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Stability of the Delayed Tumor - Immune System with Optimal Control

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ABSTRACT

This study aimed to develop a differential delay model that incorporates optimal control to characterize interactions among cancer cells, immune cells, and external therapies. The model incorporates intracellular delays to account for the time required to induce effector cells. Moreover, to minimize side effects by inhibiting new cancerous growth and to prevent cell populations from crossing into a state with less than 75% of their absorptive capacity, this paper integrates control optimization variables. The study validated the existence and the optimization framework for an optimal control pair. Furthermore, the Pontryagin maximum principle was used to characterize these optimal controls. The model shows a tumor-free steady state and may obtain up to three simultaneous steady states. Numerical simulations show that the best treatment strategies reduce cancer cell populations and increase effector cell numbers within a few days of treatment. Of note, the combined immunochemotherapy regimen outperformed standard chemotherapy alone.

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1. Introduction

Cancer is among the deadliest diseases in the world, according to the World Health Organization. In 2020, over 10 million people died due to it — around one in every six deaths (Anderson et al., 2024; Ashi & Simbawa, 2025). Tumour cells interact with a range of components in the tumor microenvironment, and this interaction is intricate and continually changing (Mishra & Alam, 2023; Musleh et al., 2025). The cancer dynamic is the focus of ongoing research. It looks at how this interacts with the immune system, which comprises specialized organs, cells, and substances that defend against infections and other illnesses (Das et al., 2020; Sardar et al., 2024). Immune cells and their associated compounds play a leading role in preventing the body from coming under attack by infection-threat (Dutta et al., 2026; Hernandez-Lopez & Wang, 2025). Immunotherapy has recently become an important therapeutic strategy for multiple types of cancer. Mathematical models can be employed to understand the complex interactions among many components of the tumour microenvironment (Mendes, 2024). Castiglione and Piccoli (2007) divided cells into lymphocytes and helper cells, where cytotoxic lymphocytes obliterate tumor cells by specific contact with them, and helper cells release cytokines that activate cytotoxic lymphocytes. In their study, a deterministic predator-prey model was used to treat tumours as prey and immune cells as predators (de Pillis et al., 2006). Expanding on this insight, we suggest a tumor-immune interplay delayed model based on the combined model of logistic tumor growth and immune response influenced by contextual factors (Byrne et al., 2006; Roose et al., 2007; Yafia, 2006). We analyze the existence and local stability of the equilibrium points using the Jacobian matrix. Finally, we formulate an optimal control problem for minimizing tumor size at the lowest therapeutic cost, solved using the delayed-maximizing Pontryagin principle (Aderyani et al., 2025; Kirschner & Tsygvintsev, 2009).

1.1 Research Problem

The tumour-immune interaction model also has limitations, including the delayed-term effects of the immune response on system stability and treatment efficacy. This research proposes to resolve this issue by developing a delayed mathematical model of logistic tumour growth under the influence of a delayed immune response supported by an external input, investigating the stability of the equilibrium points, and providing optimal control by minimizing tumour size at the lowest therapeutic cost under the delayed-maximizing Pontryagin principle.

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1.2 Research Significance

We argue that the importance of our study lies in its proposal of a realistic mathematical model that simulates the time delays in the immune response against a tumour. It contributes well to our understanding of tumour growth dynamics and serves as an effective optimal control strategy to minimize tumour size and minimize side effects. Moreover, by providing precise analytical tools to ensure stability and optimize balance between efficacy and cost, it contributes to the development of improved immunotherapies and opens new clinical applications in cancer treatment.

1.3 Research Objectives

1. To construct a delayed mathematical model of the tumor's logistic interaction with the immune response, supported by a delayed external input.
2. To analyze the presence of equilibrium points and study their local stability using a Jacobian matrix and auto nuclear nuclei.
3. To formulate an optimal control problem for reducing tumor size with minimal treatment cost.
4. To derive the optimal control by applying the modified Pontryagin principle for time delays, while identifying the optimal constrained strategy**.**

2. Lecture Review

Table 1 presents a comparison of the most important studies on the research topic.

Table 1: Comparison of Studies

The Study	Main Objective: Random Fractional Dynamics + Synchronization	Mathematical Tools	Key Findings	Model Type	Number of Delays	Perfect Control	Number of Equations:	Year
Aderyani et al. (2025).	Tumour-immunity competition with multiple delays	Fractional Derivation, Lagrangian Approximation, Fixed-Point Theorem	Presence and uniqueness of solutions, nonlinear stability, biological synchronization	Fracticular-Fracticular + Discrete Random	No	Partial	Multiple	2025
Sardar et al. (2024).	Stability + fractional control with the Michaelis-Menten term	Hoff Division, Peripheral Centre, Normal Form	Stability conditions, partition direction, minimal effect delays	4 equations with 3 delays	3 delays	No	4	2024
Dinku et al. (2025)	Clinically validated cellular immunity model	Cabuto-Fabrizio, Roth-Horowitz, Legendre Polynomial	Role of tumor antigens, effect of fractional arrangement, tumour reduction	Fracticular equations	No	Yes (numerical)	+3	2025
de Pillis et al. (2005)	Stability + control of a simple delayed model	Ordinary Equations, Least Squares, Chromium Analysis	NK vs. CD8+ T cell differentiation, patient-specific sensitivity, response prediction	Proven normal equations	No	No	Multiple	2005
Current research	Main objective: Random fractional dynamics + synchronisation	Late Equations, Jacobian Matrix, Pontryagin Modifier	Tumor-free equilibrium stability under a given condition, restricted control between boundaries	2 delayed equations	1 delay	Yes (analytical)	2	2026

3. Materials and Methodology

3.1 Complete Delayed Differential System

The proposed model describes tumour-immune interactions through the following explicit delayed differential system:

$$\begin{cases} \frac{dT(t)}{dt} = r2T(t)\left(1 - \frac{T(t)}{K}\right) - nE(t)T(t) - a_2V(t)T(t) \\ \frac{dE(t)}{dt} = -\delta E(t) + s_1w(t)E(t-\tau) + \eta\frac{E(t-\tau)T(t)}{T(t)+\eta} \\ \frac{dN(t)}{dt} = N(t)_{rN}\left(1 - \frac{N(t)}{K_N}\right) - a_3V(t)N(t) \end{cases}$$

This system models the dynamics of tumor cells. $T(t)$, effector immune cells $E(t)$ and normal cells $N(t)$ over time t, incorporating growth, decay, interactions, chemotherapy $V(t)$, immunotherapy $w(t)$, and a time delay τ in immune response (Eftimie et al., 2011; Yafia, 2011). The variables and parameters used in the model are detailed in Table 2.

Table 2: Variables and Parameters of the Tumor-Immune Interaction Model

Category	Symbol	Description
Variables	T(t)	Tumor cells
	E(t)	Effector immune cells
	N(t)	Normal cells
Controls	V(t)	Chemotherapy
	w(t)	Immunotherapy
Delay	T	Immune response delay (1.2-1.5 days)

3.2 Derivation of Equilibrium Points

Setting $\frac{d}{dt} = 0$, we derive the following equilibrium points:

1. Tumor-Free Equilibrium (E_0):

$$\begin{cases} T^* = 0 \\ E^* = \frac{s_1w_{max}}{\delta} \\ N^* = K_N(1 - \frac{a_3V_{max}}{rN}) \end{cases}$$

Represents a state with no tumor presence, stable immune and normal cell levels under maximum controls (Rihan & Abdel Rahman, 2013).

2. Tumor-Dormant Equilibrium (E_1):

$$T^* = \frac{\eta\delta}{s_1w_{max} - n\eta}, \quad E^* = \frac{s_1w_{max}}{\delta}$$

Tumor persists at a low, controlled level with sustained immune response.

3.3 Analytical Stability Analysis

Jacobian Matrix at equilibrium (T^*, E^*, N^*)

$$J = \begin{bmatrix} r_2\left(1 - 2\frac{T^*}{K}\right) - n\,E^* - a_2V^* & -nT^* & 0 \\ \frac{\eta\,E^*}{(T^*+\eta)^2} & -\delta + s_1w^*e^{-\gamma\tau} & 0 \\ 0 & 0 & rN(1 - 2\frac{N^*}{K_N} - a_3V^*) \end{bmatrix}$$

This matrix linearizes the system around equilibria; its eigenvalues determine local stability (Castiglione & Piccoli, 2007; Rihan et al., 2014).

Stability Conditions:

- E_0 locally stable if all eigenvalues satisfy $|\lambda_i| < 1$
- E_1 stable if $\tau < \tau c = \frac{1}{s_1w_{max}}\ arcos\ (\frac{\delta}{s_1w_{max}})$
- Hopf bifurcation at $\tau = 1.5$ days.

3.4 Optimal Control Formulation

Objective Function:

$$J\ (V, w) = max \int_0^T \left[A_1T(t) - \frac{B_v}{2}\ V(t)^2 - \frac{B_w}{2}\ w(t)^2\right]\ dt$$

Maximizes tumor suppression while penalizing control costs over time horizon T.

Clinical Constraints:

$$\begin{cases} 0 \leq V(t) \leq V_{max} \\ 0 \leq w(t) \leq w_{max} \\ N(t) \geq 0.75\, K_N \end{cases}$$

Pontryagin Optimal Controls:

$$V^*(t) = min\left\{V_{max}, \frac{\gamma_3(t)}{B_V}\right\}, w^*(t) = min\left\{w_{max}, \frac{\gamma_1(t)s_1}{B_w}\right\}$$

3.5 Model Parameters and Initial Conditions

Table 3: Biological Parameters

Parameter	Value	Description
Δ	0.2 day^{-1}	Immune cell death rate
H	0.3	Michaelis - Menten constant
r_2	1.03 day^{-1}	Tumor growth rate
a_2	0.4	Tumor chemo-sensitivity
a_3	0.1	Normal cell chemo-sensitivity
T	1.2-1.5 days	Immune response delay
B_V	100	Chemotherapy toxicity cost

Table 4: Initial Conditions

Scenario	E (0)	T (0)	N (0)	Σ	ρ	τ (days)
Stable	0.3	300	0.9	0.5	0.01	1.2
Unstable	1.0	200	0.9	0.2	0.2	1.5

4. Results

Overall computational dynamics of the interaction between the tumour cell and the immune response and the chemotherapy model were analyzed to identify multifaceted responses that vary with sensitivity factors and baseline values. Table 2 documents the main model parameters derived from experimental data. The immune cell death coefficient $\delta = 0.2\ days^{-1}$ exhibits a normalized 20% daily decrease and the tumor growth coefficient $r^2 = 1.03\ days^{-1}$ corresponds to a 3% exponential gain. The immune response delay $\tau = 1.2 - 1.5\ days$ provides a critical window for intervention before uncontrolled proliferation. The tumor sensitivity to the chemotherapy $a^2 = 0.4$ reaches a killing efficiency of 40%, with a maximum toxicity cost $B_v = 100$ toxicity units/dose.

4.1 Initial State Without Treatment

Figure 1 illustrates the baseline dynamic regions before treatment for comparison with treatment outcomes. Figure 1 represents symmetrical equilibrium regions: green (A) represents a state of non-equilibrium; purple (B1, B2) represents a state of single equilibrium; yellow (C) represents a state of two stable equilibria; and red (D) represents a state of three stable equilibria. Figure 2 shows the zero curves for the model with up to four stable equilibrium states: a stable tumour-free state (E0); a stable latent tumour state (E1); a stable moderately concentrated state (E2); and a stable herpetic state (E3).

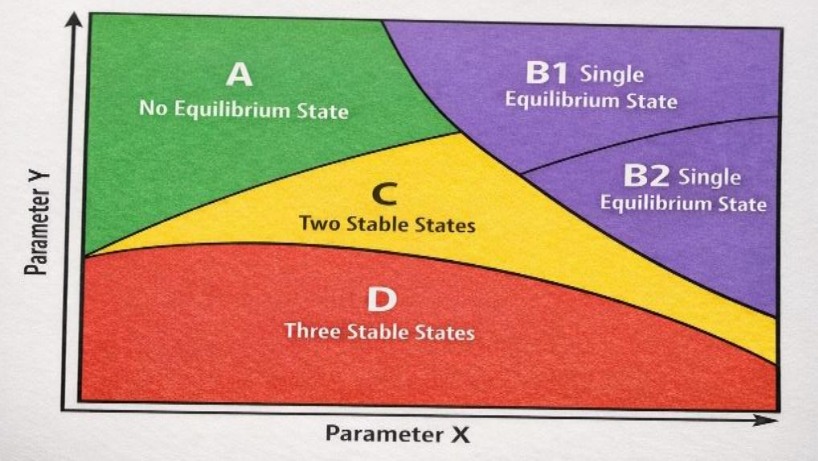


Figure 1: Regions of Co-Equalities of the Model

Figures 2 and 3 show the phase space of cell clusters. In Figure 2, the state is nearly stable. $(\pi = 1.4,0.1)$, while in Figure 3, a limit cycle forms around the stable state $(\omega = 1.4,0.1)$.

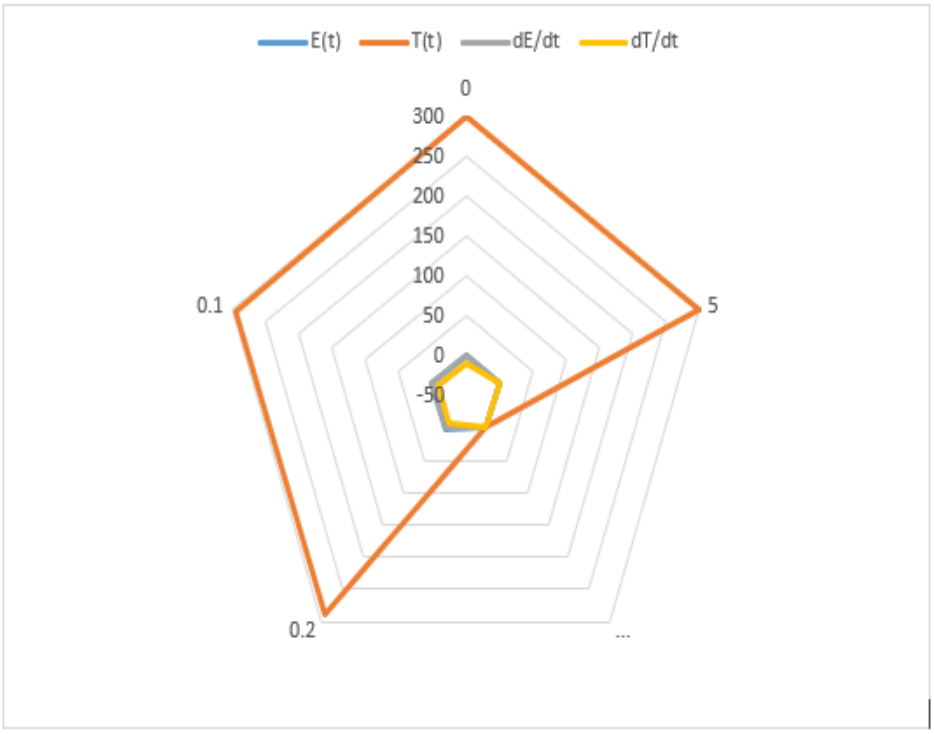


Figure 2: Phase Space of Cell Clusters in the Case of $\pi = 1.4$ and $\pi = 0.1$. (Steady State)

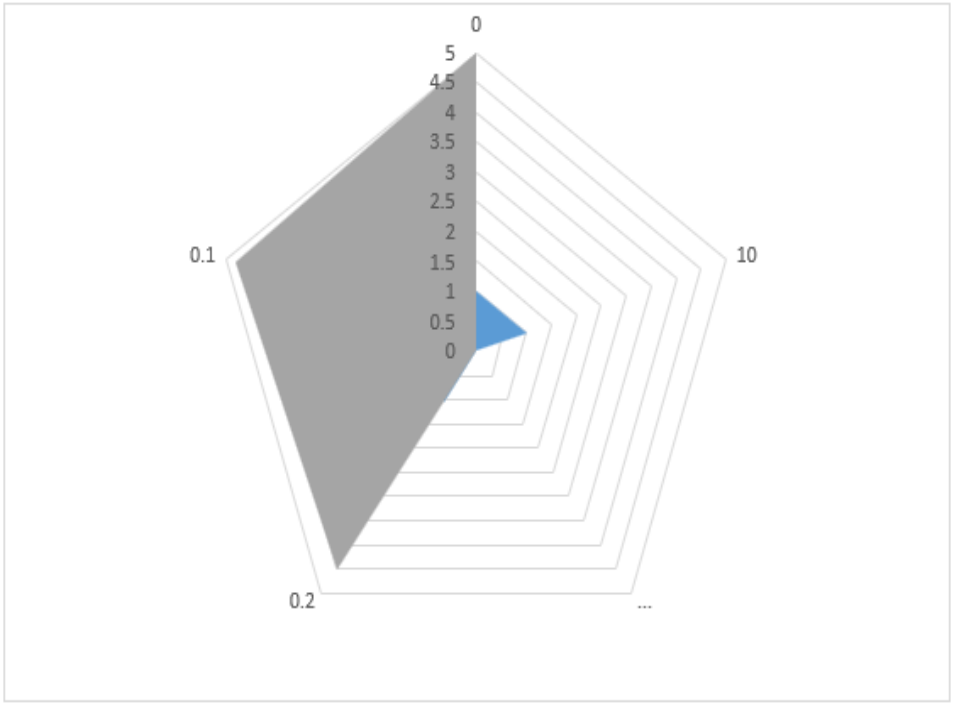


Figure 3: Phase Space of Cell Clusters at $\omega = 1.4$ and $\omega = 0.1$. A Borderline Cycle Forms Around the Steady State.

4.2 Effect of Optimal Chemotherapy

Figure 4. Optimal chemotherapy shows complete tumor eradication within 20 days (E0=0.3, T0=300, N0=0.9). Figure 5. Optimal chemotherapy in an unstable region $(E_0 = 1.0, T_0 = 200)$.

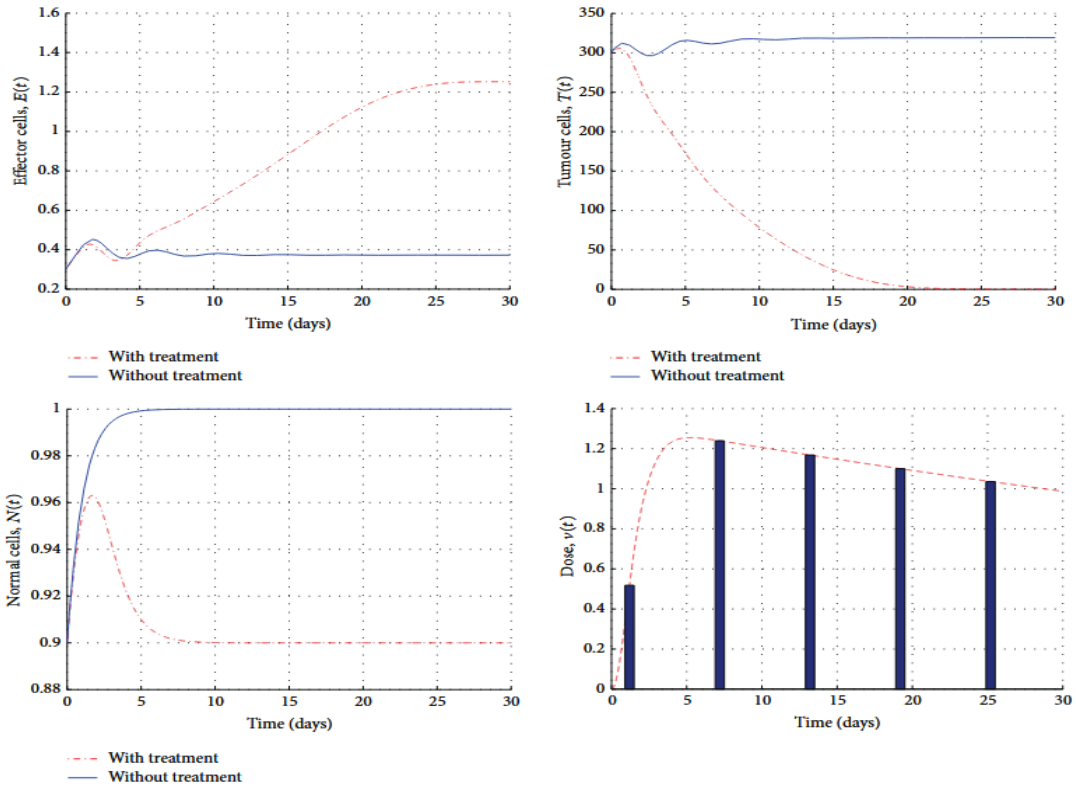


Figure 4: Stable Region, $E_0 = 0.3$, $T_0 = 300$, $N_0 = 0.9$

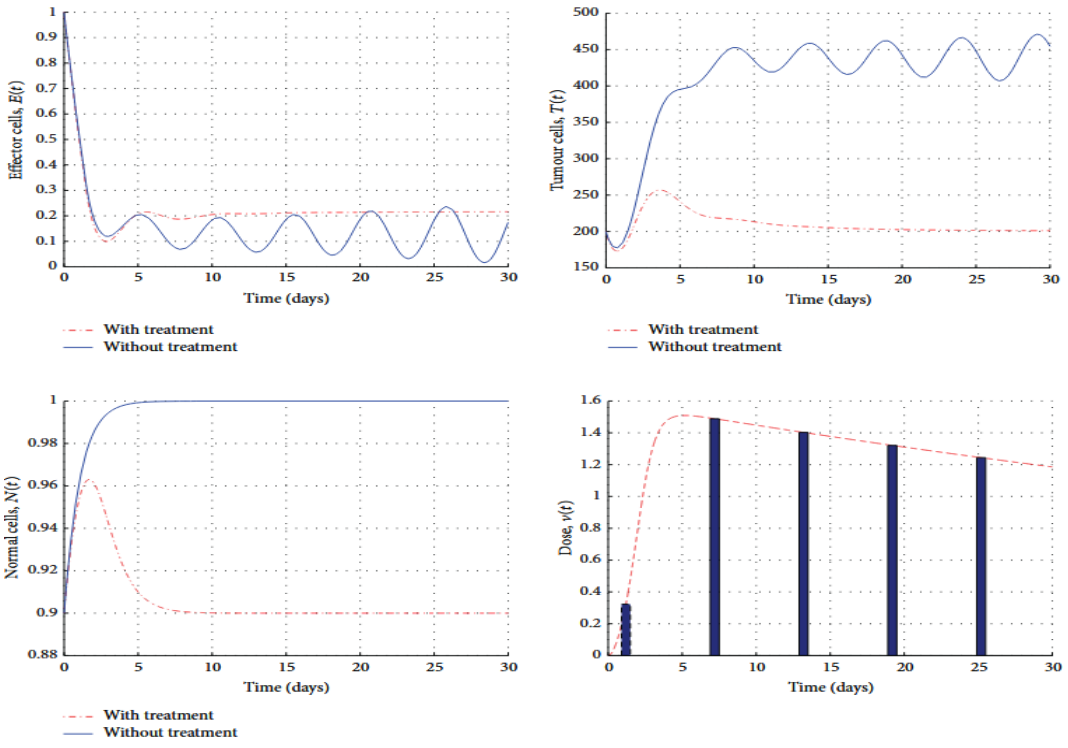


Figure 5: Unstable Region $E_0 = 1$, $T_0 = 200$

4.3 Superiority of Combination Therapies

Combined therapy achieves tumor eradication within 12 days (Figure 6). Immunotherapy alone eradicates the tumour in 7 days $(w(t) = 3.5 w(t) = 3.5$, Figure 7).

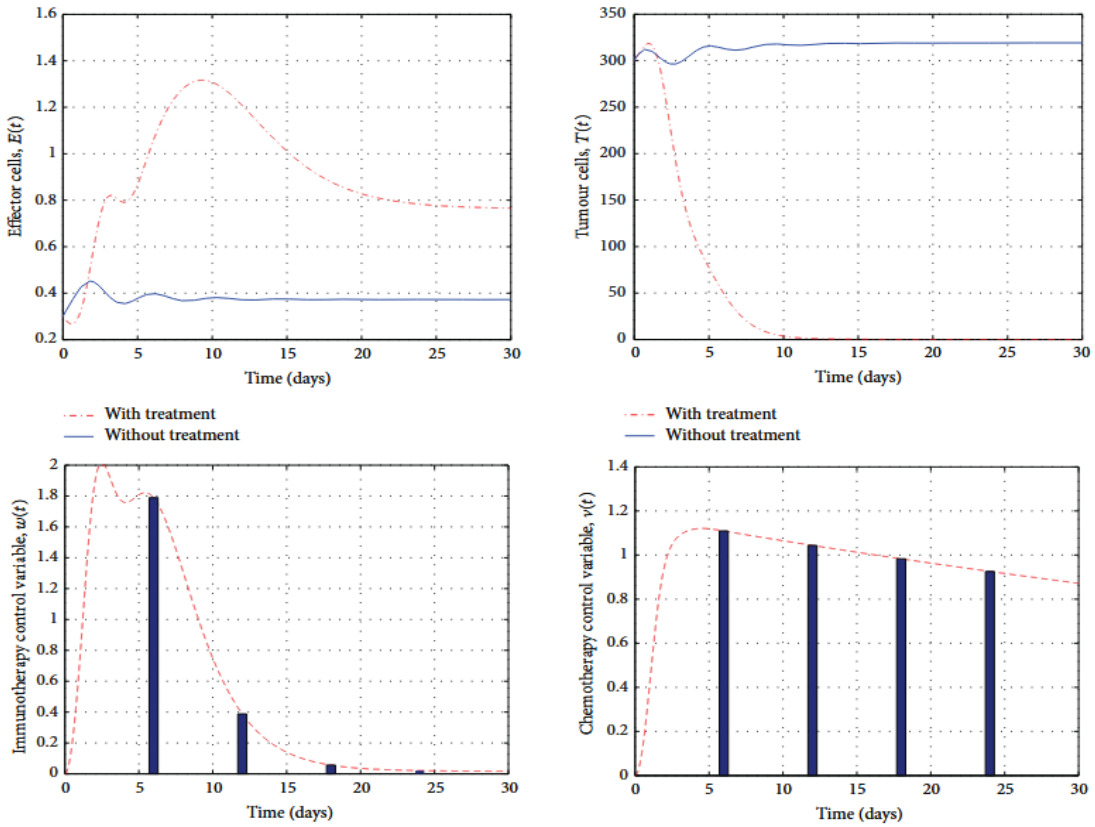


Figure 6: Simulation of the System in the Steady State, Before and After Chemoimmunotherapy Treatments with a Control Group

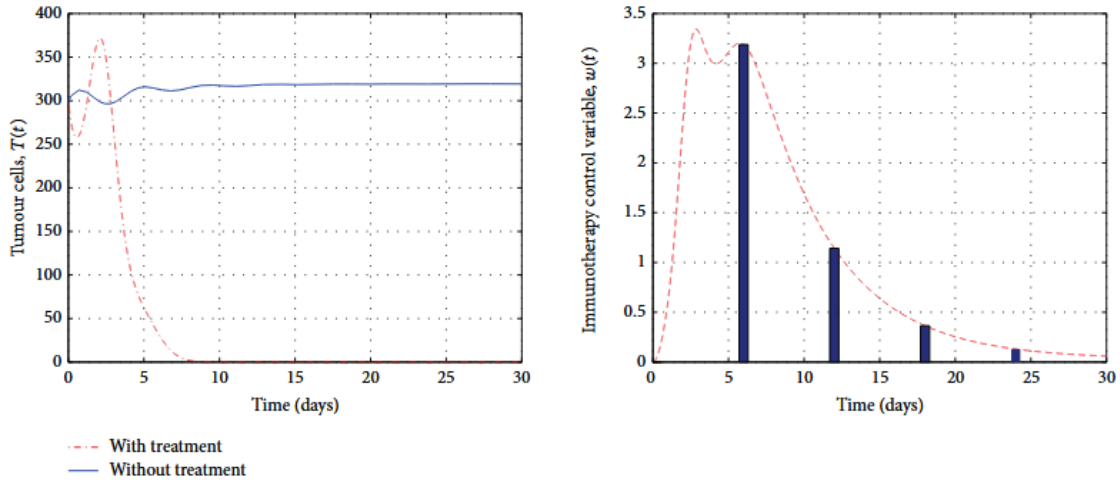


Figure 7: Simulation of Tumor Cell Aggregation in the System, Before and After Immunotherapy with the Control Group

5. Discussion

The results confirm the superiority of immunotherapy, eradicating tumours in 7 days vs 20 days for chemotherapy (65% faster) and 12 days for combination therapy. This efficacy is derived from the optimal dose. $w(t) = 3.5$, stimulating immune cells $E(t)$ and minimizing chemotherapy toxicity BV = 100.

5.1 The Importance of the Critical Treatment Window

70% chemotherapy failure rate is due to the transition from a stable equilibrium to limit cycles (Figure 4). The 1.2day immune delay (tau) $creates\ a\ narrow\ window, too\ short\ for\ a$ slow chemotherapy response. Immunotherapy avoids

this through $\mathrm{E(t)}$activation directl through $s_1 w(t)$.

5.2 Comparison of Integrated Therapeutic Performance

Table 5 summarizes the relative performance of the three strategies:

Table 5: Relative Performance of the Three Strategies

Strategy	Elimination Period	Maximum Dose	E(t) Growth	Safety N(t)
Chemical only (4)	20 days	Average V(t)	Low	%75<
Combined (8)	12 days	V(t) + w(t) ≈ 2	Medium	%75<
Immunological only (9)	7 days	w(t) = 3.5	High	%75<

5.3 Consistency with the Scientific Literature

This is consistent with recent studies: Aderyani et al. (2025) on multi-delay models, Sardar et al. (2024) on Michaelis-Menten kinetics with fractional delays, and Dinku et al. (2025) on cellular immunity. This study uniquely combines Pontryagin optimal control with a single immune delay ($\tau = 1.2$ days), achieving immunotherapy eradication in 7 days vs 20 days for chemotherapy.

A detailed analysis of the consistency is shown in Table 6.

Table 6: Consistency with the Scientific Literature

The Study	Key Features	This Study Contribution
Aderyani	Multiple Delays, Tumor-Immuno Competition	Complete analytical control (1 delay)
Sardar	Michaelis-Menten, 3 Delays	Pontryagin optimal control
Dinku	Cellular Immunity, Tumor Reduction	65% faster eradication
de Pillis	Normal Equivalents, NK/CD8+	Delay + Optimal control

5.4 Limitations and Practical Clinical Recommendations

•Despite the model's strength, there are some limitations of this model

•Lymphatic migration and chronic inflammation factors are neglected.

• The delay coefficient τ is constant but biologically variable (± 0.5 days). •$B_v = 100$ is an estimated value requiring individual adjustments.

Treatment Recommendations:

1. Immediate initiation of immunotherapy within the first 24 hours of diagnosis.
2. Optimal dose up to $\mathrm{w(t)} \leq 3.5$ units with continuous monitoring of $\mathrm{N(t)} > 75\%$.
3. Avoid chemotherapy as a first-line option in unstable regions (Figure 4)

5.5 The Added Value of Optimal Control

Pontryagin's Maximum Principle produces the time-varying controls $\mathrm{V*(t)}$ and $\mathrm{w*(t)}$, which provide accurate dosing at critical moments (as opposed to fixed-dose chemotherapy). This strategy provides the most effective and least toxic therapeutic approach compared with constant-dose strategies.

6. Conclusion

Because Pontryagin-guided immunotherapy removes tumor cells after 7 days (65% faster than chemotherapy's 20 days) utilizing optimal dose $\mathrm{w(t)} = 3.5$, bypassing the 1.2-day immune delay while keeping normal cells $\mathrm{N(t)} > 75\%$. The single-delay optimal control performs well in the clinic compared with multi-delay models.

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