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Analyzing Drug Therapy on the Interaction Between Tumor and Immune Cells Based on Optimal Fractional Control Theory

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Abstract. Cancer is a class of diseases characterized by uncontrolled cell growth that affects immune cells. There are several treatment options available, including surgery, chemotherapy, hormonal therapy, radiation therapy, targeted therapy, and palliative care. Among these, chemotherapy is one of the most widely used and recognized methods. This paper presents a novel model designed to control cancer cell growth based on a system of nonlinear fractional differential equations with delay in chemotherapy. The model focuses on the competition between tumor and immune cells to minimize the number of tumor cells and determine the optimal dosage of the administered drug. It can simulate various scenarios and predict the outcomes of different chemotherapy regimens. By employing discretization and the Grunwald-Letnikov method, we aim to gain insights into why some patients respond well to chemotherapy while others do not. The results may also help identify potential drug targets and optimize existing treatments.

Keywords. Growth process, Grunwald-Letnikov method, Immune cells, Optimal fractional control theory, Tumor.

MSC. 49-XX; 11A55; 26A33.

1 Introduction

Fokas et al. and Adimy et al. presented mathematical models for Chronic Myelogenous Leukemia (CML), a type of blood cancer, in 1991 and 2005, respectively [12] and [1]. Utilizing these models to analyze cancer responses to drug therapy can assist physicians in determining appropriate treatment strategies.

The response of a tumor to treatment is influenced by several factors, including tumor severity, treatment application, the patient's immune system capability, cancer type and stage, overall health, and patient preferences. Over the past few decades, mathematical modeling has been developed to evaluate tumor growth and predict treatment outcomes. These models can aid in controlling a tumor size and assessing the immune system's effect on tumor cells, as well as in specifying optimal drug treatments and timing for surgery. Given the known damaging side effects of chemotherapy, various models have been applied to cancer growth in conjunction with chemotherapy, aiming to minimize the total drug dosage used.

Several researchers have explored mathematical modeling of the chemotherapy's effects on cancer treatment. They have employed various types of differential equations to represent these effects. For instance, De Pillis et al. developed a mathematical model based on a system of ordinary differential equations [7, 8]. Liu and Freedom proposed a mathematical model for vascular tumor treatment using chemotherapy [14], while Namazi et al. presented a model forecasting chemotherapy effects on cancer cells [16].

All of these studies rely on the analysis of ordinary differential equations. Recently , there has been significant interest in fractional calculus, particularly for its applications in various fields such as physics and engineering [6], as well as in disease treatment. In 2012, Fang developed fractional calculus to analyze tumor growth in cancer [11]. Two years later, Bozkurt introduced a fractional order into the interaction model between Glioblastoma Multiforme (GBM) and immune system [5]. Subsequently, in 2016, Rihan et al. examined tumor-immune system dynamics with fractional order [20]. In 2018, Akman Yildiz et al. presented a cancer obesity model utilizing Caputo time fractional derivatives [2]. In 2019, researchers developed a novel fractional model to elucidate cancer immune surveillance mechanisms, employing fractional differential equations to explore the intricate relationships between various cancer cell populations and the immune system, they also proposed an efficient numerical methodology for solving these equations and an optimal control strategy to investigate chemotherapy effects [3]. Recently, in 2023, researchers introduced a fractional SIRD model to investigate Nipah virus transmission dynamics, exploring the implications of improper contact with an infected corpse as a transmission mode and examining necessary conditions for maintaining disease-free and endemic states based on the fundamental reproduction number. This study utilized the Adams-Bashforth-Moulton numerical method with fractional considerations, and provided a

comparative analysis between fractional and classical outcomes, emphasizing the significance of dangerous contact with infected corpses in viral transmission [4].

In this context, we extend the ordinary system presented by Moore and Li [15] using fractional differential equations (FDEs). We contend that our FDE model will surpass its ordinary differential equations (ODEs) counterpart, facilitating a deeper understanding of natural immune interactions within tumors and the potential adverse effects of chemotherapy on patient immune system.

We are focused on modeling and predicting the impact of chemotherapy on cancer cells through the use of fractional differential equations. We introduce a fractional differential equation model to elucidate the interaction between naive T-cells, effector T-cells, and CML cancer cells during cancer dormancy. Our primary objective is to minimize the cancer cell population and mitigate the detrimental effects of the two types of drugs on a hypothetical individual. We discuss the control model by presenting the objective functional, stating the necessary conditions for the optimal control pair, and characterizing the optimal control pair in terms of the optimal solution of the governed system, determined using the Grunwald-Letnikov method. We selected the Grunwald-Letnikov method due to its simplicity and computational efficiency in numerical implementations. Although both Caputo and Riemann-Liouville definitions are valid approaches for fractional derivatives, the Grunwald-Letnikov method aligns better with our computational framework and provides sufficient accuracy for our model. A key feature of this method is its ability to transforms the discussed problem into a set of algebraic equations that can be easily solved. The purpose of discretization is to convert one or more differential equations into a set of algebraic equations; solving this set yields values equivalent to the solutions of the differential equations at specific temporal and spatial positions. Our approach differs from previous models by incorporating fractional calculus, allowing for a more nuanced representation of cellular interactions and dynamics. The utilization of fractional equations enables us to capture long-range interactions between cells, providing a more realistic model of cancer progression. Additionally, our solution method using Grunwald-Letnikov discretization offers computational advantages over traditional methods, facilitating faster and more accurate simulations. These innovations in modeling and simulation techniques have the potential to significantly impact cancer research and treatment strategies.

Another novelty of this paper is the use of fractional differential equations (FDEs) instead of ordinary differential equations (ODEs) to demonstrate the involved control system. FDEs offer significant advantages over ODEs in cancer modeling, as they allow for more accurate modeling of this complex biological process with memory effects, crucial for capturing delayed cellular interactions in cancer. Furthermore , FDEs naturally represent anomalous diffusion patterns, offering valuable insights into metastasis processes. Also, the fractional dimension of FDEs enables modeling of systems with hereditary characteristics, facilitating the study of long-term cancer processes and drug efficacy over extended periods.

2 The CML Fractional Dynamic Model

Ordinary and partial differential equations, including heat diffusion and statistical equations, are among the mathematical tools used to derive biological models. In this paper, we extend the ODE system presented by Moore and Li [15] by incorporating FDEs. The concept applying this new model allows us to explore the optimal control strategy for Chemo-immunotherapy.

We assert that FDE model provides superior insights compared to its conventional counterparts, enhancing our understanding of the natural immune interactions in a tumor and helping potential adverse effects of chemotherapy on a patient's immune system. We will outline several advantages of our FDE model over previous approaches.

Firstly, as explained in [9], certain cells in various organs, such as breast cells, feature a rugged surface that ordinary calculus cannot adequately represent due to these surface characteristics. In contrast, studying these cells through fractional calculus may be more effective. Specifically, there are irregular points on the surface of these cells that classical derivatives struggle to describe. In such cases, fractional differentiation is advantageous because it does not require the necessary smoothness property as classical derivatives [10]. Secondly, while the definition of the classical derivative relies only on two points in the neighborhood of a given point, fractional derivatives take into account all the points in that neighborhood [13, 17]. This comprehensive approach leads to more accurate subsequent applications by utilizing all available information. The FDEs can effectively describe the dynamics of various complex and nonlocal systems that involve memory effects. The term "non-local property" reflects this concept, making FDEs increasingly popular in the study of dynamical systems [18].

Let t present time measured in days; each of the three cell populations is a function of time, t. The model we consider here is a three-cell population model describing the interaction between the cancer cell population (C), the naive T-cell population (T_n), and the effector T-cell population (T_e) [9, 15]. We assume that the effector T-cells are specific to CML, activated by the presence of CML antigen. If we suppose these three cells evolve with independent variable time, then we can present our model in the form of FDE as follows:

$$D_t^{\alpha} T_n = s_n - u_2(t) d_n T_n - k_n T_n \left(\frac{C}{C+\eta} \right), \tag{1}$$

$$D_t^{\alpha} T_e = \alpha_n k_n T_n \left(\frac{C}{C+\eta} \right) + \alpha_e T_e \left(\frac{C}{C+\eta} \right) - u_2(t) d_e T_e - \gamma_e C T_e, \tag{2}$$

$$D_t^{\alpha} C = (1 - u_1(t)) r_c C ln \left(\frac{C_{max}}{C} \right) - u_2(t) d_c C - \gamma_c C T_e. \tag{3}$$

The constants used in the system of differential equations (1)-(3) are summarized in Table 1, which includes a brief description of each constant, the initial estimates, and the ranges used for sampling later in the paper. The parameter values in our model were determined based on the described approach in reference [15]. According to this source, parameter values are derived

from empirical data and theoretical approximations, with subsequent analysis focusing on the responsiveness of system to parameter fluctuations.

For the three populations, at the initial time $t = 0$, we use the following values: $T_n(0) = 1510$, $T_e(0) = 10$, and $C(0) = 10000$. Lowercase coefficients, or parameters (e.g., s_n, α_n, and r_c) are all assumed to be constants.

Table 1: Features of patient A in the first row and patient B in the second row

s_n	d_n	d_e	d_c	k_n	η	α_n	α_e	C_{max}	r_c	λ_e	λ_c
0.29	0.35	0.40	0.012	0.066	140	0.39	0.65	160000	0.011	0.079	0.058
0.071	0.05	0.12	0.68	0.063	43	0.56	0.53	190000	0.23	0.077	0.047

We assume that changes in populations due to diffusion are negligible; that is, the numbers of pre-existing cells in each population that diffuse into and out of the blood are approximately equal. Therefore, there are no terms in the equations representing the diffusion of already-existing, mature cells into or out of the bloodstream. The first term on the right-hand side of Equation (1) is a source term for new T cells entering the blood system. We approximate this as a constant, s_n, which is a reasonable approximation except during the later stages of CML, when crowding in the bone marrow may reduce the production of naive T cells. The second term accounts for the natural attrition of T_n cells in the absence of CML. The factor d_n represents death rate constant of naive T cells, which can be understood as the reciprocal of the average lifespan of a T_n cell; it roughly approximates the fraction of the T_n population expected to die naturally in one day. The third term is a Michaelis–Menten term that captures the change in the T_n population due to encounters with CML antigen in the lymphatic system. We incorporate this term to account for the saturation effects of CML cells.

In this system, $T_n(0), T_e(0)$, and $C(0)$ are known as initial values, while the time-dependent drug efficacies are represented by $u_1(t)$ and $u_2(t)$. Setting $u_1 \equiv 0$ and $u_2 \equiv 1$ in the equations yields the same model that describes the dynamics of the disease without treatment. The variable u_1 represents a targeted therapy, such as imatinib, while u_2 corresponds to a broad cytotoxic chemotherapy, such as cytarabine or hydroxyurea, or a combination of these drugs. All of the parameter values in the equations are assumed to be positive. Furthermore, the structure of the equations ensures non-negative solutions for the variables $T_n(t)$, $T_e(t)$, and $C(t)$. The negative terms in the equations represent losses from the cell populations, whereas the positive terms act as source terms for the cell populations.

3 Discretization Method

Among the several discretization methods available for the fractional derivatives for D_t^α, we use the one generated by Grunwald-Letnikov [9]. In this method, $D^\alpha x(t)$ is approximated by

$$D^\alpha x(t) = \lim_{l\to\infty} l^{-\alpha} \sum_{j=0}^{[\frac{t}{l}]} (-1)^j \binom{\alpha}{j} x(t-jl),$$

where l is the step size and $[t]$ is the integer part of t. Using this method for system (1)-(3), $D^\alpha x(t)$ is replaced by $\sum_{j=0}^{[\frac{t_n}{l}]} C_j^\alpha x(t_{n-j})$, where $t_n = nl$ and C_j^α is Grunwald-Letnikov coefficients defined by

$$C_0^\alpha = l^{-\alpha}, \qquad C_j^\alpha = (1 - \frac{1+\alpha}{j}) c_{j-1}^\alpha, \quad j = 1, 2, 3, \ldots.$$

Now, the system (1)-(3) can be discretized as follows:

$$(T_n)_n = \frac{s_n - \sum_{j=1}^{n} c_j^\alpha (T_n)_{n-j}}{c_0 + d_n u_2(t) + k_n(\frac{c_n}{c_n+\eta})},$$

$$(T_e)_n = \frac{a_n k_n (T_n)_n (\frac{c_n}{c_n+\eta}) - \sum_{j=1}^{n} c_j^\alpha (T_e)_{n-j}}{c_0 + d_e u_2(t) + \gamma_e C_n - a_e(\frac{c_n}{c_n+\eta})},$$

$$(C)_n = \frac{- \sum_{j=1}^{n} c_j^\alpha (C)_{n-j}}{C_0 - (1 - u_1(t) r_c \ln(\frac{c_{\max}}{c_n}) + d_c u_2(t) + \gamma_c (T_e)_n}.$$

3.1 Numerical Solution in Fractional Model

The numerical results obtained using MATLAB software for two sets of parameters are presented in Table 1 (Patient A and B) with initial values of $T_n(0) = 1510$, $T_e(0) = 10$, and $C(0) = 10000$. These results are illustrated in figures for both patients, labeled A and B, for different values of derivative order α. We argue that the results from fractional order derivatives behave more naturally than those from classical order derivatives ($\alpha = 1$). As shown in Figures 1 and 2, the number of tumor cells is lower when $\alpha < 1$ compared to the case when $\alpha = 1$ (ODE case). This difference arises from the application of fractional differential instead of ordinary derivatives.

Overall, the results indicate that using fractional derivatives yields more favorable outcomes with increased efficiency. This is attributed to the non-local nature of fractional derivatives. In

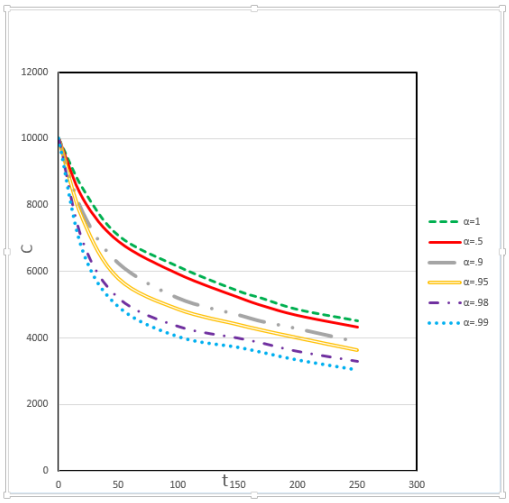

Figure 1: Numerical results for the cancer cell population (C) (patient A).

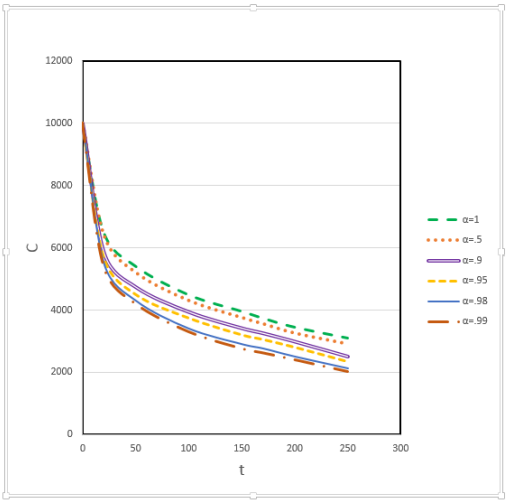

Figure 2: Numerical results for the cancer cell population (C) (patient B).

other words, when employing FDEs, we integrate information from all neighboring points, whereas ODEs rely on information from only two neighboring points. Consequently, the population of cancer cells is smaller, while the population of normal and immune cells are larger when using the fractional system compared to the ordinary one. This demonstrates the effectiveness of fractional calculus in modeling complex biological systems like cancer. The application of fractional equations allows for a more nuanced representation of cellular inter-

actions and dynamics, potentially leading to more accurate predictions and improved treatment strategies.

4 Optimal Treatment by Control Theory

In this section, we characterize the optimal control pair (u_1^*, u_2^*) that provides the optimal drug dosage for a given performance criterion. The existence of an optimal control pair is guaranteed by the compactness of the control and state spaces, as well as the convexity of the problem.

We consider the following general Bolza objective functional:

$$\text{Min} \quad J(u_1, u_2) = \int_0^{t_f} \left(C(t) + \frac{B_1}{2} u_1^2(t) + \frac{B_2}{2} u_2^2(t) \right) dt + B_3 C(t_f) - B_4 T_n(t_f),$$

where

$$u = \{u_1(t), u_2(t) | m_i \leq u_i(t) \leq M_i, u_i \text{ Lebesgue measurable}, \ i = 1, 2\} \quad t \in [0, t_f].$$

This objective functional aims to minimize the total cancer cell population over the treatment time interval $[0, t_f]$ through the first term in the integrand, as well as at the final time using a salvage term $B_3 C(t_f)$. We also aim to minimize the systemic costs associated with the two drugs u_1 and u_2. It is anticipated that the effects of the drugs are non-linear; therefore, we select quadratic cost terms $u_1^2(t)$ and $u_2^2(t)$ to reflect these effects. The coefficients B_1 and B_2 serve as weight constants for the controls and account for the toxicity of the drugs to the body. A higher weight indicates greater toxicity.

The salvage term $B_3 C(t_f)$ is included to account for potential increases in cancer cell count if the controls taper off earlier. Conversely, the term $-B_4 T_n(t_f)$ penalizes low values of T_n, as this impacts the patient's ability to combat other diseases. The coefficients B_3 and B_4 allow for different weighting of the salvage terms compared to the integral terms (all coefficients B_1, B_2, B_3 and B_4 are positive).

The lower bounds for u_1 and u_2 correspond to no therapy. For u_1, this lower bound is $m_1 = 0$, while for u_2, it is $m_2 = 1$. We assume $M_1 < 1$, as $M_1 = 1$ would imply no new cancer cells. The upper bound M_2 is greater than 1 and is determined by the parameters d_c, d_e, and d_n such that $M_2 = \min\left\{\frac{1}{d_c}, \frac{1}{d_n}, \frac{1}{d_e}\right\}$.

There are several methods for solving optimal control problems, including Euler-Lagrange method, Pontryagin's minimum principle, numerical methods based on finite differences, finite element methods, and semi-linearization techniques. In this section, we apply fractional Pontryagin's minimum principle to solve the optimal control problem [19]. The Hamiltonian H is calculated as follows:

$$H = C(t) + \frac{B_1}{2} u_1^2(t) + \frac{B_2}{2} u_2^2(t) + \varphi_1(t) \left[s_n - u_2(t) d_n T_n - k_n T_n \left(\frac{C}{C + \eta} \right) \right]$$

$$+\varphi_2(t)\left[\alpha_n k_n T_n\left(\frac{C}{C+\eta}\right)+\alpha_e T_e\left(\frac{C}{C+\eta}\right)-u_2(t)d_e T_e-\gamma_e C T_e)\right]$$
$$+\varphi_3(t)\left[(1-u_1(t))r_c C ln\left(\frac{C_{max}}{C}\right)-u_2(t)d_c C-\gamma_c C T_e\right]. \quad (4)$$

We aim to utilize the Grunwald-Letnikov discretization method to solve the problem. A fundamental issue challenge with this method is that we require initial values for the system, while only the final moment values, denoted as φ, are available. To address this issue, we have developed a method that employs variable transformation. In this case, we change the variable by setting $\varphi_i(t)=\lambda_i(t_f-t)$; thus , we obtain $\varphi_i(t_f)=\lambda_i(0)$.

By applying the fractional form, we can derive the following optimality conditions:

$$D_t^\alpha\lambda_1(t_f-t)=-\frac{\partial H}{\partial T_n}=\lambda_1(t_f-t)\left(u_2 d_n+k_n(\frac{C}{C+\eta})\right)-\lambda_2(t_f-t)\alpha_n k_n(\frac{C}{C+\eta}),$$
$$D_t^\alpha\lambda_2(t_f-t)=-\frac{\partial H}{\partial T_e}=\lambda_2(t_f-t)\left(-\alpha_e(\frac{C}{C+\eta})+u_2 d_e+\gamma_e C\right)+\lambda_3(t_f-t)\gamma_c C,$$
$$D_t^\alpha\lambda_3(t_f-t)=-\frac{\partial H}{\partial C}=\lambda_1(t_f-t)k_n T_n\frac{\eta}{(C+\eta)^2}$$
$$-(\lambda_2(t_f-t)\frac{\eta}{(C+\eta)^2})(\alpha_e T_e+\alpha_n k_n T_n)+\lambda_2(t_f-t)\gamma_e T_e-\lambda_3(t_f-t)$$
$$((1-u_1)r_c\left(\ln\frac{C_{\max}}{C}-1\right)-u_2 d_c-T_e\gamma_c\Big)-1,$$
$$D_t^\alpha T_n(t)=-\frac{\partial H}{\partial\lambda_1(t_f-t)}=s_n-u_2(t)d_n T_n-k_n T_n\left(\frac{C}{C+\eta}\right),$$
$$D_t^\alpha T_e(t)=-\frac{\partial H}{\partial\lambda_2(t_f-t)}=\alpha_n k_n T_n\left(\frac{C}{C+\eta}\right)+\alpha_e T_e\left(\frac{C}{C+\eta}\right)$$
$$-u_2(t)d_e T_e-\gamma_e C T_e,$$
$$D_t^\alpha C(t)=-\frac{\partial H}{\partial\lambda_3(t_f-t)}=(1-u_1(t))r_c C\ln\left(\frac{C_{\max}}{C}\right)-u_2(t)d_c C-\gamma_c C T_e,$$
$$\lambda_1(t_f-t)=-B_4,\quad \lambda_2(t_f-t)=0,\quad \lambda_3(t_f-t)=B_3.$$

By using the change of variable $\varphi_i(t)=\lambda_i(t_f-t)$, we obtain the following results: $\lambda_1(0)=-B_4$, $\lambda_2(0)=0$, and $\lambda_3(0)=B_3$. Additionally, we have the optimality condition stated below:

$$\frac{\partial H}{\partial u_1}=B_1u_1-\lambda_3(t_f-t)r_c C\ln\left(\frac{C_{\max}}{C}\right)=0, \quad (5)$$
$$\frac{\partial H}{\partial u_2}=B_2u_2-\lambda_1(t_f-t)d_n T_n-\lambda_2(t_f-t)d_e T_e-\lambda_3(t_f-t)d_c C=0. \quad (6)$$

By solving systems (5) and (6), we can obtain the optimal values for u_1 and u_2. Therefore, given the constraints $m_1<u_1(t)<M_1$ and $m_2<u_2(t)<M_2$, we have:

$${u_1}^*=\frac{\lambda_3 r_c C\ln(\frac{C_{\max}}{C})}{B_1},\quad {u_2}^*=\frac{\lambda_1 d_n T_n+\lambda_2 d_e T_e+\lambda_3 d_c C}{B_2}.$$

We can now apply the Grunwald-Letnikov method to discretize the optimal control problem, and the numerical results will be generated using MATLAB software.

$$(\lambda_1)_n = \frac{-\sum_{j=1}^{n} c_j^{\alpha}(\lambda_1)_{n-j} - (\lambda_2)_n \alpha_n k_n(\frac{C_n}{C_n+\eta})}{c_0 - u_2^* d_n - k_n(\frac{C_n}{C_n+\eta})}, \tag{7}$$

$$(\lambda_2)_n = \frac{-\sum_{j=1}^{n} c_j^{\alpha}(\lambda_2)_{n-j} + (\lambda_3)_n \gamma_e C_n}{c_0 + \alpha_e(\frac{C_n}{C_n+\eta}) - u_2^*(t) d_e - \gamma_e C_n}, \tag{8}$$

$$(\lambda_3)_n = \frac{-\sum_{j=1}^{n} c_j^{\alpha}(\lambda_3)_{n-j} + \frac{\eta}{C_n+\eta}\left[(\lambda_1)_n k_n(T_n)_n - (\lambda_2)_n(\alpha_n k_n(T_n)_n - \alpha_e)\right] - 1}{c_0 + (1-u_1^*(t)) r_c(\ln \frac{C_{\max}}{C_n} - 1) + u_2^*(t) d_c + (T_e)_n \gamma_c}, \tag{9}$$

$$(T_n)_n = \frac{s_n - \sum_{j=1}^{n} c_j^{\alpha}(T_n)_{n-j}}{c_0 + d_n u_2^*(t) + k_n \frac{C_n}{C_n+\eta}}, \tag{10}$$

$$(T_e)_n = \frac{\alpha_n k_n(T_n)_n \frac{C_n}{C_n+\eta} - \sum_{j=1}^{n} c_j^{\alpha}(T_e)_{n-j}}{c_0 + d_e u_2^*(t) + \gamma_e C_n - \alpha_e \frac{C_n}{C_n+\eta}}, \tag{11}$$

$$(C)_n = \frac{\sum_{j=1}^{n} c_j^{\alpha} C_{n-j}}{c_0 - (1-u_1^*(t)) r_c \ln \frac{C_{\max}}{C_n} + \gamma_c(T_e)_n + d_c u_2^*(t)}. \tag{12}$$

To determine the solution to the optimal control problem, we need to solve the above set of algebraic equations while considering the initial conditions $T_n(0) = 1510$, $T_e(0) = 10$, and $C(0) = 10000$. The numerical values of the control parameters are provided in Table 2:

Table 2: The numerical values of the control parameters

Parameters	B_1	B_2	B_3	B_4
Patient A	1000	500	1	10000
Patient B	100	50	0.1	10000

For the control system, the treatment duration is set to 250 days, and the step size is taken as $L = 1$ (one day). From the sequential representation of the resulting points over time, we can derive the optimal graphs for each function. Figures 3 and 4 illustrate the population of cancer cells in relation to the partial derivatives and the reduction in this population under controlled drug levels.

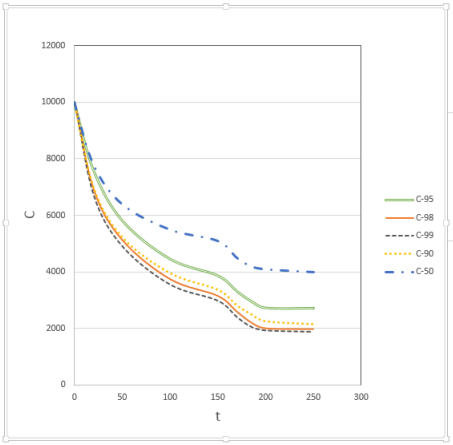

Figure 3: Numerical results for the cancer cell population (C) with u^* (patient A).

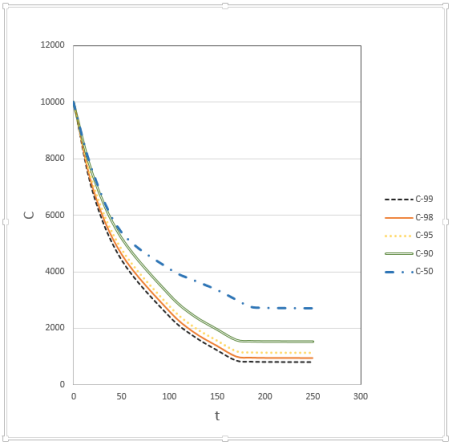

Figure 4: Numerical results for the cancer cell population (C) with u^* (patient B).

5 Conclusion

In this study , we have developed a mathematical model utilizing fractional order derivatives to depict a dynamic interactions between body immunology and drug variables. We introduced a three-cell population framework that captures the interaction between chronic myeloid leukemia (CML) and naive T cells, and effector T cell populations, initially operating in the absence of treatment, represented via fractional differential equations (FDE). The Local stability analyses of fixed points for this FDE system were validated against its ordinary differential equation (ODE) counterpart and and supported by numerical simulations from discretized FDE systems employing the Grunwald-Letnikov method. Our findings indicate that tumor cell pop-

ulations tend to rise to their maximum values when initiated with positive initial conditions . In light of this, we extended the model to include chemotherapy treatment to enhance its reliability. An optimal control study was conducted to determine the optimal drug dosage reducing tumor cell, naive T cell, and effector T cells. The resulting optimal drug doses were derived from combinations of targeted therapies and broad cytotoxic treatments. We adapted the existence and characteristic optimal control theorems originally formulated for ODE systems, to our FDE system. Given the non-local characteristics of FDEs, we assert that this model provides enhanced accuracy compared to traditional ODE models; however, this assertion necessitates further validation through clinical treatment data. Our approach presents several advantages over traditional modeling techniques , offering a nuanced representation of cellular interactions and dynamics, particularly in capturing long-range effects between cells. The comprehensive nature of the model accounts for competitive interactions among tumor cells, normal cells, and immune cells, thereby providing a holistic perspective on cancer progression. Nonetheless, there are potential limitations to address, including challenges in implementation for some researchers and the necessity for precise parameter estimation, notably regarding immune response parameters. Additionally, biological processes have been simplified, underscoring the need for extensive experimental validation to corroborate our predictions. This model holds significant promise for advancing cancer research and treatment strategies, paving the way for innovative modeling paradigms and computational approaches.

Declarations

Availability of Supporting Data

All data generated or analyzed during this study are included in this published paper.

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Competing Interests

The authors declare that they have no competing interests relevant to the content of this paper.

Authors' Contributions

The main text of manuscript is collectively written by the authors.

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