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Optimal control for cancer treatment mathematical model using Atangana–Baleanu–Caputo fractional derivative

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Abstract

In this work, optimal control for a fractional-order nonlinear mathematical model of cancer treatment is presented. The suggested model is determined by a system of eighteen fractional differential equations. The fractional derivative is defined in the Atangana–Baleanu Caputo sense. Necessary conditions for the control problem are derived. Two control variables are suggested to minimize the number of cancer cells. Two numerical methods are used for simulating the proposed optimal system. The methods are the iterative optimal control method and the nonstandard two-step Lagrange interpolation method. In order to validate the theoretical results, numerical simulations and comparative studies are given.

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1 Introduction

It is well known that one of the most dangerous diseases all over the world is cancer ([1–4]). Modeling and simulations are important tools to discover tumor cells ([5–7]). Well-known treatment modalities are surgery, radiotherapy and chemotherapy. Sadly, every of those varieties of treatment has its own disadvantages, for more details see [5–20]. However, progress within the fight against cancer continues to be made with novel modes; for more details see [12–19].

In [21] an interesting mathematical model for cancer treatment is presented. This model is governed by a system of eighteen differential equations. The first aim of this paper is to develop this model in order to control the cancer cells. In [22], optimal control of a fractional-order delay model for cancer treatment is presented. Here the fractional-order derivative is defined in the Caputo sense.

Applications of fractional calculus have increased in the last few decades, after centuries of small advancements. Examples can be found in a variety of scientific areas: engineer-

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ing, biology, epidemiology, amongst others ([23–37]). In most cases, the fractional-order differential equations (FODEs) models seem more consistent with the real phenomena than the integer order models. This is due to the fact that fractional derivatives and integrals enable the description of the memory and hereditary properties inherent in various materials and processes that exist in most biological systems.

In [14–16, 38], some fractional optimal control problems (FOCPs) have been introduced. Sweilam and AL-Mekhlafi, studied optimal control of some biology models in [22, 30, 39–42]. In [2], Torres et al. introduced and analyzed a multiobjective formulation of an optimal control problem, where the two conflicting objectives are minimization of the number of HIV-infected individuals with AIDS clinical symptoms and co-infected with AIDS and active TB and costs related to prevention and treatment of HIV and/or TB measures. More recently, in the Atangana–Baleanu Caputo sense (ABC) one defined a modified Caputo fractional derivative by introducing a generalized Mittag-Leffler function as the nonlocal and non-singular kernel ([43]). These new types of derivatives have been used in modeling of real life applications in different fields ([44, 45]). In [46–49] necessary optimality conditions for FOCPs are obtained in the Riemann–Liouville sense and numerically studied by a finite difference method. In [50], the spectral method is developed for a distributed-order fractional optimal control problem. In [51] Baleanu et al., used a central difference scheme for solving FOCPs.

In this paper, we introduced the fractional mathematical model without singular kernel for a cancer treatment model with modified parameters ([52]). Minimizing of tumor cells of FOCPs for the proposed model is the aim of this article. Two numerical techniques are introduced to study the nonlinear FOCPs. The techniques are: the iterative optimal control method (IOCM) ([22, 30, 42]) and the nonstandard two-step Lagrange interpolation method (N2LIM), which is presented here as an adaptation for the two-step Lagrange interpolation method. Numerical simulations are given. To the best of our knowledge the fractional optimal control without singular kernel for cancer treatment based on synergy between anti-angiogenic model was never explored before.

This paper organized as follows: The fractional-order model with two controls is given in Sect. 2. In Sect. 3, the optimality conditions are derived. In Sect. 4, numerical methods for FOCPs are presented. In Sect. 5, numerical experiments and simulations are presented. Finally the conclusions are given in Sect. 6.

2 The model problem

In the following, the cancer treatment fractional model based on synergy between immune cell therapies and an anti-angiogenic method with modified parameters is presented. It is important to notice that all the parameters here depend on the fractional order α as an extension of the model of integer order which is given in [21]. The model consists of eighteen variables dependent on the time. Two control variables $u_M(t)$, $u_A(t)$ are given for measuring the immunotherapy and the anti-angiogenic therapy, respectively. The variables can be identified as follows:

- $T(t)$: Number of cancer cells.
- $U(t)$: Number of mature unlicensed dendritic cells.
- $D(t)$: Number of mature licensed dendritic cells.
- $A_E(t)$: Number of activating/proliferating effector memory $CD8^+T$ cells.
- $E(t)$: Number of activated effector memory $CD8^+T$ cells.

- $A_H(t)$: Number of activating/proliferating memory helper $CD4^+$ T cells.
- H : Number of activated memory helper $CD4^+$ T cells.
- $A_R(t)$: Number of activating/proliferating regulatory T cells.
- $R(t)$: T cells number of activated regulatory.
- $Y(t)$: Endothelial cells number.
- $C(t)$: Concentration of $IL - 2$.
- $S(t)$: Concentration of $TGF - \beta$.
- $I(t)$: Concentration of $IL - 10$.
- $A_1(t)$: Concentration of angiopoietin-1.
- $A_2(t)$: Concentration of angiopoietin-2.
- $V(t)$: Concentration of free $VEGF$.
- $V_a(t)$: Concentration of anti- $VEGF$.
- $B(t)$: Length of tumor vasculature.

The parameters of the model are described in [21, 53, 54]. The new system can be described by fractional-order differential equations as follows:

$${}^{ABC}D_t^\alpha T = \gamma_1^\alpha T \left(1 - \frac{T}{B^\alpha \lambda_B^\alpha} \right) - \left(\frac{r_0^\alpha T}{(1 + k_2^\alpha \frac{T}{E})(1 + k_3^\alpha \frac{R}{E})(1 + \frac{S}{s_1^\alpha})(1 + \frac{V}{v_1^\alpha})} \right), \tag{1}$$

$${}^{ABC}D_t^\alpha U = \frac{\alpha^\alpha T}{(1 + \frac{V}{v_3^\alpha})(1 + \frac{I}{I_1^\alpha})(1 + \frac{R}{R_1^\alpha})} - \frac{\lambda^\alpha U}{1 + \frac{U}{M_H^\alpha}} - \delta_u^\alpha U, \tag{2}$$

$${}^{ABC}D_t^\alpha D = \frac{\lambda^\alpha U}{1 + \frac{U}{M_H^\alpha}} - \delta_D^\alpha D, \tag{3}$$

$${}^{ABC}D_t^\alpha A_E = \frac{\alpha_1 M_E^\alpha}{1 + k_4^\alpha \frac{M}{D}} - \delta_A^\alpha A_E, \tag{4}$$

$${}^{ABC}D_t^\alpha E = \frac{\alpha_2 A_E C}{(1 + \frac{V}{v_1^\alpha})(1 + \frac{S}{s_2^\alpha})(c_1^\alpha + C)} - \delta_E^\alpha E + \omega_1^\alpha u_M, \tag{5}$$

$${}^{ABC}D_t^\alpha A_H = \frac{\alpha_3 M_H^\alpha}{1 + k_4^\alpha \frac{M}{(U+D)}} - \delta_A^\alpha A_H, \tag{6}$$

$${}^{ABC}D_t^\alpha H = \frac{\alpha_4 A_H C}{(1 + \frac{V}{v_1^\alpha})(1 + \frac{S}{s_2^\alpha})(c_1^\alpha + C)} - \frac{\alpha_7 HS}{s_3^\alpha + S} - \delta_H^\alpha H, \tag{7}$$

$${}^{ABC}D_t^\alpha A_R = \frac{\alpha_5 M_R^\alpha}{1 + k_4^\alpha \frac{M}{D}} - \delta_A^\alpha A_R, \tag{8}$$

$${}^{ABC}D_t^\alpha R = \frac{\alpha_6 A_R C}{c_1^\alpha + C} + \frac{\alpha_7 HS}{s_3^\alpha + S} - \delta_R^\alpha R, \tag{9}$$

$${}^{ABC}D_t^\alpha C = \frac{p_c^\alpha A_H}{(1 + \frac{S}{s_4^\alpha})(1 + \frac{I}{I_1^\alpha})} - \frac{C}{\tau^\alpha}, \tag{10}$$

$${}^{ABC}D_t^\alpha S = p_1^\alpha R + p_2^\alpha T - \frac{S}{\tau_s^\alpha}, \tag{11}$$

$${}^{ABC}D_t^\alpha I = p_3^\alpha R + p_4^\alpha T - \frac{I}{\tau_I^\alpha}, \tag{12}$$

$${}^{ABC}D_t^\alpha A_1 = \alpha_{A_1}^\alpha B - \delta_{A_1}^\alpha A_1, \tag{13}$$

$${}^{\text{ABC}}D_t^\alpha A_2 = \alpha_{A_1}^\alpha B \left(\frac{T}{\theta_{A_2}^\alpha + T} \right) - \delta_{A_2}^\alpha A_2, \tag{14}$$

$${}^{\text{ABC}}D_t^\alpha V = \alpha_v^\alpha T + \alpha_{v_2}^\alpha T \left(\frac{T}{\theta_v^\alpha B + T} \right) - \delta_v^\alpha V - \tau^\alpha V_a V, \tag{15}$$

$$\begin{aligned} {}^{\text{ABC}}D_t^\alpha Y &= \alpha_y^\alpha Y \left(\frac{V}{\theta_y^\alpha Y + V} \right) - \omega^\alpha Y \left(\frac{A_1}{\theta_B^\alpha A_2 + A_1} \right) \left(\frac{V}{\rho^\alpha Y + V} \right) \\ &\quad - \delta_y^\alpha Y \left(1 + \frac{V}{\theta_y^\alpha Y + V} \right) + \omega_2^\alpha u_A, \end{aligned} \tag{16}$$

$$\begin{aligned} {}^{\text{ABC}}D_t^\alpha B &= \frac{1}{s^\alpha} \omega^\alpha Y \left(\frac{A_1}{\theta_B^\alpha A_2 + A_1} \right) \left(\frac{V}{\rho^\alpha Y + V} \right) \\ &\quad - \gamma_B^\alpha B \left(\frac{A_2^4}{(\theta_{EC}^\alpha A_1)^4 + A_2^4} \right) \left(1 - \frac{V}{\rho^\alpha Y + V} \right), \end{aligned} \tag{17}$$

$${}^{\text{ABC}}D_t^\alpha V_a = -\tau^\alpha V_a V - \rho_{v_a}^\alpha V_a. \tag{18}$$

The parameters ω_1^α and ω_2^α are the weight factors.

3 The FOCs

Consider the state system (1)–(18), in R^{18} , let

$$\Omega = \{ (u_A(\cdot), u_M(\cdot)) \text{ are Lebesgue measurable, } 0 \leq u_A(\cdot), u_M(\cdot) \leq 1, \forall t \in [0, T_f] \},$$

be the admissible control set. The objective functional is defined as follows:

$$J(u_A, u_M) = \int_0^{T_f} (AT(t) + B_1 u_A^2(t) + C u_M^2(t)) dt, \tag{19}$$

where the weight constant of cancer cell numbers is A . Moreover, B_1 , is the weight constant of immunotherapy and C is the weight constant of anti-angiogenic therapy.

Now, the aim is to minimize the following objective functional:

$$\begin{aligned} J(u_A, u_M) &= \int_0^{T_f} \eta(T, U, D, A_E, E, A_H, H, A_R, R, C, S, I, A_1, A_2, V, \\ &\quad Y, B, V_a, u_A, u_M, t) dt, \end{aligned} \tag{20}$$

subject to the constraints

$$\begin{aligned} {}^{\text{ABC}}D_t^\alpha T &= \xi_1, & {}^{\text{ABC}}D_t^\alpha U &= \xi_2, & {}^{\text{ABC}}D_t^\alpha D &= \xi_3, \\ {}^{\text{ABC}}D_t^\alpha A_E &= \xi_4, & {}^{\text{ABC}}D_t^\alpha E &= \xi_5, & {}^{\text{ABC}}D_t^\alpha A_H &= \xi_6, \\ {}^{\text{ABC}}D_t^\alpha H &= \xi_7, & {}^{\text{ABC}}D_t^\alpha A_R &= \xi_8, & {}^{\text{ABC}}D_t^\alpha R &= \xi_9, \\ {}^{\text{ABC}}D_t^\alpha C &= \xi_{10}, & {}^{\text{ABC}}D_t^\alpha S &= \xi_{11}, & {}^{\text{ABC}}D_t^\alpha I &= \xi_{12}, \\ {}^{\text{ABC}}D_t^\alpha A_1 &= \xi_{13}, & {}^{\text{ABC}}D_t^\alpha A_2 &= \xi_{14}, & {}^{\text{ABC}}D_t^\alpha V &= \xi_{15}, \\ {}^{\text{ABC}}D_t^\alpha Y &= \xi_{16}, & {}^{\text{ABC}}D_t^\alpha B &= \xi_{17}, & {}^{\text{ABC}}D_t^\alpha V_a &= \xi_{18}, \end{aligned}$$

where

$$\xi_i = \xi(T, U, D, A_E, E, A_H, H, A_R, R, C, S, I, A_1, A_2, V, Y, B, V_a, u_A, u_M, t), \quad i = 1, \dots, 18,$$

with the following initial conditions:

$$\begin{aligned} T(0) &= T_0, & U(0) &= u_0, & D(0) &= d_0, & A_E(0) &= a_{E_0}, & E(0) &= e_0, \\ A_H(0) &= a_{h_0}, & H(0) &= h_0, & A_R(0) &= a_{R_0}, & C(0) &= c_0, & S(0) &= s_0, \\ I(0) &= i_0, & A_1(0) &= a_{1_0}, & A_2(0) &= a_{2_0}, & V(0) &= v_0, & Y(0) &= y_0, \\ B(0) &= b_0, & V_a(0) &= v_{a_0}. \end{aligned}$$

The modified objective functional is defined as follows ([30]):

$$\begin{aligned} \tilde{J} &= \int_0^{T_f} [H_a(T, U, D, A_E, E, A_H, H, A_R, R, C, S, I, A_1, A_2, V, Y, B, V_a, u_A, u_M, t) \\ &\quad - \sum_{i=1}^{18} \lambda_i \xi_i(T, U, D, A_E, E, A_H, H, A_R, R, C, S, I, A_1, A_2, V, Y, B, V_a, u_A, u_M, t)] dt, \end{aligned} \tag{21}$$

where the Hamiltonian is given as follows:

$$\begin{aligned} H_a(T, U, D, A_E, E, A_H, H, A_R, R, C, S, I, A_1, A_2, V, Y, B, V_a, u_A, u_M, \lambda_i, t) \\ = \eta(T, U, D, A_E, E, A_H, H, A_R, R, C, S, I, A_1, A_2, V, Y, B, V_a, u_A, u_M, t) \\ + \sum_{i=1}^{18} \lambda_i \xi_i(T, U, D, A_E, E, A_H, H, A_R, R, C, S, I, A_1, A_2, V, Y, B, V_a, u_A, u_M, t). \end{aligned} \tag{22}$$

From (21) and (22) the necessary conditions for FOPCs ([46–49]) are

$$\begin{aligned} {}_t^{ABC} D_{t_f}^\alpha \lambda_1 &= \frac{\partial H_a}{\partial T}, & {}_t^c D_{t_f}^\alpha \lambda_2 &= \frac{\partial H_a}{\partial U}, \\ {}_t^{ABC} D_{t_f}^\alpha \lambda_3 &= \frac{\partial H_a}{\partial D}, & {}_t^c D_{t_f}^\alpha \lambda_4 &= \frac{\partial H_a}{\partial A_E}, \\ {}_t^{ABC} D_{t_f}^\alpha \lambda_5 &= \frac{\partial H_a}{\partial E}, & {}_t^c D_{t_f}^\alpha \lambda_6 &= \frac{\partial H_a}{\partial A_H}, \\ {}_t^{ABC} D_{t_f}^\alpha \lambda_7 &= \frac{\partial H_a}{\partial H}, & {}_t^c D_{t_f}^\alpha \lambda_8 &= \frac{\partial H_a}{\partial A_R}, \\ {}_t^{ABC} D_{t_f}^\alpha \lambda_9 &= \frac{\partial H_a}{\partial R}, & {}_t^c D_{t_f}^\alpha \lambda_{10} &= \frac{\partial H_a}{\partial C}, \\ {}_t^{ABC} D_{t_f}^\alpha \lambda_{11} &= \frac{\partial H_a}{\partial S}, & {}_t^c D_{t_f}^\alpha \lambda_{12} &= \frac{\partial H_a}{\partial I}, \\ {}_t^{ABC} D_{t_f}^\alpha \lambda_{13} &= \frac{\partial H_a}{\partial A_1}, & {}_t^c D_{t_f}^\alpha \lambda_{14} &= \frac{\partial H_a}{\partial A_2}, \\ {}_t^{ABC} D_{t_f}^\alpha \lambda_{15} &= \frac{\partial H_a}{\partial V}, & {}_t^c D_{t_f}^\alpha \lambda_{16} &= \frac{\partial H_a}{\partial Y}, \\ {}_t^{ABC} D_{t_f}^\alpha \lambda_{17} &= \frac{\partial H_a}{\partial B}, & {}_t^c D_{t_f}^\alpha \lambda_{18} &= \frac{\partial H_a}{\partial V_a}, \end{aligned} \tag{23}$$

$$0 = \frac{\partial H}{\partial u_k}, \tag{24}$$

$$\begin{aligned} {}_0^{ABC}D_t^\alpha T &= \frac{\partial H_a}{\partial \lambda_1}, & {}_0^{ABC}D_t^\alpha U &= \frac{\partial H_a}{\partial \lambda_2}, \\ {}_0^{ABC}D_t^\alpha D &= \frac{\partial H_a}{\partial \lambda_3}, & {}_0^{ABC}D_t^\alpha A_E &= \frac{\partial H_a}{\partial \lambda_4}, \\ {}_0^{ABC}D_t^\alpha E &= \frac{\partial H_a}{\partial \lambda_5}, & {}_0^{ABC}D_t^\alpha A_H &= \frac{\partial H_a}{\partial \lambda_6}, \\ {}_0^{ABC}D_t^\alpha H &= \frac{\partial H_a}{\partial \lambda_7}, & {}_0^{ABC}D_t^\alpha A_R &= \frac{\partial H_a}{\partial \lambda_8}, \\ {}_0^{ABC}D_t^\alpha R &= \frac{\partial H_a}{\partial \lambda_9}, & {}_0^{ABC}D_t^\alpha C &= \frac{\partial H_a}{\partial \lambda_{10}}, \\ {}_0^{ABC}D_t^\alpha S &= \frac{\partial H_a}{\partial \lambda_{11}}, & {}_0^{ABC}D_t^\alpha I &= \frac{\partial H_a}{\partial \lambda_{12}}, \\ {}_0^{ABC}D_t^\alpha A_1 &= \frac{\partial H_a}{\partial \lambda_{13}}, & {}_0^{ABC}D_t^\alpha A_2 &= \frac{\partial H_a}{\partial \lambda_{14}}, \\ {}_0^{ABC}D_t^\alpha V &= \frac{\partial H_a}{\partial \lambda_{15}}, & {}_0^{ABC}D_t^\alpha Y &= \frac{\partial H_a}{\partial \lambda_{16}}, \\ {}_0^{ABC}D_t^\alpha B &= \frac{\partial H_a}{\partial \lambda_{17}}, & {}_0^{ABC}D_t^\alpha V_a &= \frac{\partial H_a}{\partial \lambda_{18}} \end{aligned} \tag{25}$$

$$\lambda_j(T_f) = 0, \tag{26}$$

where $\lambda_j, j = 1, 2, 3, \dots, 18$, are the Lagrange multipliers.

Theorem 3.1 *If u_M^*, u_A^* be the optimal controls with corresponding states $T^*, U^*, D^*, A_E^*, E^*, A_H^*, H^*, A_R^*, R^*, C^*, S^*, I^*, A_1^*, A_2^*, V^*, Y^*, B^*$, and V_a^* , then there exist adjoint variables $\lambda_j^*, j = 1, 2, 3, \dots, 18$, satisfying the following. (i) Adjoint equations:*

$$\begin{aligned} {}_t^{ABC}D_{t_f}^\alpha \lambda_1^* &= A + \lambda_1^* \left(\gamma_1^\alpha - \frac{2\gamma_1^\alpha T^*}{\lambda_B^\alpha B^*} \right) + \frac{r_0^\alpha (1 + k_2^\alpha \frac{T^*}{E^*}) - (\frac{k_2^\alpha T^*}{E^*})}{(1 + k_2^\alpha \frac{T^*}{E^*})^2 (1 + k_3^\alpha \frac{R^*}{E^*}) (1 + \frac{S^*}{s_1^*}) (1 + \frac{V^*}{v_1^*})} \\ &+ \lambda_2^* \left(\frac{a^\alpha}{(1 + \frac{V^*}{v_3^*}) (1 + \frac{I^*}{i_1^*}) (1 + \frac{R^*}{r_1^*})} \right) + \lambda_{12}^* p_4^\alpha \\ &+ \lambda_{15}^* \left(\frac{2\alpha^\alpha v_2 T^* (\theta_v^\alpha B^* + T^*) - \alpha_{v_2}^\alpha T^{2*}}{(\theta_v^\alpha B^* + T^*)^2} + \alpha_v^\alpha \right) \\ &+ \lambda_{14}^* \left(\frac{\alpha_{A_2} B^* (\theta_{A_2} + T^*) - \alpha_{A_2} B^* T^*}{(\theta_{A_2} + T^*)^2} \right), \end{aligned} \tag{27}$$

$${}_t^{cABC}D_{t_f}^\alpha \lambda_2^* = \lambda_2^* \left(-\delta_u^\alpha - \frac{\lambda^\alpha + \frac{2\lambda^\alpha U^*}{M_H^\alpha}}{(1 + \frac{U^*}{M_H^\alpha})^2} \right) + \lambda_3^* \frac{\lambda^\alpha}{(1 + \frac{U^*}{M_H^\alpha})^2} - \lambda_6^* \frac{\frac{k_4^\alpha M^\alpha \alpha_3^\alpha M_H^\alpha}{(U^* + D^*)^2}}{(1 + \frac{k_4^\alpha M^\alpha}{U^* + D^*})^2}, \tag{28}$$

$${}_t^{ABC}D_{t_f}^\alpha \lambda_3^* = \lambda_3^* (-\delta_D^\alpha) - \lambda_4^* \left(\frac{\frac{k_4^\alpha M}{D^{2*}}}{1 + \frac{k_4^\alpha M}{D^*}} \right) - \lambda_6^* \left(\frac{\frac{k_4^\alpha M}{(U^* + D^*)^2}}{(1 + \frac{k_4^\alpha M}{(U^* + D^*)^2})} \right) + \lambda_8^* \frac{\alpha_5^\alpha M_R \frac{k_4^\alpha M}{D^{2*}}}{(1 + k_4^\alpha \frac{M}{D^*})^2}, \tag{29}$$

$${}_t^{ABC}D_{t_f}^\alpha \lambda_4^* = \lambda_4^* (-\delta_A^\alpha) + \lambda_5^* \left(\frac{\alpha_2 C^*}{(1 + \frac{V^*}{v_2^*}) (1 + \frac{S^*}{s_2^*}) (c_1^\alpha + C^*)} \right), \tag{30}$$

$${}^{\text{ABC}}D_{t_f}^{\alpha} \lambda_5^* = \lambda_1^* \left(\frac{-\frac{k_2^{\alpha} T^*}{E^{2*}} (1 + k_3^{\alpha} \frac{R^*}{E^*}) + (1 + \frac{k_2^{\alpha} T^*}{E^*}) \frac{k_3^{\alpha} R^*}{E^{2*}}}{(1 + \frac{k_2^{\alpha} T^*}{E^*})^2 (1 + \frac{k_3^{\alpha} R^*}{E^*})^2 (1 + \frac{S^*}{s_1^{\alpha}}) (1 + \frac{V^*}{v_1^{\alpha}})} \right) - \lambda_5^* \delta_E^{\alpha}, \tag{31}$$

$${}^{\text{ABC}}D_{t_f}^{\alpha} \lambda_6^* = -\lambda_6^* \delta_A^{\alpha} + \lambda_7^* \frac{\alpha_4^{\alpha} C^*}{(1 + \frac{V^*}{v_2^{\alpha}}) (1 + \frac{S^*}{s_2^{\alpha}}) (c_1 + C^*)} + \lambda_{10}^* \frac{p_c^{\alpha}}{(1 + \frac{S^*}{s_4^{\alpha}}) (1 + \frac{I^*}{I_2^{\alpha}})}, \tag{32}$$

$${}^{\text{ABC}}D_{t_f}^{\alpha} \lambda_7^* = -\lambda_7^* \left(\frac{\alpha_7 S^*}{s_3^{\alpha} + S^*} - \delta_H^{\alpha} \right) + \lambda_9^* \left(\frac{\alpha_7^{\alpha} S^*}{(s_3^{\alpha} + S^*)} \right), \tag{33}$$

$${}^{\text{ABC}}D_{t_f}^{\alpha} \lambda_8^* = -\lambda_8^* \delta_A^{\alpha} + \lambda_9^* \frac{\alpha_6^{\alpha} C^*}{(c_1 + C^*)}, \tag{34}$$

$${}^{\text{ABC}}D_{t_f}^{\alpha} \lambda_9^* = \lambda_1^* \frac{-r_0^{\alpha} \frac{Tk_3^{\alpha}}{E^*}}{(1 + k_2^{\alpha} \frac{T^*}{E^*}) (1 + k_3^{\alpha} \frac{R^*}{E^*})^2 (1 + \frac{S^*}{s_1^{\alpha}}) (1 + \frac{V^*}{v_1^{\alpha}})} - \lambda_2^* \frac{\frac{a^{\alpha} T^*}{R_1^{\alpha}}}{(1 + \frac{R^*}{R_1^{\alpha}})^2 (1 + \frac{V^*}{v_3^{\alpha}}) (1 + \frac{I^*}{I_1^{\alpha}})} - \delta_{R^*}^{\alpha} \lambda_9^*, \tag{35}$$

$${}^{\text{ABC}}D_{t_f}^{\alpha} \lambda_{10}^* = \lambda_5^* \frac{\alpha_2 A_E^* (c_1^{\alpha} + C^*) - \alpha_2^{\alpha} A_E^* C^*}{(c_1^{\alpha} + C^*)^2 (1 + \frac{V^*}{v_2^{\alpha}}) (1 + \frac{S^*}{s_2^{\alpha}})} + \lambda_7^* \frac{\alpha_4 A_H^* (c_1^{\alpha} + C^*) - \alpha_4^{\alpha} A_H^* C^*}{(c_1^{\alpha} + C^*)^2 (1 + \frac{V^*}{v_2^{\alpha}}) (1 + \frac{S^*}{s_2^{\alpha}})} + \lambda_9^* \left(\frac{\alpha_6 A_R^* (c_1^{\alpha} + C^*) - \alpha_6^{\alpha} A_R^* C^*}{(c_1^{\alpha} + C^*)^2} \right) - \lambda_{10}^* \frac{1}{\tau_c^{\alpha}}, \tag{36}$$

$${}^{\text{ABC}}D_{t_f}^{\alpha} \lambda_{11}^* = \lambda_1^* \left(-r_0^{\alpha} \frac{\frac{T^*}{s_1^{\alpha}}}{(1 + \frac{S^*}{s_1^{\alpha}})^2 (1 + \frac{k_2^{\alpha} T^*}{E^*}) (1 + \frac{k_3^{\alpha} R^*}{E^*}) (1 + \frac{V^*}{v_1^{\alpha}})} \right) + \lambda_5^* \left(\frac{\alpha_2 A_E^* (1 + \frac{S^*}{s_2^{\alpha}} - \frac{\alpha_2^{\alpha} A_E^* C^*}{s_2^{\alpha}})}{(1 + \frac{S^*}{s_2^{\alpha}})^2 (c_1^{\alpha} + C^*) (1 + \frac{V^*}{v_2^{\alpha}})} \right) + \lambda_9^* \left(\frac{\alpha_7^{\alpha} H (s_3^{\alpha} + S^*) - \alpha_7^{\alpha} H^* S^*}{(s_3^{\alpha} + S^*)^2} \right) + \lambda_{10}^* \left(\frac{p_c^{\alpha} \frac{A_H^*}{s_4^{\alpha}}}{(1 + \frac{S^*}{s_4^{\alpha}}) (1 + \frac{I^*}{I_2^{\alpha}})^2} \right) - \frac{\lambda_{11}^*}{\tau_s^{\alpha}}, \tag{37}$$

$${}^{\text{ABC}}D_{t_f}^{\alpha} \lambda_{12}^* = \lambda_2^* \left(\frac{\frac{-a^{\alpha} T^*}{I_1^{\alpha}}}{(1 + \frac{V^*}{v_3^{\alpha}}) (1 + \frac{R^*}{R_1^{\alpha}}) (1 + \frac{I^*}{I_1^{\alpha}})^2} \right) - \lambda_{10}^* \left(\frac{p_c^{\alpha} A_H^* \frac{1}{I_2^{\alpha}}}{(1 + \frac{S^*}{s_4^{\alpha}}) (1 + \frac{I^*}{I_2^{\alpha}})^2} \right) - \frac{\lambda_{12}^*}{\tau_I^{\alpha}}, \tag{38}$$

$${}^{\text{ABC}}D_{t_f}^{\alpha} \lambda_{13}^* = \lambda_{16}^* \left(\frac{-\omega^{\alpha} Y^* V^* + \omega^{\alpha} Y^* A_1^*}{(\rho^{\alpha} Y^* + V^*) (\theta_B^{\alpha} A_2^* + A_1^*)^2} \right) + \lambda_{17}^* \left(\frac{\frac{1}{S^*} \omega^{\alpha} Y^* V^* - \frac{1}{S^*} \omega^{\alpha} Y^* A_1^*}{(\rho^{\alpha} Y^* + V^*) (\theta_B^{\alpha} A_2^* + A_1^*)^2} \right) - \delta_{A_1}^{\alpha} \lambda_{13}^*, \tag{39}$$

$${}^{\text{ABC}}D_{t_f}^{\alpha} \lambda_{14}^* = \lambda_{16}^* \left(\frac{\omega A_1^* Y^* V^* \theta_B^{\alpha}}{(\rho^{\alpha} Y^* + V^*) (\theta_B^{\alpha} A_2^* + A_1^*)^2} \right) + \lambda_{17}^* \left(\frac{\frac{1}{S^*} \omega^{\alpha} Y^* V^* A_1^* \theta_B^{\alpha}}{(\rho^{\alpha} Y^* + V^*) (\theta_B^{\alpha} A_2^* + A_1^*)^2} \right) - \delta_{A_2}^{\alpha} \lambda_{14}^*, \tag{40}$$

$$\begin{aligned}
 {}^{\text{ABC}}D_{t_f}^\alpha \lambda_{15}^* &= \lambda_{15}^* (-\delta_v^\alpha - \tau^\alpha V_a^*) + \lambda_{16}^* \left(\frac{\alpha_y^\alpha Y^{2*} \theta_{v_a}^\alpha}{(\theta_{v_a}^\alpha Y^* + V^*)^2} \right. \\
 &\quad \left. - \left(\frac{\omega^\alpha Y^* A_1^*}{\theta_B^\alpha A_2^* + A_1^*} \right) \left(\frac{\rho^\alpha Y^*}{(\rho^\alpha Y^* + V^*)^2} \right) + \left(\frac{\delta_y^\alpha \theta_y^\alpha Y^{2*}}{(\theta_y^\alpha Y^* + V^*)^2} \right) \right) \\
 &\quad + \lambda_{17}^* \left(\frac{1}{S^*} \omega^\alpha Y \left(\frac{A_1^*}{(\theta_B A_2^* + A_1^*)} \right) \left(\frac{\rho^\alpha Y^*}{(\rho^\alpha Y^* + V^*)^2} \right) \right. \\
 &\quad \left. + \left(\frac{\gamma_B^\alpha B^* A_2^{4*} \rho^\alpha Y^*}{((\theta_{EC}^\alpha A_1^*)^4 + A_2^{4*})(\rho^\alpha Y^* + V^*)^2} \right) \right) - \lambda_{18}^* \tau^\alpha V_a^* \\
 &\quad + \lambda_2^* \left(\frac{-\alpha T^*}{v_3^\alpha} \right) \left(\frac{1 + \frac{V^*}{v_3^\alpha}}{(1 + \frac{V^*}{v_3^\alpha})^2} \left(1 + \frac{R^*}{R_1^*} \right) \left(1 + \frac{I^*}{I_1^*} \right) \right), \tag{41}
 \end{aligned}$$

$$\begin{aligned}
 {}^{\text{ABC}}D_{t_f}^\alpha \lambda_{16}^* &= \lambda_{16}^* \left(\frac{\alpha_y^\alpha V^{2*}}{(\theta_{v_a}^\alpha Y^* + V^*)^2} - \frac{V^{2*} \omega^\alpha A_1^*}{(\theta_B^\alpha A_2^* + A_1^*)(\rho^\alpha Y^* + V^*)^2} \right) \\
 &\quad - \delta_y^\alpha + \frac{\delta_y^\alpha V^{2*}}{(\theta_y^\alpha Y^* + V^*)^2} \\
 &\quad + \lambda_{17}^* \left(\frac{\gamma_B^\alpha B^* A_2^{4*}}{((\theta_{EC}^\alpha A_1^*)^4 + A_2^{4*})} \left(\frac{\rho^\alpha V^*}{(\rho^\alpha Y^* + V^*)^2} \right) \right), \tag{42}
 \end{aligned}$$

$$\begin{aligned}
 {}^{\text{ABC}}D_{t_f}^\alpha \lambda_{17}^* &= \lambda_{16}^* \left(\frac{-\gamma_B^\alpha A_2^{4*}}{((\theta_{EC}^\alpha A_1^*)^4 + A_2^{4*})} \left(1 - \frac{V^*}{\rho^\alpha Y^* + V^*} \right) \right) \\
 &\quad - \lambda_{15}^* \left(\frac{\alpha_{v_2}^\alpha T^2 \theta_v^\alpha}{(\theta_v^\alpha B^* + T^*)^2} \right) + \lambda_{14}^* \frac{\alpha_{A_2}^\alpha T^*}{\theta_{A_2}^\alpha + T^*} \\
 &\quad + \lambda_{13}^* \alpha_{A_1}^\alpha + \lambda_1^* \frac{\gamma_1^\alpha T^{2*} \lambda_B^\alpha}{(\lambda_B^\alpha B^*)^2}, \tag{43}
 \end{aligned}$$

$${}^{\text{ABC}}D_{t_f}^\alpha \lambda_{18}^* = \lambda_{18}^* (-\tau^\alpha V^* - \delta_{v_a}^\alpha) + \lambda_{15}^* (\tau^\alpha V^*). \tag{44}$$

(ii) *Transversality conditions*

$$\lambda_j^*(T_f) = 0, \quad j = 1, 2, \dots, 18. \tag{45}$$

(iii) *Optimality conditions:*

$$\begin{aligned}
 &H_a(T^*, U^*, D^*, A_E^*, E^*, A_H^*, H^*, A_R^*, R^*, C^*, S^*, I^*, A_1^*, A_2^*, V^*, Y^*, B^*, V_a^*, u_A^*, u_M^*, \lambda) \\
 &= \min_{0 \leq u_A, u_M \leq 1} H(T^*, U^*, D^*, A_E^*, E^*, A_H^*, H^*, A_R^*, R^*, C^*, S^*, I^*, A_1^*, A_2^*, V^*, \\
 &\quad Y^*, B^*, V_a^*, u_A, u_M, \lambda^*). \tag{46}
 \end{aligned}$$

Furthermore, the control functions u_A^*, u_M^* are given by

$$u_A^* = \min \left\{ 1, \max \left\{ 0, \frac{-\lambda_5^* W_1^\alpha}{2B_1} \right\} \right\}, \tag{47}$$

$$u_M^* = \min \left\{ 1, \max \left\{ 0, \frac{-\lambda_{12}^* W_2^\alpha}{2C} \right\} \right\}. \tag{48}$$

Proof We can claim (27)–(44) using the conditions (23) where the Hamiltonian H_a^* is given by

$$\begin{aligned}
 H_a^* = & A + Bu_A^{2*} + Cu_M^{2*} + \lambda_{1a}^{*c} D_t^\alpha T^* + \lambda_{2a}^{*c} D_t^\alpha U^* \\
 & + \lambda_{3a}^{*c} D_t^\alpha D^* + \lambda_{4a}^{*c} D_t^\alpha A_E^* + \lambda_{5a}^{*c} D_t^\alpha E^* + \lambda_{6a}^{*c} D_t^\alpha A_H^* \\
 & + \lambda_{7a}^{*c} D_t^\alpha H^* + \lambda_{8a}^{*c} D_t^\alpha A_R^* + \lambda_{9a}^{*c} D_t^\alpha R^* + \lambda_{10a}^{*c} D_t^\alpha C^* \\
 & + \lambda_{11a}^{*c} D_t^\alpha S^* + \lambda_{12a}^{*c} D_t^\alpha I^* + \lambda_{13a}^{*c} D_t^\alpha A_1^* + \lambda_{14a}^{*c} D_t^\alpha A_2^* \\
 & + \lambda_{15a}^{*c} D_t^\alpha V^* + \lambda_{16a}^{*c} D_t^\alpha Y^* + \lambda_{17a}^{*c} D_t^\alpha B^* + \lambda_{18a}^{*c} D_t^\alpha V_a^*. \tag{49}
 \end{aligned}$$

Moreover, $\lambda_j^*(T_f) = 0, j = 1, \dots, 18$, hold. The optimal controls (47)–(48) can be claimed from the minimization condition (46). Substituting u_A^*, u_M^* in (1)–(18), we get the state system as follows:

$${}_a^{ABC} D_t^\alpha T^* = \gamma_1^\alpha T^* \left(1 - \frac{T^*}{B^* \lambda_B} \right) - \left(\frac{r_0^\alpha T^*}{(1 + k_2^\alpha \frac{T^*}{E^*})(1 + k_3^\alpha \frac{R^*}{E^*})(1 + \frac{S^*}{s_1^\alpha})(1 + \frac{V^*}{v_1^\alpha})} \right), \tag{50}$$

$${}_a^{ABC} D_t^\alpha U^* = \frac{a^\alpha T^*}{(1 + \frac{V^*}{v_3^\alpha})(1 + \frac{I^*}{I_1^\alpha})(1 + \frac{R^*}{R_1^\alpha})} - \frac{\lambda U^*}{1 + \frac{U^* V^*}{M_H^\alpha}} - \delta_u^\alpha U^*, \tag{51}$$

$${}_a^{ABC} D_t^\alpha D^* = \frac{\lambda U^*}{1 + \frac{U^*}{M_H^\alpha}} - \delta_D^\alpha D^*, \tag{52}$$

$${}_a^{ABC} D_t^\alpha A_E^* = \frac{\alpha_1^\alpha M_E^\alpha}{1 + k_4^\alpha \frac{M}{D^*}} - \delta_A^\alpha A_E^*, \tag{53}$$

$${}_a^{ABC} D_t^\alpha E^* = \frac{\alpha_2^\alpha A_E^* C^*}{(1 + \frac{V^*}{v_1^\alpha})(1 + \frac{S^*}{s_2^\alpha})(c_1^\alpha + C^*)} - \delta_E^\alpha E^* + \omega_1^\alpha u_M^*, \tag{54}$$

$${}_a^{ABC} D_t^\alpha A_H^* = \frac{\alpha_3^\alpha M_H^\alpha}{1 + k_4^\alpha \frac{M}{(U^* + D^*)}} - \delta_A^\alpha A_H^*, \tag{55}$$

$${}_a^{ABC} D_t^\alpha H^* = \frac{\alpha_4^\alpha A_H^* C^*}{(1 + \frac{V^*}{v_1^\alpha})(1 + \frac{S^*}{s_2^\alpha})(c_1^\alpha + C^*)} - \frac{\alpha_7 H^* S^*}{s_3^\alpha + S^*} - \delta_H^\alpha H^*, \tag{56}$$

$${}_a^{ABC} D_t^\alpha A_R^* = \frac{\alpha_5^\alpha M_R^\alpha}{1 + k_4^\alpha \frac{M}{D^*}} - \delta_A^\alpha A_R^*, \tag{57}$$

$${}_a^{ABC} D_t^\alpha R^* = \frac{\alpha_6^\alpha A_R^* C^*}{c_1^\alpha + C^*} + \frac{\alpha_7 H^* S^*}{s_3^\alpha + S^*} - \delta_R^\alpha R^*, \tag{58}$$

$${}_a^{ABC} D_t^\alpha C^* = \frac{p_c^\alpha A_H^*}{(1 + \frac{S^*}{s_4^\alpha})(1 + \frac{I^*}{I_1^\alpha})} - \frac{C^*}{\tau^\alpha}, \tag{59}$$

$${}_a^{ABC} D_t^\alpha S^* = p_1^\alpha R^* + p_2^\alpha T^* - \frac{S^*}{\tau_s^\alpha}, \tag{60}$$

$${}_a^{ABC} D_t^\alpha I^* = p_3^\alpha R^* + p_4^\alpha T^* - \frac{I^*}{\tau_I^\alpha}, \tag{61}$$

$${}_a^{ABC} D_t^\alpha A_1^* = \alpha_{A_1}^\alpha B^* - \delta_{A_1}^\alpha A_1^*, \tag{62}$$

$${}_a^{ABC} D_t^\alpha A_2^* = \alpha_{A_1}^\alpha B^* \left(\frac{T^*}{\theta_{A_2}^\alpha + T^*} \right) - \delta_{A_2}^\alpha A_2^*, \tag{63}$$

$${}^{\text{ABC}}D_t^\alpha V^* = \alpha_v^\alpha T^* + \alpha_{v_2}^\alpha T^* \left(\frac{T^*}{\theta_v^\alpha B^* + T^*} \right) - \delta_v^\alpha V^* - \tau^\alpha V_a V^*, \tag{64}$$

$$\begin{aligned} {}^{\text{ABC}}D_t^\alpha Y^* &= \alpha_y^\alpha Y^* \left(\frac{V^*}{\theta_y^\alpha Y^* + V^*} \right) - \omega^\alpha Y^* \left(\frac{A_1^*}{\theta_B A_2^* + A_1^*} \right) \left(\frac{V^*}{\rho Y^* + V^*} \right) \\ &\quad - \delta_y^\alpha Y^* \left(1 + \frac{V^*}{\theta_y^\alpha Y^* + V^*} \right) + \omega_2^\alpha u_A^*, \end{aligned} \tag{65}$$

$$\begin{aligned} {}^{\text{ABC}}D_t^\alpha B^* &= \frac{1}{s^\alpha} \omega^\alpha Y^* V^* \left(\frac{A_1^*}{\theta_B^\alpha A_2^* + A_1^*} \right) \left(\frac{V^*}{\rho^\alpha Y^* + V^*} \right) \\ &\quad - \gamma_B^\alpha B^* \left(\frac{A_2^{4*}}{(\theta_{EC}^\alpha A_1^*)^4 + A_2^{4*}} \right) \left(1 - \frac{V^*}{\rho^\alpha Y^* + V^*} \right), \end{aligned} \tag{66}$$

$${}^{\text{ABC}}D_t^\alpha V_a^* = -\tau^\alpha V_a^* V^* - \rho_{v_a}^\alpha V_a^*. \tag{67}$$

□

3.1 Existence of an optimal control pair

The existence of the optimal control pair can be directly obtained using the results in Fleming and Rishel [55] and Lukes [56]; more precisely, we have the following theorem.

Theorem 3.2 *There exists an optimal control pair $(u_M^*, u_A^*) \in \Omega$ such that*

$$J(u_M^*, u_A^*) = \min_{(u_A, u_M) \in \Omega} J(u_M, u_A).$$

Proof To prove the existence of an optimal control, we use the result in [56]. Note that the control and the state variables are nonnegative values. In this minimizing problem, the necessary convexity of the objective functional in u_A, u_M are satisfied. The set of all the control variables $(u_M, u_A) \in \Omega$ is also convex and closed by definition. The optimal system is bounded, which determines the compactness needed for the existence of the optimal control. In addition, the integrand in functional (19), “ $AT + u_A^2 + Cu_M^2$,” is convex on the control set Ω . Also we can claim that there exist a constant $\mu > 1$ and numbers c_1, c_2 such that

$$J(u_M, u_A) \geq c_1 (u_A^2 + u_M^2)^{\frac{\mu}{2}} - c_2,$$

because the state variables are bounded, it completes the existence of an optimal control. □

4 Numerical method for solving FOCP

4.1 Nonstandard two-step Lagrange interpolation method

For simplicity consider the FODEs in the following general form:

$$\begin{aligned} {}^{\text{ABC}}D_t^\alpha y(t) &= Q(t, y(t)), \quad 0 < t \leq T, 0 < \alpha \leq 1, \\ y(0) &= y_0. \end{aligned} \tag{68}$$

The Atangana–Baleanu fractional-order derivative in the Caputo sense is given as follows ([43]):

$${}^{\text{ABC}}D_t^\alpha y(t) = \frac{M(\alpha)}{(1-\alpha)} \int_0^t E_\alpha \left(-\alpha \frac{(t-q)^\alpha}{(1-\alpha)} \right) \dot{y}(q) dq, \tag{69}$$

where $M(\alpha) = 1 - \alpha + \frac{\alpha}{\Gamma(\alpha)}$ is the normalization function, E_α is the Mittag-Leffler function.

Thanks to the fundamental theorem of fractional calculus with (69), we have

$$y(t) = y(0) + \frac{1 - \alpha}{M(\alpha)} Q(t, y(t)) + \frac{\alpha}{\Gamma(\alpha)M(\alpha)} \int_0^t Q(\theta, y(\theta))(t - \theta)^{\alpha-1} d\theta,$$

at t_{n+1} we have

$$y_{n+1} = y_0 + \frac{\Gamma(\alpha)(1 - \alpha)}{\Gamma(\alpha)(1 - \alpha) + \alpha} Q(t_n, y(t_n)) + \frac{\alpha}{\Gamma(\alpha) + \alpha(1 - \Gamma(\alpha))} \sum_{m=0}^n \int_{t_m}^{t_{m+1}} Q(\theta, y(\theta))(t - \theta)^{\alpha-1} d\theta. \tag{70}$$

The two-step Lagrange interpolation is given as follows:

$$P_k := \frac{Q(t_m, y_m)}{h} (\theta - t_{m-1}) - \frac{Q(t_{m-1}, y_{m-1})}{h} (\theta - t_m), \tag{71}$$

Equation (71) is replaced in (70) and performing the same steps as in [57], we obtain

$$y_{n+1} = y_0 + \frac{\Gamma(\alpha)(1 - \alpha)}{\Gamma(\alpha)(1 - \alpha) + \alpha} Q(t_n, y(t_n)) + \frac{1}{(1 + \alpha)(1 - \alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n h^\alpha Q(t_m, y(t_m))(1 + n - m)^\alpha \times (2 + n - m + \alpha) - (2 + n - m + 2\alpha)(n - m)^\alpha - h^\alpha Q(t_{m-1}, y(t_{m-1}))(1 + n - m)^{\alpha+1} - (n - m + 1 + \alpha)(n - m)^\alpha. \tag{72}$$

To obtain high stability [58], we used a simple modification in (72). This modification is to replace the step size h with $\phi(h)$ such that $\phi(h) = h + O(h^2)$, $0 < \phi(h) \leq 1$. For more details on NSFDM see [40, 59–62]. The nonstandard two-step Lagrange interpolation method (NS2LIM) is given as follows:

$$y_{n+1} - y_0 = \frac{\Gamma(\alpha)(1 - \alpha)}{\Gamma(\alpha)(1 - \alpha) + \alpha} Q(t_n, y(t_n)) + \frac{1}{(1 + \alpha)(1 - \alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q(t_m, y(t_m))(1 + n - m)^\alpha \times (n - m + 2 + \alpha) - (2 + n - m + 2\alpha)(n - m)^\alpha - \phi(h)^\alpha Q(t_{m-1}, y(t_{m-1}))(1 + n - m)^{\alpha+1} - (1 + n - m + \alpha)(n - m)^\alpha. \tag{73}$$

Then we use the new scheme to numerically solve the state system (50)–(67) and we use the nonstandard implicit finite difference method to solve the co-state system (27)–(44) with transversality conditions $\lambda_i(T_f) = 0, i = 1, \dots, 18$.

4.2 Construction of the N2LIM for the fraction order cancer model

Using the nonstandard technique and Eq. (73) we obtain the following nonstandard scheme for system (50)–(67). Let in system (50)–(67)

$$\begin{aligned}
 {}_a^{ABC}D_t^\alpha T^* &= Q_1, & {}_a^{ABC}D_t^\alpha U^* &= Q_2, & {}_a^{ABC}D_t^\alpha D^* &= Q_3, \\
 {}_a^{ABC}D_t^\alpha A_E^* &= Q_4, & {}_a^{ABC}D_t^\alpha E^* &= Q_5, & {}_a^{ABC}D_t^\alpha A_H^* &= Q_6, \\
 {}_a^{ABC}D_t^\alpha H^* &= Q_7, & {}_a^{ABC}D_t^\alpha A_R^* &= Q_8, & {}_a^{ABC}D_t^\alpha R^* &= Q_9, \\
 {}_a^{ABC}D_t^\alpha C^* &= Q_{10}, & {}_a^{ABC}D_t^\alpha S^* &= Q_{11}, & {}_a^{ABC}D_t^\alpha I^* &= Q_{12}, \\
 {}_a^{ABC}D_t^\alpha A_1^* &= Q_{13}, & {}_a^{ABC}D_t^\alpha A_2^* &= Q_{14}, & {}_a^{ABC}D_t^\alpha V_a^* &= Q_{15}, \\
 {}_a^{ABC}D_t^\alpha Y^* &= Q_{16}, & {}_a^{ABC}D_t^\alpha B^* &= Q_{17}, & {}_a^{ABC}D_t^\alpha V_a^* &= Q_{18},
 \end{aligned}$$

where

$$Q_i = Q(t, u_A^*, u_M^*, T^*, U^*, D^*, A_E^*, E^*, A_H^*, H^*, A_R^*, R^*, C^*, S^*, I^*, A_1^*, A_2^*, V_a^*, Y^*, B^*, V_a^*), \quad i = 1, \dots, 18,$$

$$Q_i^m := Q(t^m, u_A^{m*}, u_M^{m*}, T^{m*}, U^{m*}, D^{m*}, A_E^{m*}, E^{m*}, A_H^{m*}, H^{m*}, A_R^{m*}, R^{m*}, C^{m*}, S^{m*}, I^{m*}, A_1^{m*}, A_2^{m*}, V_a^{m*}, Y^{m*}, B^{m*}, V_a^{m*}), \quad i = 1, \dots, 18,$$

$$Q_i^{n*} := Q(t^n, u_A^{n*}, u_M^{n*}, T^{n*}, U^{n*}, D^{n*}, A_E^{n*}, E^{n*}, A_H^{n*}, H^{n*}, A_R^{n*}, R^{n*}, C^{n*}, S^{n*}, I^{n*}, A_1^{n*}, A_2^{n*}, V_a^{n*}, Y^{n*}, B^{n*}, V_a^{n*}), \quad i = 1, \dots, 18,$$

$$\begin{aligned}
 T_{n+1}^* - T_0^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_1^n \\
 &+ \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_1^m (1+n-m)^\alpha \\
 &\times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
 &- \phi(h)^\alpha Q_1^{m-1} (n+1-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha,
 \end{aligned}$$

$$\begin{aligned}
 U_{n+1}^* - U_0^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_2^n \\
 &+ \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_2^m (1+n-m)^\alpha \\
 &\times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
 &- \phi(h)^\alpha Q_2^{m-1} (n+1-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha,
 \end{aligned}$$

$$\begin{aligned}
D_{n+1}^* - D_0^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_3^n \\
&\quad + \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_3^m (1+n-m)^\alpha \\
&\quad \times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
&\quad - \phi(h)^\alpha Q_3^{m-1} (n+1-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha, \\
A_{E_{n+1}}^* - A_{E_0}^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_4^n \\
&\quad + \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_4^m (1+n-m)^\alpha \\
&\quad \times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
&\quad - \phi(h)^\alpha Q_4^{(m-1)} (n+1-m)^{\alpha+1} - (n-m+1+\alpha)(n-m)^\alpha, \\
E_{n+1}^* - E_0^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_5^n \\
&\quad + \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_5^m (1+n-m)^\alpha \\
&\quad \times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
&\quad - \phi(h)^\alpha Q_5^{m-1} (n+1-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha, \\
A_{H_{n+1}}^* - A_{H_0}^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_6^n \\
&\quad + \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_6^m (1+n-m)^\alpha \\
&\quad \times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
&\quad - \phi(h)^\alpha Q_6^{m-1} (n+1-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha, \\
H_{n+1}^* - H_0^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_7^n \\
&\quad + \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_7^m (1+n-m)^\alpha \\
&\quad \times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
&\quad - \phi(h)^\alpha Q_7^{m-1} (n+1-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha, \\
A_{R_{n+1}}^* - A_{R_0}^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_8^n \\
&\quad + \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_8^m (n+1-m)^\alpha \\
&\quad \times (n-m+2+\alpha) - (n-m)^\alpha (n-m+2+2\alpha) \\
&\quad - \phi(h)^\alpha Q_8^{m-1} (1+n-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha,
\end{aligned}$$

$$\begin{aligned}
 R_{n+1}^* - R_0^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_9^n \\
 &+ \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_9^m (1+n-m)^\alpha \\
 &\times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
 &- \phi(h)^\alpha Q_9^{m-1} (n+1-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha, \\
 C_{n+1}^* - C_0^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_{10}^n \\
 &+ \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_{10}^m (1+n-m)^\alpha \\
 &\times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
 &- \phi(h)^\alpha Q_{10}^{m-1} (n+1-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha, \\
 S_{n+1}^* - S_0^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_{11}^n \\
 &+ \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_{11}^m (1+n-m)^\alpha \\
 &\times (2+n-m+\alpha) - (n-m+2+2\alpha)(n-m)^\alpha \\
 &- \phi(h)^\alpha Q_{11}^{m-1} (n+1-m)^{\alpha+1} - (n-m)^\alpha (n-m+1+\alpha), \\
 I_{n+1}^* - I_0^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_{12}^n \\
 &+ \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_{12}^m (1+n-m)^\alpha \\
 &\times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
 &- \phi(h)^\alpha Q_{12}^{m-1} (n+1-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha, \\
 A_{1n+1}^* - A_{10}^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_{13}^n \\
 &+ \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_{13}^m (1+n-m)^\alpha \\
 &\times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
 &- \phi(h)^\alpha Q_{13}^{m-1} (n+1-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha, \\
 A_{2n+1}^* - A_{20}^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_{14}^n \\
 &+ \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_{14}^m (1+n-m)^\alpha \\
 &\times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
 &- \phi(h)^\alpha Q_{14}^{m-1} (n+1-m)^{\alpha+1} - (n-m+1+\alpha)(n-m)^\alpha,
 \end{aligned}$$

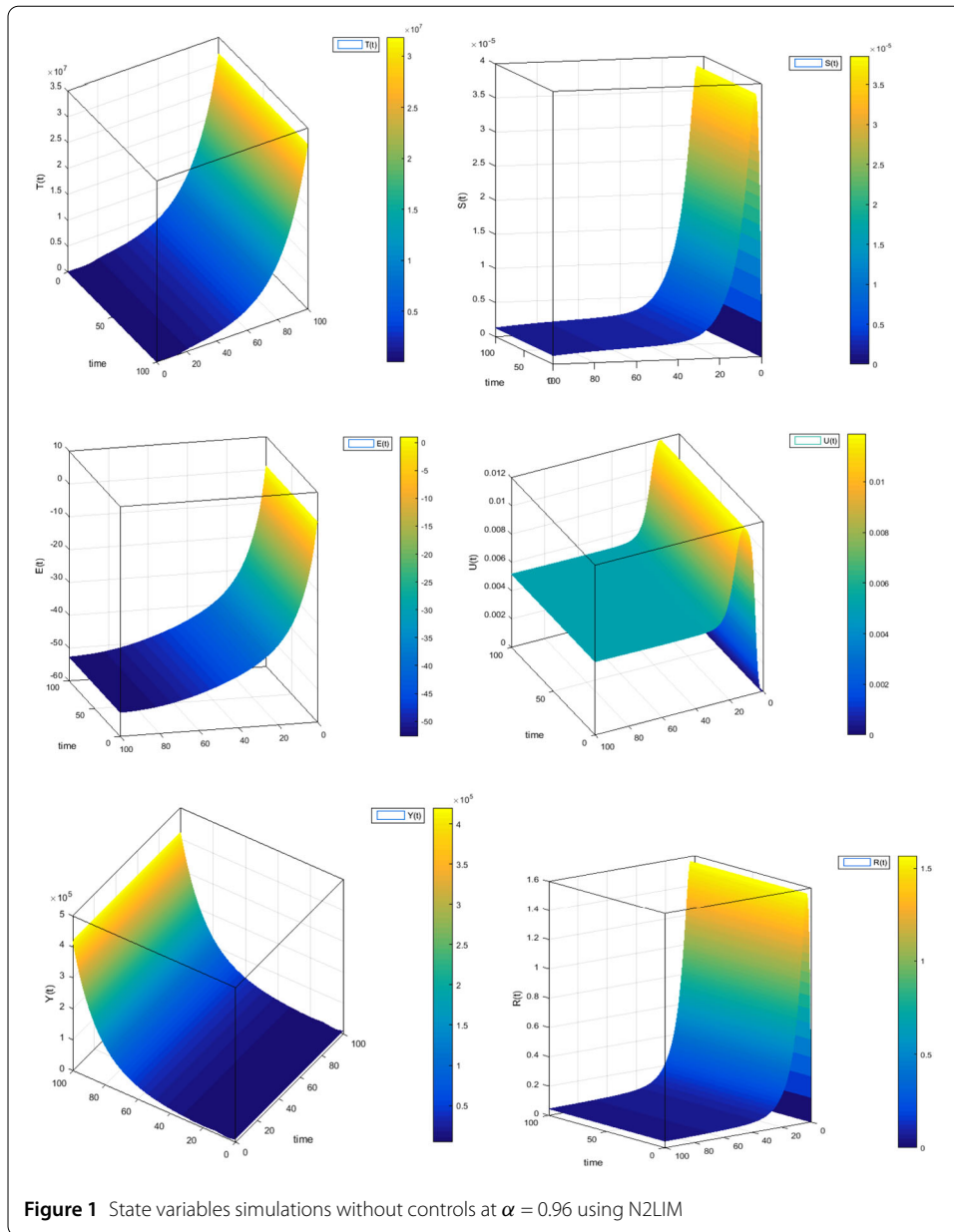
$$\begin{aligned}
 V_{n+1}^* - V_0^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_{15}^n \\
 &+ \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_{15}^m (1+n-m)^\alpha \\
 &\times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
 &- \phi(h)^\alpha Q_{15}^{m-1} (n+1-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha, \\
 Y_{n+1}^* - Y_0^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_{16}^n \\
 &+ \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_{16}^m (1+n-m)^\alpha \\
 &\times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
 &- \phi(h)^\alpha Q_{16}^{m-1} (n+1-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha, \\
 B_{n+1}^* - B_0^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_{17}^n \\
 &+ \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_{17}^m (1+n-m)^\alpha \\
 &\times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
 &- \phi(h)^\alpha Q_{17}^{m-1} (n+1-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha, \\
 V_{a_{n+1}}^* - V_{a_0}^* &= \frac{\Gamma(\alpha)(1-\alpha)}{\Gamma(\alpha)(1-\alpha) + \alpha} Q_{18}^n \\
 &+ \frac{1}{(1+\alpha)(1-\alpha)\Gamma(\alpha) + \alpha} \sum_{m=0}^n \phi(h)^\alpha Q_{18}^m (1+n-m)^\alpha \\
 &\times (2+n-m+\alpha) - (2+n-m+2\alpha)(n-m)^\alpha \\
 &- \phi(h)^\alpha Q_{18}^{m-1} (n+1-m)^{\alpha+1} - (1+n-m+\alpha)(n-m)^\alpha.
 \end{aligned}$$

5 Numerical results

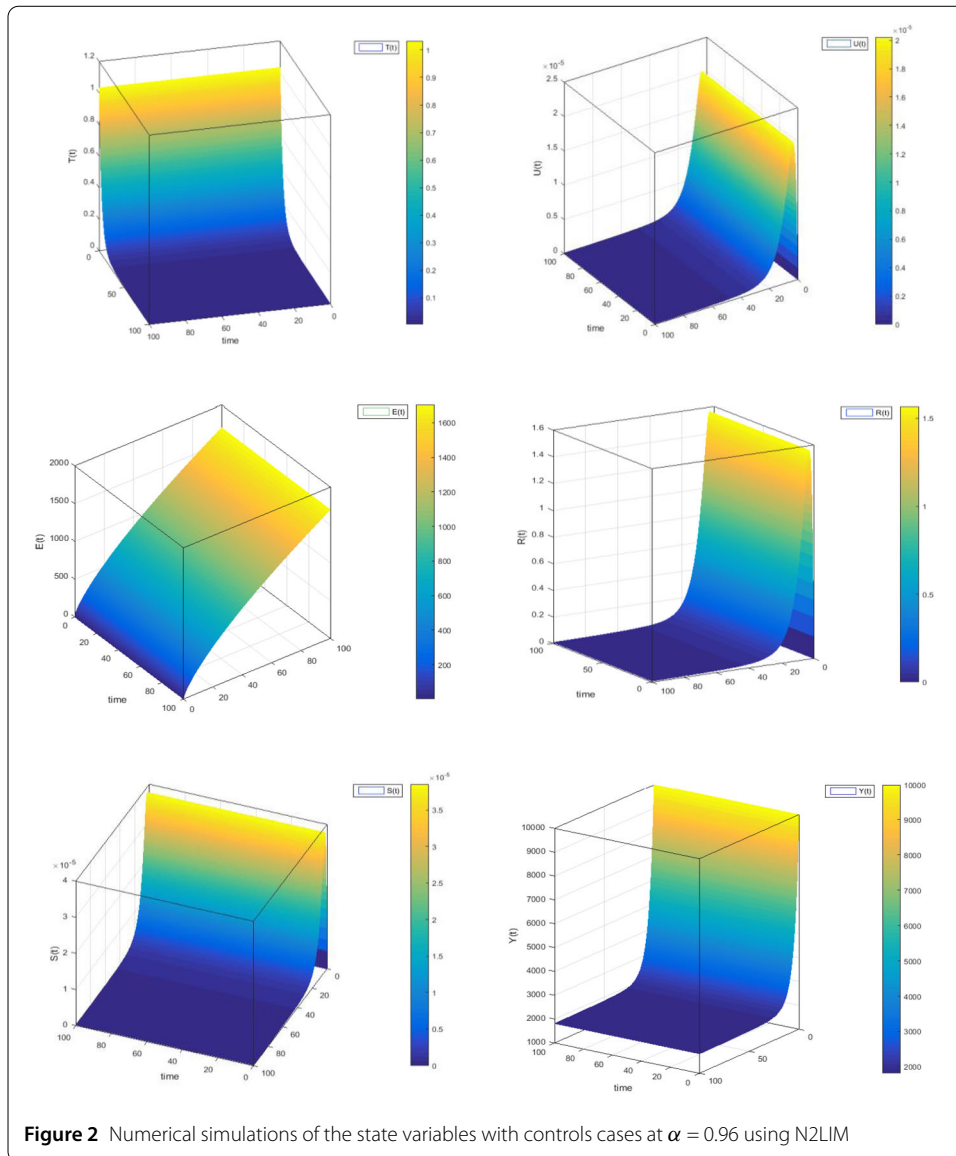
In the following, N2LIM is applied to solve the optimality system (50)–(67) and (27)–(44) with the transversality conditions $\lambda_j^*(T_f) = 0, j = 1, \dots, 18$. The state Eqs. (50)–(67) have initial conditions $T^*(0) = 1, U^*(0) = 0, D^*(0) = 1, A_E^*(0) = 0, E^*(0) = 1, A_H^*(0) = 0, H^*(0) = 0, A_R^*(0) = 0, R^*(0) = 0, Y^*(0) = 10,000, C^*(0) = 1, S^*(0) = 0, I^*(0) = 1, A_1^*(0) = 10, A_2^*(0) = 1, V^*(0) = 0, V_a^*(0) = 0, B^*(0) = 1000, \omega_1 = 1000, \omega_2 = 1000$. The values of the parameters are taken from [21] with the power $\alpha, 0 < \alpha \leq 1$. These state equations are initially solved by the proposed methods. Then we will solve the co-state equations (27)–(44) by using a nonstandard finite difference method with back step in the time.

Figure 1 shows the approximate solutions at $\alpha = 0.96$ of the state variables without controls. Figure 2 shows the behavior of approximate solutions $E(t), I(t)$ and $T(t)$ in two cases with and without controls using N2LIM. We noted that, in controlled case the increment of $E(t)$ and $Y(t)$ lead to decrease the number of cancer cells $T(t)$.

Figure 3 shows the approximate solutions of the state variables T, U, E, Y, S and R with control case and $B_1 = 100, C = 1000$ at different α using N2LIM. It is clear that the best result is at $\alpha = 0.98$ because the number of cancer cells is minimal. Also, these results show



the fractional model is more general than the integer model. Figure 4, shows the values of u_A^* , u_M^* in a units of days with different values of α by using N2LIM. It is clear that the best result at $\alpha = 0.98$ in (a) and in (b) is at $\alpha = 0.7$. Table 1 shows the comparison between the values of the objective functional using N2LIM with and without controls at $T_f = 100$ and different values of α and $\phi(h)$. We note that the best result is at $\phi(h) = 0.025(1 - e^{-h})$. The values of objective functional (19) by the IOCM ([22, 30, 42]) and N2LIM at different values of α are shown in Table 2. We note that the N2LIM results are better than the IOCM results. We use Matlab on a computer with Windows 7 home premium, RAM 4 GB and system type 64-bit operating system.



6 Conclusions

In this paper, numerical solutions for optimal control of fractional order with generalized Mittag-Leffler function for cancer treatment based on synergy between anti-angiogenic and immune cell therapies are presented. The necessary optimality conditions are proved, where two controls $u_A(t)$, $u_M(t)$ are added to reduce the cancer cells number. N2LIM is developed to study the model problem. We present some simulations that support our theoretical findings and show the effectiveness of the model. Comparative studies with IOCM are implemented, it is found that the values of the objective functional which are obtained by N2LIM are better than the results obtained by IOCM. Moreover, N2LIM can be applied to solve the fractional optimal control problem simply and effectively.

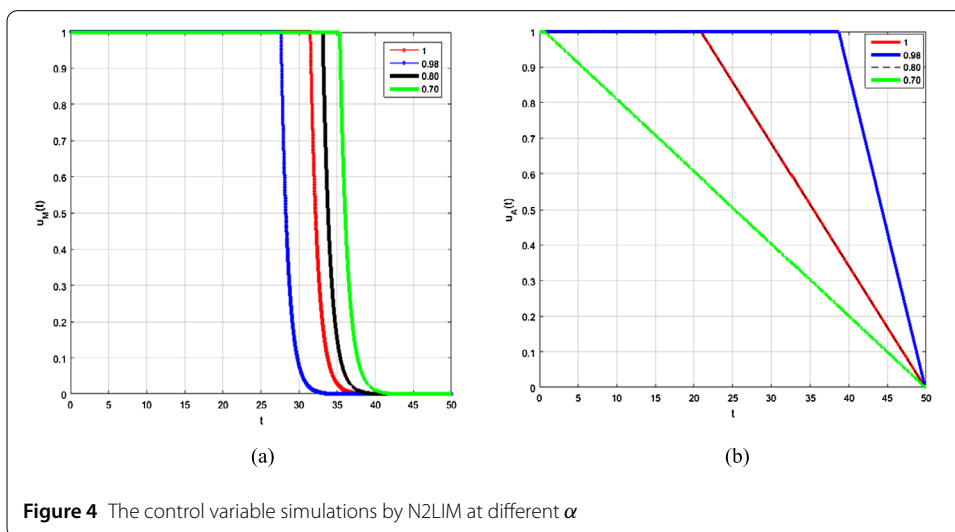
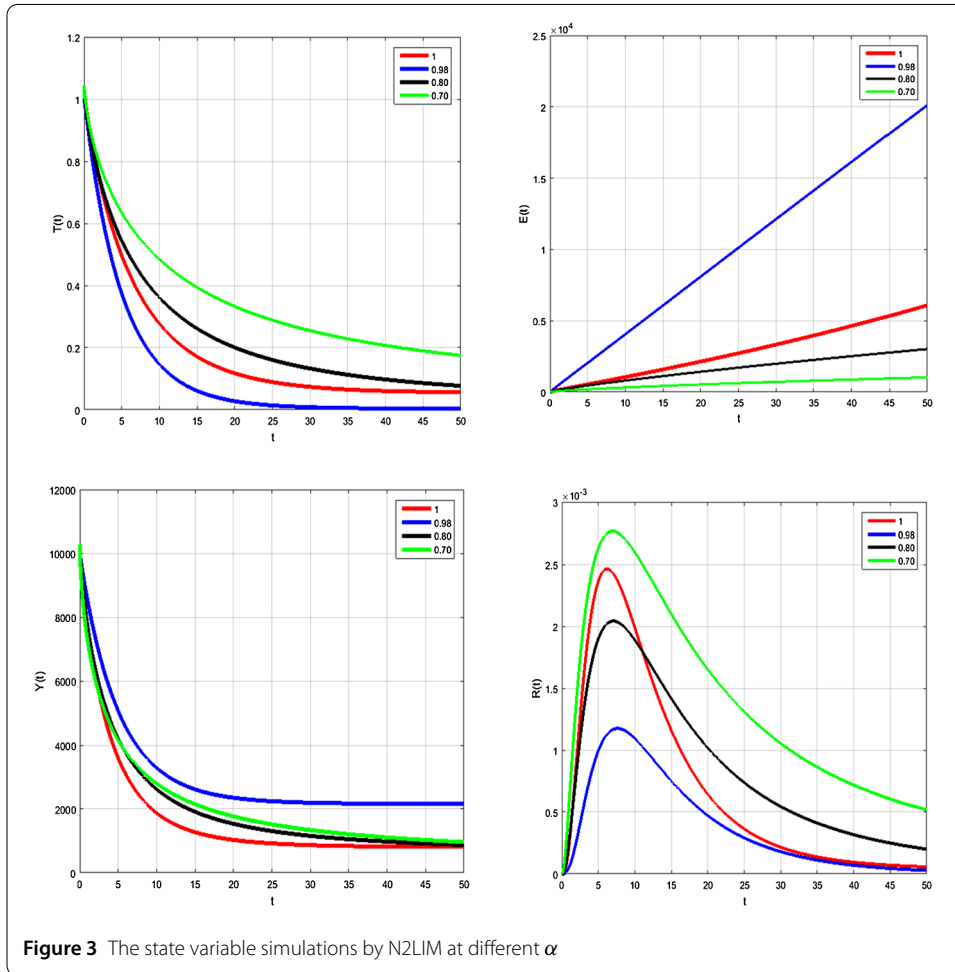


Table 1 Comparisons between objective functional values using N2LIM with and without control cases and $T_f = 100$

α	J without control	$J(u_A^*, u_M^*)$ with two controls $\phi(h) = 0.1(1 - e^{-h})$	$J(u_A^*, u_M^*)$ with two controls $\phi(h) = 0.25(1 - e^{-h})$	$J(u_A^*, u_M^*)$ with two controls $\phi(h) = 0.025(1 - e^{-h})$
1	2.7175×10^8	3.4031×10^4	7.8020×10^4	2.1007×10^3
0.9	8.2497×10^8	2.0944×10^4	7.0124×10^4	1.2715×10^3
0.8	2.9802×10^9	6.4809×10^3	3.0513×10^4	327.5621
0.6	5.0357×10^8	4.1936×10^3	9.9418×10^3	119.6221
0.5	2.3932×10^7	8.4199×10^4	6.0894×10^4	105.3185

Table 2 Comparisons between IOCM, N2LIM and $T_f = 50, B_1 = 100, C = 1000$

α	Methods	$J(u_A^*, u_M^*)$
1	IOCM	4.4325×10^4
	N2LIM	2.3616×10^4
0.98	IOCM	4.3766×10^4
	N2LIM	2.0580×10^4
0.90	IOCM	3.9290×10^4
	N2LIM	9.8979×10^3
0.80	IOCM	3.0162×10^4
	N2LIM	4.6516×10^3
0.70	IOCM	1.5232×10^4
	N2LIM	3.0171×10^3
0.60	IOCM	7.1517×10^3
	N2LIM	2.6444×10^3

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Availability of data and materials

Please contact the corresponding author for data requests.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The authors contributed equally to this paper. All authors read and approved the final manuscript.

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