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Optimal chemotherapy and immunotherapy schedules for a cancer-obesity model with Caputo time fractional derivative

Tuğba Akman Yıldız[1] | Sadia Arshad[2] | Dumitru Baleanu[3,4,5]

[1]Department of Logistics Management, University of Turkish Aeronautical Association, Ankara, Turkey

[2]Department of Mathematics, COMSATS Institute of Information Technology, Lahore, Pakistan

[3]Department of Mathematics, Çankaya University, Ankara, Turkey

[4]Institute of Soft Matter Mechanics, Department of Engineering MechanicsHohai University, Nanjing, Jiangsu, China

[5]Institute of Space Sciences, Magurele-Bucharest, Romania

Correspondence
Tuğba Akman Yıldız, Department of Logistics Management, University of Turkish Aeronautical Association, 06790 Ankara, Turkey.
Email: tr.tugba.akman@gmail.com

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This work presents a new mathematical model to depict the effect of obesity on cancerous tumor growth when chemotherapy and immunotherapy have been administered. We consider an optimal control problem to destroy the tumor population and minimize the drug dose over a finite time interval. The constraint is a model including tumor cells, immune cells, fat cells, and chemotherapeutic and immunotherapeutic drug concentrations with the Caputo time fractional derivative. We investigate the existence and stability of the equilibrium points, namely, tumor-free equilibrium and coexisting equilibrium, analytically. We discretize the cancer-obesity model using the L1 method. Simulation results of the proposed model are presented to compare three different treatment strategies: chemotherapy, immunotherapy, and their combination. In addition, we investigate the effect of the differentiation order α and the value of the decay rate of the amount of chemotherapeutic drug to the value of the cost functional. We find out the optimal treatment schedule in case of chemotherapy and immunotherapy.

KEYWORDS
chemotherapy, fractional differential equations, immunotherapy, optimal control, stability

1 | INTRODUCTION

Obesity is associated with increased incidence and mortality of multiple cancers, with risk ratios correlating directly with body mass index (BMI) in a dose-dependent fashion. Obesity not only affects cancer incidence and long-term cancer-specific mortality but also impacts survival and recurrence among those diagnosed with cancer. Multiple variables regulate the obesity-cancer risk equation. Gender and ethnic differences exist; risk ratios for obesity are significantly higher in men than in women for colon cancer incidence. For example, Asians suffer increased breast cancer risk at lower BMI than do non-Asians. Obesity is associated with a state of chronic systemic inflammation. The link between nutrient excess and inflammation is rooted in the chemical nature of nutrients, bioenergetic molecules capable of participating in energy-intensive reactions that are potentially damaging to cells. In addition, obesity is associated with an increased risk of a number of nutrient deficiencies that have been implicated in cancer pathogenesis, including vitamin D, selenium, and magnesium. To understand the influence of obesity on cancer better, Ku-Carrillo et al developed a mathematical model in[1] that incorporates the interaction between the immune system and adipose cells.

Among evolving treatment modalities, immunotherapy has progressed rapidly into an auspicious field of medicine. The aim of cancer immunotherapy is to assist the immune system to efficiently recognize and attack cancerous cells. This treatment strategy has been investigated in terms of mathematical models, too. For example, an extended mathematical

model to depict interactions between cancer cells and adaptive immune system in mouse is proposed by Qomlaqi et al[2] to optimize protocol of immunotherapy with dendritic cell vaccine. Their model includes tumor cells, natural killers, naive and mature cytotoxic T cells, regulatory T cells, naive and mature helper T cells, dendritic cells, and interleukin 2 cytokine. In the study,[3] importance of scheduling immunotherapy is underlined to eradicate and control tumor population. Moreover, immune competition is analyzed in case of tumor population by Brazzoli et al.[4] In the work by Robertson-Tessi et al,[5] the effect of chemotherapy and immunotherapy on control of the tumor growth has been presented. The combined effect of immunotherapy and chemotherapy is investigated on the basis of optimal control theory by Pang et al.[6]

The aim behind chemotherapy is to eliminate the tumor cells. The cytotoxic drugs, which have a fast dividing rate, are distributed to different parts of the body through the blood circulation system. Chemotherapy also affects mitosis rate of some other kinds of cells that have rapid growth naturally, including hair cells, in an undesirable way.[7] In several clinical contexts, it is important to minimize, or rather, optimize the amount of drug(s) used in order to regulate the potentially lethal side effects of chemotherapy in cancer treatment. Much remarkable work has been done on modeling chemotherapy treatment by using optimal control theory. For example, optimal control is used to examine the ability of a heterogeneous tumor to counteract the chemotherapeutic drug in the study.[8] To achieve this goal, it is underlined that the drug must be injected at the maximum rate.[9] Models for chemotherapy schedule have been reviewed on the basis of optimal control in the study of Schättler and Ledzewicz.[10] The study[11] offers a discussion of the prospective application of optimal control theory. Moreover, four optimal control problems (OCPs) for chemotherapy schedule are investigated by Engelhart et al,[11] and different choices of the objective functions in the framework of chemotherapy are compared. The combination of chemotherapy and radiotherapy to eradicate the cancer with metastasis is discussed by Ghaffari et al.[12] An adaptive robust control is proposed to adjust the drug dosages with an extended Kalman filter observer by Rokhforoz et al.[13] An optimal control strategy based on a linear time-varying approximation technique is proposed by Itik et al.[14] On the other hand, an OCP with a free final time is solved for tumor-immune interactions with the aim of minimizing not only the tumor population but also the treatment period by Alkama et al.[15] A model-free method for chemotherapy based on reinforcement learning is proposed by Padmanabhan et al[16] using the closed-loop control. In particular, they developed an optimal controller using Q-learning algorithm for cancer chemotherapy treatment. In the study of De Pillis and Radunskaya,[17] they modeled the chemotherapy treatment based on optimal control theory, and their objective is to minimize the tumor cells while keeping the healthy cells above a fixed level. In the study,[18] the interactions between tumor cells, immune cells, and chemotherapeutic and immunotherapeutic drug concentrations are given by a system of ordinary differential equations. On the other hand, De Pillis and Radunskaya[19] have proposed a system for tumor cells, immune cells, normal cells, and chemotherapeutic drug concentration. Recently, the effect of obesity on cancer growth has been investigated by Ku-Carrillo et al[20] by extending the model of De Pillis and Radunskaya with fat cells.

Fractional differentiation and integration operators, which are the generalization of classical integer-order counterparts, are capable of capturing memory effects due to their nonlocal nature.[21-23] It is a useful tool to develop suitable models for describing real-world problems, which cannot be expressed by using integer-order differential equations. There are several epidemiological models that have been investigated using fractional derivative. A fractional-order susceptible-infected-recuperated (SIR) epidemic model is examined by He and Banerjee[24] under the influence of both parametric seasonality and the external noise. It is shown that the system has rich dynamical behaviors with different system parameters, fractional derivative order, and the degree of seasonality and noise. An epidemic model of dengue transmission based on the SIR model with a fractional-order derivative is introduced by Hamdan and Kilicman,[25] and the threshold quantity value similar to the basic reproduction number is derived using the next-generation matrix approach. A fractional-order Ebola virus epidemic model with delayed immune response on heterogeneous complex networks is investigated by Latha et al.[26] A fractional susceptible-exposed-infectious-recovered (SEIR) model with treatment as control measure is proposed by Almeida.[27] A fractional-order Izhikevich model is studied by Teka et al[28]; they analyzed different kinds of oscillations that emerge from the fractional dynamics. The model produces a wide range of neuronal spike responses, including regular spiking, fast spiking, intrinsic bursting, mixed-mode oscillations, regular bursting, and chattering, by adjusting only the fractional order. In the context of tumor-growth models, we can mention the following papers: A cancer model with two immune effectors is investigated in terms of the Caputo fractional derivative in the study of Ahmed et al,[29] while a model for HIV infection of CD4+T cells is generalized with the Caputo derivative the paper.[30] Existence and uniqueness of the solution of a cancer model with the Caputo-Fabrizio derivative have been justified by Dokuyucu et al,[31] while the Mittag-Leffler derivative has been used in the study of Gómez-Aguilar et al.[32] For fractional OCPs (FOCPs), we can mention the study of Pinto and Tenreiro[33] where a fractional malaria transmission model is investigated on the basis of optimal control techniques. In addition, HIV infection is investigated by Elal et al,[34] and the West Nile virus model with the Caputo derivative is presented by Sweilam et al[35] in terms of Caputo derivative. On the other

hand, an optimal control strategy is proposed for a nonlinear multistrain tuberculosis model with the Caputo derivatives by Sweilam and AL-Mekhlafi.[36]

The aim of this paper is to investigate a FOCP governed by a Caputo time fractional cancer-obesity model. We note that the proposed model is based on Sharma and Samanta's model,[18] which presents the growth/decay of immune and tumor cells when chemotherapeutic and immunotherapeutic drugs have been injected, and Ku-Carrillo et al's work,[20] which offers a model for cancer-obesity relation. However, influence of obesity to cancer growth is not considered in the model of Sharma and Samanta.[18] Our model expresses the intercommunication of tumor cells, immune cells, fat cells, and chemotherapeutic and immunotherapeutic drug concentrations in terms of the Caputo time fractional derivative. To the best of our knowledge, this is the first study investigating the optimal treatment strategy for a cancerous tumor-growth model in terms of a fractional derivative. Moreover, we investigate the existence and stability of the equilibrium points, namely, tumor-free equilibrium and coexisting equilibrium, analytically. We solve the OCP using forward-backward sweep method after discretizing the fractional differential equation (FDE) applying the so-called L1 method. We illustrate the contribution of the use of fractional derivatives by solving the FOCP for different orders of differentiation. In addition, we examine the influence of the decay rate of amount of chemotherapeutic drug to the value of the cost functional. To sum up, we find out the optimal treatment schedule in case of chemotherapy and immunotherapy for a generalized cancer-obesity model.

The rest of the paper is organized as follows: In Section 2, we introduce the FOCP governed by cancer-obesity model and present the optimality system. In Section 3, existence of the equilibrium points and their stability conditions are discussed. In Section 4, we explain the discretization of the FOCP. In Section 5, we present some numerical results to compare different treatment strategies, namely, chemotherapy, immunotherapy, and their combination. Then, the paper ends with summary and conclusion.

2 | FRACTIONAL OPTIMAL CONTROL PROBLEM

In the literature, several fractional derivatives have been defined. One of the mostly used fractional differentiation operators is the Caputo derivative.[21] In this section, we briefly mention the required definitions and properties of the Caputo derivative in order to derive the optimality system.

Firstly, we define the (left) Caputo fractional differentiation operator for $0 < \alpha < 1$ as in the study of Podlubny[21]:

$$ {}^{\mathrm{C}}_{A}\mathcal{D}^{\alpha}_{t}\varphi(t) = \frac{1}{\Gamma(1-\alpha)}\int_{A}^{t}\frac{\varphi'(s)}{(t-s)^{\alpha}}\,ds. \tag{1} $$

The corresponding right differentiation operator is defined as

$$ {}^{\mathrm{C}}_{t}\mathcal{D}^{\alpha}_{B}\varphi(t) = -\frac{1}{\Gamma(1-\alpha)}\int_{t}^{B}\frac{\varphi'(s)}{(s-t)^{\alpha}}\,ds. \tag{2} $$

In addition, the right Riemann-Liouville differentiation operator is written in the form

$$ {}^{\mathrm{RL}}_{t}\mathcal{D}^{\alpha}_{B}\varphi(t) = -\frac{d}{dt}\int_{t}^{B}\frac{\varphi(s)}{(s-t)^{\alpha}}\,ds. \tag{3} $$

On the other hand, the fractional integral is given by

$$ {}_{A}\mathcal{I}^{\alpha}_{t}\varphi(t) = \frac{1}{\Gamma(\alpha)}\int_{A}^{t}(t-s)^{\alpha-1}\varphi(s)\,ds. \tag{4} $$

Lastly, we mention a useful relation between the right Caputo and Riemann-Liouville differentiation operators

$$ {}^{\mathrm{RL}}_{t}\mathcal{D}^{\alpha}_{B}\varphi(t) = {}^{\mathrm{C}}_{t}\mathcal{D}^{\alpha}_{B}\varphi(t) + \varphi(B)\frac{(B-t)^{-\alpha}}{\Gamma(1-\alpha)}. \tag{5} $$

In this study, we consider a FOCP governed by a generalized cancer-obesity model. The model describes the interaction between the state variables, namely, tumor cells $T(t)$, immune cells $I(t)$, fat cells $F(t)$, and chemotherapeutic and immunotherapeutic drug concentrations $D_1(t)$ and $D_2(t)$, respectively. The control variables $u_1(t)$ and $u_2(t)$ denote the doses of the chemotherapeutic and immunotherapeutic drugs, respectively. The aim behind the OCP is to minimize the value of the cost functional $J(u_1, u_2)$, which is equivalent to minimizing the tumor population and the drug administered over a finite time interval, where the interaction of tumor cells, immune cells, fat cells, and drug concentrations is governed by a time fractional–coupled system of differential equations.

We shortly denote

$$T := T(t),\ I := I(t),\ F := F(t),\ D_1 := D_1(t),\ D_2 := D_2(t)$$

and propose the following FOCP:

$$\min_{u=(u_1,u_2)\in U_{\text{ad}}} J(u_1, u_2) = \int_0^{t_{\text{f}}} (T + \omega_1 u_1^2 + \omega_2 u_2^2)\, dt \tag{6}$$

subject to

$$\begin{cases} {}_0^{\text{C}}\mathcal{D}_t^{\alpha} T &= r^{\alpha} T(1 - pT) - \xi_1^{\alpha} TI + c_1^{\alpha} TF - q_1^{\alpha} D_1 T, \\ {}_0^{\text{C}}\mathcal{D}_t^{\alpha} I &= s^{\alpha} + \frac{\rho^{\alpha} T^2 I}{h + T^2 + F^2} + \frac{\beta^{\alpha} D_2 I}{g + D_2} - \xi_2^{\alpha} TI - \mu^{\alpha} I - q_2^{\alpha} D_1 I, \\ {}_0^{\text{C}}\mathcal{D}_t^{\alpha} F &= d^{\alpha} F(1 - \epsilon F) - c_2^{\alpha} FT - q_3^{\alpha} D_1 F, \\ {}_0^{\text{C}}\mathcal{D}_t^{\alpha} D_1 &= u_1 - \gamma_1^{\alpha} D_1, \\ {}_0^{\text{C}}\mathcal{D}_t^{\alpha} D_2 &= u_2 - \gamma_2^{\alpha} D_2, \\ T(0) &= T_0,\ I(0) = I_0,\ F(0) = F_0,\ D_1(0) = D_{10},\ D_2(0) = D_{20}, \end{cases} \tag{7}$$

where the admissible space of controls is given by

$$U_{\text{ad}} = \{u = (u_1, u_2) \mid u_1, u_2 \text{ are measurable with } 0 \le u_1, u_2 \le 1,\ t \in [0, t_{\text{f}}]\}.$$

Therefore, the aim is to find the optimal control $u^* = (u_1^*, u_2^*) \in U_{\text{ad}}$ such that $J(u_1^*, u_2^*) = \min_{u=(u_1,u_2)\in U_{\text{ad}}} J(u_1, u_2)$ holds.

Now, we proceed with the positivity of the solution of the model (7). Then, we obtain the optimality system for OCP (6) and (7).

2.1 | Existence of positive solutions of the cancer-obesity model

We denote $\mathbb{R}_+^5 = \{x \in \mathbb{R}^5 \mid x \ge 0\}$ and $x(t) = (T, I, F, D_1, D_2)^T$.

Theorem 1. *The solution of FDE (7) is unique, and it remains in* $\mathbb{R}_+^5$.

Proof. From Lin,[37, Theorem 3.1, Remark 3.2] existence of the unique solution to FDE (7) is proven on $(0, \infty)$. Then, we show that the nonnegative orthant $\mathbb{R}_+^5$ is a positively invariant region. Since

$$\begin{aligned} &{}_0^{\text{C}}\mathcal{D}_t^{\alpha} T|_{T=0} = 0, \quad {}_0^{\text{C}}\mathcal{D}_t^{\alpha} I|_{I=0} = s^{\alpha} \ge 0, \quad {}_0^{\text{C}}\mathcal{D}_t^{\alpha} F|_{F=0} = 0, \\ &{}_0^{\text{C}}\mathcal{D}_t^{\alpha} D_1|_{D_1=0} = u_1 \ge 0, \quad {}_0^{\text{C}}\mathcal{D}_t^{\alpha} D_2|_{D_2=0} = u_2 \ge 0, \end{aligned}$$

on each hyperplane bounding the nonnegative orthant, the vector field points into $\mathbb{R}_+^5$. The solution will remain in $\mathbb{R}_+^5$.[38] □

2.2 | Optimality system

We derive the necessary optimality conditions for the OCP (6)-(7).

Theorem 2. *Given a pair of optimal controls $u^* = (u_1^*, u_2^*)$ and the state solutions $(T^*, I^*, F^*, D_1^*, D_2^*)$ corresponding to (7) that minimize objective functional (6), there exist adjoint variables $(\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5)$ satisfying*

$$\begin{cases} {}_t^{\mathrm{C}}\mathcal{D}_{t_\mathrm{f}}^{\alpha}\lambda_1 = (r^\alpha - 2r^\alpha pT - \xi_1^\alpha I + c_1^\alpha F - q_1^\alpha D_1)\lambda_1 \\ \qquad\qquad + \left(\frac{2\rho^\alpha TI(h+F^2)}{(h+T^2+F^2)^2} - \xi_2^\alpha I\right)\lambda_2 - c_2^\alpha F\lambda_3 + 1, \\ {}_t^{\mathrm{C}}\mathcal{D}_{t_\mathrm{f}}^{\alpha}\lambda_2 = -\xi_1^\alpha T\lambda_1 + \left(\frac{\rho^\alpha T^2}{h+T^2+F^2} + \frac{\beta^\alpha D_2}{g+D_2} - \xi_2^\alpha T - \mu^\alpha - q_2^\alpha D_1\right)\lambda_2, \\ {}_t^{\mathrm{C}}\mathcal{D}_{t_\mathrm{f}}^{\alpha}\lambda_3 = c_1^\alpha T\lambda_1 - \frac{2\rho^\alpha T^2 IF}{(h+T^2+F^2)^2}\lambda_2 + (d^\alpha - 2d^\alpha\epsilon F - c_2^\alpha T - q_3^\alpha D_1)\lambda_3, \\ {}_t^{\mathrm{C}}\mathcal{D}_{t_\mathrm{f}}^{\alpha}\lambda_4 = -q_1^\alpha T\lambda_1 - q_2^\alpha I\lambda_2 - q_3^\alpha F\lambda_3 - \gamma_1^\alpha\lambda_4, \\ {}_t^{\mathrm{C}}\mathcal{D}_{t_\mathrm{f}}^{\alpha}\lambda_5 = \frac{\beta^\alpha gI}{(g+D_2)^2}\lambda_2 - \gamma_2^\alpha\lambda_5, \end{cases} \tag{8}$$

with transversality conditions

$$\lambda_1(t_\mathrm{f}) = 0,\ \lambda_2(t_\mathrm{f}) = 0,\ \lambda_3(t_\mathrm{f}) = 0,\ \lambda_4(t_\mathrm{f}) = 0,\ \lambda_5(t_\mathrm{f}) = 0. \tag{9}$$

Moreover, the pair of optimal controls $u^* = (u_1^*, u_2^*)$ is represented by

$$\begin{cases} u_1^* = \min\left(\max\left(-\frac{\lambda_4}{2\omega_1}, 0\right), 1\right), \\ u_2^* = \min\left(\max\left(-\frac{\lambda_5}{2\omega_2}, 0\right), 1\right). \end{cases} \tag{10}$$

Proof. Following the proof in the study of Sweilam and AL-Mekhlafi,[36, Theorem 5.1] we note that existence of a pair of optimal controls $u^* = (u_1^*, u_2^*)$, and the associated state solution $(T^*, I^*, F^*, D_1^*, D_2^*)$ is obtained owing to the convexity of $J(u_1, u_2)$ with respect to controls and the constraint, which satisfies the Lipschitz property with respect to state variables.

The optimality system can be derived by constructing the Lagrangian as

$$\begin{aligned} &\mathcal{L}(T, I, F, D_1, D_2, u_1, u_2, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5) \\ &= \int_0^{t_\mathrm{f}} ((T + \omega_1 u_1^2 + \omega_2 u_2^2) \\ &\quad - \lambda_1^T\left(\{{}_0^{\mathrm{C}}\mathcal{D}_t^\alpha T - r^\alpha T(1 - pT) + \xi_1^\alpha TI - c_1^\alpha TF + q_1^\alpha D_1 T\right) \\ &\quad - \lambda_2^T\left({}_0^{\mathrm{C}}\mathcal{D}_t^\alpha I - s^\alpha - \frac{\rho^\alpha T^2 I}{h + T^2 + F^2} - \frac{\beta^\alpha D_2 I}{g + D_2} + \xi_2^\alpha TI + \mu^\alpha I + q_2^\alpha D_1 I\right) \\ &\quad - \lambda_3^T({}_0^{\mathrm{C}}\mathcal{D}_t^\alpha F - d^\alpha F(1 - \epsilon F) + c_2^\alpha FT + q_3^\alpha D_1 F) \\ &\quad - \lambda_4^T\left({}_0^{\mathrm{C}}\mathcal{D}_t^\alpha D_1 - u_1 + \gamma_1^\alpha D_1\right) - \lambda_5^T\left({}_0^{\mathrm{C}}\mathcal{D}_t^\alpha D_2 - u_2 + \gamma_2^\alpha D_2\right)\ )\ dt \\ &\quad + \eta_1 u_1 + \eta_2(1 - u_1) + \mu_1 u_2 + \mu_2(1 - u_2) \\ &\quad - \lambda_1(0)(T(0) - T_0) - \lambda_2(0)(I(0) - I_0) - \lambda_3(0)(F(0) - F_0) \\ &\quad - \lambda_4(0)(D_1(0) - D_{10}) - \lambda_5(0)(D_2(0) - D_{20}), \end{aligned} \tag{11}$$

where $\lambda_i(t)'$s are the adjoint or costate variables; $\eta_1 \geq 0, \eta_2 \geq 2, \mu_1 \geq 0, \mu_2 \geq 0$ are penalty multipliers satisfying

$$\eta_1 u_1 = 0, \quad \eta_2(1 - u_1) = 0, \quad \mu_1 u_2 = 0, \quad \mu_2(1 - u_2) = 0,$$

at the optimal $u^* = (u_1^*, u_2^*)$.

The optimality system associated with (6) is obtained through the first variation of $\mathcal{L}$ in (11), which must be zero for all variations $\delta T, \delta I, \delta F, \delta D_1, \delta D_2, \delta u_1, \delta u_2$, and $\delta\lambda_i$'s with the specified final condition. In particular, we present the derivation of the fractional derivative of the adjoint equation. We apply the method of fractional integration by parts, for example, to the term $\lambda_1^T(t)\left({}_0^{\mathrm{C}}\mathcal{D}_t^{\alpha}\delta T(t)\right)$ in (11) following the study of Agrawal[39, Sec. 2] as

$$\int_0^{t_\mathrm{f}} \lambda_1^T(t)\left({}_0^{\mathrm{C}}\mathcal{D}_t^{\alpha}\delta T(t)\right)\,dt = \int_0^{t_\mathrm{f}} \left({}_t^{\mathrm{RL}}\mathcal{D}_{t_\mathrm{f}}^{\alpha}\lambda_1(t)\right)^T \delta T(t)\,dt, \tag{12}$$

with the condition $\lambda_1(t_\mathrm{f}) = 0$. Then, we proceed as

$$\begin{aligned}\int_0^{t_\mathrm{f}} \left({}_t^{\mathrm{RL}}\mathcal{D}_{t_\mathrm{f}}^{\alpha}\lambda_1(t)\right)^T \delta T(t)\,dt &\underbrace{=}_{(2.5)} \int_0^{t_\mathrm{f}} \left({}_t^{\mathrm{C}}\mathcal{D}_{t_\mathrm{f}}^{\alpha}\lambda_1(t) + \frac{\overbrace{\lambda_1(t_\mathrm{f})}^{=0}\,(t_\mathrm{f}-t)^{-\alpha}}{\Gamma(1-\alpha)}\right)^T \delta T(t)\,dt \\ &= \int_0^{t_\mathrm{f}} \left({}_t^{\mathrm{C}}\mathcal{D}_{t_\mathrm{f}}^{\alpha}\lambda_1(t)\right)^T \delta T(t)\,dt.\end{aligned} \tag{13}$$

Then, we substitute (13) into (11). For the first variation to be equal to zero, all factors multiplied by a variation in Equation 13 must vanish, and we reach the adjoint Equation 8 with final condition (9) and the gradient (10). □

3 | EQUILIBRIUM POINTS AND STABILITY ANALYSIS

In this section, we will examine the existence of the equilibrium points of system (7), namely, *tumor-free equilibrium* and *coexisting equilibrium*, and determine the conditions under which they are stable. Firstly, we fix the doses of chemotherapeutic and immunotherapeutic drugs as $u_1(t) = u_1$ and $u_2(t) = u_2$, respectively. Then, we solve the following system of FDEs for $T(t), I(t), F(t), D_1(t)$, and $D_2(t)$:

$${}_0^{\mathrm{C}}\mathcal{D}_t^{\alpha}T = 0, \quad {}_0^{\mathrm{C}}\mathcal{D}_t^{\alpha}I = 0, \quad {}_0^{\mathrm{C}}\mathcal{D}_t^{\alpha}F = 0, \quad {}_0^{\mathrm{C}}\mathcal{D}_t^{\alpha}D_1 = 0, \quad {}_0^{\mathrm{C}}\mathcal{D}_t^{\alpha}D_2 = 0. \tag{14}$$

3.1 | Tumor-free equilibrium point

We consider the case that no tumor cells exist; that is, $\hat{T} = 0$. We solve system (14) and find the tumor-free equilibrium point $\hat{\mathrm{E}} = (0, \hat{\mathrm{I}}, \hat{F}, \hat{D}_1, \hat{D}_2)$ where

$$\begin{aligned}\hat{\mathrm{I}} &= \frac{s^{\alpha}(g+\hat{D}_2)}{(\mu^{\alpha}+q_2^{\alpha}\hat{D}_1)(g+\hat{D}_2)-\beta^{\alpha}\hat{D}_2}, \\ \hat{F} &= \frac{1}{\epsilon} - \frac{q_3^{\alpha}}{d^{\alpha}\epsilon}\hat{D}_1, \\ \hat{D}_1 &= \frac{u_1}{\gamma_1^{\alpha}}, \quad \hat{D}_2 = \frac{u_2}{\gamma_2^{\alpha}}.\end{aligned} \tag{15}$$

The equilibrium point $\hat{\mathrm{E}}$ exists if $\hat{\mathrm{I}} > 0$, $\hat{F} > 0$, $\hat{D}_1 > 0$, and $\hat{D}_2 > 0$. We note that $\hat{D}_1 > 0$ and $\hat{D}_2 > 0$ are automatically satisfied with $u_1 > 0$ and $u_2 > 0$ according to (15). Now, we must assure that $\hat{\mathrm{I}} > 0$ and $\hat{F} > 0$ hold. Then, we obtain the following inequalities:

$$\begin{aligned}\hat{\mathrm{I}} &= \frac{s^{\alpha}(g+\hat{D}_2)}{(\mu^{\alpha}+q_2^{\alpha}\hat{D}_1)(g+\hat{D}_2)-\beta^{\alpha}\hat{D}_2} \\ &= \frac{s^{\alpha}\gamma_1^{\alpha}(\gamma_2^{\alpha}g+u_2)}{\mu^{\alpha}g\gamma_1^{\alpha}\gamma_2^{\alpha}+q_2^{\alpha}gu_1\gamma_2^{\alpha}+q_2^{\alpha}u_1u_2+u_2\gamma_1^{\alpha}(\mu^{\alpha}-\beta^{\alpha})} > 0,\end{aligned}$$

and

$$\hat{F} = \frac{1}{\epsilon} - \frac{q_3^\alpha}{d^\alpha \epsilon}\hat{D}_1 = \frac{1}{\epsilon} - \frac{q_3^\alpha}{d^\alpha \epsilon}\frac{u_1}{\gamma_1^\alpha} > 0.$$

Therefore, we find the following conditions:

$$\mu^\alpha g\gamma_1^\alpha\gamma_2^\alpha + q_2^\alpha g u_1\gamma_2^\alpha + q_2^\alpha u_1 u_2 + u_2\gamma_1^\alpha\mu^\alpha > u_2\gamma_1^\alpha\beta^\alpha, \quad d^\alpha\gamma_1^\alpha > q_3^\alpha u_1,$$

so that the equilibrium point $\hat{E}$ exists.

Now, we discuss the stability of $\hat{E}$ by investigating the signs of the eigenvalues of the Jacobian associated with the model (7).

Theorem 3. *The equilibrium point $\hat{E} = (0, \hat{I}, \hat{F}, \hat{D}_1, \hat{D}_2)$ of system (7) exists under the condition that*

$$\mu^\alpha g\gamma_1^\alpha\gamma_2^\alpha + q_2^\alpha g u_1\gamma_2^\alpha + q_2^\alpha u_1 u_2 + u_2\gamma_1^\alpha\mu^\alpha > u_2\gamma_1^\alpha\beta^\alpha, \quad d^\alpha\gamma_1^\alpha > q_3^\alpha u_1. \tag{16}$$

Moreover, $\hat{E} = (0, \hat{I}, \hat{F}, \hat{D}_1, \hat{D}_2)$ is locally asymptotically stable if the following conditions

$$\begin{aligned} &q_3^\alpha u_1 < d^\alpha\gamma_1^\alpha, \\ &\beta^\alpha\gamma_1^\alpha u_2 < (\gamma_1^\alpha\mu^\alpha + q_2^\alpha u_1)(\gamma_2^\alpha g + u_2), \\ &I^* > \frac{r^\alpha}{\xi_1^\alpha} + \frac{c_1^\alpha}{\xi_1^\alpha\epsilon} - \left(\frac{c_1^\alpha q_3^\alpha}{\xi_1^\alpha d^\alpha\epsilon} + \frac{q_1^\alpha}{\xi_1^\alpha\gamma_1^\alpha}\right)u_1, \end{aligned} \tag{17}$$

together with (16) hold.

Proof. The Jacobian of the system (7) evaluated at $\hat{E} = (0, \hat{I}, \hat{F}, \hat{D}_1, \hat{D}_2)$ is given by

$$J(E^*) = \begin{pmatrix} \omega_1 & 0 & 0 & 0 & 0 \\ \omega_2 & \omega_3 & 0 & \omega_4 & \omega_5 \\ \omega_6 & 0 & \omega_7 & \omega_8 & 0 \\ 0 & 0 & 0 & \omega_9 & 0 \\ 0 & 0 & 0 & 0 & \omega_{10} \end{pmatrix},$$

where

$$\begin{aligned} &\omega_1 = r^\alpha - \xi_1^\alpha\hat{I} + c_1^\alpha\hat{F} - q_1^\alpha\hat{D}_1, \quad \omega_2 = -\xi_2^\alpha\hat{I}, \\ &\omega_3 = -\mu^\alpha - q_2^\alpha\hat{D}_1 + \beta^\alpha\frac{\hat{D}_2}{g + \hat{D}_2}, \quad \omega_4 = -q_2^\alpha\hat{I}, \quad \omega_5 = \frac{g\beta^\alpha\hat{I}}{(g + \hat{D}_2)^2}, \\ &\omega_6 = -c_2^\alpha\hat{F}, \quad \omega_7 = d^\alpha - 2d^\alpha\epsilon\hat{F} - q_3^\alpha\hat{D}_1, \\ &\omega_8 = -q_3^\alpha\hat{F}, \quad \omega_9 = -\gamma_1^\alpha, \quad \omega_{10} = -\gamma_2^\alpha. \end{aligned}$$

The eigenvalues of $J(\hat{E})$ are computed as

$$\begin{aligned} \lambda_1 &= \omega_9 = -\gamma_1^\alpha, \\ \lambda_2 &= \omega_{10} = -\gamma_2^\alpha, \\ \lambda_3 &= \omega_3 = \frac{\beta^\alpha u_2}{\gamma_2^\alpha g + u_2} - \left(\mu^\alpha + q_2^\alpha\frac{u_1}{\gamma_1^\alpha}\right), \\ \lambda_4 &= \omega_7 = \frac{q_3^\alpha u_1}{\gamma_1^\alpha} - d^\alpha, \\ \lambda_5 &= \omega_1 = r^\alpha - \xi_1^\alpha\hat{I} + c_1^\alpha\hat{F} - q_1^\alpha\hat{D}_1 \\ &= -\xi_1^\alpha\hat{I} + r^\alpha + \frac{c_1^\alpha}{\epsilon} - \left(\frac{c_1^\alpha q_3^\alpha}{d^\alpha\epsilon} + \frac{q_1^\alpha}{\gamma_1^\alpha}\right)u_1. \end{aligned}$$

Tumor-free equilibrium point $\hat{E}$ is locally asymptotically stable if all eigenvalues λ_i of $J(\hat{E})$ are negative. The requirement $\lambda_1 < 0$ and $\lambda_2 < 0$ are automatically satisfied. For $\lambda_3, \lambda_4, \lambda_5$ to be negative, we reach the conditions in (17). □

3.2 | Coexisting equilibrium point

In this case, tumor cells coexist; ie, $\overline{T} \neq 0$. By keeping this in mind, we solve (14) for $\overline{T} > 0, \overline{I} > 0, \overline{F} > 0, \overline{D}_1 > 0, \overline{D}_2 > 0$ to reach the coexisting equilibrium point $\overline{E} = (\overline{T}, \overline{I}, \overline{F}, \overline{D}_1, \overline{D}_2)$.

We find that

$$\begin{aligned}
&\overline{D}_1 = \frac{u_1}{\gamma_1^\alpha}, \quad \overline{D}_2 = \frac{u_2}{\gamma_2^\alpha},\\
&\overline{F} = \frac{1}{\epsilon d^\alpha}(d^\alpha - q_3^\alpha \overline{D}_1 - c_2^\alpha \overline{T}) = k_1 + k_2 \overline{T},\\
&\overline{T} = \frac{1}{pr^\alpha}(r^\alpha - \xi_1^\alpha \overline{I} - q_1^\alpha \overline{D}_1 + c_1^\alpha \overline{F}) = k_4 + k_5 \overline{I},
\end{aligned} \tag{18}$$

where

$$\begin{aligned}
&k_1 = \frac{1}{\epsilon} - \frac{q_3^\alpha}{\epsilon d^\alpha}\overline{D}_1, \quad k_2 = -\frac{c_2^\alpha}{\epsilon d^\alpha}, \quad k_3 = \frac{1}{p} - \frac{q_1^\alpha}{pr^\alpha}\overline{D}_1,\\
&k_4 = \frac{k_3^\alpha pr^\alpha + k_1 c_1^\alpha}{pr^\alpha - c_1^\alpha k_2} = \frac{\epsilon d^\alpha (k_3^\alpha pr^\alpha + k_1 c_1^\alpha)}{\epsilon d^\alpha pr^\alpha + c_1^\alpha c_2^\alpha},\\
&k_5 = -\frac{\xi_1^\alpha}{pr^\alpha - c_1^\alpha k_2} = -\frac{\epsilon d^\alpha \xi_1^\alpha}{\epsilon d^\alpha pr^\alpha + c_1^\alpha c_2^\alpha}.
\end{aligned}$$

For simplification purposes, we put

$$\begin{aligned}
&\overline{F} = k_1 + k_2(k_4 + k_5 \overline{I}) = k_6 + k_7 \overline{I},\\
&\overline{I} = \frac{s^\alpha (h + \overline{T}^2 + \overline{F}^2)(g + \overline{D}_2)}{(\mu^\alpha + \alpha_2^\alpha \overline{T} + q_2^\alpha \overline{D}_1)(h + \overline{T}^2 + \overline{F}^2)(g + \overline{D}_2) - \overline{T}^2(\rho^\alpha (g + \overline{D}_2) + \beta^\alpha \overline{D}_2) - \beta^\alpha \overline{D}_2(\overline{F}^2 + h)},
\end{aligned}$$

where $k_6 = k_1 + k_2 k_4, k_7 = k_2 k_5$. After arranging the terms, we obtain the following polynomial in $\overline{I}$:

$$m_4 \overline{I}^4 + m_3 \overline{I}^3 + m_2 \overline{I}^2 + m_1 \overline{I} + m_0 = 0, \tag{19}$$

where

$$\begin{aligned}
m_4 &= \theta_1 k_5 (k_5^2 + k_7^2),\\
m_3 &= \theta_1 (3k_4 k_5^2 + k_4 k_7^2 + 2k_5 k_6 k_7) + \theta_2 k_7^2 + \theta_3 k_5^2,\\
m_2 &= \theta_1 (3k_4^2 k_5 + 2k_4 k_6 k_7 + k_5 k_6^2) + \theta_2 (2k_6 k_7) + \theta_3 (2k_4 k_5) + \theta_4 k_5 + \theta_5 (k_5^2 + k_7^2),\\
m_1 &= \theta_1 (k_4^3 + k_4 k_6^2) + \theta_2 k_6^2 + \theta_3 k_5^2 + \theta_4 k_4 + \theta_5 (2k_4 k_5 + 2k_6 k_7) + \theta_6,\\
m_0 &= \theta_5 (k_4^2 + k_6^2) + \theta_7,\\
\theta_1 &= (g + \overline{D}_2)\xi_2^\alpha,\\
\theta_2 &= (g + \overline{D}_2)(\mu^\alpha + q_2^\alpha \overline{D}_1) - \beta^\alpha \overline{D}_2,\\
\theta_3 &= (g + \overline{D}_2)(\mu^\alpha + q_2^\alpha \overline{D}_1) - (\rho^\alpha g + \rho^\alpha \overline{D}_2 + \beta^\alpha \overline{D}_2),\\
\theta_4 &= (g + \overline{D}_2)\xi_2^\alpha h,\\
\theta_5 &= -(g + \overline{D}_2)s^\alpha,\\
\theta_6 &= (g + \overline{D}_2)(h\mu^\alpha + q_2^\alpha h \overline{D}_1) - \beta^\alpha h \overline{D}_2,\\
\theta_7 &= -(g + \overline{D}_2)s^\alpha h.
\end{aligned}$$

We observe that

$$\begin{aligned}
&m_4 = \theta_1 k_5 (k_5^2 + k_7^2) < 0,\\
&m_0 = \theta_5 (k_4^2 + k_6^2) + \theta_7 = -(g + \overline{D}_2)s^\alpha (k_4^2 + k_6^2 + h) < 0.
\end{aligned}$$

We obtain following conditions on m_1, m_2, m_3 through the use of the Descartes rule so that Equation (19) may have nontrivial positive roots:

1. If $m_1 < 0, m_2 < 0, m_3 < 0$, then there is no change of sign, so no positive roots of Equation (19) exists.
2. If $m_1 > 0, m_2 < 0, m_3 < 0$, two or no positive roots of Equation (19) exist.
3. If $m_1 < 0, m_2 > 0, m_3 < 0$, two or no positive roots of Equation (19) exist.
4. If $m_1 > 0, m_2 > 0, m_3 < 0$, two or no positive roots of Equation (19) exist.
5. If $m_1 < 0, m_2 < 0, m_3 > 0$, two or no positive roots of Equation (19) exist.
6. If $m_1 < 0, m_2 > 0, m_3 > 0$, two or no positive roots of Equation (19) exist.
7. If $m_1 > 0, m_2 > 0, m_3 > 0$, two or no positive roots of Equation (19) exist.
8. If $m_1 > 0, m_2 < 0, m_3 > 0$, four or two or no positive roots of Equation (19) exist.

Hence, $\overline{I}$ is not trivially positive if any one of the above seven conditions (2-8) is satisfied. We note that $\overline{D}_1 > 0$ and $\overline{D}_2 > 0$ hold owing to the nonnegative dosage of drugs $u_1 > 0$ and $u_2 > 0$. Now, we must find the conditions so that $\overline{T} > 0$ and $\overline{F} > 0$ hold. According to Equation (18), we find that

$$\overline{F} > 0 \text{ if } k_1 + k_2\overline{T} > 0, \quad \text{ie,} \quad \overline{T} < -\frac{k_1}{k_2} = \frac{d^\alpha\gamma_1^\alpha - q_3^\alpha u_1}{\gamma_1^\alpha c_2^\alpha},$$

$$\overline{T} > 0 \text{ if } k_4 + k_5\overline{I} > 0, \quad \text{ie,} \quad \overline{I} < -\frac{k_4}{k_5} = \frac{k_3 p r^\alpha + k_1 c_1^\alpha}{\xi_1^\alpha}.$$

We summarize the conditions on existence of the equilibrium point $\overline{E} = (\overline{T}, \overline{I}, \overline{F}, \overline{D}_1, \overline{D}_2)$ in the following theorem.

Theorem 4. *The equilibrium point $\overline{E} = (\overline{T}, \overline{I}, \overline{F}, \overline{D_1}, \overline{D_2})$ of system (7) exists under the condition that*

$$\overline{T} < \frac{d^\alpha\gamma_1^\alpha - q_3^\alpha u_1}{\gamma_1^\alpha c_2^\alpha}, \qquad \overline{I} < \frac{k_3 p r^\alpha + k_1 c_1^\alpha}{\xi_1^\alpha}, \tag{20}$$

and any one of the seven conditions (2-8) above is satisfied; ie, at least one of m_1, m_2, m_3 is positive.

We proceed with investigation of the stability of the coexisting equilibrium point $\overline{E} = (\overline{T}, \overline{I}, \overline{F}, \overline{D_1}, \overline{D_2})$. We note that if the eigenvalues, namely, λ_i's, of the Jacobian matrix evaluated at $\overline{E}$ satisfy the condition

$$|\arg(\lambda_i)| > \frac{\alpha\pi}{2}, \quad (i = 1, 2, 3, 4, 5), \tag{21}$$

then the system is asymptotically stable at $\overline{E}$.[40,41] In detail, the Jacobian matrix of system (7) evaluated at $\overline{E} = (\overline{T}, \overline{I}, \overline{F}, \overline{D}_1, \overline{D}_2)$ is given by

$$J(\overline{E}) = \begin{pmatrix} \omega_1 & \omega_2 & \omega_3 & \omega_4 & 0 \\ \omega_5 & \omega_6 & \omega_7 & \omega_8 & \omega_9 \\ \omega_{10} & 0 & \omega_{11} & \omega_{12} & 0 \\ 0 & 0 & 0 & \omega_{13} & 0 \\ 0 & 0 & 0 & 0 & \omega_{14} \end{pmatrix},$$

where

$$\omega_1 = r^\alpha - 2r^\alpha p\overline{T} - \xi_1^\alpha\overline{I} + c_1^\alpha\overline{F} - q_1^\alpha\overline{D}_1, \quad \omega_2 = -\xi_1^\alpha\overline{T},$$

$$\omega_3 = c_1^\alpha\overline{T}, \quad \omega_4 = -q_1^\alpha\overline{T}, \quad \omega_5 = \frac{2\rho^\alpha\overline{T}\overline{I}(h + \overline{F}^2)}{(h + \overline{T}^2 + \overline{F}^2)^2} - \xi_2\overline{I},$$

$$\omega_6 = \frac{\rho^\alpha\overline{T}^2}{h + \overline{T}^2 + \overline{F}^2} + \frac{\beta^\alpha\overline{D}_2}{g + \overline{D}_2} - \xi_2^\alpha\overline{T} - \mu^\alpha - q_2^\alpha\overline{D}_1,$$

$$\omega_7 = -\frac{2\rho^\alpha\overline{T}^2\overline{I}\overline{F}}{(h + \overline{T}^2 + \overline{F}^2)^2}, \quad \omega_8 = -q_2^\alpha\overline{I}, \quad \omega_9 = \frac{\beta^\alpha g\overline{I}}{(g + \overline{D}_2)^2},$$

$$\omega_{10} = -c_2^\alpha\overline{F}, \quad \omega_{11} = d^\alpha - 2d^\alpha\epsilon\overline{F} - c_2^\alpha\overline{T} - q_3^\alpha\overline{D}_1,$$

$$\omega_{12} = -q_3^\alpha\overline{F}, \quad \omega_{13} = -\gamma_1^\alpha, \quad \omega_{14} = -\gamma_2^\alpha.$$

The eigenvalues of $J(\overline{E})$ are the roots of the following characteristic polynomial:

$$p(\lambda) = -(\lambda - \omega_{13})(\lambda - \omega_{14})\underbrace{(\lambda^3 + c_1\lambda^2 + c_2\lambda + c_3)}_{:=q(\lambda)}, \tag{22}$$

where

$$\begin{aligned} c_1 &= (\omega_1 + \omega_6 + \omega_{11}), \\ c_2 &= (-\omega_1\omega_6 + \omega_2\omega_5 - \omega_1\omega_{11} + \omega_3\omega_{10} - \omega_6\omega_{11}), \\ c_3 &= (\omega_1\omega_6\omega_{11} - \omega_2\omega_5\omega_{11} + \omega_2\omega_7\omega_{10} - \omega_3\omega_6\omega_{10}). \end{aligned} \tag{23}$$

We can directly deduce that two of the eigenvalues satisfy $\lambda_1 = \omega_{13} = -\gamma_1^\alpha < 0$ and $\lambda_2 = \omega_{14} = -\gamma_2^\alpha < 0$. Therefore, we proceed with the roots of the polynomial $q(\lambda)$. We note that the discriminant of $q(\lambda)$ is given by

$$D(q) = 18c_1c_2c_3 + (c_1c_2)^2 - 4c_3c_1^3 - 4c_2^3 - 27c_3^2.$$

Then, we list the following conditions for model (7) so that condition (21) holds according to the Routh-Hurwitz criteria.[41]

Corollary 1. *Assume that the conditions of Theorem 4 hold so that the coexisting equilibrium point exists. Then, the equilibrium point $\overline{E} = (\overline{T}, \overline{I}, \overline{F}, \overline{D_1}, \overline{D_2})$ is locally asymptotically stable if one of the following conditions holds for polynomial $q(\lambda)$, which is given as in Equation 22, and coefficients c_1, c_2, c_3, which are given as in Equation 23.*

(i) If $D(q) > 0$, then the necessary and sufficient condition for the equilibrium point $\overline{E}$ to be locally asymptotically stable is $c_1 > 0, c_3 > 0, c_1c_2 > c_3$.
(ii) If $D(q) < 0$, $c_1 \geq 0, c_2 \geq 0, c_3 > 0$, then $\overline{E}$ is locally asymptotically stable for $\alpha < 2/3$.
(iii) If $D(q) < 0$, $c_1 > 0, c_2 > 0, c_1c_2 = c_3$, then $\overline{E}$ is locally asymptotically stable.

4 | DISCRETIZATION TECHNIQUE

Let $0 = t_0 < t_1 < \cdots < t_N = t_f$ be a subdivision of $I = (0, t_f]$ with constant time step $\Delta t = T/N$. We denote the approximate value of $\varphi(t)$ at $t = t_j$ as φ_j.

We present the derivation of the discrete (left/right) Caputo fractional derivative.

4.1 | Discrete state equation

The L1 method for (left) Caputo fractional derivative has been presented in the paper of Lin and Xu.[42, Sec.3] We follow the same idea to obtain

$$\begin{aligned} {}_0^{\mathrm{C}}\mathbb{D}_t^\alpha \varphi(t)|_{t=t_k} &= \frac{1}{\Gamma(1-\alpha)} \sum_{j=1}^{k} \frac{\varphi_j - \varphi_{j-1}}{\Delta t} \int_{t_{j-1}}^{t_j} (t_k - s)^{-\alpha}\, ds \\ &= B_0 \sum_{j=1}^{k} (\varphi_j - \varphi_{j-1}) \left(\delta_{j,k}^{\mathrm{C}}\right), \end{aligned} \tag{24}$$

where $B_0 = \frac{-\Delta t^{-\alpha}}{\Gamma(2-\alpha)}$, $\delta_{j,k}^{\mathrm{C}} = ((k-j)^{1-\alpha} - (k-j+1)^{1-\alpha})$.

We apply scheme (24) to the state equation (7). Then, the nonlinear state equation is linearized by the Newton method for $1 \leq k \leq N$, and the solution is obtained by solving the following system iteratively:

$$\begin{pmatrix} \delta_{k,k}^{\mathrm{C}} B_0 - J_{11} & -J_{12} & -J_{13} & -J_{14} & 0 \\ -J_{21} & \delta_{k,k}^{\mathrm{C}} B_0 - J_{22} & -J_{23} & -J_{24} & -J_{25} \\ -J_{31} & 0 & \delta_{k,k}^{\mathrm{C}} B_0 - J_{33} & -J_{34} & 0 \\ 0 & 0 & 0 & \delta_{k,k}^{\mathrm{C}} B_0 - J_{44} & 0 \\ 0 & 0 & 0 & 0 & \delta_{k,k}^{\mathrm{C}} B_0 - J_{55} \end{pmatrix} \begin{pmatrix} \delta T \\ \delta I \\ \delta F \\ \delta D_1 \\ \delta D_2 \end{pmatrix} = \begin{pmatrix} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \end{pmatrix}, \tag{25}$$

where

$$\begin{cases} R_1 =_0^{\mathrm{C}} \mathbb{D}_t^{\alpha} T(t)|_{t=t_k} - (r^{\alpha} T_k(1-pT_k) - \xi_1^{\alpha} T_k I_k + c_1^{\alpha} T_k F_k - q_1^{\alpha}(D_1)_k T_k), \\ R_2 =_0^{\mathrm{C}} \mathbb{D}_t^{\alpha} I(t)|_{t=t_k} - (s^{\alpha} + \frac{\rho^{\alpha} T_k^2 I_k}{h+T_k^2+F_k^2} + \frac{\beta^{\alpha}(D_2)_k I_k}{g+(D_2)_k} - \xi_2^{\alpha} T_k I_k - \mu^{\alpha} I_k - q_2^{\alpha}(D_1)_k I_k), \\ R_3 =_0^{\mathrm{C}} \mathbb{D}_t^{\alpha} F(t)|_{t=t_k} - (d^{\alpha} F_k(1-\epsilon F_k) - c_2^{\alpha} F_k T_k - q_3^{\alpha}(D_1)_k F_k), \\ R_4 =_0^{\mathrm{C}} \mathbb{D}_t^{\alpha} D_1(t)|_{t=t_k} - ((u_1)_k - \gamma_1^{\alpha}(D_1)_k), \\ R_5 =_0^{\mathrm{C}} \mathbb{D}_t^{\alpha} D_2(t)|_{t=t_k} - ((u_2)_k - \gamma_2^{\alpha}(D_2)_k), \end{cases} \tag{26}$$

$$\begin{cases} J_{11} = r^{\alpha} - 2r^{\alpha} pT_k - \xi_1^{\alpha} I_k + c_1^{\alpha} F_k - q_1^{\alpha}(D_1)_k, \quad J_{12} = -\xi_1^{\alpha} T_k, \\ J_{13} = c_1^{\alpha} T_k, \quad J_{14} = -q_1^{\alpha} T_k, \quad J_{21} = \frac{2\rho^{\alpha} T_k I_k (h+F_k^2)}{(h+T_k^2+F_k^2)^2} - \xi_2 I_k, \\ J_{22} = \frac{\rho^{\alpha} T_k^2}{h+T_k^2+F_k^2} + \frac{\beta^{\alpha}(D_2)_k}{g+(D_2)_k} - \xi_2^{\alpha} T_k - \mu^{\alpha} - q_2^{\alpha}(D_1)_k, \\ J_{23} = -\frac{2\rho^{\alpha} T_k^2 I_k F_k}{(h+T_k^2+F_k^2)^2}, \quad J_{24} = -q_2^{\alpha} I_k, \quad J_{25} = \frac{\beta^{\alpha} g I_k}{(g+(D_2)_k)^2}, \\ J_{31} = -c_2^{\alpha} F_k, \quad J_{33} = d^{\alpha} - 2d^{\alpha}\epsilon F_k - c_2^{\alpha} T_k - q_3^{\alpha}(D_1)_k, \\ J_{34} = -q_3^{\alpha} F_k, \quad J_{44} = -\gamma_1^{\alpha}, \quad J_{55} = -\gamma_2^{\alpha}. \end{cases} \tag{27}$$

4.2 | Discrete adjoint equation

The discrete adjoint equation can be derived similarly as

$$\begin{aligned} {}_t^{\mathrm{C}}\mathbb{D}_{t_f}^{\alpha} \varphi(t)|_{t=t_k} &= -\frac{1}{\Gamma(1-\alpha)} \sum_{j=k+1}^{N-1} \frac{\varphi_j - \varphi_{j-1}}{\Delta t} \int_{t_{j-1}}^{t_j} (s-t_k)^{-\alpha}\, ds \\ &= C_0 \sum_{j=k+1}^{N-1} (\varphi_{j-1} - \varphi_j) \left(\zeta_{j,k}^{\mathrm{C}}\right), \end{aligned} \tag{28}$$

where $C_0 = -B_0$, $\zeta_{j,k}^{\mathrm{C}} = ((j-k)^{1-\alpha} - (j-k-1)^{1-\alpha})$.

The discrete scheme (28) is applied to the equation (8) to obtain the following system of equations for $N-2 \geq k \geq 0$:

$$\begin{pmatrix} \delta_{k,k+1}^{\mathrm{C}} C_0 - J_{11} & -J_{21} & -J_{31} & 0 & 0 \\ -J_{12} & \delta_{k,k+1}^{\mathrm{C}} C_0 - J_{22} & 0 & 0 & 0 \\ -J_{13} & -J_{23} & \delta_{k,k+1}^{\mathrm{C}} C_0 - J_{33} & 0 & 0 \\ -J_{14} & -J_{24} & -J_{34} & \delta_{k,k+1}^{\mathrm{C}} C_0 - J_{44} & 0 \\ 0 & -J_{25} & 0 & 0 & \delta_{k,k+1}^{\mathrm{C}} C_0 - J_{55} \end{pmatrix} \begin{pmatrix} (\lambda_1)_{k+1} \\ (\lambda_2)_{k+1} \\ (\lambda_3)_{k+1} \\ (\lambda_4)_{k+1} \\ (\lambda_5)_{k+1} \end{pmatrix}$$

$$= \begin{pmatrix} 1 + E_0 \sum_{j=k+2}^{N} (\lambda_1)_j \left(\delta_{k,j-1}^{\mathrm{C}} - \delta_{k,j}^{\mathrm{C}}\right) \\ E_0 \sum_{j=k+2}^{N} (\lambda_2)_j \left(\delta_{k,j-1}^{\mathrm{C}} - \delta_{k,j}^{\mathrm{C}}\right) \\ E_0 \sum_{j=k+2}^{N} (\lambda_3)_j \left(\delta_{k,j-1}^{\mathrm{C}} - \delta_{k,j}^{\mathrm{C}}\right) \\ E_0 \sum_{j=k+2}^{N} (\lambda_4)_j \left(\delta_{k,j-1}^{\mathrm{C}} - \delta_{k,j}^{\mathrm{C}}\right) \\ E_0 \sum_{j=k+2}^{N} (\lambda_5)_j \left(\delta_{k,j-1}^{\mathrm{C}} - \delta_{k,j}^{\mathrm{C}}\right) \end{pmatrix}. \tag{29}$$

TABLE 1 Values of the parameters

Parameter	Description	Unit	Value
r	Per capita growth rate of tumor cells	d^{-1}	0.004 31 (Sharma and Samanta[18])
p	Reciprocal carrying capacity of tumor cells	$cells^{-1}$	1.02×10^{-9} (Sharma and Samanta[18])
ξ_1	Competition term of tumor cells with immune cells	$d^{-1}\ cells^{-1}$	6.41×10^{-11} (Sharma and Samanta[18])
ξ_2	Competition term of immune cells with tumor cells	$d^{-1}\ cells^{-1}$	3.42×10^{-6} (Sharma and Samanta[18])
c_1	Competition term of fat cells with tumor cells	$d^{-1}\ cells^{-1}$	ξ_1 (estimated)
c_2	Competition term of fat cells with tumor cells	$d^{-1}\ cells^{-1}$	ξ_2 (estimated)
q_1	Response of tumor cells to chemotherapeutic drug	d^{-1}	0.08 (Sharma and Samanta[18])
q_2	Response of immune cells to immunotherapeutic drug	d^{-1}	2×10^{-11} (Sharma and Samanta[18])
q_3	Response of fat cells to immunotherapeutic drug	d^{-1}	q_2 (estimated)
s	Immune source rate	d^{-1} cells	0.33 (Sharma and Samanta[18])
ρ	Recruitment rate of immune cells by tumor cells	d^{-1}	0.0125 (Sharma and Samanta[18])
h	Immune response stimulated by tumor cells	$cells^2$	20 200 000 (Sharma and Samanta[18])
μ	Per capita death rate of immune cells	d^{-1}	0.204 (Sharma and Samanta[18])
β	Recruitment rate of immune cells by D_2	d^{-1}	0.125 (Sharma and Samanta[18])
g	Steepness coefficient of the β	None	20 000 000 (Sharma and Samanta[18])
d	Per capita growth rate of fat cells	d^{-1}	$r/2$ (estimated)
ϵ	Reciprocal carrying capacity of fat cells	$cells^{-1}$	$p/2$ (estimated)
γ_1	Decay rate of D_1	d^{-1}	0.1 (Sharma and Samanta[18])
γ_2	Decay rate of D_2	d^{-1}	1 (Sharma and Samanta[18])

5 | NUMERICAL RESULTS

In this section, we present some numerical results to compare three different treatment strategies: chemotherapy, immunotherapy, and their combination. In addition, we investigate the effect of the order of differentiation α and the value of the decay rate of amount of chemotherapeutic drug γ_1 to the value of the cost functional J_{γ_1}. For this purpose, we solve the FOCP for $\alpha \in \{0.65, 0.75, 0.85, 0.95\}$ and $\gamma_1 \in \{0.1, 0.5, 0.9\}$. We set the values of the parameters as in Table 1, otherwise stated.

We fix the initial conditions as $T_0 = 2$, $I_0 = 0.1$, $F_0 = 1$, $D_{10} = 0.5$, and $D_{20} = 0.5$, and the initial doses are taken as $u_1 = 0.5$ and $u_2 = 0.5$. The final time of the treatment is set as 120 days with a constant time step size $\Delta t = 0.025$. We implement the so-called forward-backward sweep method under MATLAB to solve the OCP (Equations (6) and (7)).[43 Chap. 5] The algorithm can be summarized as follows:

Algorithm 1 Forward-backward sweep method

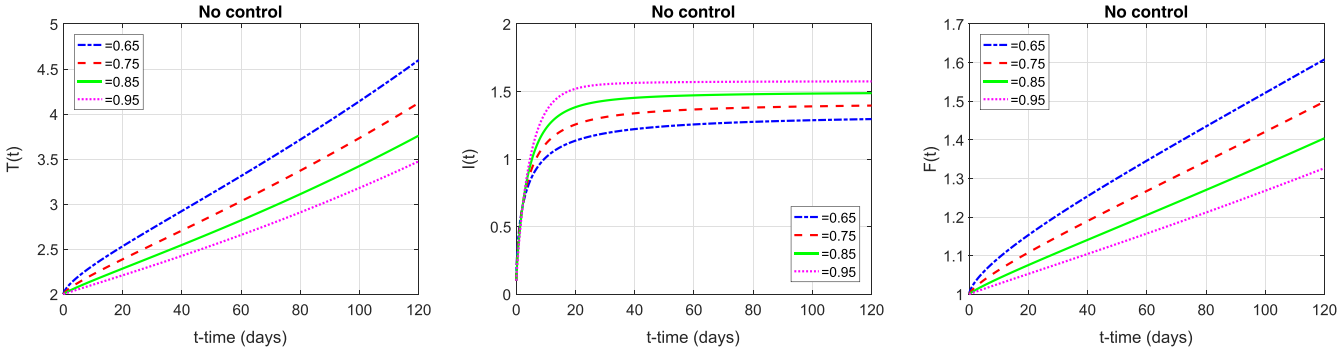
1: Fix $\psi = -1$, $\delta = 0.001$.
2: Initiate the control $(u_{old})_1$, $(u_{old})_2$, the state $x_{old} = \{T_{old}, I_{old}, F_{old}, (D_{old})_1, (D_{old})_2\}$ and adjoint $p_{old} = \{(\lambda_{old})_1, (\lambda_{old})_2, (\lambda_{old})_3, (\lambda_{old})_4, (\lambda_{old})_5\}$.
3: **while** $\psi < 0$ **do**
4: Solve the state Equation 7 for $x = \{T, I, F, D_1, D_2\}$ using $T_0, I_0, F_0, D_{10}, D_{20}, (u_{old})_1, (u_{old})_2$ forward in time.
5: Solve the adjoint Equation 8 for $p = \{\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5\}$ using $\lambda_i(t_f) = 0, x = \{T, I, F, D_1, D_2\}$ backward in time.
6: Update the control using the gradient Equation 10 to reach u_1, u_2.
7: Compute $\chi_i = \delta\|x_i\| - \|x_i - (x_{old})_i\|$, $\upsilon_j = \delta\|u_j\| - \|u_j - (u_{old})_j\|$, $\rho_i = \delta\|p_i\| - \|p_i - (p_{old})_i\|$ and calculate $\psi = \min\{\chi_i, \upsilon_j, \rho_i\}$ for $i, j \in \{1, 2, 3, 4, 5\}, k \in \{1, 2\}$.
8: **end while**

Before investigating the optimal treatment strategy, we solve the uncontrolled cancer-obesity model for different values of the order of differentiation α to observe whether an appropriate treatment strategy is needed to cure the disease or if the body can heal itself or not. In Figure 1, we present the number of tumor cells, immune cells, and fat cells obtained by taking $u_1 = 0$ and $u_2 = 0$ in FDE (7). We observe that the populations of tumor and fat cells are increasing over time

for different values of α, while the number of immune cells approaches to a fixed value. According to these results, an optimal treatment strategy is required to eliminate tumor burden as time passes. Now, we proceed with the comparison of aforementioned treatment strategies.

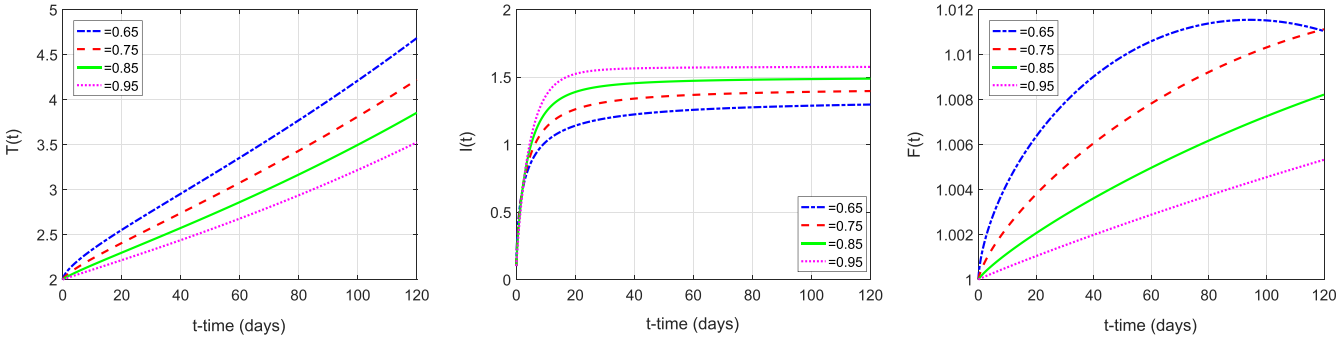
5.1 | Immunotherapeutic treatment

Firstly, we will examine the contribution of immunotherapy to cure the disease by taking $u_1 = 0$. In Figure 2, the number of tumor cells, immune cells, and fat cells is depicted. We can deduce from the figures that immunotherapeutic treatment has no positive effect on tumor burden, since the tumor cell population cannot be eliminated or decreased in size.



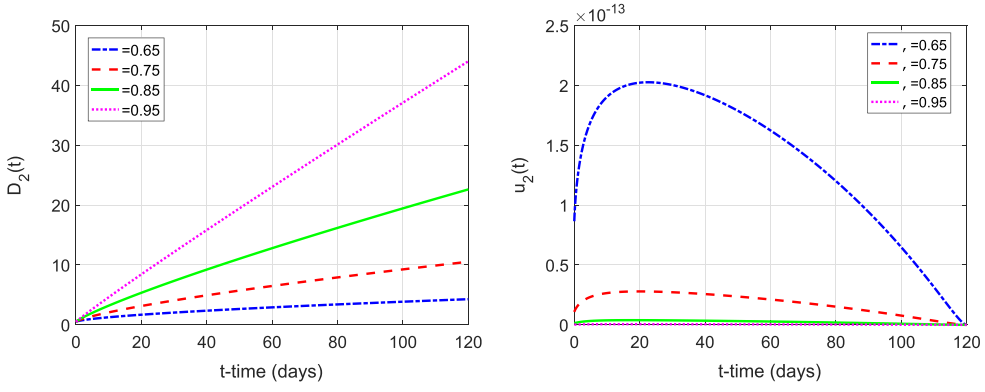
(A) Tumor cells $T(t)$. (B) Immune cells $I(t)$. (C) Fat cells $F(t)$.

FIGURE 1 Number of cells for uncontrolled case [Colour figure can be viewed at wileyonlinelibrary.com]



(A) Tumor cells $T(t)$. (B) Immune cells $I(t)$. (C) Fat cells $F(t)$.

FIGURE 2 Number of cells for immunotherapy [Colour figure can be viewed at wileyonlinelibrary.com]



(A) Drug $D_2(t)$. (B) Control $u_2(t)$.

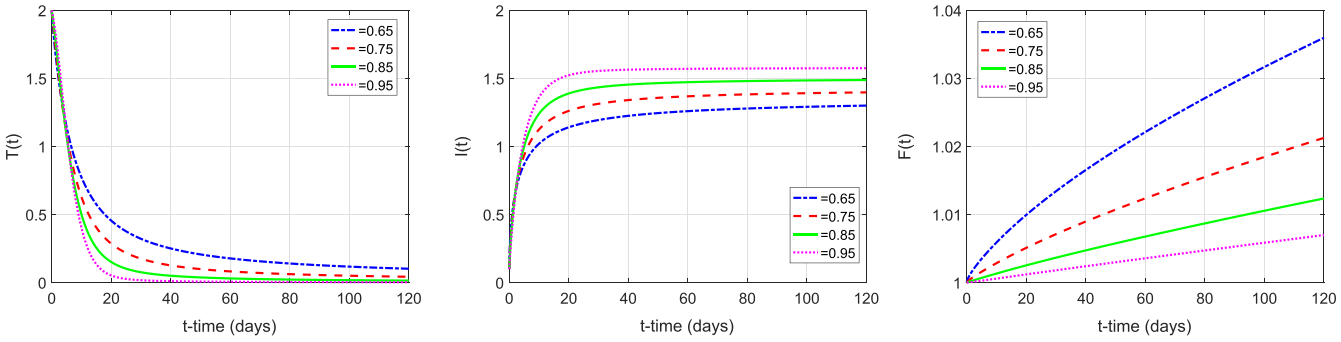
FIGURE 3 Concentration and dose of immunotherapeutic drug [Colour figure can be viewed at wileyonlinelibrary.com]

In Figure 3, we depict the immunotherapeutic drug concentration $D_2(t)$ and drug dose $u_2(t)$. We notice that immunotherapy has no contribution on tumor population, although drug concentration is increased over time. In addition, the drug dose is quite small, which is not enough to minimize the tumor population. Therefore, we should apply another treatment strategy to cure the disease.

5.2 | Chemotherapeutic treatment

We proceed with chemotherapeutic treatment by taking $u_2 = 0$. In Figure 4, populations of tumor, immune, and fat cells are presented. We immediately see that tumor population is successfully minimized over time despite increasing number of fat cells in the system, while the population of immune cells is not destroyed over time.

We investigate the effect of the order α and the decay rate γ_1 to the value of the cost functional J_{γ_1}, and we record the values in Table 2. Firstly, we notice that the value of J_{γ_1} decreases as we increase α. It indicates a reverse relation between the order α and the cost functional J. On the contrary, a smaller value of J_{γ_1} is measured for smaller values of the decay rate γ_1, since more drug is contained in the system. A FOCP with a smaller value of α can be regarded as a model containing information about history. Therefore, the system with a small value of α is more vulnerable to environmental changes, because less information is inserted into the model about the past stages of the current phenomenon.

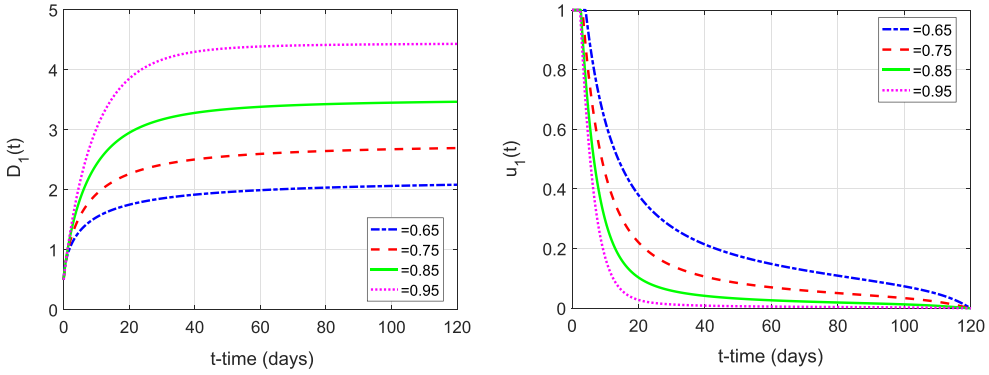


(A) Tumor cells $T(t)$. (B) Immune cells $I(t)$. (C) Fat cells $F(t)$.

FIGURE 4 Number of cells for chemotherapy [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Values of the cost functional J_{γ_1} for chemotherapy

α	$J_{\gamma_1=0.1}$	$J_{\gamma_1=0.5}$	$J_{\gamma_1=0.9}$
0.65	109.8614	176.6794	220.6039
0.75	93.3870	147.8597	191.8046
0.85	83.7488	125.4692	167.0782
0.95	78.6649	109.5484	147.4113



(A) Drug $D_1(t)$. (B) Control $u_1(t)$.

FIGURE 5 Concentration and dose of chemotherapeutic drug [Colour figure can be viewed at wileyonlinelibrary.com]

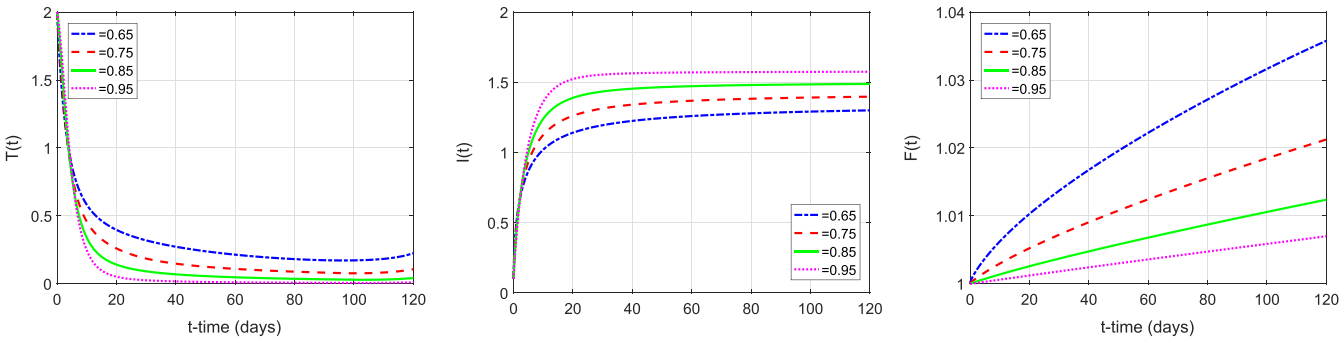
In Figure 5, we present the chemotherapeutic drug concentration $D_1(t)$ and drug dose $u_1(t)$. We observe that the reverse relation between the order α and the value of J_{γ_1} is revealed, since drug concentration gets higher as α increases. Thus, more tumor cells are destroyed owing to higher drug concentration. On the other hand, the drug dose decreases as time passes, which means that the functional J_{γ_1} has been minimized successfully over time.

5.3 | Combination of chemotherapeutic and immunotherapeutic treatment

We proceed with the combination of chemotherapeutic and immunotherapeutic treatments with $u_1 \neq 0$ and $u_2 \neq 0$. In Figure 6, the number of tumor cells, immune cells, and fat cells is depicted. We observe that the tumor population is decreased, while the population of fat cells is increasing slowly over time. In addition, the number of immune cells approaches a fixed value. There is not a visible difference between chemotherapeutic treatment and combined therapy. Therefore, we will record some values of J_{γ_1} to assess the contribution of combined therapy over usual chemotherapy.

In Table 3, we present the values of J_{γ_1} for different values of α and γ_1. As we increase γ_1, J_{γ_1} decreases, while the fractional order has a reverse effect on the cost functional. If we compare Table 3 with Table 2, then we deduce that combined therapy gives much better results than chemotherapy does. In other words, smaller values of the cost functional are reached. On account of a stronger immune system, immune cells fight with tumor cells much better and tumor population shrinks in size. We think that a system including memory effect, which corresponds to the use of fractional-order derivatives in the underlying model, can be regarded as a model associated with a population, which can correctly adjust itself to environmental changes and which can rebound itself on account of previous experiences.

In Figure 7, we present the drug concentrations and doses for chemotherapeutic and immunotherapeutic treatments. As time passes, drug concentrations $D_1(t)$ and $D_2(t)$ decrease. Otherwise, it might be harmful for healthy and immune cells. Doses $u_1(t)$ and $u_2(t)$ lie within the admissible set U_{ad}, and they decrease over time. Although the control u_2 seems too small, immunotherapeutic treatment leads J_{γ_1} to decrease more than 50% than single chemotherapy does.

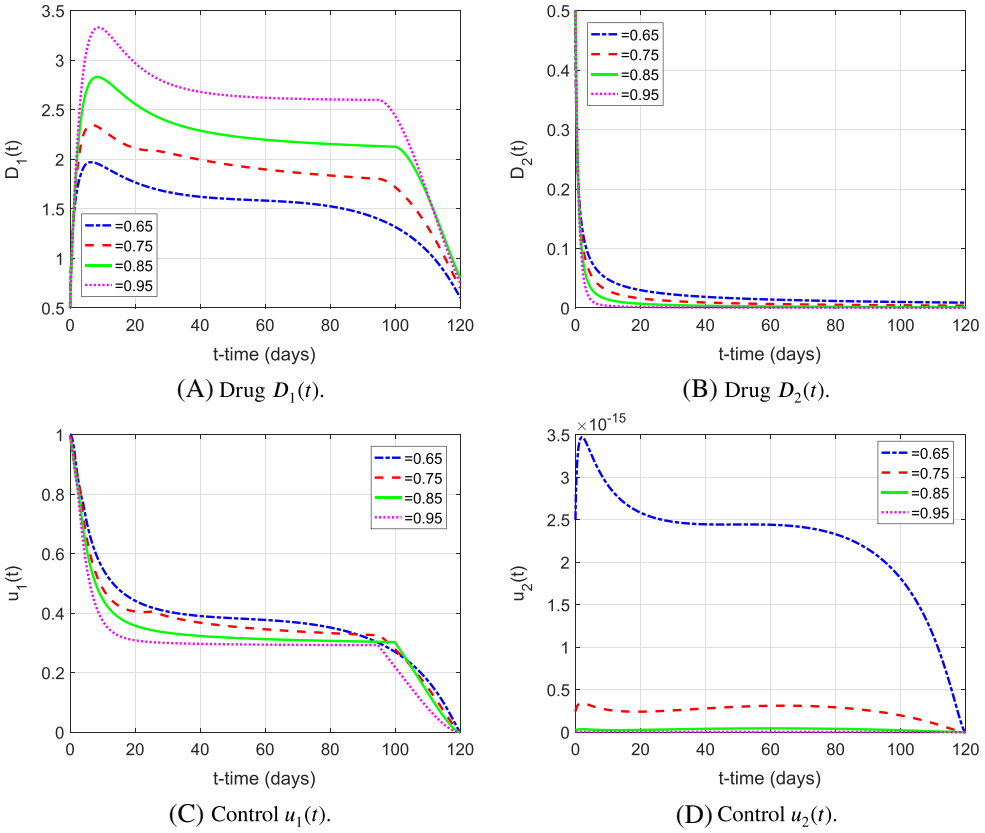


(A) Tumor cells $T(t)$. (B) Immune cells $I(t)$. (C) Fat cells $F(t)$.

FIGURE 6 Number of cells for combination of chemotherapy and immunotherapy [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Values of the cost functional J_{γ_1} for combination of chemotherapy and immunotherapy

α	$J_{\gamma_1=0.1}$	$J_{\gamma_1=0.5}$	$J_{\gamma_1=0.9}$
0.65	56.9001	100.2467	125.6317
0.75	42.2034	79.9290	105.4514
0.85	31.6144	61.8146	86.5216
0.95	24.4067	45.1141	68.4444



(A) Drug $D_1(t)$. (B) Drug $D_2(t)$.

(C) Control $u_1(t)$. (D) Control $u_2(t)$.

FIGURE 7 Concentration of drug and control [Colour figure can be viewed at wileyonlinelibrary.com]

6 | SUMMARY AND CONCLUSION

In this study, we investigate the optimal treatment strategy for a cancer-obesity model. Interaction between tumor cells, immune cells, fat cells, and chemotherapeutic and immunotherapeutic drug concentrations are modeled with the Caputo time fractional derivative. The aim is to find a pair of controls, which correspond to drug doses, to minimize the number of tumor cells over a finite time period with the optimal drug dose injected to the system. We compare immunotherapy, chemotherapy, and their combination to treat the tumor. We find out that mixed immune-chemotherapy gives the smallest values of the cost functional J. Moreover, we notice that the values of J decrease as we increase the order of differentiation α. We think that a system including memory effect, which corresponds to the use of fractional-order derivatives in the underlying model, can be regarded as a model associated with a population, which can correctly adjust itself to environmental changes and which can rebound itself on account of previous experiences. As a future work, we will investigate the optimal treatment strategy through the use of a fractional derivative with nonsingular kernel.

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ORCID

Tuğba Akman Yıldız http://orcid.org/0000-0003-1206-2287

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