

A study of a fractional-order cancer biomarker model theoretical analysis and numerical simulation

Bushra M. Al-Smadi¹, Shaher M. Momani^{1,2}, Iqbal M. Batiha^{2,3*}, Sara A. Khalil⁴, and Sana Abughurra⁴

¹Department of Mathematics, Faculty of Science, The University of Jordan, Amman, Jordan

²Nonlinear Dynamics Research Center (NDRC), Ajman University, Ajman, United Arab Emirates

³Department of Mathematics, Al Zaytoonah University of Jordan, Amman, Jordan

⁴Department of Mathematics, Applied Science Private University, Amman, Jordan

bsr8220262@ju.edu.jo; s.momani@ju.edu.jo; i.batiha@zu.edu.jo; s_khalil@asu.edu.jo;

s_abugurrah@asu.edu.jo

ARTICLE INFO

Article history:

Received: June 19, 2026

Revised: July 7, 2026

Accepted: July 10, 2026

Published Online: July 31, 2026

Keywords:

Fractional-order cancer model

Cancer biomarkers

Existence and uniqueness

Local stability

Generalized fractional taylor expansion

Particle swarm optimization

ABSTRACT

This paper presents a fractional-order mathematical model for describing the dynamics of cancer biomarkers based on the Caputo fractional derivative. The proposed model incorporates memory effects inherent in biological systems, which provides a more realistic framework than the corresponding classical integer-order model. The existence and uniqueness of solutions are established using fixed-point theory, while the local stability of the equilibrium point is investigated through suitable stability criteria. Numerical solutions are obtained using the Generalized Fractional Taylor Expansion (GFTE), and the effectiveness and accuracy of the proposed numerical scheme are demonstrated. Furthermore, Particle Swarm Optimization (PSO) is employed for determining the optimal model parameters and nanoparticle dosage to improve tumor size estimation. The numerical results reveal the influence of the fractional-order parameter on biomarker dynamics and show that the proposed fractional-order model offers a flexible and robust framework for cancer biomarker analysis, early tumor detection, and optimization-based parameter estimation.



1. Introduction

Cancer is a complex and multifaceted disease, and despite ongoing advances in detection and treatment, it remains one of the leading causes of death worldwide. One of the key challenges in oncology lies in the accurate modeling and analysis of cancer biomarkers, which play a critical role in early diagnosis, monitoring treatment responses, and predicting disease progression.

Classical models used to describe biomarker behavior are typically based on classical integer-order differential equations. However, such models are often inadequate when dealing with biological systems that exhibit memory effects, hereditary properties, and anomalous diffusion. At

the same time, recent developments in computational mathematics have focused on constructing numerically stable polynomial approximation frameworks that improve the robustness of stability analysis and nonlinear computations.¹ These limitations have led to growing interest in fractional calculus, which extends the concept of differentiation and integration to non-integer orders, enabling more realistic and flexible modeling of complex biological processes.

In addition to tumor-related mathematical modeling, recent studies have extensively investigated the qualitative and dynamical behavior of nonlinear fractional-order systems arising in various scientific fields including ecological models,

*Corresponding Author

chemical kinetics, chaotic systems, and stochastic dynamical systems. For instance, fractional-order ecological systems have been studied in the context of synchronization and boundedness analysis, highlighting complex dynamical behaviors such as combination synchronization and ultimate boundedness. Similarly, synchronization phenomena in coupled integer, fractional, and delay chaotic systems have been examined to understand the interaction between different dynamical regimes.² Moreover, fractional-order models have been successfully applied in chemical kinetics, such as catalytic processes, demonstrating the versatility of fractional calculus in describing memory-dependent reaction dynamics.³ In addition, stochastic and spatially dependent predator–prey systems have been analyzed using both analytical and numerical techniques to capture randomness and spatial effects in biological interactions.⁴ Furthermore, recent studies on tumor–immune interaction models and delayed predator–prey systems have focused on the existence and uniqueness of solutions, stability analysis, bifurcation phenomena, and control strategies, including delay feedback and hybrid controllers.^{5–9} Despite these advances, most existing works address either ecological, chaotic, or tumor–immune systems independently, while limited attention has been given to fractional-order cancer biomarker models integrated with nanoparticle-based detection and optimization techniques for tumor size estimation.

The authors in¹⁰ developed a mathematical model of cancer biomarkers. The effectiveness of cancer treatment largely depends on the ability to detect the disease at an early stage. However, existing biomarker technologies lack sufficient predictive capability to identify cancer early enough to significantly improve patient outcomes. Current imaging techniques and blood-based biomarkers are generally limited to detecting tumors only after they reach a minimum diameter of 1 cm, a process that may take up to ten years. Furthermore, most existing biosensor models do not provide a mechanism for estimating or tracking tumor size. In,¹¹ the authors developed an ultra-sensitive tumor-penetrating nanosensor capable of detecting tumors smaller than 5 mm; however, the model presented in¹⁰ does not include a method for quantifying tumor size. In,¹² the authors aim to enhance the mathematical model of the activity-based nanosensor by incorporating a measurable indicator of tumor size, based on the hypothesis that the concentration of cleavable reporters in urine increases as tumor size grows. This paper focuses on the existence

and uniqueness theory for a fractional-order cancer model.

Despite the significant progress achieved in cancer biomarker modeling and nanoparticle-based sensing technologies, existing mathematical models are primarily formulated using classical integer-order differential equations, which are unable to adequately represent the memory-dependent and hereditary characteristics of biological processes. Moreover, most available studies focus on biomarker detection or tumor–immune interactions without providing a comprehensive mathematical framework that combines rigorous theoretical analysis, efficient numerical approximation, and optimization for cancer biomarker dynamics. Therefore, there remains a need for a reliable fractional-order mathematical model capable of accurately describing biomarker evolution while supporting optimal tumor size estimation.

The main motivation of this study is to develop a mathematically reliable fractional-order framework to describe the dynamics of cancer biomarkers and nanoparticle-based detection systems. Since biological processes inherently exhibit memory and hereditary characteristics, fractional-order models provide a more realistic representation than classical integer-order models. In this context, investigating the stability of the proposed model is essential because it ensures that biomarker concentrations remain bounded and converge toward biologically meaningful equilibrium states under small perturbations. Establishing the stability of the proposed model ensures that the predicted biomarker dynamics remain biologically meaningful and mathematically reliable, thereby providing a solid theoretical foundation for tumor size estimation, numerical simulation, and optimization.

Recent advances have demonstrated the growing importance of fractional-order modeling in complex engineering and biomedical applications. For instance, fractional fuzzy Roesser and Fornasini–Marchesini models have been developed to investigate granular fuzzy continuous-time systems with fractional dynamics. Furthermore, fuzzy fractional epidemic models based on the Caputo derivative have been successfully employed to describe the transmission dynamics of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) over complex heterogeneous networks. In addition, fuzzy fractional formulations of the generalized Bagley–Torvik equation have been proposed to address uncertainty in engineering systems using Caputo generalized Hukuhara differentiability. These studies demonstrate the

versatility and effectiveness of fractional calculus in modeling complex systems with memory effects. However, to the best of our knowledge, similar concepts have not yet been employed for optimizing a fractional-order cancer biomarker model integrated with Particle Swarm Optimization (PSO) and solved using the Generalized Fractional Taylor Expansion (GFTE), which constitutes the main novelty of the present work.^{13–15}

Motivated by the limitations of existing cancer biomarker models, this work proposes a comprehensive fractional-order mathematical framework for analyzing cancer biomarker dynamics using the Caputo fractional derivative. Unlike previous studies, which mainly focus on either theoretical analysis or numerical simulations, the proposed approach integrates rigorous mathematical analysis, efficient numerical approximation, and parameter optimization within a unified framework. Specifically, the existence and uniqueness of solutions are established using fixed-point theory, the local stability of the equilibrium point is investigated, the Generalized Fractional Taylor Expansion (GFTE) is employed to obtain accurate numerical approximations, and Particle Swarm Optimization (PSO) is utilized to determine the optimal nanoparticle dosage for improved tumor size estimation. Therefore, the proposed framework provides both theoretical guarantees and practical computational tools for cancer biomarker modeling, contributing to more reliable strategies for early cancer detection.

2. Preliminaries

This section introduces the essential mathematical principles, theorems, and methodologies that form the foundation of this study. A rigorous understanding of these foundational concepts is critical for deriving and validating the results presented in subsequent sections. In particular, this section covers key topics such as Banach spaces, fixed-point theorems, fractional calculus operators, and stability analysis.

Definition 1.¹⁶ Let (X, d) be a metric space. We say that (X, d) is complete if every Cauchy sequence in X converges to an element of X .

Definition 2.¹⁷ A norm $\|\cdot\| : X \rightarrow \mathbb{R}$ on a vector space X must satisfy the following:

- (1) $\|x\| \geq 0$ and $\|x\| = 0 \iff x = 0$.
- (2) $\|\alpha x\| = |\alpha| \cdot \|x\|$, $\forall \alpha \in \mathbb{R}$ (or $\mathbb{C}$). where $x, y \in X$ and α is a scalar.
- (3) $\|x + y\| \leq \|x\| + \|y\|$.

In this work, we utilize the supremum Norm (L^∞ -norm). Let $B(X, \mathbb{R})$ denote the space of

all real valued bounded functions of on X . The supremum norm is defined as

$$\|f\|_\infty = \sup_{x \in X} |f(x)|.$$

Theorem 1.¹⁶ [Cauchy–Schwarz Inequality] For any two vectors $\mathbf{u}, \mathbf{v} \in \mathbb{R}^n$, we have

$$\left| \sum_{i=1}^n u_i v_i \right| \leq \left(\sum_{i=1}^n |u_i|^2 \right)^{1/2} \left(\sum_{i=1}^n |v_i|^2 \right)^{1/2}, \quad (1)$$

or equivalently,

$$|\mathbf{u} \cdot \mathbf{v}| \leq \|\mathbf{u}\|_2 \cdot \|\mathbf{v}\|_2, \quad (2)$$

where $\mathbf{u} = (u_1, u_2, \dots, u_n)$ and $\mathbf{v} = (v_1, v_2, \dots, v_n) \in \mathbb{R}^n$.

Remark 1. At each point $t \in [a, b]$ we have

$$\|\mathbf{X}(t)\|_2 \leq \sup_{\tau \in [a, b]} \|\mathbf{X}(\tau)\|_2 = \|\mathbf{X}\|_{c,2}, \quad (3)$$

where $\|\mathbf{X}\|_{c,2}$ is the supremum norm of Euclidean norm.

Definition 3.¹⁸ The system is said to satisfy the Lipschitz condition if there exists $L > 0$ such that $\|P(t, \mathbf{x}) - P(t, \mathbf{y})\| \leq L \|\mathbf{x} - \mathbf{y}\|$, $\forall \mathbf{x}, \mathbf{y} \in \Omega, \forall t \geq t_0$ where $\Omega \subset \mathbb{R}^n$ is the admissible state space, L is the Lipschitz constant.

Definition 4.¹⁷ An operator $T : X \rightarrow X$ is called a contraction if there exists a constant $l \in (0, 1)$ such that for all $x, y \in X$:

$$\|T(x) - T(y)\| \leq l \|x - y\|.$$

Theorem 2.¹⁷ (Banach Fixed Point Theorem) Let (X, d) be a complete metric space and let $T : X \rightarrow X$ be a contraction operator. Then there exists a unique fixed point $x \in X$ such that $T(x) = x$.

Definition 5.¹⁹ Let α be a real non-negative number. Then J_a^α defined on $L_1[a, b]$, (the set of all functions such that their absolute values are integrable on $[a, b]$), by

$$J_a^\alpha f(t) = \frac{1}{\Gamma(\alpha)} \int_a^t (t - \tau)^{\alpha-1} f(\tau) d\tau, \quad (4)$$

$$a \leq t \leq b,$$

is called the Riemann-Liouville fractional-order integral operator of order α .

Definition 6. Let $\alpha \in \mathbb{R}$ and $m = \lceil \alpha \rceil$. The Caputo operator D_a^α is defined by

$${}^c D_a^\alpha f = J_a^{m-\alpha} D^m f. \quad (5)$$

Definition 7. ¹⁹ Let $\alpha \in \mathbb{R}^+$ and $m = \lceil \alpha \rceil$ such that $m - 1 < \alpha \leq m$. Then the Caputo fractional-order derivative operator of order α is given by

$${}^c D_a^\alpha f(t) = \frac{1}{\Gamma(m - \alpha)} \int_a^t (t - \tau)^{m - \alpha - 1} f^{(m)}(\tau) d\tau, \quad (6)$$

$t > a$.

The Caputo fractional derivative is adopted in this study because it is particularly suitable for modeling real-world biological systems. One of its main advantages is that it allows the use of classical initial conditions expressed in terms of integer-order derivatives, which have clear physical and biological interpretations. Moreover, the Caputo derivative effectively captures the memory and hereditary characteristics inherent in cancer biomarker dynamics while maintaining consistency with traditional differential equations when the fractional order approaches one. These properties make it an appropriate choice for the proposed fractional-order cancer biomarker model. It should be noted that if $a = 0$ in (6), one obtains the most commonly used version of the Caputo fractional-order derivative operator. That we have

$${}^c D_*^\alpha f(t) = \frac{1}{\Gamma(m - \alpha)} \int_0^t (t - \tau)^{m - \alpha - 1} f^{(m)}(\tau) d\tau, \quad (7)$$

$t > 0$.

Definition 8. ²⁰ A dynamical system is called autonomous if its governing equations do not explicitly depend on time t .

Definition 9. ²⁰ An equilibrium point x^* is a solution of the equation

$$f(x^*) = 0.$$

Definition 10. ²¹ The Jacobian matrix of a system of equations is the square matrix of first-order partial derivatives:

$$J(x) = \frac{\partial f}{\partial x} = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_n} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_n} \end{pmatrix}.$$

Theorem 3. ¹⁹ The equilibrium solutions x^* of the autonomous Caputo system

$$D_t^\alpha x(t) = f(x(t)),$$

are locally asymptotically stable if all the eigenvalues λ_i of the Jacobian matrix J , evaluated at

the equilibrium points, satisfy

$$|\arg(\lambda_i)| > \frac{\alpha\pi}{2}, \quad (8)$$

where $\alpha \in (0, 1)$.

Theorem 4. (Generalized Fractional Taylor Formula).²² Suppose that $D^{k\rho} f(x) \in C(0, a]$ for $k = 0, 1, \dots, n + 1$, where $0 < \rho \leq 1$. Then

$$f(x) = \sum_{i=0}^n \frac{x^{i\rho}}{\Gamma(i\rho + 1)} (D^{i\rho} f)(0^+) + \frac{(D^{(n+1)\rho} f)(\xi)}{\Gamma((n+1)\rho + 1)} x^{(n+1)\rho}. \quad (9)$$

with $0 \leq \xi \leq x$, $\forall x \in (0, a]$.

2.1. Short description about PSO

A particle is a single candidate in the swarm. For a D -dimensional problem, each particle has a position and a velocity. To illustrate the main aspects of the PSO algorithm, we list them below with a brief description:

- (1) Position (x): The coordinates of the particle in the search space.
- (2) Velocity (v): The speed and direction in which the particle will move.
- (3) Personal Best (pbest): The best position that yields the best fitness value that an individual particle has found so far.
- (4) Global Best (gbest): The best position discovered by any particle in the entire swarm so far.
- (5) Fitness Function: a function that takes the position of a particle and returns a single numerical value (fitness value), representing how good the solution is. The goal is to maximize or minimize this value.
- (6) Inertia weight (w): a hyperparameter that controls the momentum of each particle. It determines how much of the previous velocity is retained at each iteration. It has two main effects:
 - (a) A high value of w that helps in searching new areas (exploration).
 - (b) A low value of w that helps in refining existing areas (exploitation).

The goal is to balance exploration and exploitation to achieve faster and more stable convergence.
- (7) Cognitive Coefficient (C_1) and Social Coefficient (C_2): these two hyper parameters control the attraction of the particle towards its own pbest and the swarm's gbest, respectively.
- (8) Random Numbers r_1 and r_2 : two random numbers between 0 and 1 ($r_1, r_2 \sim U[0, 1]$)

injected to maintain the stochastic nature of the algorithm.

The following content explains how PSO is implemented and how it can obtain the minimum or maximum value of the objective function:

2.1.1. Step 1: Initialization

- (1) Define the fitness function, the number of dimensions D (variables), and the boundaries of the search space for each dimension.
- (2) Set the swarm size (number of particles N), inertia weight w , cognitive coefficient C_1 , social coefficient C_2 , and the maximum number of iterations, typically $C_1, C_2 \in [1, 2.5]$, and $w \in [0.4, 0.9]$.
- (3) Initialize the swarm so that for each particle i in the swarm (from 1 to N):
 - (a) Initialize position (x_i) randomly.
 - (b) Initialize velocity (v_i), usually set to 0.
 - (c) Initialize personal best (pbest) by setting $pbest_i = x_i$.
- (4) Evaluate the fitness function:
 - (a) For each particle i , evaluate the fitness function $f(x_i)$.
 - (b) Identify the initial Global Best (gbest) by finding the particle with the best fitness value among all pbest and set gbest to its position.

2.1.2. Step 2: iteration loop

Repeat the process until a stopping criterion is met (e.g., a maximum number of iterations is reached or the desired fitness value is achieved). For each particle i in the swarm

- (1) Evaluate the fitness value $f(x_i)$ for the current position of the particle.
- (2) Update personal best ($pbest_i$):
 - (a) Compute $f(pbest_i)$.
 - (b) If $f(x_i) < f(pbest_i)$, then the current position is better, so set $pbest_i = x_i$.
- (3) Update global best ($gbest$):
 - (a) Compare $f(pbest_i)$ with $f(gbest)$.
 - (b) If $f(pbest_i) < f(gbest)$, then set $gbest$ to the particles $pbest_i$ position.
- (4) Update velocity (v_i): For each dimension d , apply

$$v_i(d) = w v_i(d) + c_1 r_1 (pbest_i(d) - x_i(d)) + c_2 r_2 (gbest(d) - x_i(d)). \quad (10)$$

- (5) Update position (x_i): For each dimension d , apply

$$x_i(d) = x_i(d) + v_i(d).$$

2.1.3. Step 3: output results

Once the loop ends, the algorithm outputs $gbest$ as the best-found solution and $f(gbest)$ as the best-found fitness value.

3. Model formulation

Building on the foundations of fractional calculus established in the previous chapter, this chapter develops an advanced fractional-order mathematical model for analyzing cancer biomarkers. It provides biological justifications for each term, presents the estimated parameter values, and highlights the advantages of the fractional-order model. In this section, we present the full set of modified model equations that describe the dynamics of nanoparticle (NP) transport, enzymatic cleavage, and reporter accumulation for cancer detection applications. Unlike classical integer-order models, these equations incorporate memory effects and anomalous diffusion, which is critical for capturing the complex behavior of NPs in a heterogeneous tumor microenvironment. In¹², the authors aimed to enhance the mathematical model of the activity-based nanosensor by incorporating a measurable indicator of tumor size, based on the hypothesis that the concentration of cleavable reporters in urine increases as tumor size grows. In particular, they proposed the following ordinary system:

$$\begin{aligned} \frac{dN_p}{dt} &= -\alpha N_p + \beta(N_t - N_p) - \frac{\gamma_m E_m N_p}{k_m} - \frac{\gamma_b E_b N_p}{k_p} \\ \frac{dN_t}{dt} &= \beta(N_p - N_t) - \frac{\gamma_m E_t N_t}{k_m} \\ \frac{dR_t}{dt} &= \frac{\gamma_m E_t N_t}{k_m} - \delta R_t \\ \frac{dR_p}{dt} &= \delta R_t + \frac{\gamma_m E_m N_p}{k_m} + \frac{\gamma_b E_b N_p}{k_p} - (\mu + v + w)R_p \\ \frac{dR_u}{dt} &= \mu R_p \end{aligned} \quad (11)$$

with initial conditions

$$\begin{aligned} N_t(0) &= R_t(0) = R_p(0) = R_u(0) = 0, \\ N_p(0) &= 2.5 \times 10^{-6}, \end{aligned} \quad (12)$$

where the variables and parameters of model (11)-(12) are defined in **Table 1**.

where p is defined in **Table 1** and r is the radius of the tumor.

Table 1. Model Parameters for Nanoparticle Pharmacokinetics

Variable	Description	Unit	Value
N_p	Nanoparticle in plasma	M	2.5×10^{-6}
N_t	Nanoparticle in tumor	M	0
R_t	Reporter in tumor	M	0
R_p	Reporter in plasma	M	0
R_u	Reporter in urine	M	0
α	Rate constant for NP clearance in plasma	min^{-1}	0.0462
P	Tumor permeability constant	m^{-1}	2.3×10^{-4}
γ_m	MMP9 catalytic efficiency	min^{-1}	3.99
γ_b	Catalytic efficiency in plasma	min^{-1}	0.0659
k_r	Reporter tumor diffusion rate	min^{-1}	0.09
μ	Rate of reporter filtration into urine	min^{-1}	0.032
v	MPS clearance rate	min^{-1}	0.0064
w	Rate of NP and reporter reabsorption	min^{-1}	2.89
k_m	MMP9 Michaelis constant	M	2.13×10^{-6}
k_p	Plasma protease Michaelis constant	M	1.0063×10^{-5}
β	Tumor surface-to-volume transfer coefficient	min^{-1}	Computed via $\beta = \frac{3P}{r}$
E_m	Concentration of shed proteases in blood	M	7.1623×10^{-8}
E_p	Concentration in blood	M	4×10^{-6}
E_t	Concentration of proteases in tumor	M	7.1624×10^{-7}

Using the Caputo derivative, system (11)-(12) can be reformulated as follows:

$$\begin{aligned}
D^\rho N_p(t) &= -\alpha N_p + \beta(N_t - N_p) - \frac{\gamma_m E_m N_p}{k_m} \\
&\quad - \frac{\gamma_b E_b N_p}{k_p}, \\
D^\rho N_t(t) &= \beta(N_p - N_t) - \frac{\gamma_m E_t N_t}{k_m}, \\
D^\rho R_t(t) &= \frac{\gamma_m E_t N_t}{k_m} - \delta R_t, \\
D^\rho R_p(t) &= \delta R_t + \frac{\gamma_m E_m N_p}{k_m} + \frac{\gamma_b E_b N_p}{k_p} \\
&\quad - (\mu + v + w)R_p, \\
D^\rho R_u(t) &= \mu R_p
\end{aligned} \tag{13}$$

Compared with the original integer-order model (11), the proposed fractional-order model (13) provides a more flexible mathematical framework by incorporating memory and hereditary effects through the Caputo fractional derivative. In biological systems, the current state is often influenced not only by present conditions but also

by the past evolution of the process. Consequently, the fractional-order formulation offers a more realistic description of nanoparticle transport, biomarker dynamics, and reporter accumulation in heterogeneous tumor environments. Moreover, the proposed model preserves the biological interpretation of the original system while extending its capability to capture complex temporal dynamics that cannot be adequately represented by classical integer-order differential equations.

with initial conditions

$$\begin{aligned}
N_t(0) &= R_t(0) = R_p(0) = R_u(0) = 0, \\
N_p(0) &= 2.5 \times 10^{-6},
\end{aligned} \tag{14}$$

where $0 < \rho \leq 1$. All other parameters remain as defined in the original model (11)-(12).

4. Existence and uniqueness

In this section, we study the existence and uniqueness of the proposed fractional-order model (13)-(14). This analysis verifies whether the model is well-posed.

Theorem 5. System (13)-(14) satisfies Lipschitz condition.

Proof. To prove this result, we first assume that

$$D^\alpha \mathbf{X}(t) = \mathbf{F}(t, \mathbf{X}), \quad (15)$$

where

$$\mathbf{X} = (N_p, N_t, R_t, R_p, R_u)^T,$$

and $\mathbf{F}$ is the vector representing the right-hand side functions from the five equations in system (13)-(14), such that

$$\mathbf{F} = \begin{bmatrix} -\alpha N_p + \beta(N_t - N_p) - \frac{\gamma_m E_m N_p}{k_m} \\ -\frac{\gamma_b E_b N_p}{k_p} \\ \beta(N_p - N_t) - \frac{\gamma_m E_t N_t}{k_m} \\ \frac{\gamma_m E_t N_t}{k_m} - \delta R_t \\ \delta R_t + \frac{\gamma_m E_m N_p}{k_m} + \frac{\gamma_b E_b N_p}{k_p} \\ -(\mu + v)R_p - wR_p \\ \mu R_p \end{bmatrix}^T \quad (16)$$

with initial condition $\mathbf{X}(0) = \mathbf{X}_0$, where

$$\mathbf{X}_0 = (N_p(0), N_t(0), R_t(0), R_p(0), R_u(0)). \quad (17)$$

Secondly, we need to show that

$$\|F_i(t, \mathbf{X}) - F_i(t, \mathbf{Y})\| \leq L_i \|\mathbf{X} - \mathbf{Y}\|,$$

for all $\mathbf{X}, \mathbf{Y}$ in the domain and

$$L_i > 0, \quad \forall i = 1, 2, 3, 4, 5.$$

For this purpose we let

$$\mathbf{X} = (N_p, N_t, R_t, R_p, R_u),$$

and

$$\mathbf{Y} = (N_p^*, N_t^*, R_t^*, R_p^*, R_u^*).$$

We consider the following states:

(1) For f_1 , we have

$$\begin{aligned} |F_1(\mathbf{X}) - F_1(\mathbf{Y})| = & \left| -\alpha N_p + \beta(N_t - N_p) \right. \\ & - \frac{\gamma_m E_m}{k_m} N_p - \frac{\gamma_b E_b}{k_p} N_p \\ & + \alpha N_p^* - \beta(N_t^* - N_p^*) \\ & \left. + \frac{\gamma_m E_m}{k_m} N_p^* + \frac{\gamma_b E_b}{k_p} N_p^* \right|. \end{aligned} \quad (18)$$

By the triangle inequality, we obtain

$$\begin{aligned} |F_1(\mathbf{X}) - F_1(\mathbf{Y})| \leq & (\alpha + \frac{\gamma_m E_m}{k_m} + \frac{\gamma_b E_b}{k_p}) |N_p - N_p^*| \\ & + \beta |(N_t - N_p) - (N_t^* - N_p^*)|. \end{aligned} \quad (19)$$

This implies that

$$\begin{aligned} |F_1(\mathbf{X}) - F_1(\mathbf{Y})| \leq & \left(\alpha + \beta + \frac{\gamma_m E_m}{k_m} + \frac{\gamma_b E_b}{k_p} \right) |N_p - N_p^*| \\ & + \beta |N_t - N_t^*|. \end{aligned} \quad (20)$$

Let

$$L_1 = \max \left(\alpha + \beta + \frac{\gamma_m E_m}{k_m} + \frac{\gamma_b E_b}{k_p}, \beta \right),$$

then

$$\begin{aligned} |F_1(\mathbf{X}) - F_1(\mathbf{Y})| \leq & L_1 |N_p - N_p^*| \\ & + L_1 |N_t - N_t^*|, \end{aligned}$$

or

$$\begin{aligned} |F_1(\mathbf{X}) - F_1(\mathbf{Y})| \leq & L_1 (|N_p - N_p^*| \\ & + |N_t - N_t^*|). \end{aligned} \quad (21)$$

Set $\mathbf{V} = (v_1, v_2) = (|N_p - N_p^*|, |N_t - N_t^*|)$.

Applying $|\sum_{i=1}^n v_i| \leq (\sqrt{\sum_{i=1}^n 1^2}) \|v\|_2$, we get

$$\begin{aligned} \left| \sum_{i=1}^2 v_i \right| &= |v_1 + v_2| \\ &= |N_p - N_p^*| + |N_t - N_t^*| \leq \sqrt{2} \cdot \|\mathbf{V}\|_2 \\ &= \sqrt{2} \cdot \sqrt{v_1^2 + v_2^2} \\ &= \sqrt{2} \cdot \sqrt{(N_p - N_p^*)^2 + (N_t - N_t^*)^2} \\ &\leq \sqrt{2} \cdot \sqrt{(N_p - N_p^*)^2 + (N_t - N_t^*)^2} \\ &\quad \sqrt{+(R_t - R_t^*)^2 + (R_p - R_p^*) + (R_u - R_u^*)} \\ &= \sqrt{2} \cdot \|\mathbf{X} - \mathbf{Y}\|_2. \end{aligned} \quad (22)$$

Thus,

$$|N_p - N_p^*| + |N_t - N_t^*| \leq \sqrt{2} \cdot \|\mathbf{X} - \mathbf{Y}\|_2. \quad (23)$$

Combining (21) and (23) we get

$$\begin{aligned} |F_1(\mathbf{X}) - F_1(\mathbf{Y})| \leq & L_1 (|N_p - N_p^*| \\ & + |N_t - N_t^*|) \\ & \leq \sqrt{2} L_1 \|\mathbf{X} - \mathbf{Y}\|_2. \end{aligned} \quad (24)$$

or

$$|F_1(\mathbf{X}) - F_1(\mathbf{Y})| \leq L_1^* \|\mathbf{X} - \mathbf{Y}\|_2, \quad (25)$$

where $L_1^* = \sqrt{2} L_1$.

(2) For f_2 , we have

$$\begin{aligned} |F_2(\mathbf{X}) - F_2(\mathbf{Y})| = & \left| \beta(N_p - N_t) - \frac{\gamma_m E_t}{k_m} N_t \right. \\ & - \beta(N_p^* - N_t^*) + \frac{\gamma_m E_t}{k_m} N_t^* \\ & = |\beta(N_p - N_p^*) \\ & - \left(\beta + \frac{\gamma_m E_t}{k_m} \right) (N_t - N_t^*)| \\ & \leq \beta |N_p - N_p^*| \\ & + \left(\beta + \frac{\gamma_m E_t}{k_m} \right) |N_t - N_t^*|. \end{aligned} \quad (26)$$

Let

$$L_2 = \max \left(\beta, \beta + \frac{\gamma_m E_t}{k_m} \right),$$

then

$$|F_2(\mathbf{X}) - F_2(\mathbf{Y})| \leq L_2 (|N_p - N_p^*|$$

$$+|N_t - N_t^*|).$$

By Cauchy-Schwarz inequality, we obtain

$$|F_2(\mathbf{X}) - F_2(\mathbf{Y})| \leq \sqrt{2} L_2 \|\mathbf{X} - \mathbf{Y}\|_2,$$

or equivalently,

$$|F_2(\mathbf{X}) - F_2(\mathbf{Y})| \leq L_2^* \|\mathbf{X} - \mathbf{Y}\|_2, \quad (27)$$

where $L_2^* = \sqrt{2} L_2$.

(3) For f_3 , we have

$$\begin{aligned} |F_3(\mathbf{X}) - F_3(\mathbf{Y})| &= \left| \frac{\gamma_m E_t N_t}{k_m} - \delta R_t \right. \\ &\quad \left. - \frac{\gamma_m E_t N_t^*}{k_m} - \delta R_t^* \right| \\ &\leq \frac{\gamma_m E_t}{k_m} |N_t - N_t^*| \\ &\quad + \delta |R_t - R_t^*|. \end{aligned} \quad (28)$$

Let

$$L_3 = \max \left(\frac{\gamma_m E_t}{k_m}, \delta \right),$$

then

$$|F_3(\mathbf{X}) - F_3(\mathbf{Y})| \leq L_3 (|N_t - N_t^*| + |R_t - R_t^*|).$$

By the same argument as before,

$$|F_3(\mathbf{X}) - F_3(\mathbf{Y})| \leq \sqrt{2} L_3 \|\mathbf{X} - \mathbf{Y}\|_2,$$

or equivalently,

$$|F_3(\mathbf{X}) - F_3(\mathbf{Y})| \leq L_3^* \|\mathbf{X} - \mathbf{Y}\|_2, \quad (29)$$

$$L_3^* = \sqrt{2} L_3.$$

(4) For f_4 , we have

$$\begin{aligned} |F_4(\mathbf{X}) - F_4(\mathbf{Y})| &= \left| \delta(R_t - R_t^*) \right. \\ &\quad + \frac{\gamma_m E_m}{k_m} (N_p - N_p^*) \\ &\quad + \frac{\gamma_b E_b}{k_p} (N_p - N_p^*) \\ &\quad - (\mu + v + w) \\ &\quad \left. (R_p - R_p^*) \right| \\ &\leq \delta |R_t - R_t^*| \\ &\quad + \left(\frac{\gamma_m E_m}{k_m} + \frac{\gamma_b E_b}{k_p} \right) \\ &\quad |N_p - N_p^*| \\ &\quad + (\mu + v + w) \\ &\quad |R_p - R_p^*|. \end{aligned} \quad (30)$$

Let

$$L_4 = \max \left(\delta, \frac{\gamma_m E_m}{k_m} + \frac{\gamma_b E_b}{k_p}, \mu + v + w \right),$$

then

$$\begin{aligned} |F_4(\mathbf{X}) - F_4(\mathbf{Y})| &\leq L_4 (|R_t - R_t^*| \\ &\quad + |N_p - N_p^*| + |R_p - R_p^*|). \end{aligned}$$

By the same argument,

$$|F_4(\mathbf{X}) - F_4(\mathbf{Y})| \leq \sqrt{3} L_4 \|\mathbf{X} - \mathbf{Y}\|_2, \quad (31)$$

or

$$|F_4(\mathbf{X}) - F_4(\mathbf{Y})| \leq L_4^* \|\mathbf{X} - \mathbf{Y}\|_2, \quad (32)$$

where $L_4^* = \sqrt{3} L_4$.

(5) For F_5 , we obtain

$$\begin{aligned} |F_5(\mathbf{X}) - F_5(\mathbf{Y})| &= |\mu R_p - \mu R_p^*| \\ &= \mu |R_p - R_p^*| \\ &\leq L_5^* \|X - Y\|_2, \end{aligned} \quad (33)$$

or

$$|F_5(\mathbf{X}) - F_5(\mathbf{Y})| \leq L_5^* \|\mathbf{X} - \mathbf{Y}\|_2, \quad (34)$$

where

$$L_5^* = \mu.$$

Now, to complete the proof, observe that

$$\|\mathbf{F}(\mathbf{X}) - \mathbf{F}(\mathbf{Y})\|_2 = \sqrt{\sum_{i=1}^5 |F_i(\mathbf{X}) - F_i(\mathbf{Y})|^2}. \quad (35)$$

By (25), (27), (29), (32), and (34), we obtain

$$\begin{aligned} \|\mathbf{F}(\mathbf{X}) - \mathbf{F}(\mathbf{Y})\|_2 &= \sqrt{\sum_{i=1}^5 |F_i(\mathbf{X}) - F_i(\mathbf{Y})|^2} \\ &\leq \sqrt{\sum_{i=1}^5 (L_i^*)^2 \|\mathbf{X} - \mathbf{Y}\|_2^2} \\ &= \left(\sqrt{\sum_{i=1}^5 (L_i^*)^2} \right) \|\mathbf{X} - \mathbf{Y}\|_2. \end{aligned} \quad (36)$$

Let

$$L = \sqrt{\sum_{i=1}^5 (L_i^*)^2},$$

then

$$\|\mathbf{F}(\mathbf{X}) - \mathbf{F}(\mathbf{Y})\|_2 \leq L \|\mathbf{X} - \mathbf{Y}\|_2.$$

This proves that system (13)-(14) satisfies the Lipschitz condition. $\square$

We now introduce a theoretical result establishing the existence and uniqueness of system (15)-(17), which is equivalent to system (13)-(14).

Theorem 6. Let $\rho \in (0, 1)$, $I = [0, h^*] \subseteq \mathbb{R}$ and

$$J = \{ \mathbf{X} \in \mathbb{R}^5 : \|\mathbf{X} - \mathbf{X}_0\| \leq r \}.$$

Suppose $\mathbf{F} : I \times J \rightarrow \mathbb{R}^5$ satisfies

(1) Boundedness, i.e. $\exists M > 0$ such that

$$\|\mathbf{F}(t, \mathbf{X})\| \leq M, \quad \forall (t, \mathbf{X}) \in I \times J.$$

(2) The Lipschitz condition established above.

If $\frac{Lr}{M} < 1$ and $h^* = \min \left\{ h, \left(\frac{r \Gamma(\rho+1)}{M} \right)^{\frac{1}{\rho}} \right\}$, then system (15)-(17) has a unique solution

$\mathbf{X} \in C^\rho[0, h^*]$.

Proof. Applying the Riemann–Liouville integral operator to both sides of (15), we obtain

$$J^\rho D^\rho \mathbf{X}(t) = J^\rho \mathbf{F}(t, \mathbf{X}),$$

or

$$\mathbf{X}(t) = \mathbf{X}_0 + J^\rho \mathbf{F}(t, \mathbf{X}),$$

that is,

$$\mathbf{X}(t) = \mathbf{X}_0 + \frac{1}{\Gamma(\rho)} \int_0^t (t-s)^{\rho-1} \mathbf{F}(s, \mathbf{X}(s)) ds.$$

Define the operator T on $C^\rho[0, h^*]$ as

$$T\mathbf{X}(t) = \mathbf{X}_0 + \frac{1}{\Gamma(\rho)} \int_0^t (t-s)^{\rho-1} \mathbf{F}(s, \mathbf{X}(s)) ds.$$

To prove the desired result using the Banach fixed-point theorem (Theorem 2), we show that T maps J to itself and T is a contraction. For $\mathbf{X} \in J$, we have

$$\begin{aligned} \|T\mathbf{X}(t) - \mathbf{X}_0\| &= \left\| \mathbf{X}_0 + \frac{1}{\Gamma(\rho)} \int_0^t (t-s)^{\rho-1} \mathbf{F}(s, \mathbf{X}(s)) ds - \mathbf{X}_0 \right\|, \\ &= \left\| \frac{1}{\Gamma(\rho)} \int_0^t (t-s)^{\rho-1} \mathbf{F}(s, \mathbf{X}(s)) ds \right\| \\ &\leq \frac{1}{\Gamma(\rho)} \int_0^t (t-s)^{\rho-1} \|\mathbf{F}(s, \mathbf{X}(s))\| ds, \end{aligned} \quad (37)$$

i.e.,

$$\|T\mathbf{X}(t) - \mathbf{X}_0\| \leq \frac{1}{\Gamma(\rho)} \int_0^t (t-s)^{\rho-1} \|\mathbf{F}(s, \mathbf{X}(s))\| ds.$$

Since $\mathbf{F}$ is bounded,

$$\|T\mathbf{X}(t) - \mathbf{X}_0\| \leq \frac{M}{\Gamma(\rho)} \int_0^t (t-s)^{\rho-1} ds.$$

Evaluating the above integral gives

$$\|T\mathbf{X}(t) - \mathbf{X}_0\| \leq \frac{Mt^\rho}{\rho\Gamma(\rho)} = \frac{Mt^\rho}{\Gamma(\rho+1)}.$$

As $t \in [0, h^*]$, we have $t^\rho \leq (h^*)^\rho$, so

$$\|T\mathbf{X}(t) - \mathbf{X}_0\| \leq \frac{Mt^\rho}{\Gamma(\rho+1)} \leq \frac{M(h^*)^\rho}{\Gamma(\rho+1)},$$

or

$$\|T\mathbf{X}(t) - \mathbf{X}_0\| \leq \frac{M(h^*)^\rho}{\Gamma(\rho+1)}. \quad (38)$$

Since

$$h^* = \min \left\{ h, \left(\frac{r\Gamma(\rho+1)}{M} \right)^{\frac{1}{\rho}} \right\}.$$

We consider two cases.

Case (1): If $h^* = h$, we choose h^* such that

$$\frac{M(h^*)^\rho}{\Gamma(\rho+1)} = \frac{M(h)^\rho}{\Gamma(\rho+1)} \leq r,$$

so (38) gives

$$\|T\mathbf{X}(t) - \mathbf{X}_0\| \leq \frac{M(h^*)^\rho}{\Gamma(\rho+1)} \leq r,$$

i.e.,

$$\|T\mathbf{X}(t) - \mathbf{X}_0\| \leq r.$$

Case (2): If $h^* = \left(\frac{r\Gamma(\rho+1)}{M} \right)^{\frac{1}{\rho}}$, then

$$(h^*)^\rho = \left(\frac{r\Gamma(\rho+1)}{M} \right),$$

and hence

$$\frac{M(h^*)^\rho}{\Gamma(\rho+1)} = r.$$

Thus, (38) gives

$$\|T\mathbf{X}(t) - \mathbf{X}_0\| \leq \frac{M(h^*)^\rho}{\Gamma(\rho+1)} = r,$$

or

$$\|T\mathbf{X}(t) - \mathbf{X}_0\| \leq r.$$

Hence, in both cases, we obtain

$$\|T\mathbf{X}(t) - \mathbf{X}_0\| \leq r,$$

which shows that $T\mathbf{X} \in J$ or $T : \mathbf{X} \rightarrow \mathbf{X}$. This proves the first condition of the Banach fixed-point theorem (Theorem 2). It remains to show that T is a contraction. For $\mathbf{X}, \mathbf{Y} \in T$.

$$\begin{aligned} T\mathbf{X}(t) - T\mathbf{Y}(t) &= \frac{1}{\Gamma(\rho)} \int_0^t (t-s)^{\rho-1} \\ &\quad (F(s, \mathbf{X}(s)) - F(s, \mathbf{Y}(s))) ds. \end{aligned} \quad (39)$$

Thus,

$$\begin{aligned} \|T\mathbf{X}(t) - T\mathbf{Y}(t)\| &\leq \frac{1}{\Gamma(\rho)} \int_0^t (t-s)^{\rho-1} \\ &\quad \times \|\mathbf{F}(s, \mathbf{X}(s)) - \mathbf{F}(s, \mathbf{Y}(s))\| ds. \end{aligned}$$

By the Lipschitz condition,

$$\begin{aligned} \|T\mathbf{X}(t) - T\mathbf{Y}(t)\| &\leq \frac{L}{\Gamma(\rho)} \int_0^t (t-s)^{\rho-1} \\ &\quad \|\mathbf{X}(s) - \mathbf{Y}(s)\| ds. \end{aligned}$$

Using inequality (3),

$$\|T\mathbf{X}(t) - T\mathbf{Y}(t)\| \leq \frac{L\|\mathbf{X} - \mathbf{Y}\|_{c,2}}{\Gamma(\rho)} \int_0^t (t-s)^{\rho-1} ds.$$

As a consequence, by evaluating the above integral, we get

$$\|T\mathbf{X}(t) - T\mathbf{Y}(t)\| \leq \frac{L\|\mathbf{X} - \mathbf{Y}\|_{c,2}}{\Gamma(\rho+1)} t^\rho.$$

Since $t \in [0, h^*]$,

$$\|T\mathbf{X}(t) - T\mathbf{Y}(t)\| \leq \frac{L(h^*)^\rho}{\Gamma(\rho+1)} \|\mathbf{X} - \mathbf{Y}\|_{c,2}.$$

Taking the supremum over $t \in [0, h^*]$,

$$\begin{aligned} \|T\mathbf{X} - T\mathbf{Y}\|_{c,2} &= \sup_{t \in [0, h^*]} \|T\mathbf{X}(t) - T\mathbf{Y}(t)\| \\ &\leq \frac{L(h^*)^\rho}{\Gamma(\rho+1)} \|\mathbf{X} - \mathbf{Y}\|_{c,2}. \end{aligned} \quad (40)$$

or

$$\|T\mathbf{X} - T\mathbf{Y}\|_{c,2} \leq \frac{L(h^*)^\rho}{\Gamma(\rho+1)} \|\mathbf{X} - \mathbf{Y}\|_{c,2}. \quad (41)$$

To show that T is a contraction, we need $l = \frac{L(h^*)^\rho}{\Gamma(\rho+1)} < 1$. Consider two cases.

Case 1: If $h^* = \left(\frac{r\Gamma(\rho+1)}{M}\right)^{\frac{1}{\rho}}$, then

$$\begin{aligned} l &= \frac{L(h^*)^\rho}{\Gamma(\rho+1)} \\ &= \frac{L \left(\left(\frac{r\Gamma(\rho+1)}{M} \right)^{\frac{1}{\rho}} \right)^\rho}{\Gamma(\rho+1)} \\ &= \frac{L(r\Gamma(\rho+1)/M)}{\Gamma(\rho+1)} \\ &= \frac{Lr}{M}. \end{aligned} \quad (42)$$

Consequently, by the given assumption in the theorem under construction, we get

$$l = \frac{Lr}{M} < 1.$$

Case 2: If $h^* = h$, then

$$h^* = h \leq \left(\frac{r\Gamma(\rho+1)}{M} \right)^{\frac{1}{\rho}}.$$

Thus,

$$\begin{aligned} l &= \frac{L(h^*)^\rho}{\Gamma(\rho+1)} = \frac{Lh^\rho}{\Gamma(\rho+1)} \\ &\leq \frac{L}{\Gamma(\rho+1)} \left(\left(\frac{r\Gamma(\rho+1)}{M} \right)^{\frac{1}{\rho}} \right)^\rho, \end{aligned} \quad (43)$$

or equivalently

$$l \leq \frac{L}{\Gamma(\rho+1)} \cdot \frac{r\Gamma(\rho+1)}{M} = \frac{Lr}{M} < 1, \quad (44)$$

i.e.,

$$l \leq \frac{Lr}{M} < 1.$$

which implies that T is a contraction operator. Hence, by the Banach fixed-point theorem (Theorem 2), system (16)-(17) has a unique solution. $\square$

5. Invariant region

In this section, we discuss the invariant region for the fractional system (13)-(14). The benefits of investigating this aspect lie in ensuring that the

solution $\mathbf{X} = (N_p, N_t, R_t, R_p, R_u)$ remains non-negative and bounded, which reflects a biologically realistic scenario. Furthermore, investigating the invariant region confirms the validity of the proposed mathematical model and guarantees valid predictions. In light of this discussion, we introduce a further result concerning the invariant region for the fractional-order system given in (15)-(17), which is equivalent to system (13)-(14).

Theorem 7. ²³ Consider the fractional-order system

$$D^\rho x_i = f_i(t, \mathbf{X}),$$

with $\rho \in (0, 1)$ and initial condition $\mathbf{X}(0) \geq 0$. If for each i ,

$f_i(t, \mathbf{X}) \geq 0$ whenever $x_i = 0$ and $x_j \geq 0$ for all $j \neq i$, then

$$\mathbf{X}(t) \in \mathbb{R}_+^n \quad \text{for all } t > 0.$$

The following theorem ensures that the concentrations never become negative, which is essential for the validity of the proposed model (15)-(17).

Theorem 8. (Non-negativity of solutions) If the initial conditions

$$N_t(0), N_p(0), R_t(0), R_b(0), R_u(0) \geq 0,$$

then the solutions remain non-negative for all $t \geq 0$.

Proof. The verification follows from Theorem 7, which should be checked for each state variable.

(1) For N_p : When $N_p = 0$ in the first equation of system (16), we obtain

$$\begin{aligned} D^\rho N_p|_{N_p=0} &= -\alpha(0) + \beta(N_t - 0) \\ &\quad - \frac{\gamma_m E_m}{k_m}(0) - \frac{\gamma_b E_b}{k_p}(0) \\ &= \beta N_t \geq 0, \quad (\text{since } \beta > 0 \text{ and } N_t \geq 0). \end{aligned}$$

(2) For N_t : In the second equation,

$$\begin{aligned} D^\rho N_t|_{N_t=0} &= \beta(N_p - 0) - \frac{\gamma_m E_t}{k_m}(0) = \beta N_p \geq 0, \\ &\text{since } \beta > 0 \text{ and } N_p \geq 0. \end{aligned}$$

(3) For R_t : When $R_t = 0$ in the third equation,

$$D^\rho R_t|_{R_t=0} = \frac{\gamma_m E_t}{k_m} N_t - \delta(0) = \frac{\gamma_m E_t}{k_m} N_t \geq 0,$$

since $\gamma_m, E_t, k_m > 0$ and $N_t \geq 0$.

(4) For R_p : When $R_p = 0$ in the fourth equation,

$$\begin{aligned} D^\rho R_p|_{R_p=0} &= \delta R_t + \frac{\gamma_m E_m}{k_m} N_p + \frac{\gamma_b E_b}{k_p} N_p \\ &\quad - (\mu + v)(0) - \omega(0) \\ &= \delta R_t + \left(\frac{\gamma_m E_m}{k_m} + \frac{\gamma_b E_b}{k_p} \right) N_p \geq 0, \end{aligned}$$

since all parameters are positive and $R_t, N_p \geq 0$.

(5) For R_u : When $R_u = 0$ in the fifth equation,

$$D^\rho R_u|_{R_u=0} = \mu R_p \geq 0, \\ (\text{since } \mu > 0 \text{ and } R_p \geq 0).$$

Thus, from the above cases, Theorem (7) allows us to conclude that the solutions of system (13) remain non-negative for all $t > 0$. $\square$

Theorem 9. *If the quantity*

$$Q = N_p + N_t + R_t + R_p + R_u, \quad (45)$$

satisfies $D^\rho Q \leq 0$, then

$$Q(t) \leq Q(0), \quad \forall t > 0.$$

Proof. Suppose the assumption (45) is given. By taking D^ρ of both sides of (45), we get

$$D^\rho Q = D^\rho N_p + D^\rho N_t + D^\rho R_t + D^\rho R_p + D^\rho R_u.$$

Consequently, we have

$$\begin{aligned} D^\rho Q = & [-\alpha N_p + \beta(N_t - N_p)] - \frac{\gamma_m E_m}{k_m} N_p \\ & - \frac{\gamma_b E_b}{k_p} N_p + [\beta(N_p - N_t) \\ & - \frac{\gamma_m E_t}{k_m} N_t] + \frac{\gamma_m E_t}{k_m} N_t \\ & - \delta R_t + \delta R_t + \frac{\gamma_m E_m}{k_m} N_p + \frac{\gamma_b E_b}{k_p} N_p \\ & - (\mu + \nu) R_p - \omega R_p + \mu R_p, \end{aligned}$$

which implies

$$D^\rho Q = -(\alpha N_p + (\nu + \omega) R_p). \quad (46)$$

Since $\alpha, \nu, \omega > 0$ and $N_p, R_p \geq 0$, it follows that $D^\rho Q \leq 0$.

Finally, to show $Q(t) \leq Q(0)$, we use the Caputo fractional derivative property:

$$J^\rho D^\rho Q(t) = Q(t) - Q(0),$$

or equivalently,

$$Q(t) - Q(0) = \frac{1}{\Gamma(\rho)} \int_0^t (t-s)^{\rho-1} D^\rho Q(s) ds.$$

Since $\Gamma(\rho) > 0$, $(t-s)^{\rho-1} > 0$ for $s < t$, and $D^\rho Q(s) \leq 0$, we have

$$Q(t) - Q(0) \leq 0, \quad \text{i.e., } Q(t) \leq Q(0). \quad \square$$

Remark 2. *From the previous two theorems, we can deduce that the set*

$\Omega = \{(N_p, N_t, R_t, R_p, R_u) \in \mathbb{R}_+^5 : Q(t) \leq Q(0)\}$, *is positively (non-negatively) invariant, where Q is defined in equation (45).*

6. Equilibrium of the fractional-order model

In this part, we aim to find the equilibrium of our proposed model (13)-(14) to determine whether

the NPs or reporters will be eliminated (i.e. $Q \rightarrow 0$) over time, reflecting whether the concentrations of these NPs or reporters will accumulate in the tumor. This helps to understand the long-term behavior of the drug.

Lemma 1. *System (13)-(14) has a unique equilibrium point $E^* = (0, 0, 0, 0, c)$, where $c \geq 0$.*

Proof. To determine the equilibrium points of system (13)-(14), we set the right-hand sides of the system equal to zero, yielding

$$D^\rho N_p = -\alpha N_p + \beta(N_t - N_p) \quad (47)$$

$$-\frac{\gamma_m E_m}{k_m} N_p - \frac{\gamma_b E_b}{k_p} N_p = 0, \quad (48)$$

$$D^\rho N_t = \beta(N_p - N_t) - \frac{\gamma_m E_t}{k_m} N_t = 0, \quad (49)$$

$$D^\rho R_t = \frac{\gamma_m E_t}{k_m} N_t - \delta R_t = 0, \quad (50)$$

$$D^\rho R_p = \delta R_t + \frac{\gamma_m E_m}{k_m} N_p \quad (51)$$

$$+ \frac{\gamma_b E_b}{k_p} N_p - (\mu + \nu + \omega) R_p = 0, \quad (52)$$

$$D^\rho R_u = \mu R_p = 0. \quad (53)$$

From equation (53), we obtain $R_p^* = 0$. Substituting this into equation (52), we obtain

$$\delta R_t + \left(\frac{\gamma_m E_m}{k_m} + \frac{\gamma_b E_b}{k_p} \right) N_p = 0. \quad (54)$$

Since all parameters are nonnegative, it follows that $R_t^* = 0$ and $N_p^* = 0$. Substituting $N_p^* = 0$ into equation (49) yields $N_t^* = 0$. Moreover, equation (50) is satisfied automatically.

Finally, from equation (53), we conclude that R_u^* can take any nonnegative constant value, i.e., $R_u^* = c$ with $c \geq 0$. Hence, the system has the unique equilibrium point $E^* = (0, 0, 0, 0, c)$.²⁴ $\square$

7. Local stability

In this part, we present some theoretical results, particularly the local stability theorem. This theorem serves as a theoretical validation for the nanoparticle-reporter system (13)-(14). It shows that in the absence of external perturbations, the system remains inherently stable and does not become unstable. However, before proceeding with the analysis, we first recall a well-known theorem, which is reported below for completeness.

Theorem 10. *For a block lower triangular matrix²⁵*

$$M = \begin{pmatrix} A & 0 \\ B & C \end{pmatrix}.$$

the eigenvalues of M are the union of the eigenvalues of A and C .

Theorem 11. The Jacobian matrix for system (15)–(17) is given by

$$J = \begin{pmatrix} -\alpha - \beta - \frac{\gamma_m E_m}{k_m} - \frac{\gamma_b E_b}{k_p} & \beta & 0 & 0 & 0 \\ \beta & -\beta - \frac{\gamma_m E_t}{k_m} & 0 & 0 & 0 \\ 0 & \frac{\gamma_m E_t}{k_m} & -\delta & 0 & 0 \\ \frac{\gamma_m E_m}{k_m} + \frac{\gamma_b E_b}{k_p} & 0 & \delta & -(\mu + \nu + \omega) & 0 \\ 0 & 0 & 0 & \mu & 0 \end{pmatrix} \quad (55)$$

Proof. This result follows directly by computing the Jacobian matrix of system (13):

$$J = \begin{pmatrix} \frac{\partial f_1(\mathbf{X})}{\partial N_p} & \frac{\partial f_1(\mathbf{X})}{\partial N_t} & \frac{\partial f_1(\mathbf{X})}{\partial R_t} & \frac{\partial f_1(\mathbf{X})}{\partial R_p} & \frac{\partial f_1(\mathbf{X})}{\partial R_u} \\ \frac{\partial f_2(\mathbf{X})}{\partial N_p} & \frac{\partial f_2(\mathbf{X})}{\partial N_t} & \frac{\partial f_2(\mathbf{X})}{\partial R_t} & \frac{\partial f_2(\mathbf{X})}{\partial R_p} & \frac{\partial f_2(\mathbf{X})}{\partial R_u} \\ \frac{\partial f_3(\mathbf{X})}{\partial N_p} & \frac{\partial f_3(\mathbf{X})}{\partial N_t} & \frac{\partial f_3(\mathbf{X})}{\partial R_t} & \frac{\partial f_3(\mathbf{X})}{\partial R_p} & \frac{\partial f_3(\mathbf{X})}{\partial R_u} \\ \frac{\partial f_4(\mathbf{X})}{\partial N_p} & \frac{\partial f_4(\mathbf{X})}{\partial N_t} & \frac{\partial f_4(\mathbf{X})}{\partial R_t} & \frac{\partial f_4(\mathbf{X})}{\partial R_p} & \frac{\partial f_4(\mathbf{X})}{\partial R_u} \\ \frac{\partial f_5(\mathbf{X})}{\partial N_p} & \frac{\partial f_5(\mathbf{X})}{\partial N_t} & \frac{\partial f_5(\mathbf{X})}{\partial R_t} & \frac{\partial f_5(\mathbf{X})}{\partial R_p} & \frac{\partial f_5(\mathbf{X})}{\partial R_u} \end{pmatrix},$$

where, f_i denotes the i -th component of system (13), with $\mathbf{X} = (N_p, N_t, R_t, R_p, R_u)$. $\square$

Lemma 2. Consider the quadratic equation

$$\lambda^2 + a\lambda + b = 0,$$

where $a > 0$ and $b > 0$. Then all roots of this equation have negative real parts.

Theorem 12. The equilibrium $E^* = (0, 0, 0, 0, c)$, for $c \geq 0$ of the fractional-order system (15)–(17) is locally asymptotically stable for all $\rho \in (0, 1)$.

Proof. To analyze the local stability, we compute the eigenvalues of the Jacobian matrix J at E^* i.e.

$$J^* = J_{E^*} = J.$$

Now, to find the eigenvalues J^* , we solve

$$|J - \lambda I| = 0. \quad (56)$$

The matrix J^* can be written in block lower triangular form:

$$J^* = \begin{pmatrix} A & 0 \\ B & C \end{pmatrix},$$

where

$$A = \begin{pmatrix} -\alpha - \beta - \frac{\gamma_m E_m}{k_m} - \frac{\gamma_b E_b}{k_p} & \beta \\ \beta & -\beta - \frac{\gamma_m E_t}{k_m} \end{pmatrix},$$

$$B = \begin{pmatrix} 0 & \frac{\gamma_m E_t}{k_m} \\ \frac{\gamma_m E_m}{k_m} + \frac{\gamma_b E_b}{k_p} & 0 \end{pmatrix},$$

$$C = \begin{pmatrix} -\delta & 0 & 0 \\ \delta & -(\mu + \nu + \omega) & 0 \\ 0 & \mu & 0 \end{pmatrix}.$$

For further simplification, we define

$$\begin{aligned} k_1 &= -\alpha - \beta - \frac{\gamma_m E_m}{k_m} - \frac{\gamma_b E_b}{k_p}, \\ k_2 &= -\beta - \frac{\gamma_m E_t}{k_m}, \\ k_3 &= \mu + \nu + \omega. \end{aligned} \quad (57)$$

Thus,

$$A = \begin{pmatrix} k_1 & \beta \\ \beta & k_2 \end{pmatrix}, \quad C = \begin{pmatrix} -\delta & 0 & 0 \\ \delta & -k_3 & 0 \\ 0 & \mu & 0 \end{pmatrix}$$

The characteristic equation of A is

$$\lambda^2 - (k_1 + k_2)\lambda + (k_1 k_2 - \beta^2) = 0.$$

Since

$$\begin{aligned} k_1 &= -\left(\alpha + \beta + \frac{\gamma_m E_m}{k_m} + \frac{\gamma_b E_b}{k_p}\right) < 0, \\ k_2 &= -\left(\beta + \frac{\gamma_m E_t}{k_m}\right) < 0, \end{aligned}$$

it follows that

$$-(k_1 + k_2) > 0.$$

Moreover, writing

$$k_1 = -(\beta + a), \quad k_2 = -(\beta + b), \quad a, b > 0,$$

we obtain

$$k_1 k_2 = (\beta + a)(\beta + b) > \beta^2,$$

and hence

$$k_1 k_2 - \beta^2 > 0.$$

Therefore, both coefficients of the characteristic polynomial are positive. By Lemma 2, all eigenvalues of A have negative real parts so $\lambda_1 < 0$ and $\lambda_2 < 0$.

We now find the eigenvalues of C :

$$|C - \lambda I| = 0,$$

or

$$\begin{vmatrix} -\delta - \lambda & 0 & 0 \\ \delta & -k_3 - \lambda & 0 \\ 0 & \mu & -\lambda \end{vmatrix} = 0,$$

which simplifies to

$$-\lambda(-\delta - \lambda)(-k_3 - \lambda) = 0.$$

Thus, the eigenvalues are

$$\lambda_3 = 0, \quad \lambda_4 = -\delta, \quad \lambda_5 = -k_3.$$

The eigenvalue $\lambda_3 = 0$ corresponds to a marginally stable mode. For the remaining eigenvalues, since $\lambda_i < 0$ for $i = 1, 2, 4, 5$, we have

$$|\arg(\lambda_i)| = \pi \geq \frac{\rho\pi}{2}, \quad \forall \rho \in (0, 1).$$

Therefore, by Theorem 3, the fractional-order system (15)–(17) is locally asymptotically stable at E^* . $\square$

8. Tuning parameters using PSO algorithm

In this section, Particle Swarm Optimization (PSO) is employed to determine the optimal values of the model parameters ($\rho, \alpha, \beta, \gamma_m, \gamma_b, \delta, \mu, v, w, k_m, k_p, E_m, E_b, E_t$) for the proposed fractional-order cancer biomarker model (13)–(14). The optimization process aims to improve the agreement between the mathematical model and the experimental data while enhancing the predictive capability of the proposed framework. The PSO algorithm is initialized using the parameter settings listed in **Table 2**.

Table 2. Parameters of PSO Algorithm

Parameter	Value
Population size N	30
Maximum number of iterations	50
Cognitive learning rate C_1	2
Social learning rate C_2	2
Function tolerance	1×10^{-6}
Weight factor $[w_{\min}, w_{\max}]$	$[0.6, 0.9]$

Using the PSO settings listed in **Table 2**, the optimization algorithm was run to estimate the optimal values of the model parameters. The resulting optimized parameter values are summarized in **Table 3**.

Table 3. Initial and Optimized Parameter Values with Percentage Change

Parameter	Initial	Optimized	Change (%)
ρ (fractional-order)	1	0.15	−85.0
α (plasma decay)	0.0462	0.08	+73.2
β (tumor permeability)	2.3×10^{-4}	5×10^{-4}	+117.4
γ_m (MMP-9 effect)	2.0	0.5	−75.0
γ_b (blood effect)	0.0659	0.09	+36.6
δ (reporter diffusion)	0.09	0.05	−44.4
μ (renal filtration)	0.032	0.08	+150.0
v (clearance rate)	0.0064	0.0411	+542.9
w (reabsorption rate)	2.89	0.8	−72.3
k_m (MMP-9)	150	290.22	+93.5
k_p (blood proteases)	500	300	−40.0
E_m (MMP-9 in blood)	7.1623×10^{-8}	5.6682×10^{-7}	+691.4
E_b (proteases in blood)	4.0×10^{-6}	3.9691×10^{-5}	+892.3
E_t (MMP-9 in tumor)	7.1624×10^{-7}	2.5919×10^{-6}	+261.9

Table 3 summarizes the optimized parameter values obtained using the PSO algorithm together with their percentage changes relative to the initial estimates. The optimization process significantly adjusted several model parameters, indicating that the original parameter set was not sufficient to achieve satisfactory agreement with the experimental observations. In particular, the optimized parameters enhance the description of nanoparticle transport, enzymatic activation, reporter generation, and clearance dynamics, leading to a more reliable representation of the biological system.

The fractional-order ρ , representing the memory effect in the system, was optimized to 0.15, indicating strong fractional behavior and highlighting the increased influence of system memory on nanoparticle kinetics. The plasma decay rate α and tumor permeability rate β were increased to 0.08 and 5×10^{-4} , respectively, reflecting faster

elimination of nanoparticles from plasma and enhanced transfer into the tumor compartment after optimization.

Conversely, several parameters associated with enzymatic activity and reporter kinetics underwent notable adjustments. The tumor-related MMP9 parameter γ_m decreased to 0.5, while blood-related parameters γ_b , δ , and μ were adjusted to 0.09, 0.05, and 0.08, respectively, reflecting refined enzymatic efficiency and reporter kinetics. Clearance (v) and reabsorption (w) rates were optimized to 0.0411 and 0.8, indicating more efficient systemic processing of the reporter.

Additionally, the Michaelis-Menten constants k_m and k_p for MMP9 and blood proteases were adjusted to 290.22 and 300, while the corresponding enzymatic concentrations E_m , E_b , and E_t increased to 5.6682×10^{-7} , 3.9691×10^{-5} , and 2.5919×10^{-6} , respectively. These changes collectively suggest that the optimized parameters

enhance the model's sensitivity to enzymatic activity and reporter dynamics, improving the accuracy of nanoparticle distribution and tumor-targeting predictions. The optimization process effectively balances transport, reaction, and clearance processes, resulting in a more physiologically realistic and predictive model.

Overall, the optimization process demonstrates the effectiveness of PSO as a parameter estimation tool for fractional-order biological models, allowing simultaneous calibration of multiple parameters while preserving the biological interpretation of the system.

These optimized parameter values indicate a more accurate representation of enzymatic activity and reporter kinetics and also improve the model's predictive capabilities. Specifically, the adjustments led to more efficient systemic processing of nanoparticles and reporters, resulting in an earlier detection time and higher maximal reporter concentration in urine. Overall, the optimized parameters enhance the reliability and physiological realism of the model in simulating nanoparticle distribution and tumor-targeting dynamics.

Additionally, to determine the suitable dose of nanoparticles needed to reveal tumor size, we display **Table 4**, which shows the optimization of several testing doses.

Table 4. Dose Optimization Analysis Based on Maximum Urinary Reporter Concentration

Dose ($\mu\text{g/mL}$)	Max R_u (ng/mL)	Detection time (h)
15	2.43	43.6
20	3.23	37.8
25	4.03	33.9
30	4.82	31.5
35	5.61	29.6
40	6.40	28.1
45	7.18	26.7
50	7.96	25.7
60	9.51	23.8
70	11.04	22.8
80	12.55	21.8
90	14.05	20.8
100	15.52	19.9

Table 4 shows that increasing the nanoparticle dose leads to higher urinary reporter concentrations. However, doses above $80 \mu\text{g/mL}$ result in only marginal increases in reporter levels while potentially raising toxicity and cost. Consequently, the model identifies $80 \mu\text{g/mL}$ as the optimal dose, producing a maximal urinary reporter concentration of 12.55 ng/mL , which is sufficient for early tumor detection and assessment.

This observation demonstrates the practical utility of the optimization procedure, since it identifies a dose that balances detection sensitivity with the potential risks associated with unnecessarily high nanoparticle concentrations.

To illustrate the nanoparticle dynamics of model (13)-(14) with a fractional-order of $\rho = 0.975$ and the optimal dose of $80 \mu\text{g/mL}$, **Figures 1–5** illustrate the distribution and clearance of nanoparticles and the resulting reporter kinetics over time.

To further validate the optimized parameter set, the numerical simulations obtained using the optimized parameters are compared with the corresponding experimental data.

Figure 1 shows the temporal profile of nanoparticles in plasma (N_p) following administration of the optimal dose of $80 \mu\text{g/mL}$ using the fractional-order model with $\rho = 0.975$. The plot shows a rapid decline in plasma nanoparticle concentration immediately after administration, indicating of fast distribution and clearance processes. The numerical solution closely matches the experimental data, validating the accuracy of the model in capturing the pharmacokinetic behavior of nanoparticles in plasma. This decline highlights the transient nature of nanoparticles in the systemic circulation before being taken up by tumor or other tissues.

Figure 2 shows the concentration profile of nanoparticles in the tumor compartment, denoted by $N_t(t)$, for the optimal dose of $80 \mu\text{g/mL}$ with $\rho = 0.975$. Unlike the plasma profile, the tumor concentration shows a clear accumulation phase, where $N_t(t)$ increases over time and reaches a peak value before gradually decreasing. This behavior reflects the effective transport and retention of nanoparticles within tumor tissue. The numerical simulation shows good agreement with the experimental data, indicating that the model successfully describes nanoparticle uptake, accumulation, and subsequent clearance in the tumor. These results confirm the reliability of the optimized fractional-order model in predicting nanoparticle dynamics within tumor tissues.

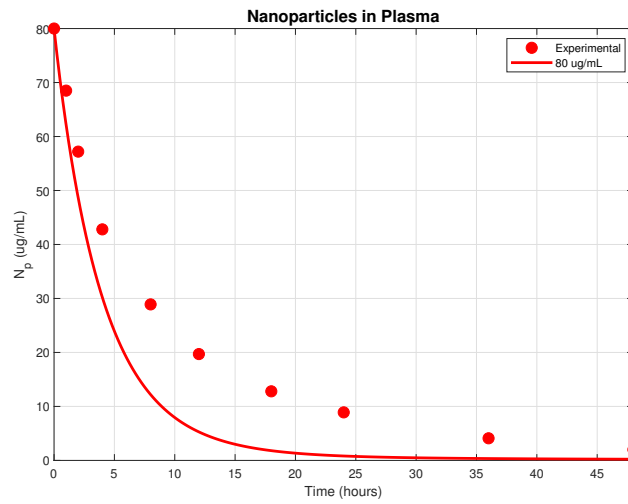


Figure 1. Comparison of experimental data and model simulation for Nanoparticles N_p

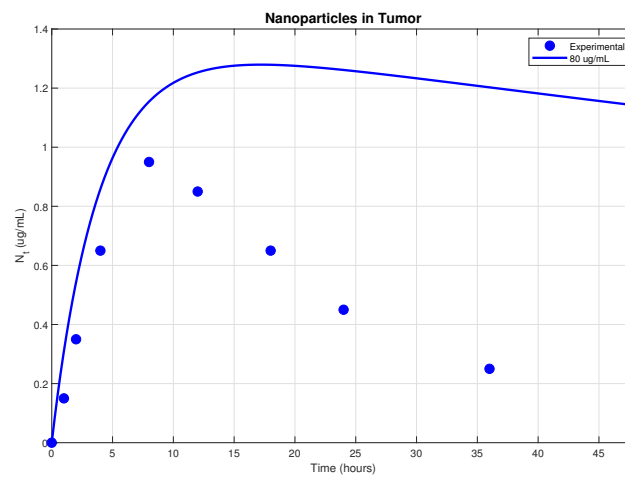


Figure 2. Comparison of experimental data and model simulation for Nanoparticles in Tumor (N_t)

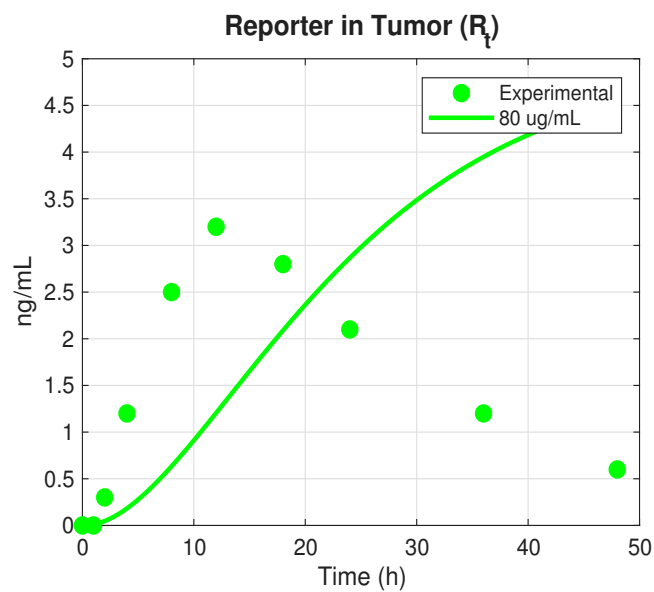


Figure 3. Comparison between the numerical simulation and experimental data of the reporter concentration in the tumor, $R_t(t)$

Figure 3 shows the temporal profile of the reporter concentration in the tumor $R_t(t)$. The data show a gradual increase in reporter concentration over time, reflecting the enzymatic activation of the nanosensors within the tumor microenvironment. The initial phase is characterized by a slow accumulation, which eventually peaks, indicating effective nanoparticle retention and reporter generation in the tumor. This pattern demonstrates that the model successfully captures the dynamic behavior of the reporter within the tumor environment, although the initial low levels may suggest delayed activation or limited immediate release.

Figure 4 shows the temporal behavior of the

reporter concentration in plasma, represented by $R_p(t)$, for the optimized dose of $80 \mu\text{g/mL}$ and fractional-order $\rho = 0.975$. The plasma reporter concentration initially increases as the reporter is released from the tumor into the bloodstream, followed by a gradual decline due to systemic clearance mechanisms. The numerical simulation shows good agreement with the experimental data, indicating that the model effectively captures the transport of the reporter from the tumor to the plasma as well as its subsequent elimination. This behavior highlights the role of plasma as a transient compartment in the overall reporter kinetics.

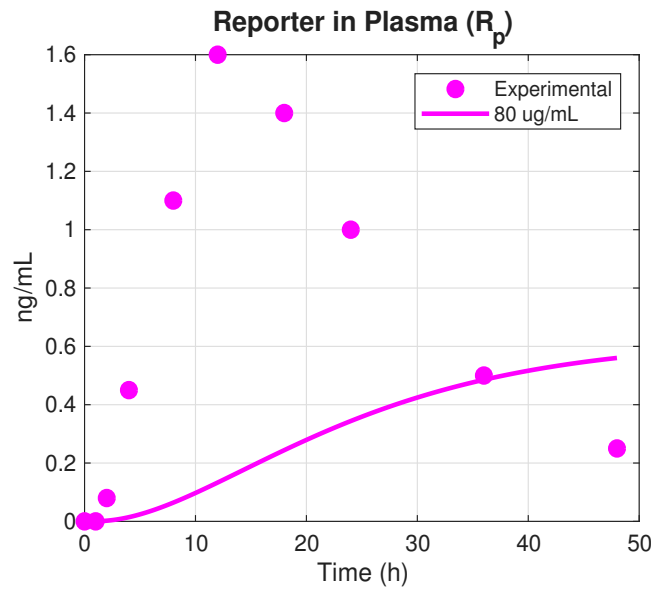


Figure 4. Comparison between the numerical simulation and experimental data of the reporter concentration in plasma, $R_p(t)$

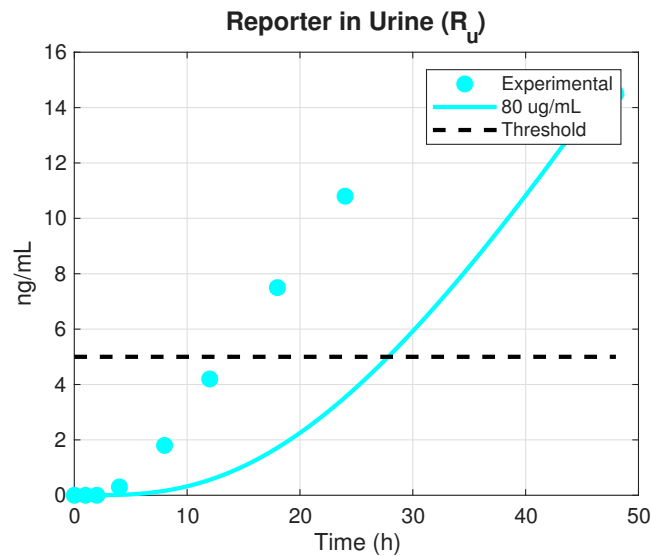


Figure 5. Comparison between the numerical simulation and experimental data of the cumulative reporter concentration in urine, $R_u(t)$

Figure 5 shows the temporal profile of the reporter concentration in urine. The data indicate that reporter levels in urine remain low during the initial time points, suggesting a delay in the excretion process. Over time, we observe a gradual increase in the urinary concentration, reflecting the eventual clearance of the reporter from the body. This pattern highlights the model's ability to capture the kinetics of reporter elimination

and its subsequent appearance in urine, providing insights into the overall pharmacokinetic profile.

Additionally, we plot **Figure 6**, which displays a chart comparing percentage changes in the parameters of model (13)-(14) between two optimization runs.

Figure 6 shows that the two runs (Run1 and Run2) exhibit clearly different changes in many parameters, indicating variability in the optimization results.

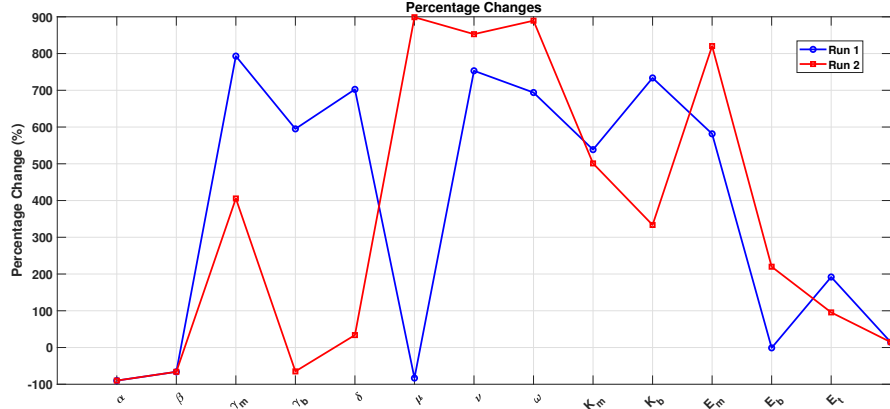


Figure 6. Comparison of percentage changes in model parameters between two optimization runs (Run1 vs Run2)

9. Numerical simulation

The Generalized Fractional Taylor Expansion (GFTE) is used in this study because it offers an efficient and reliable numerical approach for solving fractional-order differential equations. Compared with conventional numerical techniques, the GFTE naturally incorporates the fractional-order derivative while preserving the memory characteristics of the system. Furthermore, the method is computationally efficient, easy to implement, and provides accurate approximations for nonlinear fractional dynamical systems. These features make it particularly suitable for simulating the proposed fractional-order cancer biomarker model.

In this section, we derive the numerical solution for the proposed fractional model using the Generalized Fractional Taylor Formula. As presented in,²² for a function $f(t)$ satisfying certain regularity conditions, the approximate solution at $t_{k+1} = t_k + h$ can be expanded as:

$$f(t_{k+1}) \approx f(t_k) + \frac{h^\rho}{\Gamma(\rho+1)} D^\rho f(t_k) + \frac{h^{2\rho}}{\Gamma(2\rho+1)} D^{2\rho} f(t_k). \quad (58)$$

where $0 < \rho \leq 1$ is the fractional order and h is the time step size.

To streamline the numerical scheme for system (13), we first define the following auxiliary constants to simplify the notation:

$$a_m = \frac{\gamma_m E_m}{k_m}, \quad a_b = \frac{\gamma_b E_b}{k_p}, \quad a_t = \frac{\gamma_t E_t}{k_m}, \quad (59)$$

$$S = \alpha + \beta + a_m + a_b,$$

$$S_p = \mu + v + w.$$

By applying the expansion (58) to each state variable in system (13) and substituting the corresponding fractional derivatives, we obtain the following explicit recursive formulas:

9.1. Nanoparticles in plasma (N_p)

$$N_p(t_{k+1}) = A_p N_p(t_k) + B_p N_t(t_k), \quad (60)$$

where:

$$A_p = 1 - \frac{Sh^\rho}{\Gamma(\rho+1)} + \frac{(\beta^2 + S^2)h^{2\rho}}{\Gamma(2\rho+1)},$$

$$B_p = \frac{\beta h^\rho}{\Gamma(\rho+1)} - \frac{(\beta^2 + \beta a_t + S\beta)h^{2\rho}}{\Gamma(2\rho+1)}.$$

9.2. Nanoparticles in tumor (N_t)

$$N_t(t_{k+1}) = A_t N_t(t_k) + B_t N_p(t_k), \quad (61)$$

where:

$$A_t = 1 - \frac{(\beta + a_t)h^\rho}{\Gamma(\rho + 1)} + \frac{(\beta^2 + (\beta + a_t)^2)h^{2\rho}}{\Gamma(2\rho + 1)},$$

$$B_t = \frac{\beta h^\rho}{\Gamma(\rho + 1)} - \frac{\beta(S + \beta + a_t)h^{2\rho}}{\Gamma(2\rho + 1)}.$$

9.3. Reporters in tumor (R_t)

$$R_t(t_{k+1}) = A_r R_t(t_k) + B_r N_t(t_k) + C_r N_p(t_k), \quad (62)$$

where:

$$A_r = 1 - \frac{\delta h^\rho}{\Gamma(\rho + 1)} + \frac{\delta^2 h^{2\rho}}{\Gamma(2\rho + 1)},$$

$$B_r = \frac{a_t h^\rho}{\Gamma(\rho + 1)} - \frac{a_t(\beta + a_t + \delta)h^{2\rho}}{\Gamma(2\rho + 1)},$$

$$C_r = \frac{a_t \beta h^{2\rho}}{\Gamma(2\rho + 1)}.$$

9.4. Reporters in plasma (R_p)

$$R_p(t_{k+1}) = A_{Rp} R_p(t_k) + B_{Rp} R_t(t_k) + C_{Rp} N_p(t_k) + D_{Rp} N_t(t_k), \quad (63)$$

where:

$$A_{Rp} = 1 - \frac{S_p h^\rho}{\Gamma(\rho + 1)} + \frac{S_p^2 h^{2\rho}}{\Gamma(2\rho + 1)},$$

$$B_{Rp} = \frac{\delta h^\rho}{\Gamma(\rho + 1)} - \frac{(\delta^2 + \delta S_p)h^{2\rho}}{\Gamma(2\rho + 1)},$$

$$C_{Rp} = \frac{(a_m + a_b)h^\rho}{\Gamma(\rho + 1)} - \frac{((a_m + a_b)S + S_p(a_m + a_b))h^{2\rho}}{\Gamma(2\rho + 1)},$$

$$D_{Rp} = \frac{(\delta a_t + (a_m + a_b)\beta)h^{2\rho}}{\Gamma(2\rho + 1)}. \quad (64)$$

9.5. Reporters in urine (R_u)

$$R_u(t_{k+1}) = R_u(t_k) + B_{Ru} R_p(t_k) + C_{Ru} R_t(t_k) + D_{Ru} N_p(t_k), \quad (65)$$

where:

$$B_{Ru} = \frac{\mu h^\rho}{\Gamma(\rho + 1)} - \frac{\mu S_p h^{2\rho}}{\Gamma(2\rho + 1)},$$

$$C_{Ru} = \frac{\mu \delta h^{2\rho}}{\Gamma(2\rho + 1)},$$

$$D_{Ru} = \frac{\mu(a_m + a_b)h^{2\rho}}{\Gamma(2\rho + 1)}.$$

The above recursive formulas constitute the generalized Taylor-based numerical scheme used to simulate the system dynamics.

10. Numerical results and discussion

In this section, numerical simulations of the proposed fractional-order cancer biomarker model are presented using the Generalized Fractional Taylor Expansion (GFTE). The primary objective is to investigate the influence of the fractional-order parameter ρ on the biomarker dynamics and to demonstrate the effectiveness of the proposed numerical method in solving the fractional-order system.

The numerical simulations confirm the accuracy and stability of the Generalized Fractional Taylor Expansion in solving the proposed fractional-order cancer biomarker model. Consequently, the proposed approach provides an efficient computational framework for analyzing complex biological systems governed by fractional differential equations.

Figures 7–11 present the time evolution of the state variables (N_p, N_t, R_t, R_p, R_u) for $\rho \in \{0.7, 0.8, 0.9, 1\}$. The results show that the fractional parameter ρ effectively modulates the decay rates and accumulation peaks due to the memory effects of the fractional derivative.

Specifically, **Figures 7** and **8** show that decreasing ρ leads to a slower decay of nanoparticles in both plasma (N_p) and tumor (N_t) compared to the classical integer-order case ($\rho = 1$). This prolonged retention can be biologically attributed to the non-local transport properties in the tumor microenvironment. Consequently, the reporter accumulation in the tumor and plasma shows higher peak concentrations and delayed clearance for lower values of ρ , as shown in **Figures 9** and **10**. Finally, **Figure 11** shows that the accumulative reporter excretion in urine (R_u) is slower for the fractional model, reflecting the system's overall memory retention.

Overall, the numerical results demonstrate that the proposed fractional-order model offers greater flexibility than its classical integer-order counterpart. By adjusting the fractional-order parameter, the model can reproduce different dynamic behaviors while preserving the biological interpretation of the underlying processes. These findings confirm the suitability of fractional calculus for describing complex cancer biomarker dynamics involving memory and hereditary effects.

The excellent agreement between the proposed numerical method and the reference solutions confirms the accuracy and stability of the Generalized Fractional Taylor Expansion. Consequently, the proposed approach provides an efficient computational framework for analyzing fractional-order cancer biomarker models.

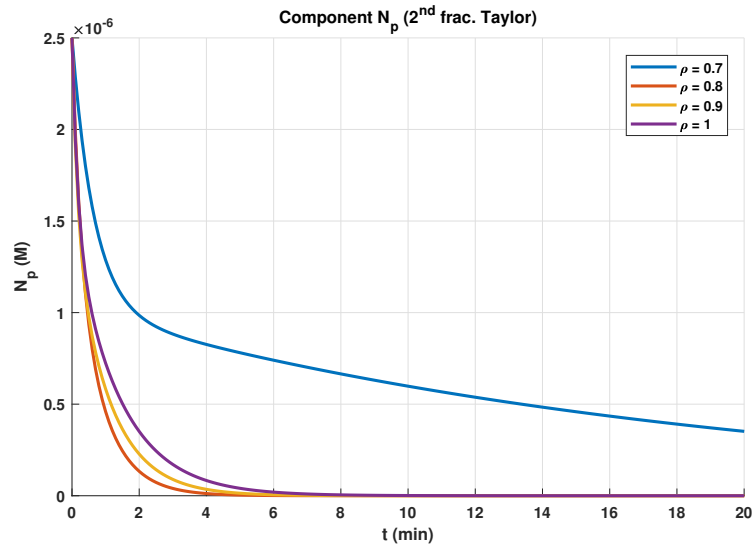


Figure 7. Simulation of nanoparticle concentration in plasma $N_p(t)$ for different fractional-orders ρ

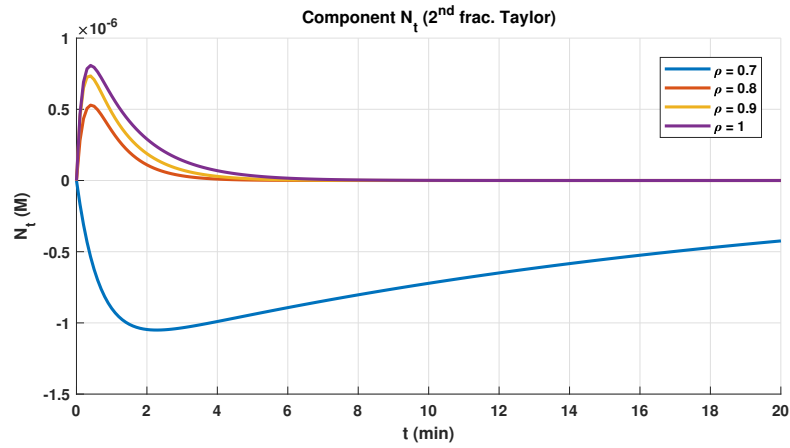


Figure 8. Simulation of nanoparticle concentration in tumor $N_t(t)$ for different fractional-orders ρ

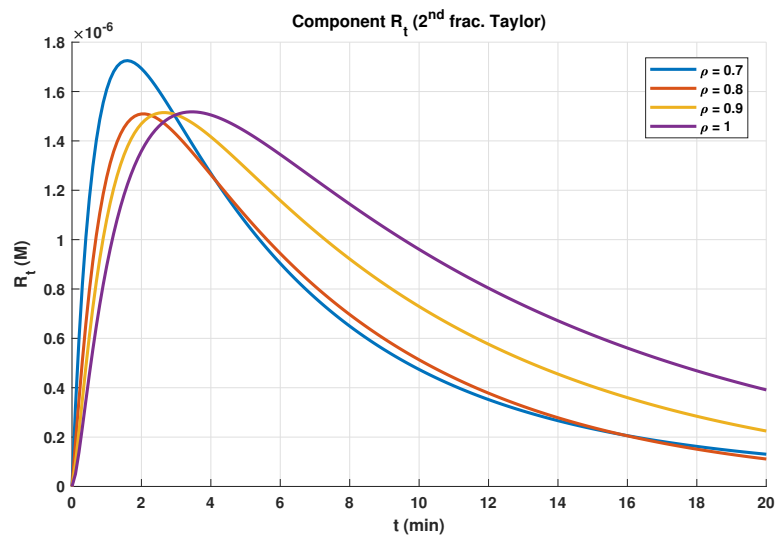


Figure 9. Simulation of reporter concentration in tumor $R_t(t)$ for different fractional-orders ρ

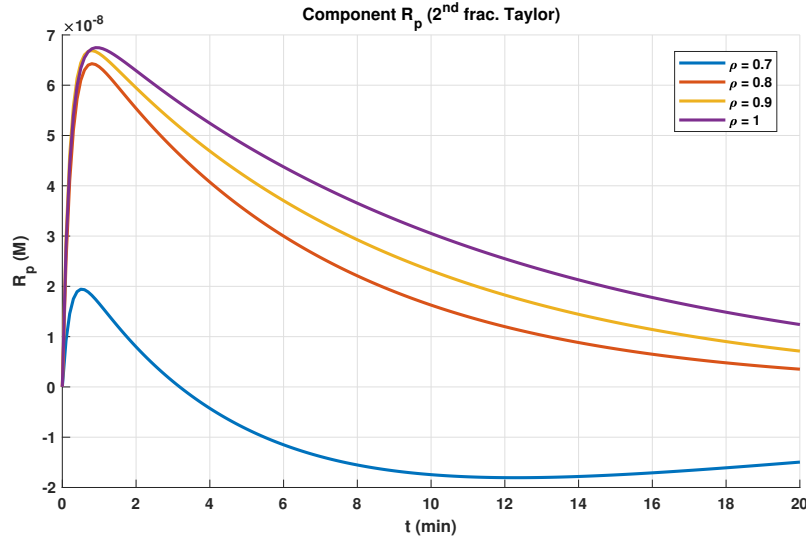


Figure 10. Simulation of reporter concentration in plasma $R_p(t)$ for different fractional-orders ρ

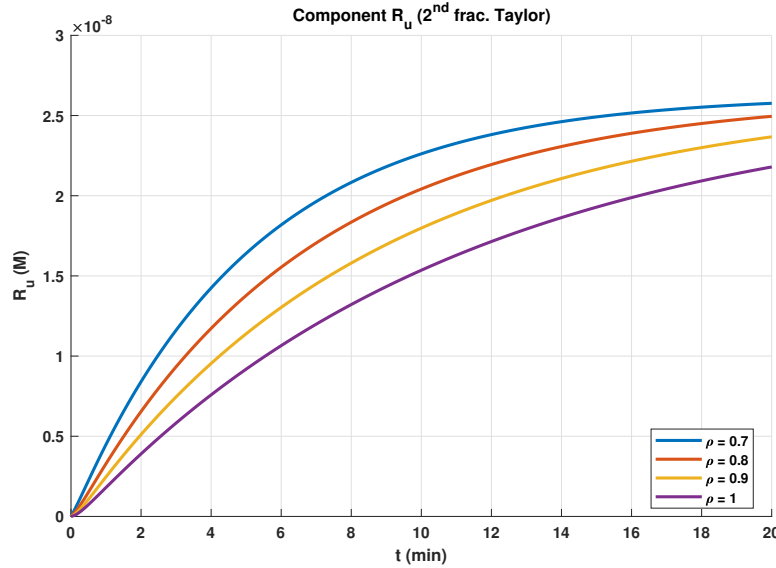


Figure 11. Simulation of reporter accumulation in urine $R_u(t)$ for different fractional-orders ρ

11. Conclusion

This paper presented a fractional-order mathematical model for cancer biomarker dynamics using the Caputo fractional derivative, which incorporates memory effects and hereditary characteristics that cannot be captured by classical integer-order models. The proposed framework was theoretically validated by establishing the existence and uniqueness of solutions and investigating the local stability of the equilibrium point. Numerical solutions were successfully obtained using the Generalized Fractional Taylor Expansion (GFTE), demonstrating that the proposed numerical method provides accurate and stable approximations for the fractional-order system.

The numerical simulations revealed that the fractional-order parameter significantly affects nanoparticle transport, reporter dynamics, and urinary biomarker accumulation, confirming the important role of memory effects in describing the underlying biological processes. Furthermore, the Particle Swarm Optimization (PSO) algorithm was employed to optimize the model parameters and determine the optimal nanoparticle dose, leading to improved model performance and enhanced tumor size estimation.

Overall, the proposed framework combines rigorous theoretical analysis, efficient numerical simulation, and artificial intelligence-based optimization within a unified mathematical model. These findings demonstrate the potential of

fractional-order modeling as a reliable computational tool for improving nanoparticle-based cancer biomarker analysis and supporting future developments in early cancer detection and quantitative tumor assessment.

Acknowledgments

This work is supported by Ajman University Internal Research Grant No. [DRGS Ref. 2025-IRG-DRG-3].

Funding

None.

Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

Conceptualization: Bushra M. Al-Smadi, Iqbal M. Batiha

Investigation: Bushra M. Al-Smadi, Iqbal M. Batiha, Sara A. Khalil, Sana Abughurra

Methodology: Bushra M. Al-Smadi, Iqbal M. Batiha, Shaher Momani

Formal analysis: Bushra M. Al-Smadi, Iqbal M. Batiha, Sara A. Khalil

Writing-original draft: Bushra M. Al-Smadi, Iqbal M. Batiha

Writing-review & editing: Bushra M. Al-Smadi, Iqbal M. Batiha, Sara A. Khalil, Sana Abughurra

Availability of data

No datasets were generated or analyzed during the current study. All results are based on theoretical analysis and numerical simulations. The MATLAB codes used to generate the numerical results are available from the corresponding author upon reasonable request.

AI tools statement

The authors declare that artificial intelligence (AI) tools were used solely to assist with language editing, grammar checking, and improving the readability of the manuscript. All scientific content, mathematical derivations, theoretical analyses, numerical simulations, interpretations, and conclusions were developed, verified, and approved by the authors, who take full responsibility for the content of this article.

Further disclosure

The authors declare that they have no competing interests and no additional disclosures to report.

References

1. Hamadneh T, Abu Falahah I, Batiha B. On the computation of the general simplicial Bernstein inclusion-isotone property for stability analysis of least-squares polynomials. *Mathematics*. 2026;14(3):517. <https://doi.org/10.3390/math14030517>
2. Shukla VK, Joshi MC, Mishra PK, Xu C. Generalized synchronization between coupled integer, fractional and delay chaotic systems. *Evolving Systems*. 2025;16(4):132. <https://doi.org/10.1007/s12530-025-09758-x>
3. Xua C, Liao M, Farman M, Shehzad A. Hydrogenolysis of glycerol by heterogeneous catalysis: A fractional order kinetic model with analysis. *MATCH Commun Math Comput Chem*. 2024;91(3):635-664. <https://doi.org/10.46793/match.91-3.635X>
4. Baber MZ, Yasin MW, Xu C, Ahmed N, Iqbal MS. Numerical and analytical study for the stochastic spatial dependent prey-predator dynamical system. *J Comput Nonlinear Dyn*. 2024;19(10):101003. <https://doi.org/10.1115/1.4066038>
5. Ali G, Marwan M, Rahman U, Hleili M. Investigation of fractional-ordered tumor-immune interaction model via fractional-order derivative. *Fractals*. 2024;32(6):2450119. <https://doi.org/10.1142/S0218348X24501196>
6. Lin J, Xu C, Zhao Y, Deng Q. Hopf bifurcation and controller design for a predator-prey model with double delays. *AIP Advances*. 2025;15(7):075329. <https://doi.org/10.1063/5.0283543>
7. Deng Q, Xu C, Lin J, Zhao Y. Bifurcation mechanism, speed feedback controller, and hybrid controller design in a delayed tumor-immune competitive model. *AIP Advances*. 2025;15(9):095009. <https://doi.org/10.1063/5.0292455>
8. Xu C, Balci E. Hunting cooperation and gestation delay in a prey-predator model with fractional derivative. *J Appl Anal Comput*. 2026;16(2):1035-1053. <https://doi.org/10.11948/20250147>
9. Lin J, Xu C, Zhao Y, Pang Y, Liu Z, Shen J. Bifurcation and control of a predator-prey system with two time delays. *J Appl Anal Comput*. 2026;16(2):807-859. <https://doi.org/10.11948/20250164>
10. Kwong GA, Dudani JS, Carrodegua E, Mazumdar EV, Zekavat SM, Bhatia SN. Mathematical framework for activity-based cancer biomarkers. *Proc Natl Acad Sci USA*. 2015;112(41):12627-12632. <https://doi.org/10.1073/pnas.1506925112>
11. Kwon EJ, Dudani JS, Bhatia SN. Ultrasensitive tumour-penetrating nanosensors of protease activity. *Nat Biomed Eng*. 2017;1(4):0054. <https://doi.org/10.1038/s41551-017-0054>

12. Bergstrom E, Gutierrez N, Masson H. Modifying a “Mathematical Framework for Activity-Based Cancer Biomarkers”: Correlating Tumor Size and Reporter Concentration. *BENG 221 Course Project Report*. La Jolla, CA: University of California San Diego; 2017. Accessed July 30, 2026. <https://isn.ucsd.edu/courses/beng221/problems/2017/Modifying%20a%20Mathematical%20Framework%20for%20Activity-Based%20Cancer%20Biomarkers.pdf>
13. Muhammad G, Akram M. Fuzzy fractional generalized Bagley-Torvik equation with fuzzy Caputo gH-differentiability. *Eng Appl Artif Intell*. 2024;133:108265. <https://doi.org/10.1016/j.engappai.2024.108265>
14. Muhammad G, Akram M, Alsulami H, Hussain N. Granular fuzzy fractional continuous-time linear systems: Roesser and Fornasini-Marchesini models. *Fractal Fract*. 2025;9(7):398. <https://doi.org/10.3390/fractalfract9070398>
15. Muhammad G, Akram M. Fuzzy fractional epidemiological model for Middle East respiratory syndrome coronavirus on complex heterogeneous network using Caputo derivative. *Inf Sci*. 2024;659:120046. <https://doi.org/10.1016/j.ins.2023.120046>
16. Rudin W. *Principles of Mathematical Analysis*. 3rd ed. New York, NY: McGraw-Hill; 1976. Accessed July 30, 2026. https://david92jackson.neocities.org/images/Principles_of_Mathematical_Analysis-Rudin.pdf
17. Kreyszig E. *Introductory Functional Analysis with Applications*. 1st Wiley ed. New York, NY: John Wiley & Sons; 1991. Accessed July 30, 2026. [https://physics.bme.hu/sites/physics.bme.hu/files/users/BMETE15AF53_kov/Kreyszig%20-%20Introductory%20Functional%20Analysis%20with%20Applications%20\(1\).pdf](https://physics.bme.hu/sites/physics.bme.hu/files/users/BMETE15AF53_kov/Kreyszig%20-%20Introductory%20Functional%20Analysis%20with%20Applications%20(1).pdf)
18. Coddington EA. *An Introduction to Ordinary Differential Equations*. New York, NY: Courier Corporation; 2012. Accessed July 30, 2026. <https://personal.math.ubc.ca/~cass/research/pdf/DE.pdf>
19. Podlubny I. *Fractional Differential Equations*. San Diego, CA: Academic Press; 1999. Accessed July 30, 2026. <https://shop.elsevier.com/books/fractional-differential-equations/podlubny/978-0-12-558840-9>
20. Perko L. *Differential Equations and Dynamical Systems*. 3rd ed. New York, NY: Springer; 2001. <https://doi.org/10.1007/978-1-4613-0003-8>
21. Hirsch MW, Smale S, Devaney RL. *Differential Equations, Dynamical Systems, and an Introduction to Chaos*. 3rd ed. Oxford, UK: Academic Press; 2013. Accessed July 30, 2026. [https://eclass.uoa.gr/modules/document/file.php/MATH626/Morris%20W.%20Hirsch%2C%20Stephen%20Smale%20and%20Robert%20L.%20Devaney%20\(Auth.\)%20-%20Differential%20Equations%2C%20Dynamical%20Systems%2C%20and%20an%20Introduction%20to%20Chaos-Academic%20Press%20\(2012\).pdf](https://eclass.uoa.gr/modules/document/file.php/MATH626/Morris%20W.%20Hirsch%2C%20Stephen%20Smale%20and%20Robert%20L.%20Devaney%20(Auth.)%20-%20Differential%20Equations%2C%20Dynamical%20Systems%2C%20and%20an%20Introduction%20to%20Chaos-Academic%20Press%20(2012).pdf)
22. Odibat ZM, Momani S. An algorithm for the numerical solution of differential equations of fractional order. *J Appl Math Inform*. 2008;26:15-27. Accessed July 30, 2026. https://www.researchgate.net/profile/Shaher-Momani/publication/264059551_An_Algorithm_for_the_numerical_solution_of_differential_equations_of_fractional_order/links/548f3e100cf2d1800d8623f0/An-Algorithm-for-the-numerical-solution-of-differential-equations-of-fractional-order.pdf
23. Podlubny I, Dorcak L, Kostial I. On fractional derivatives, fractional-order dynamic systems and $PI^{\lambda}D^{\mu}$ -controllers. In: *Proceedings of the 36th IEEE Conference on Decision and Control*. IEEE; 1997;5:4985-4990. <https://doi.org/10.1109/CDC.1997.649841>
24. Caputo M. Linear models of dissipation whose Q is almost frequency independent – II. *Geophys J Int*. 1967;13(5):529-539. <https://doi.org/10.1111/j.1365-246X.1967.tb02303.x>
25. Horn RA, Johnson CR. *Matrix Analysis*. 2nd ed. Cambridge, UK: Cambridge University Press; 2013. <https://doi.org/10.1017/CBO9780511810817>

Bushra M. Al-Smadi received the M.Sc. degree from the Department of Mathematics, The University of Jordan, Amman, Jordan, in 2026.
 <https://orcid.org/0009-0001-8123-1876>

Shaher Momani is a Distinguished Professor at Ajman University and a leading researcher in fractional calculus. Since 2009, he has been ranked among the world's top researchers in the field by Thomson Reuters. He has authored more than 500 publications and was recognized as a Highly Cited Researcher in Mathematics (2014–2017) and Cross-Field (2018) by Clarivate Analytics. Dr. Momani has held academic positions at several prestigious institutions and has received numerous awards and honors in recognition of his outstanding contributions to mathematics, fractional calculus, and applied analysis.
 <https://orcid.org/0000-0002-6326-8456>

Iqbal M. Batiha is an Assistant Professor at Al-Zaytoonah University of Jordan and a researcher at the Nonlinear Dynamics Research Center, Ajman University. He is a founding member of ICSRS Jordan and has published extensively in international journals. His research interests include fractional calculus, control theory, mathematical modeling, and numerical methods. Dr. Batiha has received several prestigious awards, including the Riemann–Liouville Award and the Oliviu Gherman Award.
 <https://orcid.org/0000-0002-8443-8848>

Sara A. Khalil is currently an assistant professor in

the Mathematics Department at Applied Science Private University (ASU), Amman, Jordan. She helped organize and participated in several international conferences. She has authored and co-authored more than 10 papers published in international peer-reviewed journals. Her research interests include partial differential equations, analysis, and numerical analysis.

 <https://orcid.org/0009-0007-3165-3484>

sor in the Mathematics Department at Applied Science Private University (ASU), Amman, Jordan. She received the B.S. and M.S. degrees in Mathematics from Mutah University, Alkarak, Jordan, in 2005 and 2008, respectively, and the Ph.D. degree in Mathematics from the University of Jordan, Amman, Jordan, in 2014.

 <https://orcid.org/0009-0003-4573-5916>

Sana Abughurra is currently an assistant profes-

An International Journal of Optimization and Control: Theories & Applications (<https://accscience.com/journal/ijocta>)



This work is licensed under a Creative Commons Attribution 4.0 International License. The authors retain ownership of the copyright for their article, but they allow anyone to download, reuse, reprint, modify, distribute, and/or copy articles in IJOCTA, so long as the original authors and source are credited. To see the complete license contents, please visit <http://creativecommons.org/licenses/by/4.0/>.