

Modeling and Simulation of Tumor Growth with Stability Analysis

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ABSTRACT

Original research paper

In this work, tumor development is investigated through a dynamical systems approach. The model incorporates tumor cells, Natural Killer (NK) cells, dendritic cells, CD8+T cells, and circulating lymphocytes. The framework is expressed as a nonlinear system of ordinary differential equations, which is solved using the finite difference method (FDM). In addition, stability of the system is analyzed for two distinct cases: the equilibrium points without therapies and the equilibrium points under therapies.

Keywords: Natural Killer cell, Dendritic cell, Cytotoxic (CD8+T) cell, Lymphocytes, Immunotherapy, Chemotherapy.

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1. Introduction

Tumor growth arises from uncontrolled cell proliferation, loss of regulatory mechanisms such as apoptosis and cell cycle checkpoints, and continuous interaction with the tissue microenvironment[1]. Unlike normal cells, tumor cells avoid regulatory mechanisms such as apoptosis and immune surveillance, allowing them to expand rapidly and attack neighboring tissues. The growth of tumors is often described using mathematical models, such as the exponential, logistic[2], and Gompertz functions, which capture different phases of cancer development ranging from rapid initial expansion to slower, resource-limited progression. In addition to intrinsic cellular mechanisms, tumor progression is strongly influenced by immune responses, nutrient availability, angiogenesis, and therapeutic interventions like chemotherapy and immunotherapy[3]. Understanding these dynamics through both experimental and mathematical

approaches is essential for predicting tumor behavior, optimizing treatment strategies, and improving patient outcomes.

A mathematical model was created by De Pillis et al.[1], [3], [4] to examine tumor growth when immunotherapy and chemotherapy are administered together. Their work used differential equations to explore the interactions between tumor cells, immune responses, and treatment outcomes. Similarly, Unni and Seshaiyer [5] developed a model incorporating tumor cell interactions, immunological responses, and drug interventions to study tumor dynamics. Their differential equation framework highlighted the roles of CD8+ T cells, dendritic cells [6], and natural killer (NK) cells in controlling tumor development, showing that combined immunotherapy and chemotherapy can effectively reduce tumor size and improve therapeutic outcomes.

In another study, Wang [7], discussed several mathematical models of tumor progression, including the logistic [2], Gompertz, and exponential equations. These models have been used to estimate the impact of therapies such as chemotherapy and to predict cancer progression, with the choice of growth model shown to be critical for accurate therapy prediction and optimization[3]. Likewise, Ira et al. [8] employed differential equations to analyze tumor progression under treatment, focusing on the interactions among the immune system, chemotherapy, and tumor cells. Their findings revealed that while high chemotherapy doses initially reduce tumor size effectively, the rate of reduction slows over time.

Logistic growth patterns were further investigated by Tsoularis and Wallace [9], who extended the classical Verhulst model by adding parameters to improve predictive accuracy. Their results indicated that logistic models can successfully describe real-world biological growth, including tumor development. Building on this line of research, other models have specifically examined tumor-immune interactions, focusing on CD8+ T cells and NK cells, and incorporating possible vaccination effects, again using differential equations to capture tumor-immune dynamics [1].

Additional approaches have modeled tumor progression from a population dynamics perspective, employing ordinary differential equations (ODEs) to assess how radiation and repair mechanisms influence tumor lifespan[5]. Control oriented frameworks have also been proposed, such as those that apply optimal control theory to chemotherapy modeling [11], with the aim of reducing tumor size while minimizing harm to healthy cells [6].

2. Main Work

By integrating C compartment, and introducing some modification in the mathematical model of [8], our developed model is expressed as:

$$\begin{aligned}\frac{dT}{dt} &= aT(1 - bT) - (c_1 N + jD + kL + K_T M)T \\ \frac{dN}{dt} &= s_1 C + \frac{g_1 N T^2}{h_1 + T^2} - (c_2 T - l_1 D + K_N M + e)N \\ \frac{dD}{dt} &= s_2 C - (f_1 L + l_2 N - l_3 T + K_D M + g)D \\ \frac{dL}{dt} &= (r_1 N + r_2 C + f_2 D - hL)T - uN L^2 + \frac{P_1 L I}{g_1 + I} - K_L ML - iL \\ \frac{dC}{dt} &= \alpha - (\beta C + K_C M)C \\ \frac{dM}{dt} &= v_M(t) - l_4 M \\ \frac{dI}{dt} &= v_I(t) - l_5 I\end{aligned}$$

The first equation of the model describes the dynamics of tumor cells, which follow logistic growth. Their population is suppressed through interactions with Natural Killer (NK) cells, dendritic cells, and cytotoxic T (CD8+T) cells at constant rates c_1, j and k , respectively. In addition, chemotherapy drugs contribute to tumor cell reduction. The second equation governs NK cells, which are

Beyond these, studies have investigated the statistical behavior of tumor growth models. For example, the logistic and Gompertz functions were analyzed under multiplicative and additive error factors to evaluate their robustness in representing biological growth across different contexts [10]. Broader reviews have also synthesized multiple modeling approaches to forecast tumor progression and guide treatment strategies [6].

Hybrid approaches have emerged as well, such as structural equation modeling (SEM) frameworks that combine logistic and constrained exponential growth functions [2], which have been compared against independent logistic and exponential models [11], [12]. Other works apply formal reaction kinetics to tumor dynamics, using experimental data to validate models and optimize treatment responses[13], [14].

Alternative perspectives include stochastic individual-based models (IBMs) that simulate birth, death, and movement processes to capture emergent population dynamics, with applications extending to cancer modeling as well as human population dispersal[15]. Finally, at the immunological level, studies of the NKG2D receptor and its ligands Rae1 and H60 have demonstrated how tumor immunity can be promoted by stimulating CD8+ T cells and NK cells, suggesting promising directions for cancer immunotherapy [14], [16], [17].

The rest of the paper is organized as follows: Section 2 explores the mathematical model of tumor growth; Section 3 describes the stability of the proposed model. Section 4 contains numerical solutions. Finally, Section 5 summarizes findings and discusses possible future research.

produced at a constant source rate s_1 in association with circulating lymphocytes. These cells are diminished through interactions with tumor cells, dendritic cells, and chemotherapy drugs at constant rates c_2, l_1 and K_N .

The dendritic cells are activated only in the presence of tumor cells and are produced at a constant rate of s_2 together with circulating lymphocytes. Their depletion occurs due to interactions with NK cells and CD8+T cells, as well as through chemotherapy and natural death, at constant rates f_1, l_2, l_3 and K_D . CD8+T cells, in turn, are stimulated by the interaction of dendritic and NK cells with tumor cells, leading to their proliferation. They are, however, eliminated by chemotherapy when inactive, and destroyed through interactions with tumor cells.

Circulating lymphocytes are supplied at a constant rate α , but are reduced by chemotherapy and natural death. Finally, the last two equations describe the concentrations of the chemotherapy drug M and the immunotherapy drug I within the body.

Table: List of parameters with description and values

Parameters	Description	Values
s_1	Source term of NK cell	1.3e4
s_2	Source term of Dendritic cell	480
K_T	Killing rate of tumor cell	0.1
K_N	Killing rate of NK cell	0.1
K_D	Killing rate of Dendritic cell	0.1
K_L	Killing rate of cytotoxic lymphocytes	0.1
K_C	Killing rate of circulating lymphocytes	0.1
a	Tumor growth rate	0.431
b	Tumor growth declaration rate	2.17e-8
c_1	Interaction between tumors and NK cell	3.5e-6
g	Decay rate of D cell	0.24
h	Interaction rate between tumor cells and cytotoxic cells	2.4
u	Elimination rate of cytotoxic cells	2.8e-8
l_1	Interaction between dendritic cells and natural killer cells	1e-6
f_1	Interaction between cytotoxic cells and dendritic cells	1e-8
f_2	Activation rate of cytotoxic cells	0.01
g_1	Proliferation rate of natural killer cell	2e4
h_1	Steepness of natural killer cell	0.16
P_I	Activeness of cytotoxic cells due to I	1.9
g_I	Steepness of cytotoxic cell	2.4
l_2	Competition rate	4.0e-4
c_2	Competition between T cells and natural killer cells	1e-7
l_3	Competition between T cells and dendritic cells	0
i	Natural decay rate	2
j	Competition between T cells and D cells	1e-7
v_I	Source term of I	1
v_M	Source term of M	1
l_4	Chemotherapy effect used	0.5
k	Competition between T cells and cytotoxic cells	1e-7
l_5	Immunotherapy effect used	0.4
η	Natural decay rate	412
α	Source term	7
β	Decay term	10

3. Stability

3.1 Stability Analysis without Therapies

3.1.1 Tumor Free Equilibrium Points

We analyze the stability of the given system, for which we consider the following:

$$\frac{dT}{dt} = \frac{dN}{dt} = \frac{dD}{dt} = \frac{dL}{dt} = \frac{dC}{dt} = 0.$$

Based on this consideration, we obtain the following system of nonlinear equations, whose solution yields the tumorfree equilibrium point.

$$\begin{aligned} 0 &= aT(1 - bT) - (c_1 N + jD + kL)T \\ 0 &= s_1 C + \frac{g_1 N T^2}{h_1 + T^2} - (c_2 T - l_1 D + e)N \\ 0 &= s_2 C - (f_1 L + l_2 N - l_3 T + g)D \\ 0 &= f_2 DT - hLT - uNL^2 + (r_1 N + r_2 C)T - iL \\ 0 &= \alpha - \beta C. \end{aligned}$$

Employing the parameter set listed in Table 1, the nonlinear system is solved numerically to determine the equilibrium point $(T^*, N^*, D^*, L^*, C^*)$. The computed values corresponding to the tumor-free equilibrium are presented below

$$\begin{aligned} T^* &= 0, \\ N^* &= 11978.3118, \\ D^* &= 21.2005, \\ L^* &= 0, \\ C^* &= 0.22 \end{aligned}$$

The associated Jacobian matrix is given by:

$$\begin{bmatrix} -0.0255 & 0.0075 & 0 & 1.3 \\ -0.0906 & -0.0302 & -0.0226 & 0.048 \\ 0 & 0 & -0.02 & 0 \\ 0 & 0 & 0 & -0.007 \end{bmatrix}$$

The eigenvalues are

$$\begin{aligned} -0.2424, \\ -5.0313, \\ -0.02, \\ -0.9, \end{aligned}$$

Since all eigenvalues have negative real parts, the system is stable according to the eigenvalue stability criterion.

To further verify stability, a test was performed by varying one parameter at a time while keeping the remaining parameters fixed at their baseline values from Table 1.

3.1.2 Tumor Present Equilibrium Points

To determine the tumor-present equilibrium of the dynamical system, we follow steps analogous to the previous case:

$$\frac{dT}{dt} = \frac{dN}{dt} = \frac{dD}{dt} = \frac{dL}{dt} = \frac{dC}{dt} = 0.$$

The resulting system of nonlinear equations is given by:

$$\begin{aligned} 0 &= aT(1 - bT) - (c_1 N + jD + kL)T \\ 0 &= s_1 C + \frac{g_1 N T^2}{h_1 + T^2} - (c_2 T - l_1 D + e)N \\ 0 &= s_2 C - (f_1 L + l_2 N - l_3 T + g)D \\ 0 &= f_2 DT - hLT - uNL^2 + (r_1 N + r_2 C)T - iL \\ 0 &= \alpha - \beta C. \end{aligned}$$

Numerical solution of this nonlinear system, with parameter values taken from Table 1, yields the equilibrium point $(T^*, N^*, D^*, L^*, C^*)$:

$$\begin{aligned} T^* &= 0, \quad N^* = 11978.3118, \quad D^* = 21.200, \\ L^* &= 0, \\ C^* &= 0.222. \end{aligned}$$

The Jacobian matrix associated with this system is:

$$\begin{bmatrix} -43.268e-10 & -16.192e-07 & -46.262e-9 & -46.262e-9 & 0 \\ 47.473e+07 & -2.3999e-1 & 1.2314e-1 & 0 & 1.3e+5 \\ 0 & -5.5415e-3 & -4.9497 & -13.854e-08 & 4.80 \\ 1.3853e+1 & -2.8749e-25 & 4.6262e-05 & -2.0001e4 & 0 \\ 0 & 0 & 0 & 0 & -7.000 \end{bmatrix}$$

The eigenvalues associated with this system are:

$$\begin{aligned} -0.120, \quad -0.120, \quad -49.4970, \\ -0.037330, \quad -0.90, \end{aligned}$$

Since all eigenvalues possess negative real parts, the eigenvalue stability criterion guarantees that the system is stable.

Stability of the system was examined through a one-at-a-time parameter variation, with all remaining parameters held at their baseline values given in Table 1.

3.2 Stability Analysis with Therapies

To examine the stability of the system, we consider the following:

$$\frac{dT}{dt} = \frac{dN}{dt} = \frac{dD}{dt} = \frac{dL}{dt} = \frac{dC}{dt} = \frac{dM}{dt} = \frac{dI}{dt} = 0.$$

From this consideration, we obtain the following system of nonlinear equations, whose solution yields the equilibrium point.

$$\begin{aligned} 0 &= aT(1 - bT) - (c_1 N + jD + kL - K_T M)T \\ 0 &= s_1 C + \frac{g_1 N T^2}{h_1 + T^2} - (c_2 T - l_1 D + K_N M + e)N \\ 0 &= s_2 C - (f_1 L + l_2 N - l_3 T + K_D M + g)D \\ 0 &= (r_1 N + r_2 C + f_2 D - hL)T - uN L^2 + \frac{P_L L I}{g_I + I} - K_L M L - iL \\ 0 &= \alpha - (\beta C + K_C M)C \\ 0 &= v_M(t) - l_4 M \\ 0 &= v_I(t) - l_5 I \end{aligned}$$

By solving the nonlinear system numerically with the parameter set from Table 1, we obtain the equilibrium point $(T^*, N^*, D^*, L^*, C^*, M^*, I^*)$. The corresponding component values are:

$$\begin{aligned} T^* &= 0.00758, \\ N^* &= 123142.795, \\ D^* &= 2.1550, \\ L^* &= 0.00427, \\ C^* &= 0.222, \\ M^* &= 2.000, \\ I^* &= 2.500. \end{aligned}$$

The associated Jacobian matrix is

$$\begin{bmatrix} 0 & -2.70e-14 & -1e-15 & -1e-15 & 0 & 4.66e1 & 0 \\ 7.79 & -2.40e-7 & 7.43e-2 & 0 & 1.30e-13 & -4.46e5 & 0 \\ 0 & -5.54e-9 & -4.95e-5 & -1.39e-13 & 4.80e-4 & 1.45e2 & 0 \\ & 1.39e-7 & 0 & 7.59e-11 & -2e-4 & 0 & -4.84e1 & 0 \\ & 0 & 0 & 0 & 0 & -7.0e-6 & 0 & 0 \\ & 0 & 0 & 0 & 0 & 0 & -9e-7 & 0 \\ & 0 & 0 & 0 & 0 & 0 & -1.0e-7 & 0 \end{bmatrix}$$

The eigenvalues associated with this system are:

$$\begin{aligned} &-0.1200, \quad -0.1200, \quad -4.94971, \quad -0.0382, \\ &-9.000, \quad -5.000, \quad -4.000, \end{aligned}$$

Since all eigenvalues possess negative real parts, the eigenvalue stability criterion guarantees that the system is stable.

The system was tested by varying one parameter at a time, while keeping all others fixed at their baseline values from Table 1.

4. Numerical Simulation

The numerical simulation of the tumor immune model illustrates the interaction between tumor cells, immune populations, and therapeutic interventions. The results show that tumor cells initially expand, reach a short-lived peak, and are subsequently eliminated due to immune and therapeutic pressures. NK cells increase steadily throughout the simulation, attaining a high saturation level that reflects their persistent surveillance role. Dendritic cells and cytotoxic T cells both exhibit transient growth, peaking early in response to tumor presence and then declining once the tumor burden diminishes, with dendritic cells stabilizing at a moderate level while cytotoxic T cells decay to near zero. Circulating lymphocytes rise monotonically and approach a stable equilibrium,

providing constant immune support. Meanwhile, chemotherapy and immunotherapy inputs increase rapidly, representing steady external treatment supplies.

These dynamics highlight the typical immune tumor interaction shaped by combined natural and therapeutic responses. The transient activation of dendritic and cytotoxic cells, the sustained expansion of NK cells, and the eventual stabilization of therapeutic agents together ensure the system converges to a tumor free steady state.

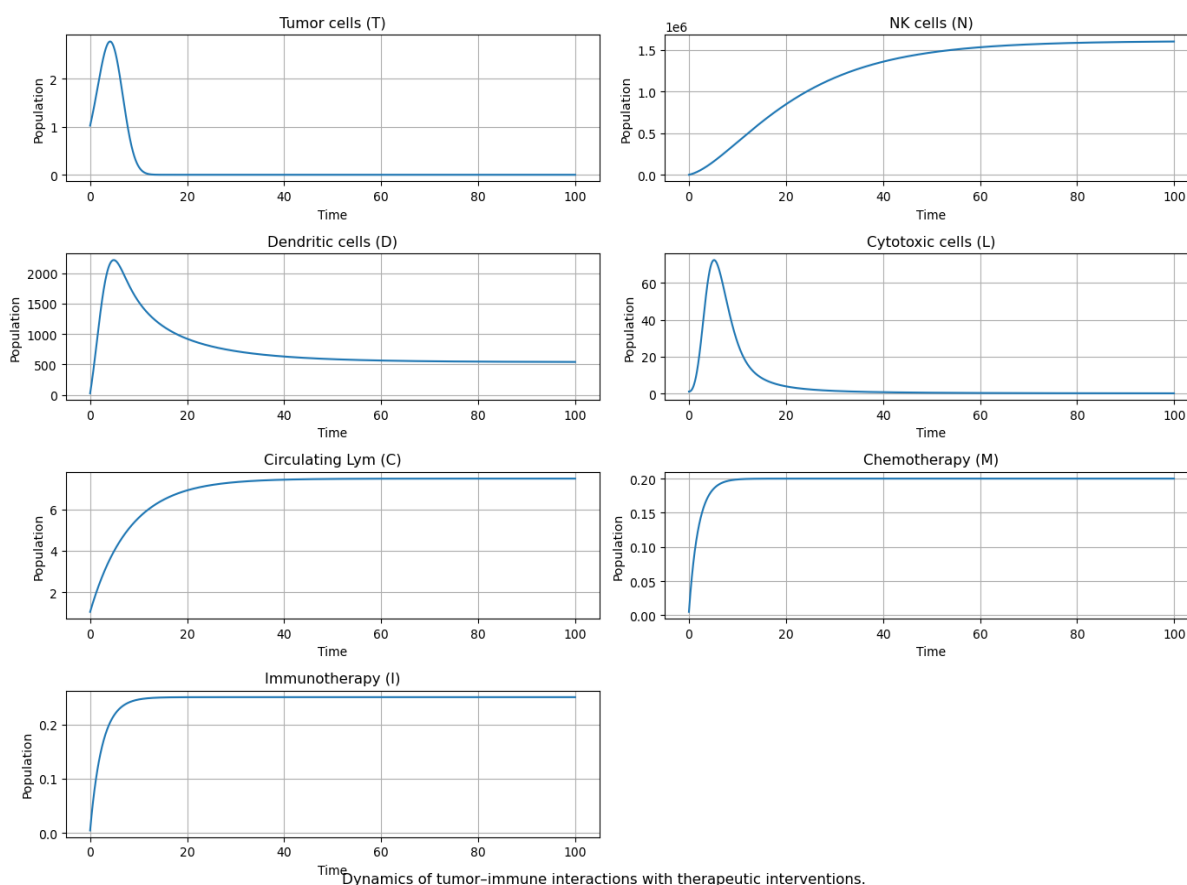


Figure 5: Dynamics of tumor-immune interactions with therapeutic interventions.

5. Conclusion

In this formulation, circulating lymphocytes (C) are explicitly incorporated into the tumor-immune-therapy framework, introducing additional regulatory interactions that more realistically capture immune support dynamics. The modified equations couple C with NK cells, dendritic cells, and cytotoxic lymphocytes, thereby strengthening their activation pathways, while also including its natural production and decay. Numerical solutions obtained using the finite difference method demonstrate that the system exhibits stable tumor elimination under combined immune and therapeutic effects, with circulating lymphocytes providing sustained baseline stimulation. Furthermore, stability analysis based on the eigenvalues of the Jacobian matrix confirms that the equilibrium remains locally stable when all eigenvalues possess negative real parts, ensuring convergence to a tumor-free steady state. This integration of circulating lymphocytes not only enriches the biological realism of the model but also emphasizes their role in maintaining long-term immune surveillance and enhancing therapeutic outcomes.

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