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Mathematical Modeling of Breast Cancer Based on the Caputo–Fabrizio Fractal-Fractional Derivative

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Abstract: Breast cancer ranks among the most prevalent malignancies affecting the female population and is a prominent contributor to cancer-related mortality. Mathematical modeling is a significant tool that can be employed to comprehend the dynamics of breast cancer progression and dissemination and to formulate novel therapeutic approaches. This paper introduces a mathematical model of breast cancer that utilizes the Caputo–Fabrizio fractal-fractional derivative. The aim is to elucidate and comprehend the intricate dynamics governing breast cancer cells and cytotoxic T lymphocytes in the context of the fractional derivative. The derivative presented herein offers a broader perspective than the conventional derivative, as it incorporates the intricate fractal characteristics inherent in the process of tumor proliferation. The significance of this study lies in its contribution to a novel mathematical model for breast cancer, which incorporates the fractal characteristics of tumor development. The present model possesses the capability to investigate the impacts of diverse treatment strategies on the proliferation of breast cancer, as well as to formulate novel treatment strategies that exhibit enhanced efficacy.

Keywords: breast cancer; mathematical modeling; fractional derivative; fractals

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1. Introduction

Breast cancer is a pathological condition characterized by the unregulated proliferation of cells within the breast tissue. Based on the data provided by "The Global Burden of Disease Cancer Collaboration", it can be observed that breast cancer demonstrates the highest prevalence when compared to other forms of cancer [1]. This pathological condition causes cellular and mammary tissue organization aberrations, resulting in unregulated cellular growth. Therefore, breast cancer presents a potential hazard to women on a global scale. Breast cancer was ranked as the second most prevalent form of cancer by the World Health Organization (WHO) in the year 2004 [2]. According to surveys conducted by the World Health Organization (WHO), it has been found that breast cancer affects approximately 8–9 percent of women on a global scale. Despite numerous studies and investigations, the precise cause of breast cancer remains uncertain. Based on the findings referenced in the sources [2,3], breast cancer was responsible for causing 685,000 fatalities in the year 2020, affecting a total of 2.3 million women. Breast cancer had become the most prevalent global disease by the conclusion of 2020, as evidenced by the diagnosis of 7.8 million women within the preceding five-year period [2]. It is worth noting that breast cancer has a global impact on women following the onset of puberty, and its occurrence tends to rise as individuals age. A comprehensive grasp of the epidemiology of breast cancer and its implications for women's health is crucial in developing impactful, preventive, and therapeutic approaches worldwide.

Cancer is widely recognized as a prominent genetic disorder, with its development primarily linked to mutations occurring in genes associated with a susceptibility to the disease [4]. Many methodologies have been devised to comprehend the fundamental mechanism of human breast cancer [5]. Loeb introduced the notion of a mutator phenotype, which holds significant importance in the progression of tumors [6]. Simultaneously, Tomlinson and Bodmer investigated the mutator phenotype hypothesis and unveiled its correlation with selective pressure for the clonal expansion of intermediate cells [7]. These investigations contribute substantially to our comprehension of the intricate dynamics underlying breast cancer's development and progression. Through the process of elucidation, these studies provide insight into the role of mutator phenotypes, thereby creating opportunities for the development of therapeutic interventions and targeted strategies to address breast cancer and other genetic disorders. The basic ideas of population genetics and the evolutionary processes driving the origin and spread of tumors are best described using mathematical models [8,9]. Various factors, including mutation, selection, and tissue types, have been observed to influence the dynamics of tumorigenesis [10,11]. It is worth noting that there is a correlation between an upsurge in cases of breast cancer incidences among women and factors such as postmenopausal status and the presence of estrogen receptors. The incorporation of mathematical modeling in the field of cancer research offers significant contributions in elucidating the intricate dynamics among these variables, thereby enhancing our comprehension of the pathogenesis of breast cancer.

Mathematical frameworks play a crucial role in facilitating the understanding of intricate disease dynamics and offering precise perspectives on disease control and prevention [12]. In the context of cancer modeling, this field of study dates back to 1954, when the first attempts were made to explain cancer behavior [13]. Following this, scholars have researched diverse facets of cancer and the proliferation of tumors using mathematical models. Dixit et al. [14] formulated a mathematical model to describe the chemotherapy treatment protocol for tumor cancers, providing a comprehensive outline of the treatment procedure. Recent research has focused on developing enhanced, streamlined, mathematical models with an improved efficiency. An experimental model employing low-dose chemotherapy and limited parameters was developed to examine the communication of angiogenic signals between blood vessels and tumors [15]. Jordao and Tavares have developed a compartmental model that incorporates both cancerous and healthy cells, thereby comprehensively examining the proposed cancer model [16]. Khajanchi and Nieto have investigated how a time delay affects the dynamics of the tumor system [17]. Mahlbacher et al. have provided an important model to understand the interactions between the immune system and malignancies, providing important insights for cancer therapy approaches [18]. Numerous mathematical models have been devised in the existing body of literature to examine, conceptualize, and depict the transmission dynamics of cancer [10]. These models play a crucial role in advancing our comprehension of cancer dynamics and they present promising opportunities for developing effective approaches to cancer research, treatment, and prevention.

Fractional calculus has developed as a fast-growing area of mathematical studies, emphasizing arbitrary order derivatives and integrals. Using fractional differential equations has attracted considerable interest in diverse scientific fields. Memory properties have been observed in various intricate phenomena across applied sciences. Researchers may obtain more precise findings using fractional derivatives instead of integer derivatives, which introduces an extra degree of freedom. The inherent non-local characteristics of fractional differential equations render them highly suitable for depicting phenomena or processes exhibiting memory, as well as hereditary properties across various disciplines, including physics, chemistry, biology, and economics [19,20]. Sabir et al. [21] introduced a stochastic framework to tackle the fractional-order differential model linked to breast cancer growth throughout the phase of immune-chemotherapeutic therapy. The proposed framework encompasses a range of control factors, such as pharmacological agents targeting cancer, a ketogenic dietary regimen, and immunomodulatory agents. The developed

model incorporates the temporal changes in tumor density during chemotherapy treatment and the immune response elicited by the interplay between healthy and cancer cells. Solis-Perez et al. [22] introduced a mathematical framework to analyze the competitive dynamics of breast cancer. The model incorporates fractional order derivatives, notably the Liouville–Caputo and Caputo–Fabrizio–Caputo fractional derivatives. The use of fractional derivatives has been shown to provide more important insights into the complexity of the dynamics inside the breast cancer competition model. Sohail et al. [22] introduced an innovative method for including atezolizumab medication in modeling breast cancer epidemiology. The researchers used a methodology based on piecewise fractional-order modeling in their investigation. Hassani et al. [23] examined the Caputo fractional derivative for the fractional order breast cancer competition model. Numerical simulations verified the developed methodology's validity, feasibility, and computational efficacy. Abaid-ur-Rehman et al. [24] examined the reduced differential transform approach for the computer solution of two cancer tumor models with fractional-order dynamics in the Caputo sense. The models used in this study are founded upon the impact of cancer chemotherapy agents, providing insight into the intricate dynamics involving chemotherapeutic medications, cancer cells, normal cells, and immune cells. Ozturk and Ozkose developed the fractional-order model of the tumor–immune system interaction [25]. The research results revealed that the fractional model had a more favorable level of conformity to the experimental data than the integer order model.

Within material and process modeling, fractional calculus emerges as a highly effective instrument, particularly in examining materials and processes that possess memory and hereditary attributes, such as electrochemical phenomena. Furthermore, fractional differentiation and integration operators have been employed to extend the applicability of diffusion and wave equations [26,27]. Additionally, these operators have been utilized to tackle contemporary challenges, such as the temperature field problem in oil strata [28]. In terms of cancer research, notable contributions have been made by Valentim et al. [29], who suggested a multistep exponential model with a fractional order to represent the evolution history of a tumor. Similarly, Farayola et al. [30] modeled a radiotherapy cancer treatment process that included radiobiological factors. These studies demonstrate the adaptability and efficacy of fractional calculus in comprehending intricate cancer-related mechanisms and have the potential to provide valuable perspectives for enhancing approaches to cancer treatment.

This article introduces a substantial expansion of a newly developed deterministic model within the Caputo–Fabrizio fractal-fractional framework. The main objective of this study is to develop a concise and inclusive mathematical model with fractional-order properties that can effectively depict the dynamic characteristics of cancer cells and CTLs. The implications of developing a fractional-order model that is less complex are extensive, particularly in terms of enhancing computational efficiency and interpretability. With the growing importance of computational methods in contemporary research, the simplicity of the proposed model has the potential to facilitate faster and more accurate simulations and predictions. The study's primary contributions pertain to the integration of theoretical concepts and empirical observations within the field of breast cancer research. Utilizing the proposed Caputo–Fabrizio fractal-fractional model can enhance our comprehension of the dynamics between cancer and the immune system. This has the possibility of unveiling innovative approaches for cancer treatment and propelling the progress of mathematical modeling in the field of oncology.

2. Mathematical Model

This study aims to investigate and analyze the breast cancer model with fractional-order derivatives, as previously explored and examined by Idrees and Sohail [31] with integer-order derivatives. Idrees and Sohail introduced a deterministic model that is based upon a set of fundamental assumptions: initially, it has been observed that cancer cells exhibit logistic growth when there is no immune response present [32]. Furthermore, it

has been observed that cytotoxic T lymphocytes exhibit the capacity to eradicate cancer cells [33]. Moreover, it has been observed that cancer cells have the ability to stimulate both naive and noncytotoxic cells [34]. Subsequent to the activation of cytotoxic T cells, their proliferation exhibits a logistic trend, eventually ceasing after a specific threshold of interactions with cancer cells has been reached [35]. Our model's basic premise is that breast cancer is homogenous, which means that every cancer cell within a tumor is thought to have the same characteristics and tendencies. Although this assumption simplifies the tumor's computational description, it could not adequately reflect the heterogeneity in breast cancers. It is hypothesized that a homogeneous distribution of immune cells exists inside the tumor microenvironment. In reality, immune cells have the potential to display spatial heterogeneity within the tumor microenvironment, hence influencing their interactions with cancer cells. Our model simplifies this distribution for computational tractability. Some parameters, such as growth rates, treatment efficacies, and immune cell activities, are considered constant throughout the simulation. In reality, these parameters may vary over time or across different patients. While we aim to capture average values, this assumption may not fully account for temporal changes.

The mathematical representation of the dynamics of cancer cells and cytotoxic T lymphocytes is described by a system of ordinary differential equations:

$$\frac{dC(t)}{dt} = \underbrace{a_1 C(t)\left(1-\frac{C(t)}{a_2}\right)}_{\text{Logistic growth of tumor cells}} - \underbrace{a_3 C(t)\left(\frac{L(t)}{a_4+L(t)}\right)}_{\text{Tumor cells killed by cytolysis}}, \tag{1}$$

$$\frac{dL(t)}{dt} = \underbrace{a_5 L(t)\left(1-\frac{L(t)}{a_6}\right)\left(\frac{C(t)}{a_7+C(t)}\right)}_{\text{Activation of CTLs by tumor and their logistic growth}} - \underbrace{a_8 C(t)L(t)}_{\text{Inactivation of CTL after interaction with tumor}} - \underbrace{a_9 L(t)}_{\text{Natural degradation}}, \tag{2}$$

where $C(t)$ represents the population of breast cancer cells, $L(t)$ represents the population of cytotoxic T lymphocytes, and a_i $(i = 1, 2, 3, \ldots, 9)$ are positive dimensionless constants. The complete process of non-dimensionalization is explained in [31]. Numerous in vitro and in vivo investigations have repeatedly shown that tumor cells proliferate exponentially while their population is small but decelerate as their population reaches higher levels. In light of this fact, it is postulated that the progression of tumor development adheres to a logistic curve characterized by an inherent growth rate denoted as α_1 and a maximum carrying capacity represented as α_2. The researchers used experimental literature, where accessible, to determine the parameters of the suggested model quantitatively. Nevertheless, due to the limited data availability, we must additionally depend on prior estimations of certain rates and values derived from other scholarly modeling publications. The estimation of the growth rate α_1 is derived from the data [36], while the determination of the carrying capacity is based on the findings from the research [37–39]. Estimating the values of parameters α_1 and α_4 is based on the analysis of experimental data [40]. The parameters of the CTL equation were determined based on a clinical investigation conducted on cancer cells and T lymphocytes in individuals diagnosed with breast cancer [41]. The complete process of the parameter estimation is described in [31].

2.1. Preliminaries of Fractional Calculus

This section discusses some fundamental definitions pertaining to the Caputo–Fabrizio fractal-fractional order derivative, which are useful when developing a fractional-order mathematical model of breast cancer.

Definition 1. *The Riemann–Liouville fractional integral of the function $g : \mathbb{R}^+ \to \mathbb{R}$ exists for $\xi > 0$ in two forms: the upper and lower. These upper and lower integrals on the closed interval $[\alpha, \beta]$ are defined as [42]:*

$$
\begin{aligned}
{}^{RL}_{\alpha}D_t^{-\xi}(g(t)) = {}^{RL}_{\alpha}I_t^{\xi}(g(t)) &= \frac{1}{\Gamma(\xi)}\int_{\alpha}^{t}(t-x)^{\xi-1}g(x)dx, \quad for \quad t > \alpha, \\
{}^{RL}_{t}D_{\beta}^{-\xi}(g(t)) = {}^{RL}_{t}I_{\beta}^{\xi}(g(t)) &= \frac{1}{\Gamma(\xi)}\int_{t}^{\beta}(x-t)^{\xi-1}g(x)dx, \quad for \quad t < \beta,
\end{aligned}
$$

where Γ is the gamma function.

Definition 2. *The existence of the Riemann–Liouville fractional derivative of the function $g : \mathbb{R}^+ \to \mathbb{R}$ is established in two distinct forms, namely the upper and lower forms. The calculation of this derivative is performed by employing the Lagrange rule for differential operators. In order to calculate the nth-order derivative with respect to the integral of order $(n - \xi)$, the derivative of order ξ is obtained. It is imperative to consider that the numerical value of n must exceed that of ξ, where n represents the smallest integer. Thus, the derivatives are defined as [42]:*

$$
{}^{RL}_{\alpha}D_t^{\xi}(g(t)) = \frac{d^n}{dt^n}{}^{RL}_{\alpha}D_t^{-(n-\xi)}(g(t)) = \frac{d^n}{dt^n}{}^{RL}_{\alpha}I_t^{n-\xi}(g(t)),
$$

$$
{}^{RL}_{t}D_{\beta}^{\xi}(g(t)) = \frac{d^n}{dt^n}{}^{RL}_{t}D_{\beta}^{-(n-\xi)}(g(t)) = \frac{d^n}{dt^n}{}^{RL}_{t}I_{\beta}^{n-\xi}(g(t)).
$$

Definition 3. *An alternative definition of the derivative, proposed by Caupto [43], was introduced to address certain limitations of the Riemann–Liouvile derivative. The alternative definition is provided below.*

$$
{}^{C}_{0}D_t^{\xi}(g(t)) = \frac{1}{\Gamma(n-\xi)}\int_{0}^{t}\frac{g^{(n)}(\Psi)}{(t-\Psi)^{\xi-n+1}}d\Psi,
$$

where $\xi \in (n-1, n)$, in which $n \in N$. Obviously, ${}^{C}_{0}D_t^{\xi}(g(t)) \to D_t^{\xi}(g(t))$ whenever $\xi \to 1$. Thus, ${}^{C}_{0}D_t^{\xi}(g(t))$ and $D_t^{\xi}(h(t))$ exist almost everywhere and let $s_1, s_2 \in R$; then, ${}^{C}_{0}D_t^{\xi}[s_1 g(t) + s_2 h(t)]$ exists almost everywhere with

$$
{}^{C}_{0}D_t^{\xi}[s_1 g(t) + s_2 h(t)] = s_1[{}^{C}_{0}D_t^{\xi}(g(t))] + s_2[{}^{C}_{0}D_t^{\xi}(h(t))].
$$

Definition 4. *Let us consider a fixed point, denoted as C^*, for the Caputo system, which is commonly referred to as its equilibrium point and is defined as follows:*

$$
{}^{C}_{0}D_t^{\xi}(C^*(t)) = g(t, C^*(t)) \Leftrightarrow g(t, C^*t) = 0, \quad where \quad 0 < \xi > 1.
$$

Definition 5. *Let $g \in H^1(a, b)$, where $H^1(a, b)$ is the Sobolev space of order 1 which is defined as*

$$
H^1(a, b) = \{g \in L^2(a, b) : D(g) \in L^2(a, b)\};
$$

then, the Caputo fractional derivative is defined as [44]

$$
{}^{C}_{0}D_t^{\xi}(g(t)) = \frac{M(\xi)}{1-\xi}\int_{a}^{t}D_t^{\xi}(g(x))exp\left(-\xi\frac{t-x}{1-\xi}\right)dx,
$$

where $M(\xi)$ is the normalization function such that $M(0) = M(1) = 1$.

Definition 6. *If the given function does not satisfy the conditions for membership in the Sobolev space, the resulting derivative is referred to as the Caputo–Fabrizio fractional derivative, which is formally defined as*

$$ {}_0^{CF}D_t^{\xi}(g(t)) = \frac{M(\xi)}{1-\xi}\int_a^t (g(t)-g(x))exp\left(-\xi\frac{t-x}{1-\xi}\right)dx. $$

Definition 7. *If a function $g(t)$ is continuous and fractally differentiable over the given interval (α, β) with fractal order τ, then the definition of the Caputo–Fabrizio fractal-fractional derivative of $g(t)$ with order ξ in the Riemann–Liouville sense is given by*

$$ {}_0^{CFF}D_t^{\xi,\tau}(g(t)) = \frac{M(\xi)}{1-\xi}\frac{d}{dt^{\tau}}\int_0^t exp\left(-\frac{\xi}{1-\xi}(t-x)\right)g(x)dx. $$

2.2. Mathematical Model with the Caputo–Fabrizio Fractal-Fractional Derivative

The Caputo–Fabrizio fractal-fractional derivative (see Definition 7) is a mathematical operator that has been specifically developed to expand the traditional notion of differentiation to include a non-integer or fractional orders. The name of this concept derives from its originators, Michele Caputo and Mauro Fabrizio, who identified the constraints of traditional fractional derivatives in effectively representing intricate and self-replicating patterns frequently observed in many natural and biological phenomena, including tumor proliferation. Caputo and Fabrizio introduced a novel conceptualization of the fractional derivative that incorporates a smooth kernel [45]. This formulation exhibits distinct representations for the temporal and spatial variables. The rationale for the interest in this novel method derives from the imperative need to use a model that accurately characterizes the dynamics of classical viscoelastic materials, thermal media, electromagnetic systems, and other related phenomena. The initial description of the fractional derivative is notably advantageous for mechanical phenomena associated with plasticity, fatigue, damage, and electromagnetic hysteresis. Utilizing the new fractional derivative appears more reasonable when these effects are absent. The inclusion of a smooth kernel in the fractional derivative concept is crucial for representing the interactions between tumor cells and their surrounding tissue. This smoothness factor can be used to model how tumor cells respond to mechanical and chemical signals from their environment, affecting their proliferation rates and migration patterns. Tumor cells often exhibit an anomalous diffusion, which means that their movement does not follow the traditional Brownian motion. The fractional derivative concept can capture this behavior more accurately, providing a better understanding of how tumor cells spread and invade surrounding tissues.

The Caputo–Fabrizio fractal-fractional derivative is an innovative fractional order operator that offers many benefits compared to conventional fractional order operators, including the Caputo and Atangana–Baleanu fractional derivatives. The Caputo–Fabrizio fractal-fractional derivative represents a broader spectrum of possibilities than other fractional order operators. It has a superior stability to other fractional order operators, making it a more dependable choice for numerical simulations. The integer-order model given in Equations (1) and (2) can be transformed into the Caputo–Fabrizio fractal-fractional derivative:

$$ {}_0^{CFF}D_t^{\xi,\tau}(C(t)) = F_1(C(t),L(t)) = a_1C(t)\left(1-\frac{C(t)}{a_2}\right) - a_3C(t)\left(\frac{L(t)}{a_4+L(t)}\right), \quad (3) $$

$$ {}_0^{CFF}D_t^{\xi,\tau}(L(t)) = F_2(C(t),L(t)) = a_5L(t)\left(1-\frac{L(t)}{a_6}\right)\left(\frac{C(t)}{a_7+C(t)}\right) - a_8C(t)L(t) - a_9L(t), \quad (4) $$

where ξ and τ are the fractional and fractal order of the model subject to the initial conditions of $C(0) = C_0(t)$ and $L(0) = L_0(t)$.

3. Numerical Solution

This study uses the Adams–Bashforth technique to solve the fractional-order model numerically [46]. To build a numerical scheme for the proposed model, it is essential to convert the model into the following form:

$$\begin{cases} {}^{CF}_{0}D^{\xi}_{t}(C(t)) = \tau t^{\tau-1}F_1(C(t), L(t)), \\ {}^{CF}_{0}D^{\xi}_{t}(L(t)) = \tau t^{\tau-1}F_2(C(t), L(t)). \end{cases} \tag{5}$$

After applying the CF integral to the system (5), we obtain

$$\begin{cases} C(t) = C(0) + \frac{\tau}{\Gamma(\xi)}\int_0^t \chi^{\tau-1}(t-\chi)^{\xi-1}F_1(\chi, C(t), L(t))d\chi, \\ L(t) = L(0) + \frac{\tau}{\Gamma(\xi)}\int_0^t \chi^{\tau-1}(t-\chi)^{\xi-1}F_2(\chi, C(t), L(t))d\chi. \end{cases}$$

This implies that

$$\begin{cases} C(t) = C_0(t) + \frac{\tau t^{\tau-1}(1-\xi)}{M(\xi)}F_1(\chi, C(t), L(t)) + \frac{\tau\xi}{M(\xi)}\int_0^t \chi^{\tau-1}F_1(\chi, C(t), (L(t)))d\chi, \\ L(t) = L_0(t) + \frac{\tau t^{\tau-1}(1-\xi)}{M(\xi)}F_2(\chi, C(t), (L(t))) + \frac{\tau\xi}{M(\xi)}\int_0^t \chi^{\tau-1}F_2(\chi, C(t), L(t))d\chi. \end{cases}$$

At t_{n+1}, we have the following scheme:

$$\begin{cases} C_{n+1}(t) = C_0(t) + \frac{\tau t^{\tau-1}(1-\xi)}{M(\xi)}F_1(\chi, C(t), L(t)) + \frac{\tau\xi}{M(\xi)}\int_0^{t_{n+1}} \chi^{\tau-1}F_1(\chi, C(t), (L(t)))d\chi, \\ L_{n+1}(t) = L_0(t) + \frac{\tau t^{\tau-1}(1-\xi)}{M(\xi)}F_2(\chi, C(t), (L(t))) + \frac{\tau\xi}{M(\xi)}\int_0^{t_{n+1}} \chi^{\tau-1}F_2(\chi, C(t), (L(t)))d\chi. \end{cases}$$

By taking the difference between consecutive terms, we obtain

$$\begin{cases} C_{n+1}(t) = & C_n(t) + \frac{\tau t^{\tau-1}(1-\xi)}{M(\xi)}F_1(t_n, C_n(t), L_n(t)) - \frac{\tau t_{n-1}^{\tau-1}(1-\xi)}{M(\xi)}F_1(t_{n-1}, C_{n-1}(t), L_{n-1}(t)) \\ & + \frac{\tau\xi}{M(\xi)}\int_{t_n}^{t_{n+1}} \chi^{\tau-1}F_1(\chi, C(t), (L(t)))d\chi, \\ L_{n+1}(t) = & L_n(t) + \frac{\tau t^{\tau-1}(1-\xi)}{M(\xi)}F_2(t_n, C_n(t), L_n(t)) - \frac{\tau t_{n-1}^{\tau-1}(1-\xi)}{M(\xi)}F_2(t_{n-1}, C_{n-1}(t), L_{n-1}(t)) \\ & + \frac{\tau\xi}{M(\xi)}\int_{t_n}^{t_{n+1}} \chi^{\tau-1}F_2(\chi, C(t), (L(t)))d\chi. \end{cases}$$

Integrating and using the Lagrange interpolation polynomial, we obtain

$$\begin{cases} C_{n+1}(t) = & C_n(t) + \frac{\tau t^{\tau-1}(1-\xi)}{M(\xi)}F_1(t_n, C_n(t), L_n(t)) - \frac{\tau t_{n-1}^{\tau-1}(1-\xi)}{M(\xi)}F_1(t_{n-1}, C_{n-1}(t), L_{n-1}(t)) \\ & + \frac{\tau\xi}{M(\xi)}\left[\frac{3h}{2}t_n^{\tau-1}F_1(t_n, C_n(t), L_n(t)) - \frac{h}{2}t_{n-1}^{\tau-1}F_1(t_{n-1}, C_{n-1}(t), L_{n-1}(t))\right], \\ L_{n+1}(t) = & L_n(t) + \frac{\tau t^{\tau-1}(1-\xi)}{M(\xi)}F_2(t_n, C_n(t), L_n(t)) - \frac{\tau t_{n-1}^{\tau-1}(1-\xi)}{M(\xi)}F_2(t_{n-1}, C_{n-1}(t), L_{n-1}(t)) \\ & + \frac{\tau\xi}{M(\xi)}\left[\frac{3h}{2}t_n^{\tau-1}F_2(t_n, C_n(t), L_n(t)) - \frac{h}{2}t_{n-1}^{\tau-1}F_2(t_{n-1}, C_{n-1}(t), L_{n-1}(t))\right]. \end{cases}$$

After simplification, we obtain

$$\begin{cases} C_{n+1}(t) = & C_n(t) + \tau t_n^{\tau-1}\left(\frac{1-\xi}{M(\xi)} + \frac{3h\xi}{2M(\xi)}\right)F_1(t_n, C_n(t), L_n(t)) \\ & -\tau t_{n-1}^{\tau-1}\left(\frac{1-\xi}{M(\xi)} + \frac{h\xi}{2M(\xi)}\right)F_1(t_{n-1}, C_{n-1}(t), L_{n-1}(t)), \\ L_{n+1}(t) = & L_n(t) + \tau t_n^{\tau-1}\left(\frac{1-\xi}{M(\xi)} + \frac{3h\xi}{2M(\xi)}\right)F_2(t_n, C_n(t), L_n(t)) \\ & -\tau t_{n-1}^{\tau-1}\left(\frac{1-\xi}{M(\xi)} + \frac{h\xi}{2M(\xi)}\right)F_2(t_{n-1}, C_{n-1}(t), L_{n-1}(t)). \end{cases} \tag{6}$$

The iterative scheme given in (6) gives the numerical solution of the proposed fractional-order mathematical model of breast cancer.

4. Results and Discussion

In this section of the article, the Adams–Bashforth method is used to analyze the intricate dynamics of our proposed breast cancer model through multiple simulations. The main goal of these simulations is to determine the input parameters that exert the greatest influence on perturbing the population levels of cancer patients. Through a numerical investigation, our objective is to enhance our understanding of the dynamics exhibited by the fractional breast cancer system. This endeavor seeks to provide a more precise and all-encompassing comprehension of the dynamics experienced by patients with breast cancer. The objective of these simulations is to augment our understanding of the fundamental mechanisms that govern the progression of breast cancer, with the ultimate goal of advancing research and treatment strategies for this disease.

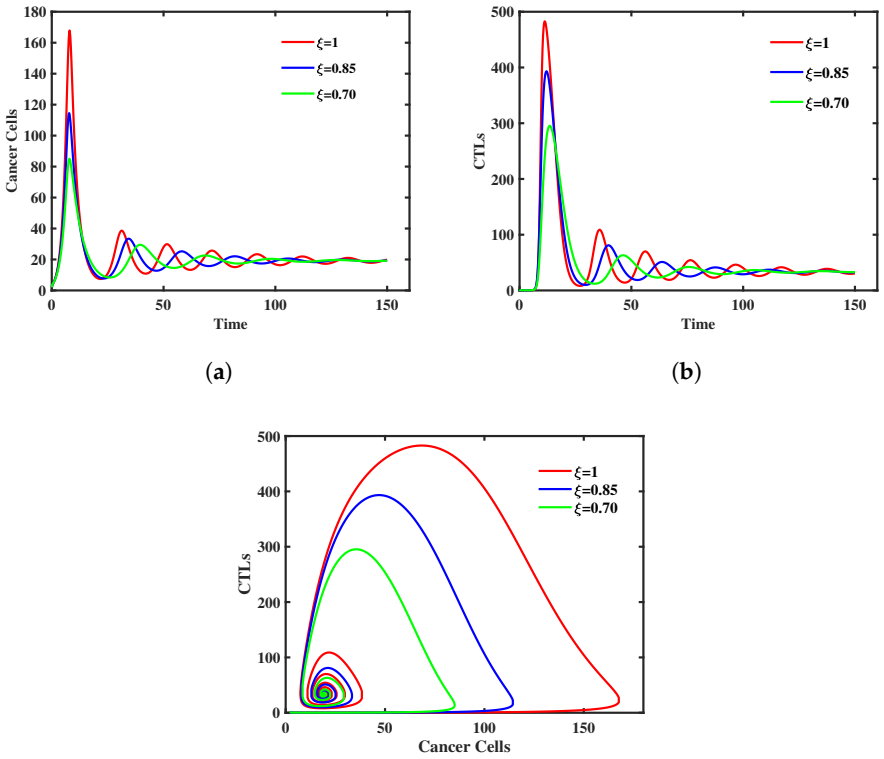
We examine three cases of simulations as a means to conceptualize the impact of the parameters on the system's dynamic behavior. We observed that both the fractal and the fraction have a substantial impact on the solution pathway of the breast cancer model in all cases.

4.1. Case I

We examine the impact of the Caputo–Fabrizio fractal-fractional order derivative on the breast cancer model at different values of the fractional order, as shown in Figure 1. For the simulations of Case I, we use the following values of the parameters: $\alpha_1 = 0.6387$, $\alpha_2 = 10^3$, $\alpha_3 = 1$, $\alpha_4 = 20$, $\alpha_5 = 5.7484$, $\alpha_6 = 8 \times 10^2$, $\alpha_7 = 10^2$, $\alpha_8 = 7.812 \times 10^{-4}$, and $\alpha_9 = 0.8729$. The proposed mathematical model possesses periodic solutions characterized by various amplitude of oscillations. However, it is important to note that these periodic solutions do not result in Hopf bifurcation. It is worth mentioning that both the cancer cells and CTLs tend to converge toward the positive equilibrium point due to the presence of oscillations within their respective populations. Moreover, it has been observed that the amplitude of oscillations exhibits a proportional increase as the fractional order is incremented. Similarly, Figure 2 shows the impact of the fractal order on the population of breast cancer cells and CTLs. The system shows more oscillations as we increase the fractal order of the model. These results contribute to a deeper comprehension of the system's dynamics and illuminate the implications of fractional order derivatives when modeling such complex phenomena. The investigation of the influence of fractional orders on the dynamics of systems has the potential to be of great importance in modeling breast cancer and future therapeutic treatments.

4.2. Case II

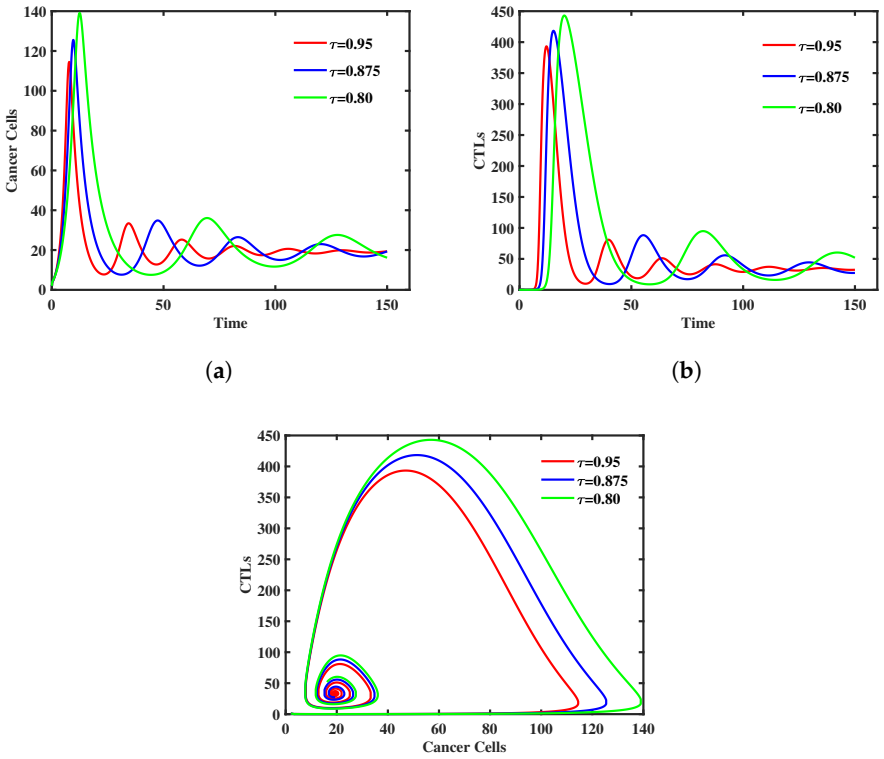
We use, in the simulations of this case, the following values of the parameters: $\alpha_1 = 0.41$, $\alpha_2 = 10^3$, $\alpha_3 = 1$, $\alpha_4 = 20$, $\alpha_5 = 5.7484$, $\alpha_6 = 8 \times 10^2$, $\alpha_7 = 10^2$, $\alpha_8 = 7.812 \times 10^{-4}$, and $\alpha_9 = 0.1287$. Figure 3 illustrates the temporal effects of fractal parameters on the behavior of CTLs and cancer cells. It is indicated that when τ is small, representing the state of tumor dormancy, there is evidence of damped oscillations. Tumor dormancy is characterized by a state in which the population of tumor cells remains stable, and both effector cells and tumor cells coexist without undergoing extinction. When the parameter τ exceeds a specific threshold, the system with a value of $\tau = 0.88$ experiences a Hopf bifurcation, resulting in the emergence of periodic or quasi-periodic solutions. The phenomenon referred to as Jeff's phenomenon, which has also been clinically observed [47], is characterized by the presence of tumor cells displaying oscillatory behavior in the absence of any treatment. The examination of fractal parameters and their impact on the dynamics of the system enhances our comprehension of tumor dormancy and oscillatory phenomena, thereby offering significant insights into the fundamental mechanisms that govern the advancement of cancer. The implications of these findings for cancer treatment strategies and the need for further investigation in the field of cancer research should be considered.



(**a**) (**b**)

(**c**)

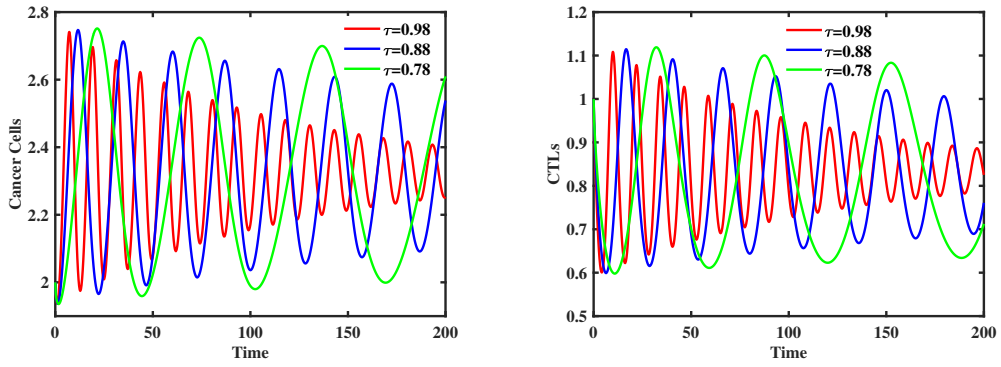
Figure 1. (**a**–**c**) Dynamics of cancer cells and CTLs at different values of ξ and a fixed value of $\tau = 0.95$.



(**a**) (**b**)

(**c**)

Figure 2. (**a**–**c**) Dynamics of cancer cells and CTLs at different values of τ and a fixed value of $\xi = 0.85$.

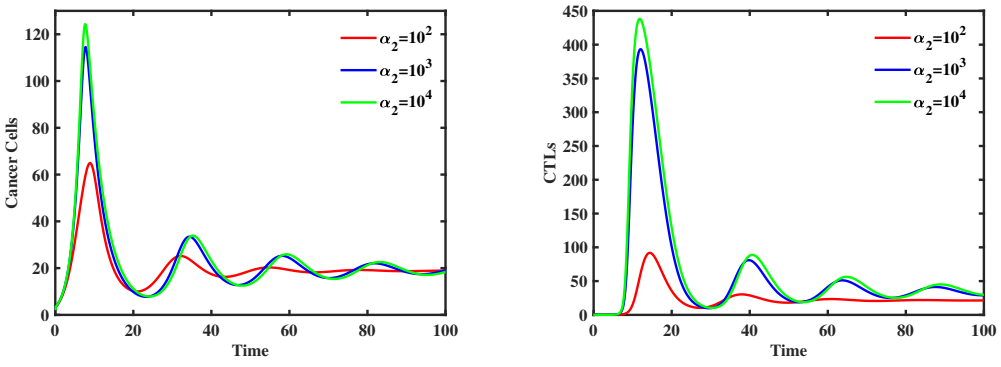


(**a**) (**b**)

Figure 3. (**a**,**b**) Dynamics of cancer cells and CTLs at different values of the fractal order and a fixed value of the fractional order.

4.3. Case III

Figure 4 depicts the impact of parameter α_2 on cancer cells and CTLs in the system with fixed values of τ and ξ. The simulations of Case III are performed with the same parametric values as given in Case I with the variation of parameter α_2. The parameter α_2 denotes the cancer cells' carrying capacity, which depends on the availability of nutrients supplied by the host organism and other growth factors. The observation of interest pertains to the significance of α_2, which represents a fundamental biological limitation. Specifically, the growth of cancer cells is inherently restricted by finite resources and spatial limitations [48]. When the parameter α_2 takes on smaller values, both CTLs and cancer cells demonstrate damped oscillatory behavior and eventually reach a stable state at the equilibrium point. Nevertheless, when α_2 reaches higher values, CTLs lose their ability to control the cancer cells effectively. As a consequence, both CTLs and cancer cells exhibit oscillatory patterns. These results have potential implications for the advancement of specific therapeutic interventions in cancer treatment. This is due to the consideration of the regulatory function of α_2 in the proliferation of cancer cells and the dynamics of the immune response. Additional investigation in this particular domain has the potential to yield significant findings pertaining to the intricacies of cancer proliferation and the interplay between the immune system and cancer cells.



(**a**) (**b**)

Figure 4. (**a**,**b**) Dynamics of cancer cells and CTLs at different values of α_2 and fixed values of $\xi = 0.85$ and $\tau = 0.95$.

The simulations conducted in this study demonstrate cyclic fluctuations, which exhibit a strong concordance with the empirical investigations of breast cancer. According to the literature, it has been shown that immune cells possess the capability to eradicate tumors during their first phases, resulting in the destruction of a majority of breast cancer cells

within a span of two days [49,50]. Also, it is evident that the population of CTLs experiences quick growth during the first phase and exhibits oscillatory behavior in the vicinity of the equilibrium point. Consequently, cancer cells demonstrate a decline in response to this swift reaction by the CTLs and remain constant at a low quantity. This phenomenon, referred to as "cancer without disease", has been extensively studied, and several experimental studies indicate that small tumors do not grow to an invasive state [51–53].

The outcomes derived from the Caputo–Fabrizio fractal-fractional order breast cancer model demonstrate a significant deviation from the traditional integer and alternative fractional-order models. The conventional model offers a fundamental comprehension of the dynamics of breast cancer. However, the Caputo–Fabrizio fractional-order method contributes a novel aspect by including the complex memory effects and nonlocal behaviors that are inherent in the evolution of the disease. The Caputo–Fabrizio formulation has enhanced convergence and accuracy in predicting long-term evolution patterns compared to other fractional-order models. This emphasizes the model's ability to effectively characterize the intricate aspects of breast cancer, making it a potentially valuable instrument for comprehending the intricacies of the condition. The potential of the Caputo–Fabrizio fractal-fractional order model to enhance breast cancer research and clinical decision-making is reinforced by its ability to encompass a wide range of patient profiles, account for anomalous diffusion, and maintain computational efficiency. This model holds promise in providing fundamental insights and practical applications in the field.

While the current mathematical model effectively assesses the interaction between breast cancer cells and CTLs, it is important to acknowledge the presence of some limitations. To provide a simplified description of cancer cells and CTLs dynamics, our model does not include all aspects of immune cell processes. The existing paradigm needs to address the self-regulatory mechanisms of CTLs adequately. Additionally, most biological systems exhibit noisy behavior as a result of the fluctuations in their constituent parts; this phenomenon is referred to as stochasticity. This problem is still open in our model. Notwithstanding potential limitations, the model in question demonstrates a satisfactory alignment with the actual data.

5. Conclusions and Future Work

This study's main aim is to thoroughly analyze the dynamic behaviors exhibited by the fractional-order breast cancer model. By conducting numerical simulations, it has been observed that the model illustrates an equilibrium point and displays various dynamic phenomena, such as quasiperiodic solutions characterized by both damped and higher amplitude oscillations and Hopf bifurcation. The emergence of these dynamic structures can be attributed to fluctuations in the fractal and fractional orders, which substantially impact the model's dynamical behaviors. Therefore, it can be deduced that the fractional-order model functions as a practical, user-friendly, and resilient computational instrument for examining interactions between cancer and immune cells.

The efficacy of treatment strategies can be evaluated over time due to the dynamic nature of our model. This dynamic aspect allows us to evaluate how treatments impact the proliferation of breast cancer cells, the activity of immune cells, and the overall tumor microenvironment. By simulating the interactions between treatments and the complex dynamics of cancer progression, we can assess how different therapies influence the course of the disease. In the future, the proposed model can be used to explore a wide range of therapeutic approaches, including chemotherapy, immunotherapy, targeted therapies, radiation therapy, and combination therapies. Each treatment type has unique mechanisms and implications, and assessing their individual and combined effects can yield valuable insights. Our model is designed to differentiate between various treatment strategies and assess their respective impacts on breast cancer dynamics. We can achieve this differentiation by incorporating specific parameters and mechanisms that represent the unique characteristics of each treatment modality. The model can be used to consider factors such

as treatment dosage, administration schedules, and the mechanisms of action inherent to each type of therapy.

Additionally, the study emphasizes the significance of input parameters in the breast cancer system, elucidating key factors essential in managing and preventing breast cancer. In future research, we intend to expand our model by incorporating delay differential equations to scrutinize the importance of time delay in the dynamics of breast cancer. Furthermore, our upcoming research endeavors will incorporate strategic interventions to mitigate the advancement of breast cancer across various stages. Through the implementation of these additional investigations, our objective is to enhance our comprehension of the dynamics of breast cancer and formulate efficacious approaches for managing and preventing this disease. Incorporating delay considerations and implementing control measures will enhance the accuracy of our model's predictions and make significant contributions to the progress of cancer research and the development of treatment methodologies.

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References

1. Fathoni, M.; Gunardi, G.; Kusumo, F.A.; Hutajulu, S.H. Mathematical model analysis of breast cancer stages with side effects on heart in chemotherapy patients. In Proceedings of the AIP Conference Proceedings, Yogyakarta, Indonesia, 29 July–1 August 2019; AIP Publishing: Melville, NY, USA , 2019.
2. Breast Cancer. Available online: https://www.who.int/news-room/fact-sheets/detail/breast-cancer (accessed on 15 July 2023).
3. DeSantis, C.E.; Bray, F.; Ferlay, J.; Lortet-Tieulent, J.; Anderson, B.O.; Jemal, A. International variation in female breast cancer incidence and mortality rates. *Cancer Epidemiol. Biomarkers Prev.* **2015**, *24*, 1495–1506. [CrossRef]
4. Michor, F.; Iwasa, Y.; Nowak, M.A. Dynamics of cancer progression. *Nat. Rev. Cancer* **2004**, *4*, 197–205. [CrossRef] [PubMed]
5. Bardelli, A.; Cahill, D.P.; Lederer, G.; Speicher, M.R.; Kinzler, K.W.; Vogelstein, B.; Lengauer, C. Carcinogen-specific induction of genetic instability. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 5770–5775. [CrossRef] [PubMed]
6. Loeb, L.A. Microsatellite instability: Marker of a mutator phenotype in cancer. *Cancer Res.* **1994**, *54*, 5059–5059.
7. Tomlinson, I.; Bodmer, W. Selection, the mutation rate and cancer: Ensuring that the tail does not wag the dog. *Nat. Med.* **1999**, *5*, 11–12. [CrossRef] [PubMed]
8. Zhang, X.; Fang, Y.; Zhao, Y.; Zheng, W. Mathematical modeling the pathway of human breast cancer. *Math. Biosci.* **2014**, *253*, 25–29. [CrossRef]
9. Enderling, H.; Chaplain, M.A.; Anderson, A.R.; Vaidya, J.S. A mathematical model of breast cancer development, local treatment and recurrence. *J. Theor. Biol.* **2007**, *246*, 245–259. [CrossRef]
10. Simmons, A.; Burrage, P.M.; Nicolau, D.V., Jr.; Lakhani, S.R.; Burrage, K. Environmental factors in breast cancer invasion: A mathematical modelling review. *Pathology* **2017**, *49*, 172–180. [CrossRef]
11. Frank, S.A.; Iwasa, Y.; Nowak, M.A. Patterns of cell division and the risk of cancer. *Genetics* **2003**, *163*, 1527–1532. [CrossRef]
12. Byrne, H.M. Dissecting cancer through mathematics: From the cell to the animal model. *Nat. Rev. Cancer* **2010**, *10*, 221–230. [CrossRef]
13. Armitage, P.; Doll, R. The age distribution of cancer and a multi-stage theory of carcinogenesis. *Br. J. Cancer* **2004**, *91*, 1983–1989. [CrossRef] [PubMed]
14. Dixit, D.S.; Kumar, D.; Kumar, S.; Johri, R. A mathematical model of chemotherapy for tumor treatment. *Adv. Appl. Math. Biosci.* **2012**, *3*, 1–10.
15. Schättler, H.; Ledzewicz, U.; Amini, B. Dynamical properties of a minimally parameterized mathematical model for metronomic chemotherapy. *J. Math. Biol.* **2016**, *72*, 1255–1280. [CrossRef] [PubMed]
16. Jordão, G.; Tavares, J.N. Mathematical models in cancer therapy. *Biosystems* **2017**, *162*, 12–23. [CrossRef]

17. Khajanchi, S.; Nieto, J.J. Mathematical modeling of tumor-immune competitive system, considering the role of time delay. *Appl. Math. Comput.* **2019**, *340*, 180–205. [CrossRef]
18. Mahlbacher, G.E.; Reihmer, K.C.; Frieboes, H.B. Mathematical modeling of tumor-immune cell interactions. *J. Theor. Biol.* **2019**, *469*, 47–60. [CrossRef]
19. Lorenzo, C.F. *Initialized Fractional Calculus*; NASA Glenn Research Center: Cleveland, OH, USA, 2000.
20. Sun, H.; Chen, W.; Wei, H.; Chen, Y. A comparative study of constant-order and variable-order fractional models in characterizing memory property of systems. *Eur. Phys. J. Spec. Top.* **2011**, *193*, 185–192. [CrossRef]
21. Sabir, Z.; Munawar, M.; Abdelkawy, M.A.; Raja, M.A.Z.; Ünlü, C.; Jeelani, M.B.; Alnahdi, A.S. Numerical investigations of the fractional-order mathematical model underlying immune-chemotherapeutic treatment for breast cancer using the neural networks. *Fractal Fract.* **2022**, *6*, 184. [CrossRef]
22. Solís-Pérez, J.; Gómez-Aguilar, J.F.; Atangana, A. A fractional mathematical model of breast cancer competition model. *Chaos Solitons Fractals* **2019**, *127*, 38–54. [CrossRef]
23. Hassani, H.; Machado, J.T.; Avazzadeh, Z.; Safari, E.; Mehrabi, S. Optimal solution of the fractional order breast cancer competition model. *Sci. Rep.* **2021**, *11*, 15622. [CrossRef]
24. Abaid Ur Rehman, M.; Ahmad, J.; Hassan, A.; Awrejcewicz, J.; Pawlowski, W.; Karamti, H.; Alharbi, F.M. The dynamics of a fractional-order mathematical model of cancer tumor disease. *Symmetry* **2022**, *14*, 1694. [CrossRef]
25. Öztürk, I.; Özköse, F. Stability analysis of fractional order mathematical model of tumor-immune system interaction. *Chaos Solitons Fractals* **2020**, *133*, 109614. [CrossRef]
26. Chen, Y.; Yi, M.; Chen, C.; Yu, C. Bernstein polynomials method for fractional convection-diffusion equation with variable coefficients. *Comput. Model. Eng. Sci.* **2012**, *83*, 639–653.
27. Ou, C.; Cen, D.; Vong, S.; Wang, Z. Mathematical analysis and numerical methods for Caputo-Hadamard fractional diffusion-wave equations. *Appl. Numer. Math.* **2022**, *177*, 34–57. [CrossRef]
28. Galue, L.; Kalla, S.L.; Al-Saqabi, B. Fractional extensions of the temperature field problems in oil strata. *Appl. Math. Comput.* **2007**, *186*, 35–44. [CrossRef]
29. Valentim, C.A.; Rabi, J.A.; David, S.A.; Machado, J.A.T. On multistep tumor growth models of fractional variable-order. *Biosystems* **2021**, *199*, 104294. [CrossRef]
30. Farayola, M.F.; Shafie, S.; Siam, F.M.; Khan, I. Mathematical modeling of radiotherapy cancer treatment using Caputo fractional derivative. *Comput. Methods Programs Biomed.* **2020**, *188*, 105306. [CrossRef]
31. Idrees, M.; Sohail, A. Bio-algorithms for the modeling and simulation of cancer cells and the immune response. *Bio-Algorithms Med-Syst.* **2021**, *17*, 55–63. [CrossRef]
32. Britton, N.F.; Britton, N. *Essential Mathematical Biology*; Springer: Berlin/Heidelberg, Germany, 2003; Volume 453.
33. Kawarada, Y.; Ganss, R.; Garbi, N.; Sacher, T.; Arnold, B.; Hammerling, G.J. NK-and CD8+ T cell-mediated eradication of established tumors by peritumoral injection of CpG-containing oligodeoxynucleotides. *J. Immunol.* **2001**, *167*, 5247–5253. [CrossRef]
34. Dudley, M.E.; Wunderlich, J.R.; Robbins, P.F.; Yang, J.C.; Hwu, P.; Schwartzentruber, D.J.; Topalian, S.L.; Sherry, R.; Restifo, N.P.; Hubicki, A.M.; et al. Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. *Science* **2002**, *298*, 850–854. [CrossRef]
35. Adam, J.A.; Bellomo, N. *A Survey of Models for Tumor-Immune System Dynamics*; Springer Science & Business Media: Berlin/Heidelberg, Germany, 1997.
36. Nawata, H.; Chong, M.; Bronzert, D.; Lippman, M.E. Estradiol-independent growth of a subline of MCF-7 human breast cancer cells in culture. *J. Biol. Chem.* **1981**, *256*, 6895–6902. [CrossRef] [PubMed]
37. de Pillis, L.G.; Gu, W.; Radunskaya, A.E. Mixed immunotherapy and chemotherapy of tumors: Modeling, applications and biological interpretations. *J. Theor. Biol.* **2006**, *238*, 841–862. [CrossRef] [PubMed]
38. López, Á.G.; Seoane, J.M.; Sanjuán, M.A. A validated mathematical model of tumor growth including tumor–host interaction, cell-mediated immune response and chemotherapy. *Bull. Math. Biol.* **2014**, *76*, 2884–2906. [CrossRef] [PubMed]
39. Fernandez, M.; Zhou, M.; Soto-Ortiz, L. A computational assessment of the robustness of cancer treatments with respect to immune response strength, tumor size and resistance. *Int. J. Tumor. Ther.* **2018**, *7*, 1–19.
40. Muller, M.R.; Grunebach, F.; Nencioni, A.; Brossart, P. Transfection of dendritic cells with RNA induces CD4- and CD8-mediated T cell immunity against breast carcinomas and reveals the immunodominance of presented T cell epitopes. *J. Immunol.* **2003**, *170*, 5892–5896. [CrossRef]
41. Gruber, I.; Landenberger, N.; Staebler, A.; Hahn, M.; Wallwiener, D.; Fehm, T. Relationship between circulating tumor cells and peripheral T-cells in patients with primary breast cancer. *Anticancer Res.* **2013**, *33*, 2233–2238.
42. Herrmann, R. *Fractional Calculus: An Introduction for Physicists*; World Scientific: Singapore, 2011.
43. Qureshi, S.; Yusuf, A.; Aziz, S. On the use of Mohand integral transform for solving fractional-order classical Caputo differential equations. *J. Appl. Math. Comput. Mech.* **2020**, *19*, 99–109. [CrossRef]
44. Jain, S. Numerical analysis for the fractional diffusion and fractional Buckmaster equation by the two-step Laplace Adam-Bashforth method. *Eur. Phys. J. Plus* **2018**, *133*, 19. [CrossRef]
45. Caputo, M.; Fabrizio, M. A new definition of fractional derivative without singular kernel. *Prog. Fract. Differ. Appl.* **2015**, *1*, 73–85.
46. Fatmawati.; Khan, M.A.; Alfiniyah, C.; Alzahrani, E. Analysis of dengue model with fractal-fractional Caputo–Fabrizio operator. *Adv. Differ. Equ.* **2020**, *2020*, 422. [CrossRef]

47. Thomlinson, R. Measurement and management of carcinoma of the breast. *Clin. Radiol.* **1982**, *33*, 481–493. [CrossRef] [PubMed]
48. Deisboeck, T.S.; Wang, Z. Cancer dissemination: A consequence of limited carrying capacity? *Med. Hypotheses* **2007**, *69*, 173–177. [CrossRef] [PubMed]
49. Vacca, P.; Munari, E.; Tumino, N.; Moretta, F.; Pietra, G.; Vitale, M.; Del Zotto, G.; Mariotti, F.R.; Mingari, M.C.; Moretta, L. Human natural killer cells and other innate lymphoid cells in cancer: Friends or foes? *Immunol. Lett.* **2018**, *201*, 14–19. [CrossRef] [PubMed]
50. Fidler, I.J. Metastasis: Quantitative analysis of distribution and fate of tumor emboli labeled with 125I-5-iodo-2′-deoxyuridine. *J. Natl. Cancer Inst.* **1970**, *45*, 773–782.
51. Folkman, J.; Kalluri, R. Cancer without disease. *Nature* **2004**, *427*, 787. [CrossRef]
52. Fehm, T.; Mueller, V.; Marches, R.; Klein, G.; Gueckel, B.; Neubauer, H.; Solomayer, E.; Becker, S. Tumor cell dormancy: Implications for the biology and treatment of breast cancer. *Apmis* **2008**, *116*, 742–753. [CrossRef]
53. Franco, O.E.; Shaw, A.K.; Strand, D.W.; Hayward, S.W. Cancer associated fibroblasts in cancer pathogenesis. *Semin. Cell Dev. Biol.* **2010**, *21*, 33–39. [CrossRef]