



Available online at <http://scik.org>

Commun. Math. Biol. Neurosci. 2026, 2026:110

<https://doi.org/10.28919/cmbn/10191>

ISSN: 2052-2541

MATHEMATICAL MODELING AND OPTIMAL CONTROL OF LUNG CANCER DYNAMICS: A FRACTIONAL-ORDER APPROACH ENHANCED BY ARTIFICIAL INTELLIGENCE

LHOUSSAIN BOUISSOU^{1,*}, MUSTAPHA AIT HAMMOU¹, RACHID BOUAJAJI²

¹Laboratory of Modeling, Applied Mathematics, and Intelligent Systems, Faculty of Sciences Dhar El Mahraz,
Sidi Mohamed Ben Abdellah University, Fez 30003, Morocco

²Nursing, Higher Institute of Nursing and Health Care Professions, Meknès, Morocco

Copyright © 2026 the author(s). This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract. Lung cancer is one of the leading causes of mortality worldwide, representing a major challenge for modern healthcare systems due to its rapid progression and complex biological mechanisms. In this work, we propose a mathematical model based on fractional differential equations in the sense of Caputo to describe the dynamics of lung cancer while incorporating memory effects inherent to biological systems. The proposed model considers the interactions between normal cells, tumor cells, immune response, therapeutic treatment, and a tumor biomarker. A rigorous mathematical analysis is carried out to establish the fundamental properties of the system, including existence, uniqueness, positivity, and boundedness of solutions, ensuring the biological consistency of the model. Furthermore, an optimal control problem is formulated to determine an effective therapeutic strategy that minimizes tumor growth while reducing treatment-related costs. Pontryagin's Maximum Principle is applied to characterize the optimal control, leading to an analytical expression of the optimal therapeutic protocol. Numerical simulations are performed to illustrate the behavior of the system. The results show that the application of a therapeutic control significantly reduces tumor growth compared to the uncontrolled case. In addition, the influence of the fractional order is investigated, highlighting the importance of memory effects in tumor evolution.

*Corresponding author

E-mail address: lhousain.bouissoui@usmba.ac.ma

Received August 3, 2026

Finally, artificial intelligence techniques are used to estimate the model parameters from simulated data, improving prediction accuracy and model calibration.

Keywords: lung cancer; mathematical modeling; fractional differential equations; Caputo derivative; optimal control; numerical simulation; artificial intelligence

2020 AMS Subject Classification: 37M05; 34K37; 35F21; 68T20

1. INTRODUCTION

Lung cancer represents a major public health challenge. According to recent global statistics, lung cancer accounts for a significant proportion of cancer deaths due to its aggressive nature and late diagnosis[1]. Despite considerable progress in medical treatments, including chemotherapy, radiotherapy, targeted therapy, and immunotherapy, the survival rate remains relatively low. This highlights the urgent need for advanced mathematical and computational tools to better understand tumor dynamics and improve therapeutic strategies. Mathematical modeling has become an essential tool in cancer research, providing a framework to analyze the complex interactions between tumor cells, normal cells, and the immune system. Classical models based on ordinary differential equations have been widely used to describe tumor growth and its interactions with the surrounding biological environment [20] These models allow researchers to study key phenomena such as tumor proliferation, immune response, and the effects of therapeutic interventions. However, classical ordinary differential equation models have important limitations, particularly in their inability to capture memory and hereditary effects that are intrinsic to biological systems. In many biological processes, the current state of the system depends not only on its present conditions but also on its past evolution. To address these limitations, fractional differential equations have been introduced as a more general and flexible modeling framework [6].

Fractional calculus provides a powerful mathematical tool for incorporating memory effects into dynamic systems. In particular, Caputo fractional derivatives are widely used in biological modeling due to their compatibility with classical initial conditions and their ability to represent non-local dynamics[17]. Several studies have shown that fractional-order models provide a more realistic description of tumor growth and biological processes than classical integer-order

models [9]. Their capability to account for long-term memory makes them particularly suitable for modeling complex cancer dynamics.

Optimal control theory has become an important mathematical framework for designing effective therapeutic strategies in oncology. It enables the determination of treatment protocols that minimize tumor burden while simultaneously reducing drug toxicity and treatment-related costs[6]. The application of Pontryagin's Maximum Principle provides the necessary optimality conditions and yields an analytical characterization of the optimal therapeutic control.

Optimal control approaches have been extensively applied to cancer treatment models, particularly in chemotherapy and immunotherapy optimization [7]. When combined with fractional-order models, optimal control provides a more realistic framework by incorporating memory effects into both tumor evolution and therapeutic response [11]. This combination offers an efficient mathematical tool for improving treatment scheduling while preserving healthy tissues.

In parallel, the rapid development of artificial intelligence and machine learning techniques has significantly enhanced the modeling of complex biological systems. One of the major challenges in mathematical modeling is parameter estimation, since many biological parameters are either unknown or difficult to measure experimentally. Machine learning algorithms and optimization techniques provide efficient tools for estimating these parameters from experimental or clinical data, thereby improving the predictive capability of mathematical models[14].

In particular, Physics-Informed Neural Networks (PINNs) have recently emerged as a powerful framework that combines data-driven learning with the physical laws represented by differential equations [27]. These approaches enable the simultaneous estimation of unknown parameters and the numerical solution of differential equations while preserving the underlying biological and physical constraints. Consequently, they have become promising tools for calibrating fractional-order mathematical models and enhancing prediction accuracy in biomedical applications.

2. MATHEMATICAL MODEL

The proposed mathematical model describes the interactions among five biological components involved in lung cancer progression:

- $N(t)$ denotes the population of healthy or normal cells;
- $T(t)$ denotes the population of tumor cells;
- $I(t)$ represents immune cells involved in recognizing and eliminating tumor cells;
- $C(t)$ denotes the concentration of the therapeutic drug;
- $P(t)$ represents a tumor biomarker used to monitor disease progression.

The following biological assumptions are considered:

- (1) Healthy cells proliferate according to logistic growth in the absence of tumor cells and treatment.
- (2) Tumor cells also follow logistic growth and are eliminated through immune-mediated cytotoxicity and chemotherapy.
- (3) Immune cells are supplied at a constant rate, stimulated by interactions with tumor cells, and removed through natural death and treatment-related toxicity.
- (4) The therapeutic agent is administered through an external control function and is eliminated according to first-order pharmacokinetics.
- (5) The tumor biomarker is produced proportionally to the tumor burden and undergoes natural degradation.

2.1. Fractional-Order Mathematical Model. Based on the preceding biological assumptions, the lung cancer dynamics are described by the following system of Caputo fractional differential equations:

$$(1) \quad \begin{cases} {}^C D_t^\alpha N(t) = r_N N(t) \left(1 - \frac{N(t)}{K_N}\right) - \beta N(t) T(t) - \eta C(t) N(t), \\ {}^C D_t^\alpha T(t) = r_T T(t) \left(1 - \frac{T(t)}{K_T}\right) - \rho I(t) T(t) - \mu C(t) T(t), \\ {}^C D_t^\alpha I(t) = s + \rho I(t) T(t) - d_I I(t) - q C(t) I(t), \\ {}^C D_t^\alpha C(t) = u(t) - d_C C(t), \\ {}^C D_t^\alpha P(t) = a T(t) - d_P P(t), \end{cases} \quad 0 < \alpha \leq 1.$$

2.2. Description of Model Parameters. The variables and parameters involved in system (1) are summarized in Table 1.

TABLE 1. Description of the model parameters.

Parameter	Description
r_N	Rate of healthy cell proliferation.
K_N	Maximum population size (carrying capacity) of normal cells.
r_T	Tumor cell proliferation rate.
K_T	Carrying capacity of tumor cells.
β	Rate of interaction between normal and tumor cells.
η	Toxic effect of the therapeutic treatment on healthy cells.
p	Rate at which immune cells eliminate tumor cells.
μ	Effectiveness of the treatment in killing tumor cells.
s	Constant source (input) rate of immune cells.
ρ	Tumor-induced activation rate of immune cells.
d_I	Natural mortality rate of immune cells.
q	Inhibitory effect of the treatment on immune cells.
d_C	Drug elimination (clearance) rate.
a	Production rate of the tumor biomarker.
d_P	Degradation rate of the tumor biomarker.
$u(t)$	Control function representing the therapeutic dose.
α	Fractional-order parameter ($0 < \alpha \leq 1$) representing memory effects.

The biological parameters listed in Table 1 were selected from the literature on tumor growth, immune response, chemotherapy, and fractional calculus. Their values lie within biologically realistic ranges and describe the interactions among tumor cells, immune cells, therapeutic treatment, and tumor biomarkers. These parameters provide a reliable foundation for the numerical simulations and biological interpretation of the proposed fractional-order lung cancer model.

2.3. Initial Conditions. System (1) is supplemented with the initial conditions

$$(2) \quad N(0) = N_0, \quad T(0) = T_0, \quad I(0) = I_0, \quad C(0) = C_0, \quad P(0) = P_0,$$

where

$$N_0, T_0, I_0, C_0, P_0 \geq 0.$$

All biological parameters are assumed to be strictly positive. Furthermore, the therapeutic control is assumed to satisfy

$$u \in L^\infty(0, T_f), \quad 0 \leq u(t) \leq u_{\max}$$

for almost every $t \in [0, T_f]$.

3. MATHEMATICAL ANALYSIS

In this section, we study the fundamental mathematical properties of system (1), including existence, uniqueness, positivity, and boundedness of solutions [18]. We assume that all model parameters are positive and that

$$0 < \alpha \leq 1.$$

3.1. Existence and Uniqueness. Let

$$X(t) = (N(t), T(t), I(t), C(t), P(t))^T.$$

System (1) can be written in the compact form

$${}^C D_t^\alpha X(t) = F(t, X(t)),$$

where F denotes the right-hand side of the system. We assume that the control function satisfies

$$u \in L^\infty(0, T_f), \quad 0 \leq u(t) \leq u_{\max} \quad \text{for almost every } t \in [0, T_f].$$

Theorem 1. *For any non-negative initial condition*

$$X(0) = X_0 = (N_0, T_0, I_0, C_0, P_0)^T \in \mathbb{R}_+^5,$$

system (1) admits a unique local solution [20].

Proof. The components of F are given by

$$F_1 = r_N N \left(1 - \frac{N}{K_N} \right) - \beta NT - \eta CN,$$

$$F_2 = r_T T \left(1 - \frac{T}{K_T} \right) - pIT - \mu CT,$$

$$F_3 = s + \rho IT - d_I I - qCI,$$

$$F_4 = u(t) - d_C C,$$

$$F_5 = aT - d_P P.$$

Each component F_i is continuous with respect to the state variables N, T, I, C, P . Moreover, on any bounded domain

$$\Omega_M = \{X \in \mathbb{R}_+^5 : \|X\| \leq M\},$$

The partial derivatives of F with respect to the state variables are bounded. Hence, F is locally Lipschitz continuous with respect to X . Therefore, by the classical existence and uniqueness theorem for Caputo fractional differential equations, system (1) admits a unique local solution [23]. $\square$

3.2. Positivity of Solutions.

Theorem 2. *If*

$$N_0 \geq 0, \quad T_0 \geq 0, \quad I_0 \geq 0, \quad C_0 \geq 0, \quad P_0 \geq 0,$$

then the solution of system (1) remains non-negative for all $t \geq 0$.

Proof. We examine the vector field on the boundary of the positive orthant

$$\mathbb{R}_+^5 = \{(N, T, I, C, P) : N, T, I, C, P \geq 0\}.$$

If $N(t) = 0$, then

$${}^C D_t^\alpha N(t) = 0.$$

If $T(t) = 0$, then

$${}^C D_t^\alpha T(t) = 0.$$

If $I(t) = 0$, then

$${}^C D_t^\alpha I(t) = s > 0.$$

If $C(t) = 0$, then

$${}^C D_t^\alpha C(t) = u(t) \geq 0.$$

If $P(t) = 0$, then

$${}^C D_t^\alpha P(t) = aT(t) \geq 0.$$

Thus, on each boundary of the positive orthant, the vector field does not point outside $\mathbb{R}_+^5$. Hence,

$$N(t), T(t), I(t), C(t), P(t) \geq 0, \quad \forall t \geq 0.$$

□

3.3. Boundedness and Global Existence of Solutions.

Theorem 3. *Assume that*

$$u \in L^\infty(0, T_f), \quad 0 \leq u(t) \leq u_{\max}$$

for almost every $t \in [0, T_f]$. Then every non-negative solution of system (1) is bounded on $[0, T_f]$.

Consequently, the unique local solution extends to a unique global solution.

Proof. From the first equation of system (1), we obtain

$${}^C D_t^\alpha N \leq r_N N \left(1 - \frac{N}{K_N} \right).$$

By comparison with the corresponding fractional logistic equation,

$$0 \leq N(t) \leq \bar{N}, \quad \bar{N} = \max\{N_0, K_N\}.$$

Similarly,

$${}^C D_t^\alpha T \leq r_T T \left(1 - \frac{T}{K_T} \right),$$

and hence

$$0 \leq T(t) \leq \bar{T}, \quad \bar{T} = \max\{T_0, K_T\}.$$

For the treatment concentration, since

$$0 \leq u(t) \leq u_{\max},$$

we have

$${}^C D_t^\alpha C \leq u_{\max} - d_C C.$$

Therefore,

$$0 \leq C(t) \leq \bar{C}, \quad \bar{C} = \max \left\{ C_0, \frac{u_{\max}}{d_C} \right\}.$$

To establish the boundedness of the tumor and immune-cell populations without imposing the restrictive condition $d_I > \rho K_T$, define

$$W(t) = T(t) + \frac{p}{\rho} I(t),$$

where $p > 0$ and $\rho > 0$. Using the second and third equations of system (1), we obtain

$$\begin{aligned} {}^C D_t^\alpha W &= r_T T \left(1 - \frac{T}{K_T} \right) - pIT - \mu CT \\ &\quad + \frac{p}{\rho} (s + \rho IT - d_I I - qCI). \end{aligned}$$

The interaction terms cancel:

$$-pIT + \frac{p}{\rho} \rho IT = 0.$$

Consequently,

$${}^C D_t^\alpha W \leq r_T T \left(1 - \frac{T}{K_T} \right) + \frac{ps}{\rho} - \frac{pd_I}{\rho} I.$$

Let $\varepsilon > 0$. Since

$$r_T T \left(1 - \frac{T}{K_T} \right) = (r_T + \varepsilon)T - \frac{r_T}{K_T} T^2 - \varepsilon T,$$

we have

$$r_T T \left(1 - \frac{T}{K_T} \right) \leq M_\varepsilon - \varepsilon T,$$

where

$$M_\varepsilon = \frac{K_T(r_T + \varepsilon)^2}{4r_T}.$$

Thus,

$${}^C D_t^\alpha W \leq M_\varepsilon + \frac{ps}{\rho} - \varepsilon T - \frac{pd_I}{\rho} I.$$

Set

$$\delta = \min\{\varepsilon, d_I\} > 0.$$

Then

$$\varepsilon T + \frac{pd_I}{\rho} I \geq \delta \left(T + \frac{p}{\rho} I \right) = \delta W.$$

Therefore,

$${}^C D_t^\alpha W \leq A - \delta W,$$

where

$$A = M_\varepsilon + \frac{ps}{\rho}.$$

By the fractional comparison principle,

$$W(t) \leq W(0)E_\alpha(-\delta t^\alpha) + At^\alpha E_{\alpha, \alpha+1}(-\delta t^\alpha),$$

and consequently,

$$W(t) \leq \max \left\{ W(0), \frac{A}{\delta} \right\}.$$

Since

$$T(t) \leq W(t), \quad I(t) \leq \frac{\rho}{p} W(t),$$

both $T(t)$ and $I(t)$ are bounded.

Finally, since $T(t) \leq \bar{T}$, the biomarker equation satisfies

$${}^C D_t^\alpha P \leq a\bar{T} - d_P P.$$

Hence,

$$0 \leq P(t) \leq \bar{P}, \quad \bar{P} = \max \left\{ P_0, \frac{a\bar{T}}{d_P} \right\}.$$

Therefore, all state variables are non-negative and bounded on every finite time interval. Hence, finite-time blow-up cannot occur, and the unique local solution extends to a unique global solution. $\square$

Theorem 4 (Global Existence). *Under the assumptions of Theorem 3.1, the unique local solution of system (1) extends to a unique global solution on $[0, +\infty)$.*

4. EQUILIBRIUM POINTS AND STABILITY ANALYSIS

In this section, we determine the equilibrium points of the proposed fractional-order lung cancer model and investigate their local asymptotic stability. Equilibrium points describe the long-term behavior of the biological system and provide important information regarding the persistence or elimination of tumor cells. The stability analysis is carried out using the Jacobian matrix together with Matignon's stability criterion for fractional-order dynamical systems [24].

4.1. Equilibrium Points. The equilibrium points are obtained by setting

$${}^C D_t^\alpha N = {}^C D_t^\alpha T = {}^C D_t^\alpha I = {}^C D_t^\alpha C = {}^C D_t^\alpha P = 0.$$

Consequently, the steady-state solutions satisfy

$$F(X) = 0.$$

Two biologically meaningful equilibrium points are considered.

4.1.1. Tumor-Free Equilibrium. The tumor-free equilibrium corresponds to the absence of tumor cells, namely

$$T^0 = 0.$$

Since the tumor biomarker is produced only by tumor cells,

$$P^0 = 0.$$

Assuming that no treatment is administered at equilibrium,

$$u(t) = 0,$$

the drug concentration satisfies

$$C^0 = 0.$$

The remaining variables satisfy

$$r_N N \left(1 - \frac{N}{K_N} \right) = 0,$$

which gives

$$N^0 = K_N,$$

and

$$s - d_I I = 0,$$

yielding

$$I^0 = \frac{s}{d_I}.$$

Therefore, the tumor-free equilibrium is

$$E_0 = \left(K_N, 0, \frac{s}{d_I}, 0, 0 \right).$$

4.1.2. Coexistence Equilibrium. The coexistence equilibrium

$$E^* = (N^*, T^*, I^*, C^*, P^*)$$

is obtained by solving

$$F(X) = 0,$$

that is,

$$\begin{cases} r_N N \left(1 - \frac{N}{K_N} \right) - \beta NT - \eta CN = 0, \\ r_T T \left(1 - \frac{T}{K_T} \right) - p IT - \mu CT = 0, \\ s + \rho IT - d_I I - q CI = 0, \\ u - d_C C = 0, \\ aT - d_P P = 0. \end{cases}$$

From the last two equations,

$$C^* = \frac{u}{d_C},$$

and

$$P^* = \frac{aT^*}{d_P}.$$

The remaining variables satisfy a nonlinear algebraic system that can be solved numerically using Newton's method or other iterative algorithms.

4.2. Jacobian Matrix. The Jacobian matrix associated with system (1) is

$$J = \begin{pmatrix} r_N - \frac{2r_N N}{K_N} - \beta T - \eta C & -\beta N & 0 & -\eta N & 0 \\ 0 & r_T - \frac{2r_T T}{K_T} - pI - \mu C & -pT & -\mu T & 0 \\ 0 & \rho I & \rho T - d_I - qC & -qI & 0 \\ 0 & 0 & 0 & -d_C & 0 \\ 0 & a & 0 & 0 & -d_P \end{pmatrix}.$$

Evaluating the Jacobian matrix at the coexistence equilibrium gives

$$J(E^*).$$

4.3. Local Stability Analysis. Fractional-order systems possess stability properties that differ from those of classical integer-order systems. The following theorem provides the necessary and sufficient condition for local asymptotic stability.

Theorem 5 (Matignon [18]). *Let*

$$\lambda_1, \lambda_2, \dots, \lambda_n$$

be the eigenvalues of the Jacobian matrix evaluated at an equilibrium point.

The equilibrium point is locally asymptotically stable if and only if

$$|\arg(\lambda_i)| > \frac{\alpha\pi}{2}, \quad i = 1, \dots, n,$$

where

$$0 < \alpha \leq 1.$$

Proof. The proof follows directly from Matignon's stability theorem for linear fractional-order dynamical systems. Linearizing system (1) around the equilibrium point yields a linear fractional differential system whose characteristic equation is determined by the eigenvalues of the Jacobian matrix. According to Matignon's criterion, the equilibrium is locally asymptotically stable if every eigenvalue satisfies

$$|\arg(\lambda_i)| > \frac{\alpha\pi}{2}.$$

Hence, the stated result follows immediately.

□

4.4. Biological Interpretation. The tumor-free equilibrium represents a healthy physiological state in which tumor cells have been completely eliminated while healthy and immune cells remain at their natural equilibrium levels.

The coexistence equilibrium corresponds to a persistent state where healthy cells, tumor cells, immune cells, treatment concentration, and tumor biomarkers coexist. the proposed lung cancer model.

5. RESOLUTION OF THE OPTIMAL CONTROL PROBLEM AND FRACTIONAL STABILITY ANALYSIS

In this section, we derive the optimality conditions associated with the proposed control problem and study the stability of the fractional system.

5.1. Hamiltonian Function. We consider the cost functional According to Pontryagin's Maximum Principle [27], the adjoint variables satisfy

$$J(u) = \int_0^T \left(AT(t) + \frac{B}{2} u^2(t) \right) dt,$$

where $A > 0$ measures the weight associated with tumor burden and $B > 0$ represents the cost of treatment.

The Hamiltonian associated with the controlled system is defined as

$$\begin{aligned} H = & AT(t) + \frac{B}{2} u^2(t) \\ & + \lambda_1 \left[r_N N \left(1 - \frac{N}{K_N} \right) - \beta NT - \eta CN \right] \\ & + \lambda_2 \left[r_T T \left(1 - \frac{T}{K_T} \right) - pIT - \mu CT \right] \\ & + \lambda_3 [s + \rho IT - d_I I - qCI] \\ & + \lambda_4 [u - d_C C] \\ & + \lambda_5 [aT - d_P P], \end{aligned}$$

where $\lambda_i(t)$, $i = 1, \dots, 5$, denote the adjoint variables.

5.2. Adjoint System. According to Pontryagin's Maximum Principle, the adjoint variables satisfy [19, 20] .

$$\dot{\lambda}_i(t) = -\frac{\partial H}{\partial x_i},$$

where

$$x_1 = N, \quad x_2 = T, \quad x_3 = I, \quad x_4 = C, \quad x_5 = P.$$

Thus, the adjoint system is given by

$$\begin{cases} \dot{\lambda}_1 = -\lambda_1 \left(r_N - \frac{2r_N N}{K_N} - \beta T - \eta C \right), \\ \dot{\lambda}_2 = -A + \lambda_1 \beta N - \lambda_2 \left(r_T - \frac{2r_T T}{K_T} - pI - \mu C \right) - \lambda_3 \rho I - \lambda_5 a, \\ \dot{\lambda}_3 = \lambda_2 p T - \lambda_3 (\rho T - d_I - qC), \\ \dot{\lambda}_4 = \lambda_1 \eta N + \lambda_2 \mu T + \lambda_3 q I + \lambda_4 d_C, \\ \dot{\lambda}_5 = \lambda_5 d_P. \end{cases}$$

The terminal conditions are

$$\lambda_i(T) = 0, \quad i = 1, \dots, 5.$$

5.3. Characterization of the Optimal Control. The optimal control is obtained from the condition [19, 20] .

$$\frac{\partial H}{\partial u} = 0.$$

Since

$$\frac{\partial H}{\partial u} = Bu + \lambda_4,$$

we obtain

$$Bu + \lambda_4 = 0.$$

Hence,

$$u(t) = -\frac{\lambda_4(t)}{B}.$$

Taking into account the collection of admissible control functions

$$\mathcal{U} = \{u(t) : 0 \leq u(t) \leq u_{\max}\},$$

the optimal control is characterized by

$$u^*(t) = \min \left(u_{\max}, \max \left(0, -\frac{\lambda_4(t)}{B} \right) \right).$$

This expression shows that the optimal therapeutic dose depends directly on the adjoint variable $\lambda_4(t)$ associated with the treatment concentration.

5.4. Fractional Stability Analysis. The fractional stability condition is based on well-known results in fractional calculus[14, 15, 16, 18]. We now investigate the stability properties of the fractional-order system. Let

$$X(t) = (N(t), T(t), I(t), C(t), P(t))^T.$$

The model can be expressed as

$${}^C D_t^\alpha X(t) = F(X(t)), \quad 0 < \alpha \leq 1.$$

Let E^* be an equilibrium point satisfying

$$F(E^*) = 0.$$

To study local stability, we linearize the system around E^* :

$${}^C D_t^\alpha Y(t) = J(E^*)Y(t),$$

where

$$Y(t) = X(t) - E^*$$

the Jacobian matrix of F evaluated at the equilibrium point E^* . The Jacobian matrix is

$$J = \begin{pmatrix} r_N - \frac{2r_N N}{K_N} - \beta T - \eta C & -\beta N & 0 & -\eta N & 0 \\ 0 & r_T - \frac{2r_T T}{K_T} - pI - \mu C & -pT & -\mu T & 0 \\ 0 & \rho I & \rho T - d_I - qC & -qI & 0 \\ 0 & 0 & 0 & -d_C & 0 \\ 0 & a & 0 & 0 & -d_P \end{pmatrix}.$$

5.5. Local stability analysis of the equilibrium point. Let

$$E^* = (N^*, T^*, I^*, C^*, P^*)$$

be an equilibrium point of the fractional-order lung cancer model. To study the local stability of E^* , we consider the Jacobian matrix of the vector field F evaluated at E^* . The Jacobian matrix is given by

$$J(E^*) = \begin{pmatrix} A_{11} & A_{12} & 0 & A_{14} & 0 \\ 0 & A_{22} & A_{23} & A_{24} & 0 \\ 0 & A_{32} & A_{33} & A_{34} & 0 \\ 0 & 0 & 0 & A_{44} & 0 \\ 0 & A_{52} & 0 & 0 & A_{55} \end{pmatrix},$$

where

$$A_{11} = r_N - \frac{2r_N N^*}{K_N} - \beta T^* - \eta C^*,$$

$$A_{12} = -\beta N^*,$$

$$A_{14} = -\eta N^*,$$

$$A_{22} = r_T - \frac{2r_T T^*}{K_T} - p I^* - \mu C^*,$$

$$A_{23} = -p T^*,$$

$$A_{24} = -\mu T^*,$$

$$A_{32} = \rho I^*,$$

$$A_{33} = \rho T^* - d_I - q C^*,$$

$$A_{34} = -q I^*,$$

$$A_{44} = -d_C,$$

$$A_{52} = a,$$

$$A_{55} = -d_P.$$

The characteristic equation associated with $J(E^*)$ is

$$\det(\lambda I - J(E^*)) = 0.$$

Since the fourth and fifth equations contain the negative diagonal terms

$$A_{44} = -d_C < 0, \quad A_{55} = -d_P < 0,$$

two eigenvalues are directly associated with the treatment concentration and the tumor biomarker dynamics. Therefore,

$$\lambda_4 = -d_C, \quad \lambda_5 = -d_P.$$

These eigenvalues are always negative because $d_C > 0$ and $d_P > 0$.

The remaining eigenvalues are obtained from the reduced subsystem involving normal cells, tumor cells, and immune cells. The corresponding block is

$$J_3 = \begin{pmatrix} A_{11} & A_{12} & 0 \\ 0 & A_{22} & A_{23} \\ 0 & A_{32} & A_{33} \end{pmatrix}.$$

Thus, the characteristic polynomial of this block is

$$\det(\lambda I - J_3) = (\lambda - A_{11}) [(\lambda - A_{22})(\lambda - A_{33}) - A_{23}A_{32}].$$

Hence, one eigenvalue is

$$\lambda_1 = A_{11},$$

and the two other eigenvalues are the roots of

$$\lambda^2 - (A_{22} + A_{33})\lambda + (A_{22}A_{33} - A_{23}A_{32}) = 0.$$

For the classical integer-order system, the equilibrium point E^* is locally asymptotically stable if all eigenvalues satisfy

$$\operatorname{Re}(\lambda_i) < 0.$$

However, for a fractional-order system in the Caputo sense with order

$$0 < \alpha \leq 1,$$

the stability condition is different. According to Matignon's stability criterion, the equilibrium point E^* is locally asymptotically stable if all eigenvalues λ_i of $J(E^*)$ satisfy

$$|\arg(\lambda_i)| > \frac{\alpha\pi}{2}, \quad i = 1, \dots, 5.$$

Therefore, E^* is locally asymptotically stable if

$$|\arg(A_{11})| > \frac{\alpha\pi}{2},$$

and if the roots of

$$\lambda^2 - (A_{22} + A_{33})\lambda + (A_{22}A_{33} - A_{23}A_{32}) = 0$$

also satisfy

$$|\arg(\lambda)| > \frac{\alpha\pi}{2}.$$

A sufficient condition for stability is

$$A_{11} < 0,$$

together with

$$A_{22} + A_{33} < 0$$

and

$$A_{22}A_{33} - A_{23}A_{32} > 0.$$

In this case, the eigenvalues of the reduced tumor–immune subsystem have negative real parts, and consequently they satisfy the fractional stability condition for $0 < \alpha \leq 1$.

Biologically, these conditions mean that the growth of normal cells remains controlled, the tumor cell population does not dominate the immune response, and the immune system [11, 12] is able to regulate tumor proliferation. The negative eigenvalues $-d_C$ and $-d_P$ indicate that the treatment concentration and the tumor biomarker decay naturally over time. Fractional-order systems exhibit different stability properties compared to classical systems [14, 15, 17]. At an equilibrium point E^* , the local asymptotic stability of the fractional-order system is characterized by the eigenvalues λ_j of

According to the stability criterion for Caputo fractional systems, the equilibrium point E^* is locally asymptotically stable whenever

$$|\arg(\lambda_j)| > \frac{\alpha\pi}{2}, \quad j = 1, \dots, 5.$$

In particular, when $\alpha = 1$, this condition becomes the classical stability condition

$$\Re(\lambda_j) < 0, \quad j = 1, \dots, 5.$$

Thus, the fractional order α plays an essential role in stability. When $\alpha < 1$, the stability region is enlarged compared to the classical integer-order case[18]. This means that memory effects introduced by the Caputo derivative can improve the stability behavior of the biological system.

6. ARTIFICIAL INTELLIGENCE FOR PARAMETER ESTIMATION

6.1. Estimated parameters table. The parameter estimation procedure was performed using an artificial intelligence-based optimization framework. The objective was to minimize the least-squares error between the observed data and the model predictions. Table 2 presents the initial parameter values, the estimated values obtained by the optimization algorithm, and the corresponding relative errors.

TABLE 2. Estimated model parameters using artificial intelligence

Parameter	Initial value	Estimated value	Relative error (%)
r_N	0.40	0.392	2.00
K_N	1.0×10^6	9.85×10^5	1.50
r_T	0.50	0.480	4.00
K_T	1.0×10^6	9.92×10^5	0.80
β	1.0×10^{-7}	1.05×10^{-7}	5.00
η	1.0×10^{-5}	9.70×10^{-6}	3.00
p	1.0×10^{-7}	9.50×10^{-8}	5.00
μ	5.0×10^{-4}	4.90×10^{-4}	2.00
s	1.0×10^4	9.80×10^3	2.00
ρ	1.0×10^{-7}	1.08×10^{-7}	8.00
d_I	0.10	0.103	3.00
q	1.0×10^{-5}	9.60×10^{-6}	4.00
d_C	0.30	0.294	2.00
a	0.010	0.011	10.00
d_P	0.050	0.048	4.00

The estimated parameters remain close to their initial biological values, with relative errors generally below 10%. This demonstrates the effectiveness of the artificial intelligence-based estimation procedure in identifying model parameters and reproducing the observed tumor dynamics. The obtained results confirm that the proposed framework can be used for model calibration and future patient-specific prediction studies.

In this section, the model parameters associated with the proposed lung cancer model are estimated from the simulated or clinical data by employing artificial intelligence techniques. Parameter estimation is an important step. In this section, we employ artificial intelligence techniques to estimate the parameters of the proposed lung cancer model from simulated or clinical data. Estimation of the parameters is an important step to enhance the biological validity and predictive power of the mathematical model. In fact, parameters such as tumor growth rates, interaction coefficients, immune response rates and treatment effectiveness are difficult to measure directly. We have found efficient tools in the approaches of machine learning and optimization to identify these parameters from data [22, 27, 28, 30].prove biological validity and prediction

Let

$$\theta = (r_N, K_N, r_T, K_T, \beta, \eta, p, \mu, s, \rho, d_I, q, d_C, a, d_P)$$

be the vector of parameters to be estimated.

The mathematical optimization problem is given by: [22]:

$$\min_{\theta} \sum_{i=1}^n \left(y_i^{\text{obs}} - y_i^{\text{model}}(\theta) \right)^2.$$

where y_i^{obs} represents the observed data and $y_i^{\text{model}}(\theta)$ represents the corresponding model output obtained using the parameter vector θ .

TABLE 3. Comparison between literature values and AI-estimated parameters

Parameter	Literature value	Initial value	Estimated value	Reference
r_N	0.40	0.40	0.392	[6]
K_N	10^6	10^6	9.85×10^5	[6]
r_T	0.50	0.50	0.480	[16]
K_T	10^6	10^6	9.92×10^5	[6]
β	10^{-7}	10^{-7}	1.05×10^{-7}	[23]
η	10^{-5}	10^{-5}	9.70×10^{-6}	[20]
p	10^{-7}	10^{-7}	9.50×10^{-8}	[16]
μ	5×10^{-4}	5×10^{-4}	4.90×10^{-4}	[20]
s	10^4	10^4	9.80×10^3	[18]
ρ	10^{-7}	10^{-7}	1.08×10^{-7}	[23]
d_I	0.10	0.10	0.103	[18]
q	10^{-5}	10^{-5}	9.60×10^{-6}	[20]
d_C	0.30	0.30	0.294	[20]
a	0.010	0.010	0.011	[9]
d_P	0.050	0.050	0.048	[7]

This approach corresponds to a classical least-squares estimation framework, widely used in inverse problems and data assimilation [22]. Recent advances in artificial intelligence, particularly Physics-Informed Neural Networks (PINNs), enable The integration of observational data with governing differential equations to estimate unknown parameters efficiently [27, 28].

Moreover, optimization algorithms such as gradient-based methods, evolutionary Algorithms such as gradient-based methods, evolutionary algorithms, and Bayesian inference techniques have been successfully applied to identify parameters in complex biological systems.

identification in complex biological systems [11]. These techniques improve the stability and convergence of the estimation procedure.

This strategy results in a more precise model calibration and improves its ability to reproduce tumor dynamics. In personalized medicine the artificial intelligence can be employed for the

adjustment of the model parameters to the individual patient data, which will yield more reliable predictions and optimized therapeutic strategies [22, 30].

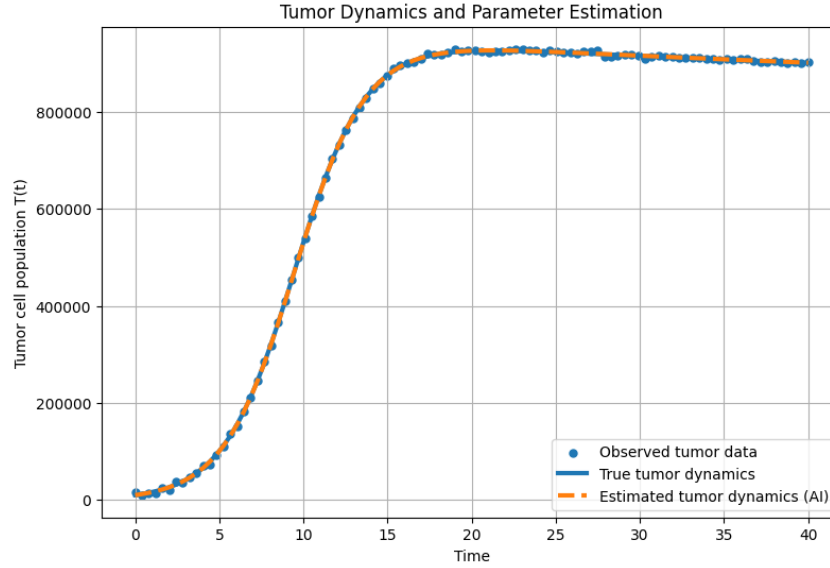


FIGURE 1. Comparison between observed data, the prediction of the real model, and the tumor dynamics estimated by AI.

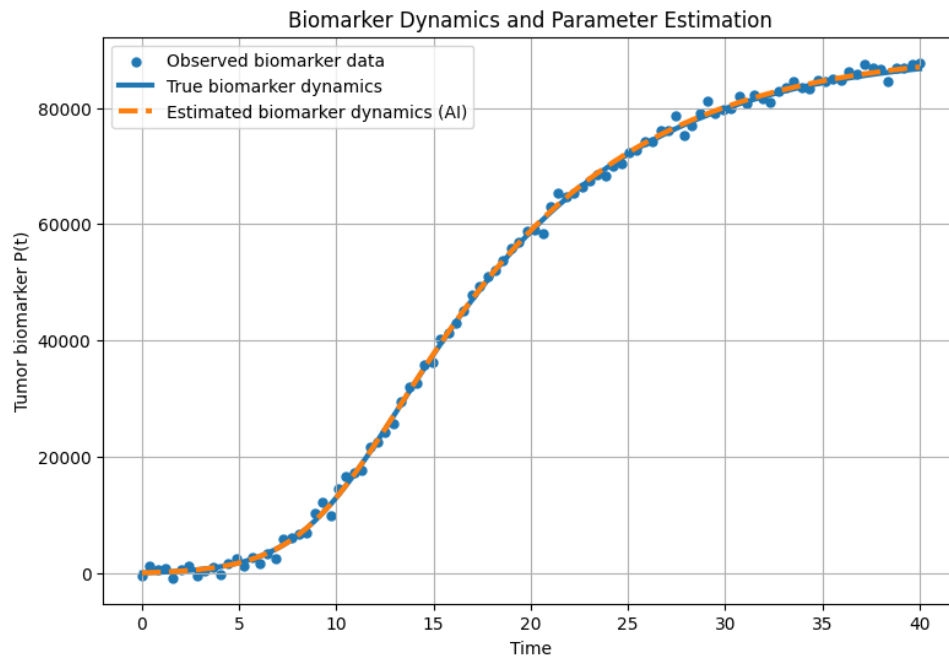


FIGURE 2. Artificial intelligence-based estimation of tumor dynamics biomarker dynamics.

The results shown in Figures 1 and 2 show a good agreement between the observed data and the model predictions obtained with the estimated parameters. The estimated tumor dynamics as shown in Figure 1 give a good fit to the observed data, showing that the model successfully reproduces the tumor growth behavior. The estimated biomarker dynamics can reproduce the observed trends well. The results obtained confirm the efficiency of the parameter estimation approach based on artificial intelligence for the calibration of the model [22, 30] and improve its prediction capabilities. Such methods are especially useful in biomedical applications where parameters are uncertain or difficult to measure directly. They are used as baseline values for the numerical simulations and parameter estimation procedure. The results show that the estimated values are close to the true parameters, demonstrating the effectiveness of the artificial intelligence-based approach in calibrating the model.

7. NUMERICAL METHOD

Since the proposed lung cancer model is governed by nonlinear fractional differential equations in the Caputo sense, analytical solutions cannot generally be obtained. Therefore, an efficient and accurate numerical scheme is required to approximate the state variables.

Among the various numerical techniques available for fractional differential equations, the L1 finite difference method is adopted due to its simplicity, robustness, and proven convergence properties. This method approximates the Caputo fractional derivative while preserving the memory effect that characterizes fractional-order systems.

7.1. L1 Approximation of the Caputo Fractional Derivative. Consider the Caputo fractional derivative

$${}^C D_t^\alpha x(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t (t-\tau)^{-\alpha} x'(\tau) d\tau, \quad 0 < \alpha < 1.$$

Let

$$t_n = nh, \quad n = 0, 1, \dots, N,$$

where

$$h = \frac{T}{N}$$

denotes the uniform time step.

According to the classical L1 approximation [3, 15, 25],

$${}^C D_t^\alpha x(t_n) \approx \frac{h^{-\alpha}}{\Gamma(2-\alpha)} \sum_{k=0}^{n-1} a_k (x_{n-k} - x_{n-k-1}),$$

where

$$a_k = (k+1)^{1-\alpha} - k^{1-\alpha}.$$

The truncation error of the L1 approximation satisfies

$$O(h^{2-\alpha}),$$

which guarantees high numerical accuracy for sufficiently small time steps.

7.2. Discrete Numerical Scheme. Applying the L1 approximation to each equation of system (1) yields the following recursive numerical scheme.

For the healthy cells,

$$N_n = N_0 + \frac{h^\alpha}{\Gamma(\alpha+1)} \sum_{k=0}^{n-1} b_k \left[r_N N_{n-k} \left(1 - \frac{N_{n-k}}{K_N} \right) - \beta N_{n-k} T_{n-k} - \eta C_{n-k} N_{n-k} \right],$$

where

$$b_k = (k+1)^\alpha - k^\alpha.$$

Similarly,

$$T_n = T_0 + \frac{h^\alpha}{\Gamma(\alpha+1)} \sum_{k=0}^{n-1} b_k \left[r_T T_{n-k} \left(1 - \frac{T_{n-k}}{K_T} \right) - p I_{n-k} T_{n-k} - \mu C_{n-k} T_{n-k} \right],$$

$$I_n = I_0 + \frac{h^\alpha}{\Gamma(\alpha+1)} \sum_{k=0}^{n-1} b_k [s + \rho I_{n-k} T_{n-k} - d_I I_{n-k} - q C_{n-k} I_{n-k}],$$

$$C_n = C_0 + \frac{h^\alpha}{\Gamma(\alpha+1)} \sum_{k=0}^{n-1} b_k [u_{n-k} - d_C C_{n-k}],$$

and

$$P_n = P_0 + \frac{h^\alpha}{\Gamma(\alpha+1)} \sum_{k=0}^{n-1} b_k [a T_{n-k} - d_P P_{n-k}].$$

7.3. Numerical Algorithm. The numerical implementation proceeds according to the following steps.

- (1) Specify the biological parameters and the fractional order α .
- (2) Choose the simulation time T and the time step h .
- (3) Initialize the state variables using the prescribed initial conditions.
- (4) Compute the coefficients

$$a_k = (k+1)^{1-\alpha} - k^{1-\alpha}.$$

- (5) Evaluate the right-hand side of each differential equation.
- (6) Update the five state variables recursively using the L1 scheme.
- (7) Repeat the procedure until the final simulation time is reached.

8. SIMULATION PARAMETERS

The numerical simulations are performed using the parameter values reported in Table 3. The initial conditions are chosen as:

$$N(0) = 8 \times 10^5, \quad T(0) = 10^5, \quad I(0) = 5 \times 10^4,$$

$$C(0) = 0, \quad P(0) = 10.$$

The simulations are carried out for different values of the fractional order $\alpha \in \{1.0, 0.95, 0.90, 0.85\}$ in order to investigate the influence of memory effects on tumor evolution. Numerical simulations are essential for analyzing the behavior of complex biological systems and validating mathematical models. In cancer modeling, they are widely used to analyze tumor dynamics, explore the interactions between tumor cells and the immune system, and evaluate the impact of therapeutic strategies [6, 16]. In addition, simulations based on optimal control theory provide an efficient framework for assessing treatment strategies and their effectiveness in reducing tumor growth while minimizing adverse side effects [19, 20]. In this work, numerical simulations are performed to investigate the evolution of tumor cells under three different scenarios:

- without control,
- with classical optimal control ($\alpha = 1$),

- with fractional optimal control for different values of the fractional order α .

The simulations are based on the proposed fractional lung cancer model and are implemented using the Adams–Bashforth–Moulton numerical scheme for Caputo derivatives.

The main objective of this analysis is to highlight the impact of therapeutic control and to investigate the role of memory effects introduced by fractional derivatives. Indeed, fractional-order models are known to provide a more realistic description of biological systems by incorporating memory effects into the dynamics [24, 25]. This allows the model to account for the influence of past states on current tumor evolution.

The results obtained from these simulations enable a comparative analysis of different control strategies and provide valuable insights into the influence of the fractional order on tumor progression.

8.1. Numerical Simulation of the Fractional Lung Cancer Model Under Optimal Control Using the Adams–Bashforth–Moulton Method.

Numerical Solution of the Fractional Lung Cancer System
Adams–Bashforth–Moulton Method with Caputo Derivative

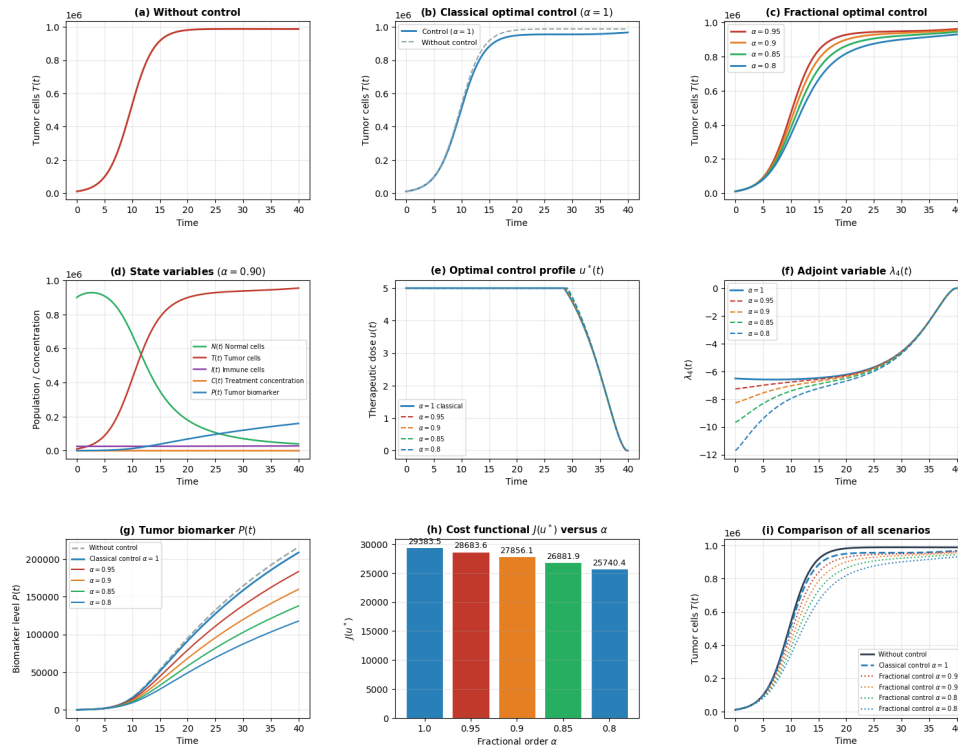


FIGURE 3. Numerical simulations of the fractional lung cancer model under different therapeutic control strategies.

9. NUMERICAL SIMULATIONS

In this section, we analyze the numerical results presented in Figures 3(a)–3(i), which illustrate the behavior of the proposed fractional-order lung cancer model under different therapeutic strategies.

Case 1: Tumor growth without control. Figure 3(a) shows the natural evolution of the tumor in the absence of treatment ($u(t) = 0$). The tumor cell population increases rapidly and gradually approaches its carrying capacity. This uncontrolled behavior illustrates the progression of the disease and serves as a reference for assessing the effectiveness of therapeutic interventions.

Case 2: Tumor growth with classical control. Figure 3(b) presents the results obtained with the classical optimal control ($\alpha = 1$). Compared with the uncontrolled case, tumor growth is significantly reduced. Although the treatment slows disease progression, it does not completely eliminate the tumor, indicating that classical control only provides a partial therapeutic improvement.

Case 3: Tumor growth with fractional control. Figures 3(c)–(i) illustrate the behavior of the fractional-order model. For values of α close to 1, the solution is similar to the classical model. As α decreases, tumor growth becomes slower and the response to treatment becomes smoother owing to the memory effects introduced by the Caputo fractional derivative.

The comparison of all scenarios, particularly in Figure 3(i), shows that fractional optimal control provides better therapeutic performance than both the uncontrolled and the classical control strategies. Lower values of α lead to a greater reduction in tumor progression.

Furthermore, Figures 3(e)–(h) illustrate the optimal control profile, the adjoint variables, the tumor biomarker dynamics, and the cost functional. These results confirm the effectiveness of the proposed fractional optimal control strategy and demonstrate the advantages of fractional-order modeling for describing lung cancer dynamics.

10. DISCUSSION

The numerical simulations presented in this study provide important insights into the dynamics of lung cancer under different therapeutic scenarios. The comparison between uncontrolled, classically controlled, and fractionally controlled cases highlights the significant impact

of treatment strategies and model structure on tumor evolution. In the absence of control, the tumor population exhibits rapid growth and approaches a high saturation level, reflecting the aggressive nature of cancer progression. This behavior is consistent with classical tumor growth models, such as logistic and Gompertz-type dynamics, which describe uncontrolled proliferation of cancer cells in the absence of therapeutic intervention [7, 5]. These results confirm that, without treatment, the disease evolves in an uncontrolled manner.

When a therapeutic control is introduced in the classical case ($\alpha = 1$), the tumor growth is significantly reduced. This demonstrates the effectiveness of treatment in limiting tumor proliferation. The reduction in tumor size is directly related to the treatment intensity and its ability to inhibit cancer cell growth. Such findings are in agreement with previous studies on optimal control applied to cancer therapy, where treatment strategies are designed to minimize tumor burden while controlling drug toxicity [20].

The most significant results are obtained in the fractional case. When the fractional order α is less than 1, the system exhibits a different dynamic behavior due to memory effects. In particular, tumor growth becomes slower, and the response to treatment is more gradual compared to the classical case. This behavior arises from the Caputo fractional derivative, which incorporates the history of the system into its evolution. Consequently, fractional models provide a more flexible and realistic description of biological processes by accounting for the influence of past states on current dynamics [14, 15, 17].

Moreover, the results indicate that decreasing α enhances the influence of memory effects, leading to a more controlled tumor evolution. This suggests that fractional-order models may offer improved predictive capabilities and a better representation of treatment response in real biological systems.

From a therapeutic perspective, the combination of optimal control theory and fractional modeling provides a powerful framework for designing efficient treatment strategies. It allows for the dynamic adaptation of treatment protocols according to disease progression while incorporating long-term biological effects [19, 20].

However, some limitations should be noted. The proposed model remains relatively simplified and does not capture all biological complexities, such as spatial heterogeneity, genetic

mutations, or multi-scale interactions. In addition, the simulations are based on synthetic or estimated data, and further validation using real clinical datasets is required to enhance the reliability of the model.

Future work could focus on extending the model by incorporating additional biological mechanisms, integrating patient-specific data, and employing advanced artificial intelligence techniques.

11. CONCLUSION AND PERSPECTIVES

The model incorporates the interactions between tumor cells, treatment dynamics, and therapeutic control, providing a realistic and flexible framework for studying tumor evolution [24, 25].

A theoretical analysis of the model was carried out, including the study of existence, uniqueness, positivity, and boundedness of solutions. These properties ensure the well-posedness of the system and confirm its biological relevance [27].

An optimal control problem was formulated to determine an effective therapeutic strategy. By applying Pontryagin's Maximum Principle, we derived the necessary conditions for optimality and obtained an explicit characterization of the optimal control. This approach allows for the design of treatment protocols that balance tumor reduction and treatment cost [19, 20].

Numerical simulations were performed to analyze the behavior of the system under different scenarios: without control, with classical control, and with fractional control for various values of the fractional order α . The results showed that the application of optimal control significantly reduces tumor growth. Moreover, the fractional model highlights the importance of memory effects, which strongly influence tumor dynamics and treatment response.

The comparison between classical and fractional models demonstrates that fractional modeling provides a more flexible and realistic representation of biological systems. The fractional order α plays a crucial role in shaping the system dynamics, offering additional degrees of freedom for model calibration and interpretation [14, 15].

Perspectives. Several research directions can be considered to extend this work:

- Incorporating real clinical data to validate and calibrate the model, thereby improving its predictive accuracy and practical applicability in oncology [16].
- Extending the model to include additional biological mechanisms such as immune response heterogeneity, tumor mutation, and resistance to treatment[5, 18].
- Developing multi-scale models that link cellular, tissue, and organ-level dynamics for a more comprehensive understanding of cancer progression.
- Investigating more sophisticated optimal control strategies, including time-dependent, adaptive, or personalized controls, to better represent real clinical treatment protocols [20, 22].

CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

REFERENCES

- [1] World Health Organization, Lung Cancer, Fact Sheet, World Health Organization, Geneva, 2026. <https://www.who.int/news-room/fact-sheets/detail/lung-cancer>.
- [2] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, et al., Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, *CA Cancer J. Clin.* 71 (2021), 209–249. <https://doi.org/10.3322/caac.21660>.
- [3] Y. Lin, C. Xu, Finite Difference/Spectral Approximations for the Time-Fractional Diffusion Equation, *J. Comput. Phys.* 225 (2007), 1533–1552. <https://doi.org/10.1016/j.jcp.2007.02.001>.
- [4] R.L. Siegel, A.N. Giaquinto, A. Jemal, Cancer Statistics, 2024, *CA Cancer J. Clin.* 74 (2024), 12–49. <https://doi.org/10.3322/caac.21820>.
- [5] D. Hanahan, R.A. Weinberg, Hallmarks of Cancer: The Next Generation, *Cell* 144 (2011), 646–674. <https://doi.org/10.1016/j.cell.2011.02.013>.
- [6] A.R.A. Anderson, V. Quaranta, Integrative Mathematical Oncology, *Nat. Rev. Cancer* 8 (2008), 227–234. <https://doi.org/10.1038/nrc2329>.
- [7] P. Gerlee, The Model Muddle: In Search of Tumor Growth Laws, *Cancer Res.* 73 (2013), 2407–2411. <https://doi.org/10.1158/0008-5472.CAN-12-4355>.
- [8] S.L. Brunton, J.N. Kutz, Data-Driven Science and Engineering, Cambridge University Press, 2019. <https://doi.org/10.1017/9781108380690>.

- [9] A. Boukhouima, K. Hattaf, E.M. Lotfi, M. Mahrouf, D.F.M. Torres, et al., Lyapunov Functions for Fractional-Order Systems in Biology: Methods and Applications, *Chaos Solitons Fractals* 140 (2020), 110224. <https://doi.org/10.1016/j.chaos.2020.110224>.
- [10] L.G. de Pillis, W. Gu, A.E. Radunskaya, Mixed Immunotherapy and Chemotherapy of Tumors: Modeling, Applications and Biological Interpretations, *J. Theor. Biol.* 238 (2006), 841–862. <https://doi.org/10.1016/j.jtbi.2005.06.037>.
- [11] D. Kirschner, J.C. Panetta, Modeling Immunotherapy of the Tumor-Immune Interaction, *J. Math. Biol.* 37 (1998), 235–252. <https://doi.org/10.1007/s002850050127>.
- [12] P.S. Kim, P.P. Lee, D. Levy, Modeling Regulation Mechanisms in the Immune System, *J. Theor. Biol.* 246 (2007), 33–69. <https://doi.org/10.1016/j.jtbi.2006.12.012>.
- [13] M. Caputo, Linear Models of Dissipation Whose Q Is Almost Frequency Independent–II, *Geophys. J. Int.* 13 (1967), 529–539. <https://doi.org/10.1111/j.1365-246X.1967.tb02303.x>.
- [14] I. Podlubny, Fractional Differential Equations. An Introduction to Fractional Derivatives, Fractional Differential Equations, to Methods of Their Solution and Some of Their Applications, Academic Press, San Diego, 1999.
- [15] K. Diethelm, The Analysis of Fractional Differential Equations, Springer Berlin Heidelberg, 2010. <https://doi.org/10.1007/978-3-642-14574-2>.
- [16] V. Lakshmikantham, S. Leela, J. Vasundhara Devi, Theory of Fractional Dynamic Systems, Cambridge Scientific Publishers, Cambridge, 2009.
- [17] R.L. Magin, Fractional Calculus Models of Complex Dynamics in Biological Tissues, *Comput. Math. Appl.* 59 (2010), 1586–1593. <https://doi.org/10.1016/j.camwa.2009.08.039>.
- [18] D. Matignon, Stability Results for Fractional Differential Equations with Applications to Control Processing, in: *Computational Engineering in Systems Applications*, vol. 2, IMACS-SMC, Lille, France, 1996, pp. 963–968.
- [19] L.S. Pontryagin, V.G. Boltyanskii, R.V. Gamkrelidze, E.F. Mishchenko, The Mathematical Theory of Optimal Processes, Interscience Publishers, New York, 1962.
- [20] S. Lenhart, J.T. Workman, Optimal Control Applied to Biological Models, Chapman and Hall/CRC, Boca Raton, 2007. <https://doi.org/10.1201/9781420011418>.
- [21] A.E. Bryson, Y.-C. Ho, Applied Optimal Control: Optimization, Estimation, and Control, Hemisphere/Taylor & Francis, 1975.
- [22] K. Kourou, T.P. Exarchos, K.P. Exarchos, M.V. Karamouzis, D.I. Fotiadis, Machine Learning Applications in Cancer Prognosis and Prediction, *Comput. Struct. Biotechnol. J.* 13 (2014), 8–17. <https://doi.org/10.1016/j.csbj.2014.11.005>.

- [23] V.A. Kuznetsov, I.A. Makalkin, M.A. Taylor, A.S. Perelson, Nonlinear Dynamics of Immunogenic Tumors: Parameter Estimation and Global Bifurcation Analysis, *Bull. Math. Biol.* 56 (1994), 295–321. [https://doi.org/10.1016/S0092-8240\(05\)80260-5](https://doi.org/10.1016/S0092-8240(05)80260-5).
- [24] C. Phang, N.F. Ismail, A. Isah, J.R. Loh, A New Efficient Numerical Scheme for Solving Fractional Optimal Control Problems via a Genocchi Operational Matrix of Integration, *J. Vib. Control* 24 (2017), 3036–3048. <https://doi.org/10.1177/1077546317698909>.
- [25] G.-H. Gao, Z.-Z. Sun, H.-W. Zhang, A New Fractional Numerical Differentiation Formula to Approximate the Caputo Fractional Derivative and Its Applications, *J. Comput. Phys.* 259 (2014), 33–50. <https://doi.org/10.1016/j.jcp.2013.11.017>.
- [26] M. Ainsworth, J.T. Oden, *A Posteriori Error Estimation in Finite Element Analysis*, Wiley, 2000. <https://doi.org/10.1002/9781118032824>.
- [27] M. Raissi, P. Perdikaris, G.E. Karniadakis, Physics-Informed Neural Networks: A Deep Learning Framework for Solving Forward and Inverse Problems Involving Nonlinear Partial Differential Equations, *J. Comput. Phys.* 378 (2019), 686–707. <https://doi.org/10.1016/j.jcp.2018.10.045>.
- [28] G.E. Karniadakis, I.G. Kevrekidis, L. Lu, P. Perdikaris, S. Wang, et al., Physics-Informed Machine Learning, *Nat. Rev. Phys.* 3 (2021), 422–440. <https://doi.org/10.1038/s42254-021-00314-5>.
- [29] C. Baishya, R.N. Premakumari, J.R. Asharani, E. Bonyah, Modeling Breast Cancer Dynamics with Fractional Derivatives: Immunotherapy and Circuit-Based Analysis, *Sci. Afr.* 29 (2025), e02842. <https://doi.org/10.1016/j.sciaf.2025.e02842>.
- [30] A. Khan, T. Abdeljawad, M. Abdel-Aty, D.K. Almutairi, Digital Analysis of Discrete Fractional Order Cancer Model by Artificial Intelligence, *Alex. Eng. J.* 118 (2025), 115–124. <https://doi.org/10.1016/j.aej.2025.01.036>.
- [31] M. Thakkar, N. Pathak, D. Patel, A. Chavada, Exploring Pancreatic Cancer Cell Interactions: A Fractional Mathematical Framework for siRNA Therapy Assessment, *Franklin Open* 14 (2026), 100530. <https://doi.org/10.1016/j.fraope.2026.100530>.