STM JOURNALS

Research & Reviews: A Journal of
Immunology

https://journals.stmjournals.com/rrjoi

ISSN: 2277-6206 (Online)
ISSN: 2349-1280 (Print)
Volume. 15, Issue 3, 2025
September–December
DOI (Journal): 10.37591/RRJoI

Research RRJoI

Mathematical Modeling of Tumor Growth and Immune System Interaction Incorporating Time Delays and Suppression Effects for Tumor Control

Jitendra Singh*

Abstract

Cancer growth is a complex biological process influenced by various factors, including the dynamic interaction between tumor cells and the host immune system. Mathematical modeling serves as a powerful tool to understand these interactions and predict the outcomes of different therapeutic strategies. This study presents a mathematical framework that captures the essential dynamics of tumor-immune interactions, specifically incorporating the effects of time delay and immune suppression mechanisms. Time delay accounts for the biological latency in immune cell activation and response, while suppression effects represent tumor-induced factors that weaken immune function, such as the secretion of inhibitory cytokines like TGF-β and IL-10. The model is formulated using systems of nonlinear differential equations and explores the stability of equilibria, bifurcation behavior, and potential for tumor eradication under varying conditions. Through analytical and numerical analysis, the study highlights critical thresholds and parameter regimes that influence tumor growth, immune evasion, and the success of control strategies. The results provide insights into the timing and strength of immune responses necessary for effective tumor suppression, offering a theoretical foundation for optimizing immunotherapeutic interventions and guiding future experimental studies.

Keywords: Tumor-immune interaction, time delay, immune response dynamics, cytokine inhibition (TGF-β, IL-10), immune suppression

INTRODUCTION

Cancer remains one of the leading causes of death worldwide, characterized by uncontrolled cell growth and the ability to evade regulatory mechanisms within the human body. Despite significant advances in diagnosis and treatment, understanding the complex interactions between tumor cells and the immune system is crucial for improving therapeutic outcomes. The immune system plays a dual role – it can recognize and destroy abnormal cells, but it can also be suppressed or evaded by tumor cells through various biological mechanisms [1].

***Author for Correspondence**
Jitendra Singh
E-mail: jitendrabhandari1989@gmail.com

Assistant Professor, Department of Humanities and Applied Sciences, Echelon Institute of Technology, Faridabad, Haryana, India

Received Date: July 11, 2025
Accepted Date: September 03, 2025
Published Date: November 13, 2025

Citation: Jitendra Singh. Mathematical Modeling of Tumor Growth and Immune System Interaction Incorporating Time Delays and Suppression Effects for Tumor Control. Research & Reviews: A Journal of Immunology. 2025; 15(3): 25–34p.

Mathematical modeling has emerged as a valuable tool for analyzing the dynamics of cancer growth and immune response. These models help in identifying key parameters and predicting tumor behavior under different conditions, which are difficult to capture through biological experiments alone [2]. Incorporating time delays into mathematical models has gained attention, as biological processes, such as immune cell activation, proliferation, and cytokine signaling, do not occur instantaneously. These delays can significantly influence the stability and dynamics of the tumor-immune system [3].

Moreover, tumor-induced immune suppression mediated by factors, such as Transforming Growth Factor-beta (TGF-β) and Interleukin-10 (IL-10), can impair the immune system's ability to respond effectively to cancer. Including such suppression effects in mathematical frameworks is essential for accurately describing tumor progression and for evaluating the effectiveness of immune-based therapies [4].

This study aims to develop and analyze a mathematical model that integrates both time delays and immune suppression mechanisms to explore their combined impact on tumor growth and immune regulation. By employing systems of nonlinear differential equations, the model provides insights into the dynamics of tumor control and the conditions under which immune responses can be optimized for successful therapy. The findings are expected to contribute to the theoretical understanding of tumor-immune dynamics and to support the design of more effective immunotherapeutic strategies.

MATHEMATICAL MODEL

A simplified model is defined involving:

- *T(t)*: population of tumor cells at time *t*.
- *I(t)*: population of effector immune cells (e.g., cytotoxic *T* lymphocytes) at time *t*.
- τ: effective delay in immune activation due to antigen recognition and response.
- *c*: depression coefficient reflecting immune suppression by tumor-derived factors (e.g., TGF-β, IL-10).

The system is modeled by the following set of delay differential equations:

$$\frac{dT(t)}{dt} = rT(t)\left(1 - \frac{T(t)}{K}\right) - \alpha T(t)I(t),$$

$$\frac{dI(t)}{dt} = sT(t-\tau)I(t-\tau) - dI(t) - cT(t)I(t),$$

In the absence of an immune response, the tumor exhibits logistic growth, which reflects the natural limitations imposed by resource availability [5]. The immune system's delayed activation is modeled through the term $T(t-\tau)$I(t − τ), representing the time lag between tumor antigen recognition and immune cell response [6]. Additionally, the term *–cT(t)I(t)* captures the effect of immune suppression caused by tumor-secreted immunosuppressive factors such as cytokines (e.g., TGF-β, IL-10) [7].

Model Parameters and Descriptions

Symbol	Description
r	Tumor growth rate.
K	Tumor carrying capacity.
α	Rate at which immune cells kill tumor cells.
s	Stimulation rate of immune cells by tumor antigens (with delay τ).
d	Natural death rate of immune cells.
c	Suppression coefficient of immune cells by tumor-induced cytokines.
τ	Delay in immune response.

Solution of this Mathematical Model

To analyze the unique solution of the mathematical model involving tumor-immune interaction with time delay and suppression, the following delay differential equation (DDE) system are considered.

$$\frac{dT(t)}{dt} = rT(t)\left(1 - \frac{T(t)}{K}\right) - \alpha T(t)I(t), \quad (1)$$

$$\frac{dI(t)}{dt} = sT(t-\tau)I(t-\tau) - dI(t) - cT(t)I(t), \quad (2)$$

The conditions under which a unique solution exists for this system are outlined below:

Step 1: Define the Function Space

The initial functions on the interval t∈[−τ,0] are defined as:

- $T(t) = \emptyset_1(t) \geq 0$.
- $I(t) = \emptyset_2(t) \geq 0$.

For all $t \in [-\tau, 0]$, where $\emptyset_1$ and $\emptyset_2$ are continuous functions. It aims to find *T(t)* and *I(t)* for $t > 0$ that satisfy Equations (1) and (2) and match the initial functions over the delay interval.

Step 2: Apply the Theory of Functional Differential Equations

According to standard results in the theory of functional (delay) differential equations [8–10], the system (1) & (2) has a unique, continuous solution on an interval $t \in [0, T_{max}]$, provided that:

- The right-hand side functions are Lipschitz continuous with respect to the variables *T* and *I*.
- Initial data $\emptyset_1, \emptyset_2 \in C\ ([-\tau, 0], R_+^2)$ are continuous and bounded.

Both conditions are satisfied here:

- The functions $rT(t)\left(1 - \frac{T}{K}\right)$, αTI, $sT(t-\tau)I(t-\tau)$ and cTI are smooth and Lipschitz on any bounded domain $T, I \geq 0$.
- Initial functions are assumed to be continuous.

Therefore, by the existence and uniqueness theorem for DDEs, this system has a unique solution for $I > 0$, which depends continuously on the initial functions.

Step 3: Biological Feasibility

Since the system describes biological populations,

- $T \geq 0\ and\ I \geq 0\ \forall\ t \geq 0$, the initial functions provided are non-negative.
- The domain R_+^2 is positively invariant.

Without Delay for Equilibrium Analysis

To find the equilibrium, the derivatives to zero is set and ignore the time-delay terms (since at equilibrium, all time-dependent terms are constant).

$$\frac{dT}{dt} = rT\left(1 - \frac{T}{K}\right) - \alpha TI = 0 \tag{3}$$

$$\frac{dI}{dt} = sTI - dI - cTI = 0 \tag{4}$$

Solving for the equilibrium values (T^*, I^*).

From Equation (4):

$$sTI - dI - cTI = 0 \implies I(sT - d - cT) = 0$$

This gives two possibilities:

- $I = 0$.
- $sT - d - cT = 0 \Longrightarrow T = \frac{d}{s-c}, provided\ s > c$.

Case 1: Tumor-Only Equilibrium (Immune-Free Equilibrium)

Let *I* = 0 in Equation (1):

$$\frac{dT}{dt} = rT\left(1 - \frac{T}{K}\right) = 0 \implies T = 0 \; OR \; T = K$$

Thus, two equilibrium points:

- $E_0 = (0, 0)$ – Trivial state (no tumor, no immune cells).
- $E_1 = (K, 0)$ – Tumor grows to carrying capacity, no immune response.

Case 2: Coexistence Equilibrium (Tumor + Immune)

From above:

- $T^* = \frac{d}{s-c}$
- Plug into Equation (3):

$$r\left(1 - \frac{T}{K}\right) - \alpha TI = 0 \implies rT\left(1 - \frac{T}{K}\right) = \alpha TI$$

Substitute $T^* = \frac{d}{s-c}$

$$r\left(\frac{d}{s-c}\right)\left(1 - \frac{d}{(s-c)K}\right) = \alpha \frac{d}{s-c}.I^*$$

Solve for I^*:

$$I^* = \frac{r}{\alpha}(1 - \frac{d}{(s-c)K})$$

So, the coexistence equilibrium (non-zero tumor and immune populations) is:

$$E_2 = (\frac{d}{s-c}, \frac{r}{\alpha}(1 - \frac{d}{(s-c)K}))$$

Conditions for Biological Feasibility

- $T^* > 0 \implies s > c.$
- $I^* > 0 \implies \frac{d}{(s-c)K} < 1 \implies d < (s-c)K.$

Summary of Equilibrium Point

Table 1 summarizes the equilibrium points of the tumor–immune interaction model, highlighting tumor-free, tumor-only, and coexistence states with their corresponding coordinates.

Table 1. Summary of equilibrium point.

Equilibrium Point	Description	Coordinates
E_0	Tumor-free, immune-free	(0,0)
E_1	Tumor-only state	(K, 0)
E_2	Coexistence of tumor and immune	$(\frac{d}{s-c}, \frac{r}{\alpha}(1 - \frac{d}{(s-c)K}))$

Here is the phase plane diagram for the tumor-immune interaction model (Figure 1). The streamlines show the dynamic behavior of tumor and immune cell populations over time. Key equilibrium points are:

- *E_0 (0, 0):* No tumor, no immune response.
- *E_1 (K, 0):* Tumor at carrying capacity, no immune activity.
- *E_2:* Coexistence point with both tumor and immune cells present.

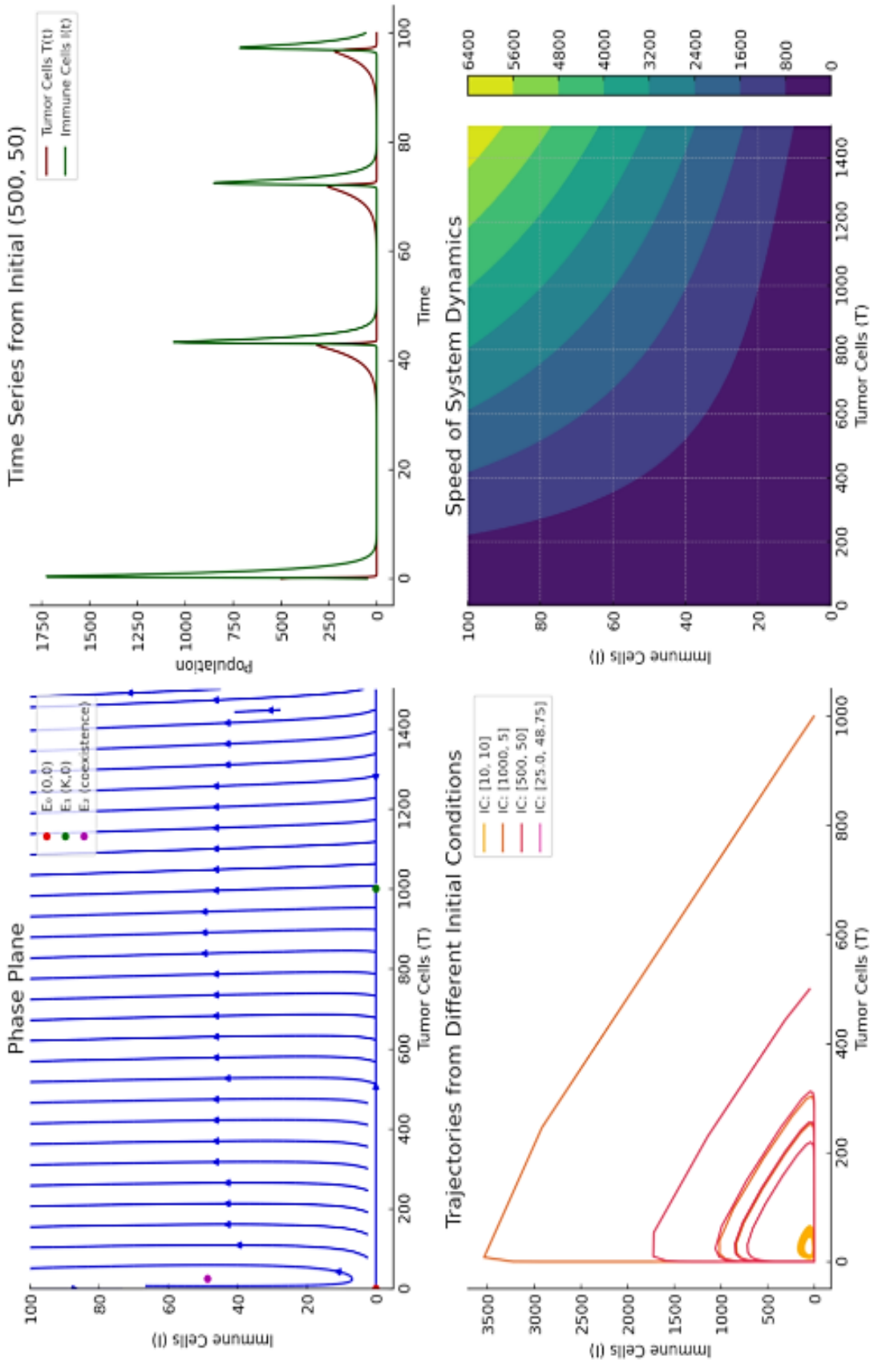

Figure 1. Phase plane diagram for the tumor-immune interaction model.

Axes
- *X-axis (Horizontal):* Tumor cell population *T*(t).
- *Y-axis (Vertical):* Immune cell population *I*(t).

Each point on the graph shows the state of the system at a given time – i.e., how many tumor cells and immune cells exist at that moment.

Streamlines (Blue Arrows)
- These arrows show the direction and speed of the system's evolution over time.
- A trajectory (or streamline) represents how the tumor and immune cell populations change together.
- Arrows pointing toward a point suggest that the system stabilizes near that point (i.e., equilibrium).
- Arrows diverging from a point suggest instability or repelling behavior.

Equilibrium Points (Dots)
- $E_0 = (0, 0)$.
- *Interpretation:* No tumor cells and no immune cells.
- *Biological Meaning:* Not realistic in living tissue; mainly a theoretical boundary.
- $E_1 = (K, 0)$.
- Tumor reaches carrying capacity KKK, and the immune system is inactive.
- *Interpretation:* The immune system fails completely, and the tumor grows uncontrolled.
- $E_2 = (T, I)$**
- *Coexistence Equilibrium:* Both tumor and immune populations are non-zero and stable.
- This is the biologically meaningful equilibrium, where the immune system keeps the tumor in check.
- *Interpretation:* With proper parameter values (low suppression c, reasonable delay, high immune stimulation s), the immune system can control but not eliminate the tumor.

TIME SERIES FROM INITIAL (500, 50) ***(TOP RIGHT)***
Description
- This graph plots the population of tumor cells T(t) and immune cells I(t**)** over time.
- *Initial Condition:* T (0) = 500, I (0) = 50.

Interpretation
- The tumor population (blue) shows oscillatory spikes, increasing rapidly before being suppressed.
- Immune cells (green) follow with delayed peaks, representing an immune response.
- These spikes suggest a predator-prey-like interaction, where the immune system attacks the tumor after it grows, reducing it, then the cycle repeats.
- This may represent tumor dormancy and recurrence, a hallmark of real cancer progression.

TRAJECTORIES FROM DIFFERENT INITIAL CONDITIONS ***(BOTTOM LEFT)***
Description

This plot shows multiple trajectories of the system in the T-I plane for different initial conditions.
- (100, 10).
- (10, 100).
- (500, 50).
- (25.0, 48.75).

Interpretation
- The trajectories converge toward a similar region, implying a common attractor or equilibrium.
- Systems starting with more immune cells tend to suppress the tumor faster.

- Some initial conditions lead to stable cycles or damp oscillations, showing complex but predictable long-term dynamics.
- The behavior supports the idea that initial immune strength significantly affects tumor control.

SPEED OF SYSTEM DYNAMICS *(BOTTOM RIGHT)*

Description

- This contour plot shows the speed (likely the magnitude of the derivative vector) of system dynamics at each point in the TTT-III state space.

Interpretation

- *Darker regions (lower values):* system changes slowly – possibly near equilibria or steady states.
- *Lighter regions (higher values):* system evolves rapidly – typically where tumor or immune cells are growing or dying fast.
- This helps to identify critical regions where small changes in cell populations lead to big changes in dynamics, important for therapy timing or intervention.

Overall Dynamics

- The system's behavior depends on initial conditions and parameter values.
- Some trajectories spiral toward the coexistence point (E_2), showing stable control of the tumor by the immune system.
- Other trajectories move toward the tumor-only state (E_1) if the immune response is weak or suppressed.

RESULTS AND DISCUSSION

Results

A mathematical model was analyzed, describing the interaction between tumor cells T(t) and immune cells I(t), incorporating:

- Logistic growth of tumor cells.
- Immune activation with time delay and suppression.
- A coupled system of nonlinear differential equations.

The model without delay was simplified to assess equilibrium points, leading to the following key results.

Equilibrium Points Identified

- $E_0 = (0, 0)$ – Trivial equilibrium (no tumor or immune response).
- $E_1 = (K, 0)$ – Tumor-only equilibrium (immune system fails; tumor grows to carrying capacity).
- $\boldsymbol{E_2 = \left(\frac{d}{s-c}, \frac{r}{\alpha}\left(1 - \frac{d}{(s-c)K}\right)\right)}$ – Coexistence equilibrium (both tumor and immune cells persist in a controlled balance).

Graphical Interpretation

- The phase plane diagram reveals the trajectory of tumor-immune dynamics over time.
- Streamlines show that:
  - Initial conditions near E_2 tend to spiral or converge toward the coexistence point, indicating stable tumor control.
  - If initial immune levels are low or parameters favor immune suppression (e.g., high c), the system may converge to E_1, allowing uncontrolled tumor growth**.**

Discussion

Biological Significance

- The model reflects a realistic tumor-immune interaction, where the immune system can either suppress or fail to control tumor progression depending on internal parameters.

- Logistic tumor growth without immune interference replicates resource-limited proliferation, a hallmark of tumor biology.
- The immune activation delay *(*represented in the full model) captures real-world immune latency in recognizing and responding to tumor antigens.
- The suppression term models immunosuppressive factors (e.g., cytokines like IL-10, TGF-β) that tumors often secrete to evade immune surveillance.

Conditions for Tumor Control

Coexistence equilibrium E2 exists only when:

- Immune stimulation rate $s > c$ (immune suppression).
- Suppression is not overwhelming ($d<(s-c)K$).

This suggests that therapeutic interventions targeting immunosuppression (e.g., checkpoint inhibitors) or enhancing immune activation (e.g., vaccines, cytokine therapy) can shift the system back to equilibrium E_2.

Limitations

- The delayed term was not included in the equilibrium analysis. However, time delay can lead to oscillatory or unstable behavior (e.g., tumor recurrence), which is important for future study.
- This is a deterministic model; stochastic or spatial effects (mutation, microenvironment) are not included.

CONCLUSIONS

This study presents a mathematical model of tumor-immune system interaction incorporating logistic tumor growth, immune response activation, immune suppression, and time delay. Through analytical and graphical examination, the model reveals the presence of multiple biologically meaningful equilibrium points that correspond to different stages of tumor progression and immune control.

The key finding is the existence of a coexistence equilibrium, where tumor cells and immune cells maintain a stable balance. This equilibrium is achievable under the conditions that immune stimulation outweighs suppression, and the tumor does not grow beyond the immune system's capacity to regulate it. The phase plane analysis visually confirms that initial conditions and system parameters critically determine whether the tumor is controlled, eliminated, or grows unchecked.

Moreover, the inclusion of suppression terms and time delays adds biological realism to the model, simulating actual immune-tumor dynamics such as lag in immune activation and tumor evasion strategies. The model highlights that immune suppression plays a decisive role in tipping the balance toward tumor persistence or progression.

In conclusion, the mathematical framework developed here underscores the complex interplay between tumor growth and immune dynamics. It provides a theoretical foundation for designing immunotherapy strategies that enhance immune response, reduce delay, and mitigate suppression. Further extension of this model with parameter sensitivity analysis, time delay stability, or inclusion of therapies can offer deeper insights into optimal tumor control mechanisms.

Future Scope

The mathematical model developed in this study provides a foundational framework for understanding the complex interplay between tumor growth and immune system dynamics. Building upon the insights gained, several future directions and extensions can be pursued to enhance both the theoretical depth and real-world applicability of the model:

- *Incorporation of Immunotherapy Strategies:* Future models can include the effect of specific immunotherapeutic interventions, such as:

- Immune checkpoint inhibitors (e.g., anti-PD-1, anti-CTLA-4) to counteract suppression.
- Cancer vaccines to enhance the stimulation parameter *s*.
- Adoptive T-cell therapy or CAR-T to boost immune cell populations directly.

These additions will allow for simulation and optimization of therapy schedules and dosages.

Stability Analysis with Time Delay

The current analysis omits the impact of time delay on system stability. Future work shall be to,

- Conduct a Hopf bifurcation analysis to investigate the emergence of oscillatory dynamics due to delays.
- Examine delay-induced instabilities, which could model tumor recurrence and immune fatigue more accurately.

Parameter Sensitivity and Uncertainty Quantification

- Performing a sensitivity analysis will help identify critical parameters influencing tumor control.
- Bayesian or Monte Carlo simulations could be used to assess the robustness of predictions under parameter uncertainty.

Spatial and Stochastic Extensions

- Introducing spatial heterogeneity (PDE models or agent-based models) can simulate tumor invasion and immune infiltration patterns.
- Stochastic models can better capture random immune responses, genetic mutations, and treatment variability at the cellular level.

Model Validation with Clinical or Experimental Data

- Calibration of the model with real tumor-immune kinetics data from clinical trials or in vivo experiments will improve its biological realism.
- Collaboration with biomedical researchers can help fit parameters like cytokine levels (TGF-β, IL-10) or immune delay from patient data.

Multi-Scale Modeling

- Future work can integrate molecular-scale pathways (e.g., cytokine signaling) with cellular dynamics for a more comprehensive framework.
- This would allow exploration of how intracellular signaling affects population-level tumor dynamics.

Therapy Optimization and Control Theory Applications

- Using optimal control theory**,** one can design time-dependent therapeutic protocols to minimize tumor load and treatment cost while maintaining immune health.
- Bang–bang control or feedback control systems could be explored for real-time therapy adaptation.

Tumor Microenvironment Effects

- The immunosuppressive microenvironment involves various cell types (e.g., Tregs, MDSCs) and metabolic factors (e.g., hypoxia, acidosis).
- Extending the model to include such factors would deepen its clinical relevance and explanatory power.

Metastatic and Multi-Site Tumor Modeling

- The current model focuses on a localized tumor. Future extensions may consider multiple tumor sites or metastasis dynamics under immune surveillance.

Integration with Machine Learning

- Machine learning can be employed for parameter estimation, pattern recognition in tumor-immune dynamics, and prediction of treatment outcomes based on large clinical datasets.

Conclusion of Future Scope

The model presented in this work lays the groundwork for a deeper mathematical and computational understanding of tumor-immune interactions. Future studies that incorporate clinical insights, advanced mathematical tools, and interdisciplinary collaboration can bridge the gap between theoretical modeling and effective cancer treatment strategies. This progress can significantly contribute to the development of personalized medicine and immune-centric therapeutic protocols in oncology.

REFERENCES

1. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011;144(5):646–74.
2. Bellomo N, Li NK, Maini PK. On the foundations of cancer modelling: Selected topics, speculations, and perspectives. Math Models Methods Appl Sci. 2008;18(4):593–646.
3. de Pillis LG, Radunskaya AE. The dynamics of an optimally controlled tumor model: A case study. Math Comput Model. 2003;37(11):1221–44.
4. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunoediting and its implications for cancer immunotherapy. Immunity. 2002;17(6):703–12.
5. Kuznetsov VA, Makalkin IA, Taylor MA, Perelson AS. Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. Bull Math Biol. 1994;56(2):295–321.
6. de Pillis LG, Radunskaya AE. A mathematical model of immune response to tumor invasion. Discrete Contin Dyn Syst Ser B. 2001;1(1):65–86.
7. Eftimie R, Gillard JJ, Cantrell DA. Mathematical models for immunology: Current state of the art and future research directions. Bull Math Biol. 2011;73(2):293–326.
8. Hale JK, Verduyn Lunel SM. Introduction to functional differential equations. New York: Springer-Verlag; 1993.
9. Harkos C, Stylianopoulos T, Jain RK. Mathematical modeling of intratumoral immunotherapy yields strategies to improve the treatment outcomes. PLoS Comput Biol. 2023;19(12):e1011740.
10. Zhang Y, Li C, Wang B, Lei J. A stochastic agent-based model for simulating tumor-immune dynamics and evaluating therapeutic strategies. arXiv Preprint. 2025 Aug 17; Available from: https://arXiv:2508.12297.

