order models distinguishes them from conventional models and permits a more detailed representation of concealed characteristics. As a result, traditional models often face difficulties in accurately representing the complex and perpetually changing dynamics of the interaction between the immune system and breast cancer. Fractional-order models offer an alternative approach distinguished by its enhanced flexibility and realism, facilitating a more comprehensive exploration of these complexities. By taking into account memory effects and nonlinearity, their capacity to unravel the intricate mechanisms driving the advancement of breast cancer and the immune response is essential. Idrees et al. [27] developed a mathematical model of breast cancer based on the Caputo–Fabrizio fractal-fractional derivative. This research made a valuable contribution by integrating the fractal properties of tumor development into an innovative mathematical model for breast cancer. Mohammadpoor et al. [28] discussed the stability of the fractional-order breast cancer model in chemotherapy patients with cardiotoxicity by applying LADM. It was determined that the days on which the maximum or minimum of the system solutions are attained are significantly influenced by the magnitude of the fractional order.

The interplay between the immune system and estrogen signalling is complex and essential to comprehend the progression of breast cancer. Fractional-order models provide a flexible methodology for accurately representing these intricacies. In addition to offering a versatile framework, they exhibit a high degree of congruence with experimental data by an additional parameter that enhances precision by incorporating observed biological processes. This precision is vital for developing reliable tools to understand and predict the behaviors of immune cells, breast cancer cells, and estrogen interactions. Additionally, fractional-order models are adept at handling the heterogeneity typical of diseases like breast cancer, which exhibit diverse subtypes with distinct behaviors. Advancements in these models bolster predictive abilities, allowing for more accurate forecasts of immune cell behavior, breast cancer dynamics, and estrogen interactions. Such predictive precision is invaluable for comprehending disease progression and tailoring personalized interventions for individual patients, marking a significant advancement in mathematical modeling for complex biological systems.

By utilizing fractional-order mathematical techniques, our study presents an innovative method for simulating the dynamics of breast cancer. As a result, we make a valuable contribution to the field of predictive modeling in oncology. By incorporating fractional-order dynamics, a more comprehensive comprehension of the progression of breast cancer can be achieved, which includes pivotal elements like estrogen dynamics and adaptive immune responses. By extending the theoretical underpinnings of cancer modeling, this interdisciplinary framework also carries substantial practical ramifications for clinical practice. Through a comprehensive analysis of the complex relationship between fractional-order dynamics and treatment interventions, our model can provide significant contributions to the understanding of tailored treatment approaches, specifically in regard to the regulation of estrogen levels.

In contrast to current fractional-order cancer mathematical models, our approach highlights the potential clinical significance of fractional-order dynamics in informing individualized treatment approaches, particularly about regulating estrogen levels. This distinctive attribute empowers us to progress precision medicine methodologies customized to specific patient attributes, thus augmenting the effectiveness and personalization of treatment regimens for breast cancer. By clarifying the complex relationship between fractional-order dynamics and treatment interventions, our model can furnish clinicians and researchers with a valuable instrument to enhance patient care and maximize therapeutic outcomes in breast cancer management.

2. Basic Definitions

This section provides a review of some fundamental definitions of fractional calculus to familiarize the readers with ongoing terms.

Definition 2.1. *The Caputo derivative of order $\alpha \in (0,1)$ for an integrable function $F(t)$ is given by [29]*

$$^{C}D^{\alpha}F(t) = \frac{1}{\Gamma(\gamma-\alpha)}\int_0^t \frac{F^{(\gamma)}(\xi)}{(t-\xi)^{\alpha-m+1}}d\xi, \qquad \gamma = [\alpha]+1.$$

The corresponding Caputo fractional integral of the function $F(t)$ is given by

$$^{C}I^{\alpha}F(t) = \frac{1}{\Gamma(\alpha)}\int_0^t (t-\xi)F(t)d\xi.$$

Definition 2.2. *The Caputo-Fabrizio derivative of order $\alpha \in (0,1)$ for the function $F(t) \in H^1(c,d)$, where $H^1(c,d)$ is Sobolev space with $c > d$, is given by [30]*

$$^{CF}D^{\alpha}F(t) = \frac{M(\alpha)}{(1-\alpha))}\int_c^t F'(\xi)e^{\frac{-\alpha}{1-\alpha}(t-\xi)}d\xi,$$

where $M(\alpha)$ is normalization function with $M(0) = M(1) = 1$. The corresponding Caputo-Fabrizio fractional integral is given by

$$^{CF}I^{\alpha}F(t) = \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)}F(t) + \frac{2\alpha}{(2-\alpha)M(\alpha)}\int_0^t F(\xi)d\xi.$$

3. Mathematical Model

A mathematical model representing the intricate interactions within the tumor's microenvironment incorporates five time-dependent ordinary differential equations (ODEs). The proposed ODEs determine a comprehensive framework for comprehending and simulating the progression of breast cancer in a spatially uniform and well-mixed microenvironment by capturing the intricate interplay between estrogen, tumor dynamics, and immune responses. The essential components of the system are represented by the model, which consists of normal cells (N), cancer cells (T), CTLs (C), helper T cells (H), and estrogen (E). The cell populations' temporal evolution is denoted by the time (t) functions for each variable.

The complex structure of breast tissue comprises epithelial cells and is contained inside the normal cell compartment. The model assumes normal cells grow and die naturally, led by unchanged DNA regulating all biological functions. According to the competition model proposed by [31], normal and cancer cells compete for limited nutrients and other resources. The following equations represent the dynamics of normal cells.

$$\frac{dN}{dt} = b_1N(1-b_2N) - b_3NT - b_4NE. \tag{3.1}$$

The first term signifies the logistic growth of normal cells with the rate b_1 (unit: per day) and inverse carrying capacity b_2 (unit: per number of cells), emphasizing the growth and limitation factors intrinsic to the breast tissues composed of epithelial cells. The second term shows the intricate interplay of genetic alterations of normal cells into cancer cells with the rate b_3 (unit: number of cells^{-1}day^{-1}). This term describes how genetic alterations in normal cells affect cancer formation, altering cell cycle control and potentially promoting the development of cancer cells. This alteration is linked to the presence of cancer cells exhibiting an uncontrolled proliferation, as highlighted in previous research [32]. The final term presents the notion of gene transactivation, proposed as a growth factor that is associated with estrogen-induced growth of breast cancer. Consequently, this stimulation may cause DNA harm, eventually decreasing the normal

cell population, which then transforms into cancerous cells with the rate b_4 (unit: number of cells^{-1}day^{-1}).
The dynamics of cancer cells are predominantly influenced by proliferation and cell death, particularly through interactions with CTLs. Cancer cells exhibit logistic growth without an immune response with a growth rate b_5 (unit: per day) and an inverse carrying capacity b_6 (unit: per number of cells). Tumor escape is approximated as the system approaches its carrying capacity. Upon immune stimulation, the interaction between cancer cells and CTLs is modeled as occurring at a rate proportional to the product of their cell numbers, with a constant of proportionality b_7 (unit: number of cells^{-1}day^{-1}). These interactions contribute to cancer cell death. By integrating these processes, we suggest the following equation to describe the temporal progression of the cancer cells.

$$\frac{dT}{dt} = b_5T(1 - b_6T) - b_7CT + b_4NE. \tag{3.2}$$

Tumor cells generate a complex chain of processes that activate and proliferate CTLs in the immune system. It commences with the recognition of specific tumor antigens, abnormal proteins expressed on the surface of cancer cells. Dendritic cells, specialized antigen-presenting cells, play a pivotal role in capturing and presenting these tumor antigens. Upon processing and presenting tumor antigens on their surface in association with major histocompatibility complex (MHC) molecules, dendritic cells signal T cells, including naive CTLs, to recognize and interact with the presented antigens. Activation of naive CTLs involves intricate signaling cascades and molecular interactions, leading to their proliferation and differentiation. The CTLs that are activated undergo clonal expansion, a critical step in the production of a more significant number of similar cells. This increase is essential for generating an effective force of CTL effectors to destroy tumor cells. The process of CTL activation and expansion in response to cancer cells is denoted by the term b_8TC (Lotka-Volterra form suggested by [33]), where b_8 (unit: number of cells^{-1}day^{-1}) represents the growth parameter. The natural decay of CTLs is modeled by the rate b_9 (unit: per day).
Helper T cells are stimulated upon encountering tumor antigens, leading to clonal expansion and differentiation. This activation is facilitated by the interaction between the T-cell receptor on the helper T cells and the tumor antigen presented by dendritic cells. Activated helper T cells release signaling molecules, such as cytokines, that play a crucial role in orchestrating and amplifying the immune response. Importantly, these cytokines, particularly interleukins, stimulate the activation and proliferation of CTLs. Activated CTLs are then equipped to specifically recognize and engage with breast cancer cells presenting the same tumor antigens. The coordinated action of helper T cells is essential for the full activation and effectiveness of CTLs in targeting and eliminating cancerous cells. The process of CTLs activation and proliferation in response to helper T cells is denied by the term $b_{10}CH$, where b_{10} (unit: number of cells^{-1}day^{-1}) represents the growth parameter. By combining these components, the following equation is derived to depict the

dynamics of CTLs.

$$\frac{dC}{dt} = b_8TC - b_9C + b_{10}CH. \tag{3.3}$$

Our proposed model focuses on the mechanisms that regulate the development of helper T cells in the tumor microenvironment in breast cancer. The evidence suggests that helper T cells are primarily influenced by three key factors: infiltration from the lymph nodes, proliferation induced by the presence of tumor cells, and natural cell death. The influx of helper T cell populations from the lymph nodes occurs at a constant rate denoted as b_{11} (unit: number of cells per day), while their natural cell death is characterized by b_{13} (unit: per day) rates. Notably, we account for the continuous production of naive T cells by hematopoietic stem cells, resulting in a constant population of these cells in the circulating bloodstream. Assuming a constant blood flow, we incorporate direct stimulation of T cells in the tumor microenvironment and a steady influx of primed T cells from the circulating blood. This assumption implicitly accommodates a consistent pool of memory T cells even in the absence of antigen stimulation, aligning with established approaches in similar models to consider a baseline level of circulating T cells [33]. In our model, we further propose that the tumor exerts a suppressive effect on the proliferation of helper T cells, indirectly impacting CTLs. Specifically, we propose that the proliferation rate of helper T cells exhibits biphasic dependence on the number of cancer cells governed by a constant of proportionality denoted as b_{12} (unit: per day). The following equation can illustrate this thorough description of the controlling regulatory mechanisms of helper T cells.

$$\frac{dH}{dt} = b_{11} + b_{12}TH - b_{13}H. \tag{3.4}$$

It is important to understand the complex interaction between estrogen and the immune system via mathematical modeling to enhance our comprehension of breast cancer. Estrogen, a key hormone, plays a pivotal role in the development and progression of breast cancer, particularly in hormone-receptor-positive cases where cancer cells express receptors for hormones like estrogen. Mathematical models provide a quantitative means to capture and simulate the complex dynamics between estrogen levels and the behavior of breast cancer cells. An increased estrogen level can cause the rapid growth of cancerous cells. Furthermore, it acts as a mitogen in breast tissue by stimulating cell proliferation [34]. Estrogen acts as a carcinogen by causing direct damage to DNA, which increases the likelihood of healthy epithelial cells becoming cancerous [35]. The following equation gives the dynamics of estrogen in which b_{14} (unit: number of cells per day) represents the continuous replenishment of excessive estrogen, while b_{15} (unit: per day) represents the natural decay

$$\frac{dE}{dt} = b_{14} - b_{15}E. \tag{3.5}$$

Combining all, we proposed the following set of ODEs to describe the time evolution of breast cancer cells along CTLs, helper T cells, and estrogen.

$$\frac{dN}{dt} = b_1N(1-b_2N) - b_3NT - b_4NE, \tag{3.6}$$

$$\frac{dT}{dt} = b_5T(1-b_6T) - b_7CT + b_4NE, \tag{3.7}$$

$$\frac{dC}{dt} = b_8TC - b_9C + b_{10}CH, \tag{3.8}$$

$$\frac{dH}{dt} = b_{11} + b_{12}TH - b_{13}H, \tag{3.9}$$

$$\frac{dE}{dt} = b_{14} - b_{15}E, \tag{3.10}$$

where $b_1, b_2, b_3, ..., b_{15}$ are positive parameters. The above mathematical model consists of five variables having different units. It is necessary to create a dimensionless mathematical model when working with variables that have different units. This necessity arises from the aim of achieving universal applicability, allowing researchers from diverse fields and locations to readily employ and understand the model without the encumbrance of unit conversions. The simplification of mathematical expressions is another crucial aspect of dimensionless modeling. By removing specific units, the model becomes more transparent and easier to analyze, facilitating a focused examination of the inherent relationships between variables without the burden of unit-related complexities.

The mathematical model (3.6)-(3.10) is non-dimensionalized using the following transformation (suggested by [25, 33, 36])

$$y_1 = \frac{N}{N_0}, y_2 = \frac{T}{T_0}, y_3 = \frac{C}{C_0}, y_4 = \frac{H}{H_0}, y_5 = \frac{E}{E_0}, \tau = b_7T_0t.$$

The dimensionless model, after replacing τ by t, is given below

$$\frac{dy_1}{dt} = a_1y_1(1-a_2y_1) - a_3y_1y_2 - a_4y_1y_5, \tag{3.11}$$

$$\frac{dy_2}{dt} = a_5y_2(1-a_6y_2) - y_3y_2 + a_7y_1y_5, \tag{3.12}$$

$$\frac{dy_3}{dt} = a_8y_2y_3 - a_9y_3 + a_{10}y_3y_4, \tag{3.13}$$

$$\frac{dy_4}{dt} = a_{11} + a_{12}y_2y_4 - a_{13}y_4, \tag{3.14}$$

$$\frac{dy_5}{dt} = a_{14} + a_{15}y_5. \tag{3.15}$$

where

$$a_1 = \frac{b_1}{b_7N_0}, a_2 = b_2N_0, a_3 = \frac{b_3}{b_7}, a_4 = \frac{b_4}{b_7}, a_5 = \frac{b_5}{b_7T_0}, a_6 = b_6T_0, a_7 = \frac{b_4N_0}{b_7T_0}, a_8 = \frac{b_8}{b_7},$$

$$a_9 = \frac{b_9}{b_7T_0}, a_{10} = \frac{b_{10}}{b_7T_0H_0}, a_{11} = \frac{b_{11}}{b_7T_0H_0}, a_{12} = \frac{b_{12}}{b_7}, a_{13} = \frac{b_{13}}{b_7T_0}, a_{14} = \frac{b_{14}}{b_7T_0E_0}, a_{15} = \frac{b_{15}}{b_7T_0}.$$

Analyzing mathematical models associated with breast cancer is crucial for improving understanding of their assessment, existence of solutions, stability, and regulation. Classical approaches to mathematical modeling often fail to achieve the requisite precision for accurately representing the dynamics of these diseases. Fractional differential equations have been introduced to address this challenge, offering a more competent framework for handling such complex problems [27]. The application of fractional differential equations extends to various applied fields, including production problems, optimization, artificial intelligence, medical diagnoses, robotics, and cosmology. Over the past few decades, fractional calculus has emerged as a valuable tool in the mathematical modeling of biological phenomena. This is primarily due to its capacity to more accurately elucidate and process materials' retention and hereditary properties than traditional integer-order models. Consequently, researchers have extended classical calculus to the fractional-order domain through fractional-order modeling, employing diverse mathematical techniques. The proposed fractional-order mathematical model under Caputo fractional derivative of order α is given by

$$D_t^\alpha(y_1) = F_1(t, Y) = a_1 y_1(1 - a_2 y_1) - a_3 y_1 y_2 - a_4 y_1 y_5, \tag{3.16}$$

$$D_t^\alpha(y_2) = F_2(t, Y) = a_5 y_2(1 - a_6 y_2) - y_3 y_2 + a_7 y_1 y_5, \tag{3.17}$$

$$D_t^\alpha(y_3) = F_3(t, Y) = a_8 y_2 y_3 - a_9 y_3 + a_{10} y_3 y_4, \tag{3.18}$$

$$D_t^\alpha(y_4) = F_4(t, Y) = a_{11} + a_{12} y_2 y_4 - a_{13} y_4, \tag{3.19}$$

$$D_t^\alpha(y_5) = F_5(t, Y) = a_{14} + a_{15} y_5, \tag{3.20}$$

where $Y \subseteq \{y_1, y_2, y_3, y_4, y_5\}$ and initial conditions are $y_1(0) = y_1^0$, $y_2(0) = y_2^0$, $y_3(0) = y_3^0$, $y_4(0) = y_4^0$, $y_5(0) = y_5^0$.

4. Model Analysis

4.1. **Boundedness and Positivity of Solutions.** The dimensionless system (3.11)-(3.15) has positive initial conditions of the form:

$$y_1(0) = y_1^0, \quad y_2(0) = y_2^0, \quad y_3(0) = y_3^0, \quad y_4(0) = y_4^0, \quad y_5(0) = y_5^0. \tag{4.1}$$

The dynamics of each population are determined by its growth rate, interactions with other populations, and external factors, thereby ensuring biological significance. The formulation of these interactions is designed to preclude the occurrence of negative values, which is consistent with the characteristics of cellular populations. We have the following theorems to prove the boundedness and positivity of solutions.

Theorem 4.1. *The solution of the system* (3.11)-(3.15) *is non-negative and remains in the region* $\Omega = \{(y_1, y_2, y_3, y_4, y_5) : y_i \in \mathcal{R}^+ \ \forall \ i = 1, 2, ..., 5\}$.

Proof. From equation (4.1) and (3.11), we have

$$\frac{dy_1}{dt} \leq a_1 y_1 - a_1 a_2 y_1^2. \tag{4.2}$$

By using the Bernoulli method, we have

$$y_1(t) \leq \frac{y_1^0}{a_2 y_1^0 + (1 - a_2 y_1^0) e^{-a_1 t}}, \tag{4.3}$$

$$y_1(t) \leq \frac{1}{a_2} \text{ as } t \longrightarrow \infty. \tag{4.4}$$

Hence, $y_1(t) > 0$ for $t > 0$. Consequently, it can be shown that $y_2(t) > 0$, $y_3(t) > 0$, $y_4(t) > 0$, $y_5(t) > 0$, for all $t > 0$. This completes the proof. □

4.2. **Stability Analysis.** The equilibrium points for the system (3.11)-(3.15) can be obtained by setting $\frac{dy_1}{dt} = 0$, $\frac{dy_2}{dt} = 0$, $\frac{dy_3}{dt} = 0$, $\frac{dy_4}{dt} = 0$, $\frac{dy_5}{dt} = 0$, and we get three equilibrium points as given by

Tumor-free equilibrium point (E_0):

$$E_0 = \left(0, 0, 0, \frac{a_{11}}{a_{13}}, \frac{a_{14}}{a_{15}}\right).$$

Tumor-dominant equilibrium point (E_1):

$$E_1 = \left(0, \frac{1}{a_6}, 0, \frac{a_{11}a_6}{a_6 a_{13} - a_{12}}, \frac{a_{14}}{a_{15}}\right).$$

Interior equilibrium point (E_2):

$$E_2 = \left(y_1^*, y_2^*, y_3^*, y_4^*, y_5^*\right).$$

The local stability of these equilibrium points can be determined by the Lyapunov linearization method and given by the following theorems.

Theorem 4.2. *The tumor-free equilibrium point (E_0) of the system* (3.11)-(3.15) *is unstable.*

Proof. The Jacobian matrix for the system (3.11)-(3.15) at E_0 is given by

$$J(E_0) = \begin{bmatrix} a_1 - \frac{a_4 a_{14}}{a_{15}} & 0 & 0 & 0 & 0 \\ \frac{a_7 a_{14}}{a_{15}} & a_5 & 0 & 0 & 0 \\ 0 & 0 & \frac{a_{10}a_{11}}{a_{13}} - a_9 & 0 & 0 \\ 0 & \frac{a_{12}a_{11}}{a_{13}} & 0 & -a_{13} & 0 \\ 0 & 0 & 0 & 0 & -a_{15} \end{bmatrix}. \tag{4.5}$$

The characteristic polynomial of $J(E_0)$ is

$$\left(\frac{a_1 a_{15} - a_4 a_{14}}{a_{15}} - \lambda\right)(a_5 - \lambda)\left(\frac{a_{10}a_{11} - a_9 a_{13}}{a_{13}} - \lambda\right)(-a_{13} - \lambda)(-a_{15} - \lambda) = 0.$$

It can be seen that one eigenvalue ($\lambda = a_5$) is positive. Hence, according to the Lyapunov linearization method, the equilibrium point E_0 is unstable. □

Theorem 4.3. *The tumor-dominant equilibrium point (E_1) of the system* (3.11)-(3.15) *is locally asymptotically stable if the inequalities $a_6 a_{13} > a_{12}$, $a_4 a_6 a_{14} + a_3 a_{15} > a_1 a_6 a_{15}$, and $a_6^2 a_9 a_{13} + a_8 a_{12} > a_6^2 a_{10} a_{11} + a_6 a_8 a_{13} + a_6 a_9 a_{12}$ hold.*

Proof. The Jacobian matrix for the system (3.11)-(3.15) at E_1 is given by

$$J(E_1) = \begin{bmatrix} a_1 - \frac{a_3}{a_6} - \frac{a_4 a_{14}}{a_{15}} & 0 & 0 & 0 & 0 \\ \frac{a_7 a_{14}}{a_{15}} & -a_5 & -\frac{1}{a_6} & 0 & 0 \\ 0 & 0 & \frac{a_8}{a_6} + \frac{a_{10}a_{11}a_6}{a_6 a_{13} - a_{12}} - a_9 & 0 & 0 \\ 0 & \frac{a_{12}a_{11}a_6}{a_6 a_{13} - a_{12}} & 0 & \frac{a_{12}}{a_6} - a_{13} & 0 \\ 0 & 0 & 0 & 0 & -a_{15} \end{bmatrix}. \tag{4.6}$$

The characteristic polynomial of $J(E_1)$ is

$$(\frac{a_1 a_6 a_{15} - a_4 a_6 a_{14} - a_3 a_{15}}{a_6 a_{15}} - \lambda)(-a_5 - \lambda)(\frac{a_8}{a_6} + \frac{a_{10}a_{11}a_6}{a_6 a_{13} - a_{12}} - a_9 - \lambda)(-\frac{a_6 a_{13} - a_{12}}{a_6} - \lambda)(-a_{15} - \lambda) = 0.$$

According to the Lyapunov linearization method, the equilibrium point E_1 is locally asymptotically stable if all eigenvalues (roots of the characteristic polynomial) are negative. It can be seen that two eigenvalues ($\lambda = -a_5$ and $\lambda = -a_{15}$) are negative and other eigenvalues will be negative if $a_6 a_{13} > a_{12}$, $a_4 a_6 a_{14} + a_3 a_{15} > a_1 a_6 a_{15}$, and $a_6^2 a_9 a_{13} + a_8 a_{12} > a_6^2 a_{10} a_{11} + a_6 a_8 a_{13} + a_6 a_9 a_{12}$. This completes the proof. □

Theorem 4.4. *The interior equilibrium point (E_2) of the system* (3.11)-(3.15) *is locally asymptotically stable if $c_i > 0$ ($i = 1, 2, ..., 13$), $c_1 c_5 c_9 c_{12} + c_1 c_6 c_{10} c_{11} + c_9 c_4 c_2 c_{12} > c_1 c_6 c_8 c_{12}$, and $c_1 c_5 c_9 + c_2 c_4 c_9 > c_1 c_6 c_8$.*

Proof. The Jacobian matrix for the system (3.11)-(3.15) at E_2 is given by

$$J(E_1) = \begin{bmatrix} -c_1 & -c_2 & 0 & 0 & -c_3 \\ c_4 & -c_5 & -c_6 & 0 & c_7 \\ 0 & c_8 & c_9 & c_{10} & 0 \\ 0 & c_{11} & 0 & c_{12} & 0 \\ 0 & 0 & 0 & 0 & -c_{13} \end{bmatrix}, \tag{4.7}$$

where $c_1 = 2a_1 a_2 y_1^* + a_3 y_2^* + a_4 y_5^* - a_1$, $c_2 = a_3 y_1^*$, $c_3 = a_4 y_1^*$, $c_4 = a_7 y_5^*$, $c_5 = 2a_5 a_6 y_2^* + y_3^* + a_5$, $c_6 = y_2^*$, $c_7 = a_7 y_1^*$, $c_8 = a_8 y_3^*$, $c_9 = a_8 y_2^* + a_{10} y_4^* - a_9$, $c_{10} = a_{10} y_3^*$, $c_{11} = a_{12} y_4^*$, $c_{12} = a_{12} y_2^* - a_{13}$, $c_{13} = a_{15}$. By using Gaussian elimination, the Eq. (4.7) can be reduced into following form:

$$J(E_1) = \begin{bmatrix} -c_1 & -c_2 & 0 & 0 & -c_3 \\ 0 & -\frac{c_5 c_1 + c_4 c_2}{c_1} & -c_6 & 0 & \frac{c_7 c_1 - c_4 c_3}{c_1} \\ 0 & 0 & \frac{c_1 c_5 c_9 - c_8 c_1 c_6 + c_2 c_4 c_9}{c_5 c_1 + c_4 c_2} & c_{10} & \frac{c_8 (c_7 c_1 - c_4 c_3)}{c_5 c_1 + c_4 c_2} \\ 0 & 0 & 0 & \frac{c_1 c_5 c_9 c_{12} - c_1 c_6 c_8 c_{12} + c_{11} c_1 c_6 c_{10} + c_2 c_4 c_9 c_{12}}{c_1 c_5 c_9 - c_8 c_1 c_6 + c_2 c_4 c_9} & \frac{c_9 c_{11} (c_7 c_1 - c_4 c_3)}{c_1 c_5 c_9 - c_8 c_1 c_6 + c_2 c_4 c_9} \\ 0 & 0 & 0 & 0 & -c_{13} \end{bmatrix}. \tag{4.8}$$

The characteristic polynomial of $J(E_2)$ is

$$(-c_1 - \lambda)(-\frac{c_5 c_1 + c_4 c_2}{c_1} - \lambda)(\frac{c_1 c_5 c_9 - c_8 c_1 c_6 + c_2 c_4 c_9}{c_5 c_1 + c_4 c_2} - \lambda)(\frac{c_1 c_5 c_9 c_{12} - c_1 c_6 c_8 c_{12} + c_{11} c_1 c_6 c_{10} + c_2 c_4 c_9 c_{12}}{c_1 c_5 c_9 - c_8 c_1 c_6 + c_2 c_4 c_9} - \lambda)(-c_{13} - \lambda) = 0.$$

According to the Lyapunov linearization method, the equilibrium point E_1 is locally asymptotically stable if all eigenvalues (roots of the characteristic polynomial) are negative. It can be seen that three eigenvalues ($\lambda = -c_1$, $\lambda = -\frac{c_5 c_1 + c_4 c_2}{c_1}$, and $\lambda = -c_{13}$) are negative and other eigenvalues

will be negative if $c_1c_5c_9c_{12} + c_1c_6c_{10}c_{11} + c_9c_4c_2c_{12} > c_1c_6c_8c_{12}$ and $c_1c_5c_9 + c_2c_4c_9 > c_1c_6c_8$. This completes the proof. □

5. Methodology of Numerical Simulation

Different numerical methods are proposed to solve fractional-order differential equations. A comprehensive analysis of these methodologies can be found in [37–39]. In this study, we use the generalized Adams-Bashforth-Moulton method to solve the proposed mathematical model. To understand the procedure, we have the following nonlinear equation

$$D_t^{\alpha}(z(t)) = f(t, z(t)), \;\; 0 \le t \le T,$$
$$z^{(q)}(0) = z_0^{(q)}, \;\; q = 0, 1, 2, 3, ..., \nu, \;\; \nu = [\eta].$$

The above equation can be written in the form of a Volterra integral equation as follows

$$z(t) = \sum_{q=0}^{\nu-1} z_0^q \frac{t^q}{q!} + \frac{1}{\Gamma(\eta)} \int_0^t (t-\xi)^{\eta-1} f(\xi, z(\xi)) d\xi \tag{5.1}$$

Tuan et al. [40] used the Adams-Bashforth-Moulton method to integrate the above equation. Following this methodology, we set $h = \frac{T}{N}$, $t_n = nh$, $n = 0, 1, 2, 3, ..., N \in Z^+$ and we can write the system (3.16)-(3.20) as follows:

$$\begin{aligned} y_1^{(n+1)} =& y_1^0 + \frac{h^{\alpha}\lambda^{1-\alpha}}{\Gamma(\alpha+2)} \left[a_1 y_{1p}^{(n+1)} (1 - a_2 y_{1p}^{(n+1)}) - a_3 y_{1p}^{(n+1)} y_{2p}^{(n+1)} - a_4 y_{1p}^{(n+1)} y_{5p}^{(n+1)} \right] \\ &+ \frac{h^{\alpha}\lambda^{1-\alpha}}{\Gamma(\alpha+2)} \sum_{i=0}^{n} a_i^{(n+1)} \left[a_1 y_1^{(i)} (1 - a_2 y_1^{(i)}) - a_3 y_1^{(i)} y_2^{(i)} - a_4 y_1^{(i)} y_5^{(i)} \right], \end{aligned} \tag{5.2}$$

$$\begin{aligned} y_2^{(n+1)} =& y_2^0 + \frac{h^{\alpha}\lambda^{1-\alpha}}{\Gamma(\alpha+2)} \left[a_5 y_{2p}^{(n+1)} (1 - a_6 y_{2p}^{(n+1)}) - y_{3p}^{(n+1)} y_{2p}^{(n+1)} + a_7 y_{1p}^{(n+1)} y_{5p}^{(n+1)} \right] \\ &+ \frac{h^{\alpha}\lambda^{1-\alpha}}{\Gamma(\alpha+2)} \sum_{i=0}^{n} a_i^{(n+1)} \left[a_5 y_2^{(i)} (1 - a_6 y_2^{(i)}) - y_3^{(i)} y_2^{(i)} + a_7 y_1^{(i)} y_5^{(i)} \right], \end{aligned} \tag{5.3}$$

$$\begin{aligned} y_3^{(n+1)} =& y_3^0 + \frac{h^{\alpha}\lambda^{1-\alpha}}{\Gamma(\alpha+2)} \left[a_8 y_{2p}^{(n+1)} y_{3p}^{(n+1)} - a_9 y_{3p}^{(n+1)} + a_{10} y_{3p}^{(n+1)} y_{4p}^{(n+1)} \right] \\ &+ \frac{h^{\alpha}\lambda^{1-\alpha}}{\Gamma(\alpha+2)} \sum_{i=0}^{n} a_i^{(n+1)} \left[a_8 y_2^{(i)} y_3^{(i)} + a_9 y_3^{(i)} + a_{10} y_3^{(i)} y_4^{(i)} \right], \end{aligned} \tag{5.4}$$

$$\begin{aligned} y_4^{(n+1)} =& y_4^0 + \frac{h^{\alpha}\lambda^{1-\alpha}}{\Gamma(\alpha+2)} \left[a_{11} + a_{12} y_{2p}^{(n+1)} y_{4p}^{(n+1)} - a_{13} y_{4p}^{(n+1)} \right] \\ &+ \frac{h^{\alpha}\lambda^{1-\alpha}}{\Gamma(\alpha+2)} \sum_{i=0}^{(n)} a_i^{(n+1)} \left[a_{11} + a_{12} y_2^{(i)} y_4^{(i)} - a_{13} y_4^{(i)} \right], \end{aligned} \tag{5.5}$$

$$y_5^{(n+1)} = y_5^0 + \frac{h^\alpha \lambda^{1-\alpha}}{\Gamma(\alpha+2)}\left[a_{14} + a_{15} y_{5p}^{(n+1)}\right] + \frac{h^\alpha \lambda^{1-\alpha}}{\Gamma(\alpha+2)} \sum_{i=0}^{n} a_i^{(n+1)} \left[a_{14} + a_{15} y_5^{(i)}\right], \tag{5.6}$$

where

$$y_{1p}^{(n+1)} = y_1^0 + \frac{\lambda^{1-\alpha}}{\Gamma(\alpha)} \sum_{i=0}^{n} \Phi_i^{(n+1)} \left[a_1 y_1^{(i)}(1 - a_2 y_1^{(i)}) - a_3 y_1^{(i)} y_2^{(i)} - a_4 y_1^{(i)} y_5^{(i)}\right], \tag{5.7}$$

$$y_{2p}^{(n+1)} = y_2^0 + \frac{\lambda^{1-\alpha}}{\Gamma(\alpha)} \sum_{i=0}^{n} \Phi_i^{(n+1)} \left[a_5 y_2^{(i)}(1 - a_6 y_2^{(i)}) - y_3^{(i)} y_2^{(i)} + a_7 y_1^{(i)} y_5^{(i)}\right], \tag{5.8}$$

$$y_{3p}^{(n+1)} = y_3^0 + \frac{\lambda^{1-\alpha}}{\Gamma(\alpha)} \sum_{i=0}^{n} \Phi_i^{(n+1)} \left[a_8 y_2^{(i)} y_3^{(i)} - a_9 y_3^{(i)} + a_{10} y_3^{(i)} y_4^{(i)}\right], \tag{5.9}$$

$$y_{4p}^{(n+1)} = y_4^0 + \frac{\lambda^{1-\alpha}}{\Gamma(\alpha)} \sum_{i=0}^{n} \Phi_i^{(n+1)} \left[a_{11} + a_{12} y_2^{(i)} y_4^{(i)} - a_{13} y_4^{(i)}\right], \tag{5.10}$$

$$y_{5p}^{(n+1)} = y_5^0 + \frac{\lambda^{1-\alpha}}{\Gamma(\alpha)} \sum_{i=0}^{n} \Phi_i^{(n+1)} \left[a_{14} + a_{15} y_5^{(i)}\right]. \tag{5.11}$$

Also, for $j = 1, 2, 3$,

$$a_i^{(n+1)} = \begin{cases} n^{\alpha_k+1} - (n-\alpha_k)(n+1)^{\alpha_k} & i = 0 \\ (n-i+2)^{\alpha_k+1} + (n-i)^{\alpha_k+1} - 2(n-i+1)^{\alpha_k+1} & 1 < i < n \\ 1 & i = n+1 \end{cases}$$

and

$$\Phi_i^{(n+1)} = \frac{h^{\alpha_k}}{\alpha_k}\left((n-i+1)^{\alpha_k} - (n-i)^{\alpha_k}\right), \quad 0 \le i \le n. \tag{5.12}$$

6. Results and Discussion

We developed an intricate mathematical framework by utilizing Caputo fractional derivatives in order to obtain the impact of fractional-order derivatives on the dynamics of breast cancer. The proposed mathematical model is simulated in MATLAB and the results are shown graphically in Figures 1 and 2.

In our fractional-order mathematical model, the α parameter denotes the fractional order of differentiation. The determination of the suitable α value involves an examination of its impact on the experimental data, taking into account the memory effects and long-range dependencies that are intrinsic to the dynamics of breast cancer progression and adaptive immune responses. In our numerical experiments, we present results for α values of 0.85, 0.9, and 0.95. These values were

chosen based on their relevance to capturing the fractional-order dynamics observed in biological systems. However, by comparing the dynamics of the proposed model to experimental data, one can determine an appropriate value. Furthermore, the results' robustness against fluctuations in the α parameter can be evaluated through sensitivity analyses. Table 1 details the values of the model parameters utilized in our numerical simulations.

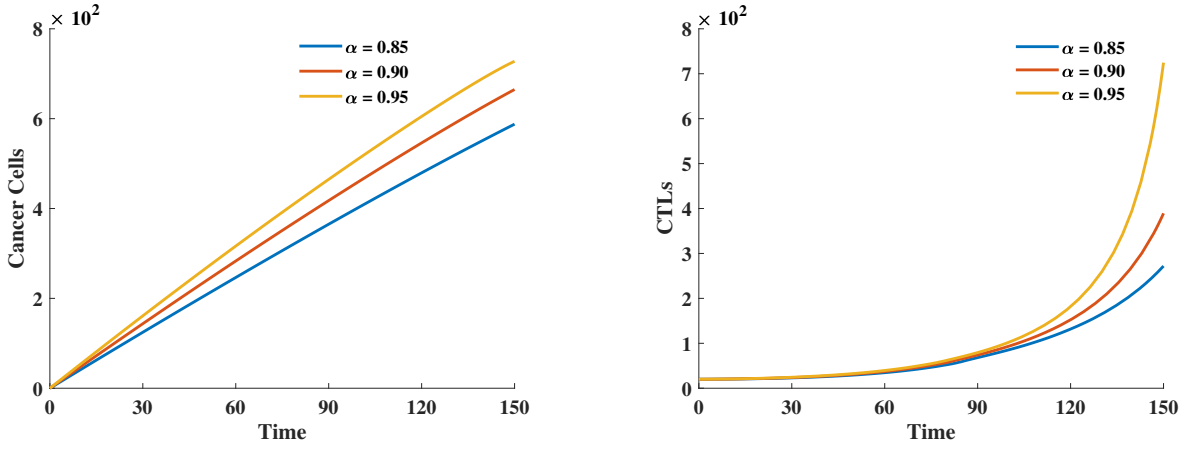
We have obtained remarkable insights into the behavior of our fractional-order mathematical model through multiple values of fractional orders via intensive simulations and research. Significantly, an upward trend in the values of the cell populations is observed as the fractional order (α) increases. This discovery implies that increasing fractional orders leads to heightened dynamics within the system, potentially signaling a proliferation of cancer cells with more aggressive characteristics. Conversely, the model forecasts that diminishing fractional order values correspond to a decrease in cell populations. This decline in fractional orders could suggest a more subdued or less assertive trajectory of cancer proliferation, as evidenced by the observed reduction.

The study's findings have substantial and wide implications, underscoring the need for fractional-order models when modeling complex biological systems such as breast cancer. Compared to the integer order model, the fractional order approach provides a relatively adaptable framework that simulates the nonlinear intricacies of biological processes, which poses the risk of simplifying dynamics and disregarding vital details. Our analysis revealed that the category of divergent models expands significantly when integer order derivatives are utilized; this is particularly true for chaotically nonlinear systems, such as tumor development. Conventional approaches may fail to detect a divergence pattern due to the intrinsic complex nonlinearity in cancer processes. On the contrary, fractional-order derivatives exhibit a greater capacity for accurately simulating these dynamics at a higher order.

Due to their ability to accurately simulate the behavioral patterns of biological systems with varying degrees of complexity, fractional-order models can be utilized effectively in clinical and biomedical practice. Fractional order enables the identification of latent patterns that facilitate the advancement of cancer, thereby reducing the development of more rational therapeutic interventions. No additional variables regarding the treatment alternative were incorporated into the current model. However, our model's application of treatment techniques might be evaluated more positively, particularly via regulating estrogens. The fractional-order model's clinical significance and utility value can be enhanced by incorporating a system of treatment strategies, such as hormone therapy or targeted therapies that regulate estrogen levels. Our model's functional applicability is currently restricted, and treatment considerations must be adopted, which will also play a part in therapeutic methods and clinical decision-making. Through simulating various treatment alternatives and assessing their capacity to modify the advancement of cancer, we devise customized therapeutic options that cater to the specific needs of every patient in terms of tumor characteristics and cellular composition.

It is critical to validate our fractional-order model for breast cancer dynamics to evaluate its practical utility and predictive effectiveness. To this end, we obtained experimental data on the number of cancer cells from [41], extracting the relevant information using the MATLAB function 'GRABIT.' Following that, a comparative analysis was performed between the forecasts produced by our model and the actual number of cancer cells extracted from [41]. This comparison was facilitated by plotting the number of cancer cells predicted by our model, considering the parametric values ($\alpha_5 = 0.629$ and $\alpha_7 = 0.173$) alongside the experimental data, as illustrated in Figure 3. Our analysis revealed that the model's predictions, particularly when utilizing a fractional-order parameter of $\alpha = 0.9$, closely aligned with the experimental data, demonstrating a superior fit compared to the integer-order case ($\alpha = 1$). This successful validation underscores the practical applicability of our fractional-order model in accurately predicting breast cancer dynamics, as evidenced by its close correspondence with observed data points. These findings affirm the model's ability to capture the complexities of breast cancer progression and highlight its potential as a valuable tool for guiding clinical decision-making and treatment optimization.

The dynamics of the fractional-order model are more closely aligned with experimental data than the traditional derivative model, as illustrated in Figure 3. This comparison demonstrates that the fractional-order model is more capable of capturing the intricate dynamics of breast cancer progression. We emphasize the practicality of fractional calculus in biological modeling by providing numerical outcomes demonstrating the benefits of employing the fractional-order approach in achieving congruence with experimental observations. Furthermore, Figure 3 shows the advantages of using the fractional-order model over the traditional derivative model. A comparative analysis of different alpha values with experimental data makes it possible to clarify that the fractional-order model provides a more precise portrayal of breast cancer dynamics.

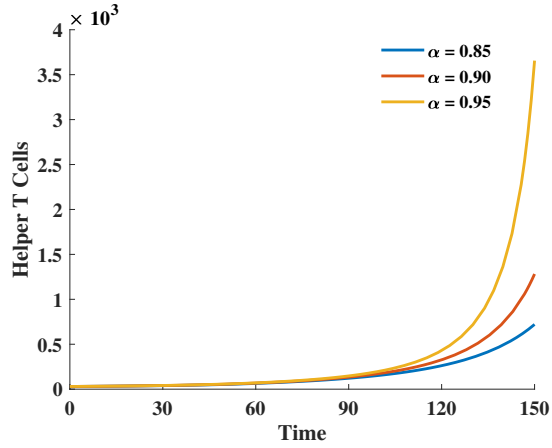


(A) Dynamics of cancer cells at different values of α. (B) Dynamics of CTLs at different values of α.

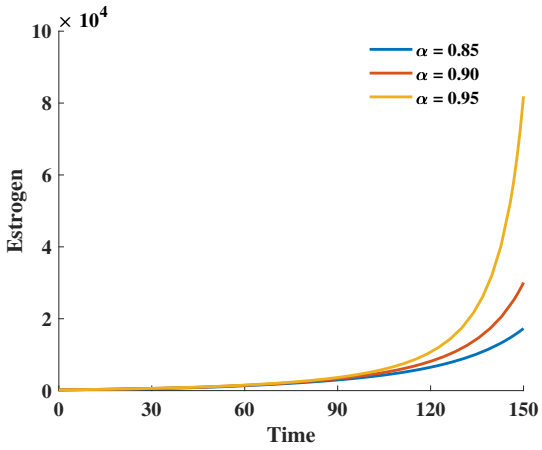
FIGURE 1. Dynamics of cancer cells and CTLs at different values of α.

TABLE 1. Description of parameters and their values.

Symbols	Definitions	Values	References
α_1	Logistic growth rate of normal cells	0.2-0.8	Varies
α_2	Inverse carrying capacity of normal cells	10^{-3}	Assumed
α_3	Mutation rate of normal cells into cancer cells	0.001-0.005	Assumed
α_4	Mutation rate of normal cells into cancer cells due to estrogen	0.001-0.005	Assumed
α_5	Logistic growth rate of cancer cells	0.4-0.8	[42, 43]
α_6	Inverse carrying capacity of cancer cells	10^{-3}	Assumed
α_7	Growth rate of cancer cells due to estrogen	0.05-0.2	Varies
α_8	Growth rate of CTLs	0.04	[33]
α_9	Natural degradation rate of CTLs	0.8729	[43, 44]
α_{10}	Growth rate of CTLs due to helper T cells	0.001-0.015	[33]
α_{11}	Supply of helper T cells	10^2-10^3	Varies
α_{12}	Growth rate of helper T cells due to cancer cells	0.015-0.02	[33]
α_{13}	Natural degradation rate of helper T cells	0.055	[33]
α_{14}	Supply of estrogen	10^2-10^3	Varies
α_{15}	Natural degradation rate of estrogen	0.03-0.07	[34, 43]



(A) Dynamics of helper T cells at different values of α.



(B) Dynamics of estrogen at different values of α.

FIGURE 2. Dynamics of helper T cells and estrogen at different values of α.

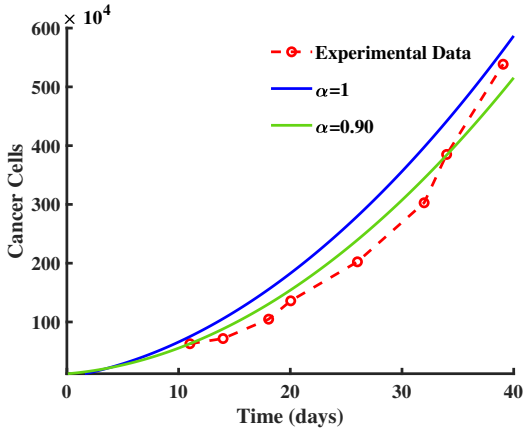


FIGURE 3. Comparison of cancer cells at different values of α with experimental data.

7. CONCLUSIONS

We emphasize the significance of incorporating fractional calculus into biological modeling using a fractional-order mathematical framework that enhances understanding of breast cancer dynamics. The variations in cell populations highlight the importance of fractional-order dynamics in understanding the complex nonlinear aspects of cancer advancement. Our results emphasize the potential practical use of fractional-order models in directing individualized treatment approaches, mainly by adjusting estrogen levels. Incorporating treatment considerations into our framework presents an avenue for refining therapeutic approaches and informing clinical decision-making. By leveraging the capabilities of fractional-order modeling, we aim to advance precision medicine initiatives to combat breast cancer and improve patient outcomes.

Acknowledgments: The authors extend their appreciation to the Deanship of Scientific Research at Imam Mohammad Ibn Saud Islamic University (IMSIU).

Conflicts of Interest: The authors declare that there are no conflicts of interest regarding the publication of this paper.

REFERENCES

[1] M. Akram, M. Iqbal, M. Daniyal, A.U. Khan, Awareness and Current Knowledge of Breast Cancer, Biol. Res. 50 (2017), 33. https://doi.org/10.1186/s40659-017-0140-9.

[2] S. Lei, R. Zheng, S. Zhang, S. Wang, R. Chen, K. Sun, H. Zeng, J. Zhou, W. Wei, Global Patterns of Breast Cancer Incidence and Mortality: A Population-based Cancer Registry Data Analysis from 2000 to 2020, Cancer Commun. 41 (2021), 1183–1194. https://doi.org/10.1002/cac2.12207.

[3] Y. Kim, K.Y. Yoo, M.T. Goodman, Differences in Incidence, Mortality and Survival of Breast Cancer by Regions and Countries in Asia and Contributing Factors, Asian Pac. J. Cancer Prev. 16 (2015), 2857–2870. https://doi.org/10.7314/apjcp.2015.16.7.2857.

[4] E. Mallon, The Basic Pathology of Human Breast Cancer, J. Mammary Gland Biol. Neoplasia 5 (2000), 139–163. https://doi.org/10.1023/a:1026439204849.

[5] K. Polyak, Breast Cancer: Origins and Evolution, J. Clin. Invest. 117 (2007), 3155–3163. https://doi.org/10.1172/jci33295.

[6] E.A. McSherry, S. Donatello, A.M. Hopkins, S. McDonnell, Common Molecular Mechanisms of Mammary Gland Development and Breast Cancer: Molecular Basis of Invasion in Breast Cancer, Cell. Mol. Life Sci. 64 (2007), 3201–3218. https://doi.org/10.1007/s00018-007-7388-0.

[7] U. Testa, G. Castelli, E. Pelosi, Breast Cancer: A Molecularly Heterogenous Disease Needing Subtype-Specific Treatments, Med. Sci. 8 (2020), 18. https://doi.org/10.3390/medsci8010018.

[8] G. Jerusalem, J. Collignon, H. Schroeder, L. Lousberg, Triple-Negative Breast Cancer: Treatment Challenges and Solutions, Breast Cancer: Targets Therapy 8 (2016), 93–107. https://doi.org/10.2147/BCTT.S69488.

[9] D.G. DeNardo, L.M. Coussens, Inflammation and Breast Cancer. Balancing Immune Response: Crosstalk between Adaptive and Innate Immune Cells during Breast Cancer Progression, Breast Cancer Res. 9 (2007), 212. https://doi.org/10.1186/bcr1746.

[10] D. Martorelli, E. Muraro, A. Merlo, R. Turrini, A. Rosato, R. Dolcetti, Role of CD4+ Cytotoxic T Lymphocytes in the Control of Viral Diseases and Cancer, Int. Rev. Immunol. 29 (2010), 371–402. https://doi.org/10.3109/08830185.2010.489658.

[11] S. Mocellin, E. Wang, F.M. Marincola, Cytokines and Immune Response in the Tumor Microenvironment, J. Immunotherapy 24 (2001), 392–407.

[12] N.R. Maimela, S. Liu, Y. Zhang, Fates of CD8+ T Cells in Tumor Microenvironment, Comp. Struct. Biotechnol. J. 17 (2019), 1–13. https://doi.org/10.1016/j.csbj.2018.11.004.

[13] C. Gu-Trantien, S. Loi, S. Garaud, C. Equeter, M. Libin, A. De Wind, et al. CD4+ Follicular Helper T Cell Infiltration Predicts Breast Cancer Survival, J. Clin. Invest. 123 (2013), 2873–2892. https://doi.org/10.1172/JCI67428.

[14] H.I. Jacobson, J.A. Bennett, G.J. Mizejewski, Inhibition of Estrogen-Dependent Breast Cancer Growth by a Reaction Product of α-Fetoprotein and Estradiol, Cancer Res. 50 (1990), 415–420.

[15] P. Bhardwaj, C.C. Au, A. Benito-Martin, H. Ladumor, S. Oshchepkova, R. Moges, K.A. Brown, Estrogens and Breast Cancer: Mechanisms Involved in Obesity-Related Development, Growth and Progression, J. Steroid Biochem. Mol. Biol. 189 (2019), 161–170. https://doi.org/10.1016/j.jsbmb.2019.03.002.

[16] L.R. Nelson, S.E. Bulun, Estrogen Production and Action, J. Amer. Acad. Dermatol. 45 (2001), S116–S124. https://doi.org/10.1067/mjd.2001.117432.

[17] G.A. Colditz, B.A. Rosner, W.Y. Chen, M.D. Holmes, S.E. Hankinson, Risk Factors for Breast Cancer According to Estrogen and Progesterone Receptor Status, J. Nat. Cancer Inst. 96 (2004), 218–228. https://doi.org/10.1093/jnci/djh025.

[18] A.M. Jarrett, M.J. Bloom, W. Godfrey, A.K. Syed, D.A. Ekrut, L.I. Ehrlich, T.E. Yankeelov, A.G. Sorace, Mathematical Modelling of Trastuzumab-Induced Immune Response in an in Vivo Murine Model of HER2+ Breast Cancer, Math. Med. Biol.: J. IMA 36 (2019), 381–410. https://doi.org/10.1093/imammb/dqy014.

[19] H.C. Wei, Mathematical Modeling of Tumor Growth: The MCF-7 Breast Cancer Cell Line, Math. Biosci. Eng. 16 (2019), 6512–6535. https://doi.org/10.3934/mbe.2019325.

[20] L. Anderson, S. Jang, J. Yu, Qualitative Behavior of Systems of Tumor–CD4+ –Cytokine Interactions with Treatments, Math. Meth. Appl. Sci. 38 (2015), 4330–4344. https://doi.org/10.1002/mma.3370.

[21] S. Banerjee, R.R. Sarkar, Delay-Induced Model for Tumor–Immune Interaction and Control of Malignant Tumor Growth, Biosystems 91 (2008), 268–288. https://doi.org/10.1016/j.biosystems.2007.10.002.

[22] K.J. Mahasa, R. Ouifki, A. Eladdadi, L.D. Pillis, Mathematical Model of Tumor–Immune Surveillance, J. Theor. Biol. 404 (2016), 312–330. https://doi.org/10.1016/j.jtbi.2016.06.012.

[23] A. El-Gohary, Chaos and Optimal Control of Cancer Self-Remission and Tumor System Steady States, Chaos Solitons Fractals 37 (2008), 1305–1316. https://doi.org/10.1016/j.chaos.2006.10.060.

[24] A. El-Gohary, I.A. Alwasel, The Chaos and Optimal Control of Cancer Model with Complete Unknown Parameters, Chaos Solitons Fractals 42 (2009), 2865–2874. https://doi.org/10.1016/j.chaos.2009.04.028.

[25] V. Kuznetsov, I. Makalkin, M. Taylor, A. Perelson, Nonlinear Dynamics of Immunogenic Tumors: Parameter Estimation and Global Bifurcation Analysis, Bull. Math. Biol. 56 (1994), 295–321. https://doi.org/10.1016/S0092-8240(05)80260-5.

[26] D. Kirschner, J.C. Panetta, Modeling Immunotherapy of the Tumor - Immune Interaction, J. Math. Biol. 37 (1998), 235–252. https://doi.org/10.1007/s002850050127.

[27] M. Idrees, A. Alnahdi, M. Jeelani, Mathematical Modeling of Breast Cancer Based on the Caputo–Fabrizio Fractal-Fractional Derivative, Fractal Fract. 7 (2023), 805. https://doi.org/10.3390/fractalfract7110805.

[28] H. Mohammadpoor, N. Eghbali, L. Sajedi, M. Nosrati Sahlan, Stability Analysis of Fractional Order Breast Cancer Model in Chemotherapy Patients with Cardiotoxicity by Applying LADM, Adv. Contin. Discr. Models 2024 (2024), 6. https://doi.org/10.1186/s13662-024-03800-z.

[29] S.G. Samko, Fractional Integrals and Derivatives, Theory and Applications, Gordon and Breach, 1993.

[30] M. Caputo, M. Fabrizio, A New Definition of Fractional Derivative Without Singular Kernel, Progr. Fract. Diff. Appl. 1 (2015), 73–85.

[31] R.A. Gatenby, The Potential Role of Transformation-Induced Metabolic Changes in Tumor-Host Interaction, Cancer Res. 55 (1995), 4151–4156.

[32] C. Mufudza, W. Sorofa, E.T. Chiyaka, Assessing the Effects of Estrogen on the Dynamics of Breast Cancer, Comp. Math. Meth. Med. 2012 (2012), 473572. https://doi.org/10.1155/2012/473572.

[33] Y. Dong, R. Miyazaki, Y. Takeuchi, et al. Mathematical Modeling on Helper T Cells in a Tumor Immune System, Discr. Contin. Dyn. Syst. - B 19 (2014), 55–72. https://doi.org/10.3934/dcdsb.2014.19.55.

[34] V. Valayannopoulos, F. Bajolle, J.B. Arnoux, S. Dubois, N. Sannier, et al. Successful Treatment of Severe Cardiomyopathy in Glycogen Storage Disease Type III With D,L-3-Hydroxybutyrate, Ketogenic and High-Protein Diet, Pediatric Res. 70 (2011), 638–641. https://doi.org/10.1203/PDR.0b013e318232154f.

[35] S. Nagl, The Role of Model Integration in Complex Systems Modelling: An Example from Cancer Biology, Springer, Berlin 2010.

[36] H. Dritschel, S. Waters, A. Roller, H. Byrne, A Mathematical Model of Cytotoxic and Helper T Cell Interactions in a Tumour Microenvironment, Lett. Biomath. 5 (2018), S36–S68. https://doi.org/10.30707/LiB5.2Dritschel.

[37] K.M. Owolabi, A. Atangana, Numerical Methods for Fractional Differentiation, Springer, Singapore, 2019. https://doi.org/10.1007/978-981-15-0098-5.

[38] C. Li, C. Tao, On the Fractional Adams Method, Comp. Math. Appl. 58 (2009), 1573–1588. https://doi.org/10.1016/j.camwa.2009.07.050.

[39] M. Weilbeer, Efficient Numerical Methods for Fractional Differential Equations and Their Analytical Background, Papierflieger Clausthal-Zellerfeld, Germany, 2006.

[40] N.H. Tuan, H. Mohammadi, S. Rezapour, A Mathematical Model for COVID-19 Transmission by Using the Caputo Fractional Derivative, Chaos Solitons Fractals 140 (2020), 110107. https://doi.org/10.1016/j.chaos.2020.110107.

[41] N. Brünner, M. Spang-Thomsen, K. Cullen, The T61 Human Breast Cancer Xenograft: An Experimental Model of Estrogen Therapy of Breast Cancer, Breast Cancer Res. Treat. 39 (1996), 87–92. https://doi.org/10.1007/BF01806080.

[42] S.E. Wardell, A.P. Yllanes, C.A. Chao, Y. Bae, K.J. Andreano, et al. Pharmacokinetic and Pharmacodynamic Analysis of Fulvestrant in Preclinical Models of Breast Cancer to Assess the Importance of Its Estrogen Receptor-α Degrader Activity in Antitumor Efficacy, Breast Cancer Res. Treat. 179 (2020), 67–77. https://doi.org/10.1007/s10549-019-05454-y.

[43] A.S. Alnahdi, M. Idrees, Nonlinear Dynamics of Estrogen Receptor-Positive Breast Cancer Integrating Experimental Data: A Novel Spatial Modeling Approach, Math. Biosci. Eng. 20 (2023), 21163–21185. https://doi.org/10.3934/mbe.2023936.

[44] M. Idrees, A. Sohail, Bio-Algorithms for the Modeling and Simulation of Cancer Cells and the Immune Response, Bio-Algor. Med-Syst. 17 (2021), 55–63. https://doi.org/10.1515/bams-2020-0054.