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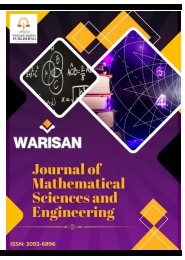

Modelling the Impact of Immune Response and Drug Intervention on Tumor Growth using Ordinary Differential Equation

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ABSTRACT

Cancer progression often occurs due to immune evasion and the limitations of conventional treatments such as chemotherapy, which may also damage healthy cells. Mathematical modelling provides a useful framework for understanding the interactions between tumor growth, immune response, and drug intervention. This study presents a mathematical model based on a system of ordinary differential equations to investigate how tumor growth is affected by immune response and chemotherapy. The study aims to develop mathematical models describing tumor-immune interactions, analyze their stability across three scenarios which is the absence of immune response and drug, presence of immune response without drug, and presence of both and conduct numerical simulations of tumor-immune-drug dynamics. Stability analysis is discussed for each case, with numerical simulations using the Runge-Kutta (RK4) method in MATLAB for selected parameters within the stability region. The findings demonstrate that combining immune response with drug intervention enhances tumor suppression compared to either approach alone.

1. Introduction

Cancer remains a leading cause of death in Malaysia, primarily due to uncontrolled cell division that invades surrounding tissues and organs [1]. The immune system, particularly cytotoxic T lymphocytes (CTLs), plays a crucial role in targeting tumor cells, but tumors often develop mechanisms to evade immune detection [2-4]. Chemotherapy, commonly used to treat cancer, targets rapidly dividing cells but causes significant side effects due to its lack of selectivity [5-7]. Hence,understanding the interaction between tumors, immune responses, and drugs is essential to improve treatment strategies.

The mathematical modeling, especially through ordinary differential equations (ODEs), provides a powerful tool to represent tumor dynamics and treatment effects over time [8,9]. Early models by de Pillis and Radunskaya [10], and later by Robertson-Tessi *et al*., [11], focused on tumor-immune system interactions. Villasana and Radunskaya [12] proposed a phase-specific model that integrated

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immune response and chemotherapy, though it only covered partial scenarios. More comprehensive models by de Pillis and Radunskaya [13] incorporated tumor, immune, host, and drug effects using a four-population model with optimal control, highlighting the importance of balancing treatment efficacy with immune preservation [14-16].

Based on previous studies, mathematical models have been developed by researchers to understand, analyze, and investigate tumor growth, particularly focusing on the interaction between tumor cells and the immune system. However, most of these studies concentrate on only one factor either the immune response or drug treatment and rarely combine both in a comprehensive model. Furthermore, the stability of these models under varying treatment parameters has received limited attention. In addition, several important parameters are often missing in existing models, making it difficult to fully represent real treatment scenarios. These limitations have led to a restricted understanding of actual tumor dynamics, especially in clinical contexts.

To address these gaps, this study develops a mathematical model that simultaneously integrates the interaction between tumor cells, the immune system, and drug treatment within a single framework. Unlike previous studies that focus on only one or two components, this model combines all three elements at the same time. By doing so, it provides a more realistic and comprehensive representation of actual treatment conditions.

2. The Mathematical Model

The detailed representation of mathematical model that integrates tumor growth, immune response, and chemotherapy are describe in Table 1.

Table 1
Modelling differential equation for each cases

Case 1 : With the absence of both the immune response and drug.
$\frac{dT_I}{dt} = 2a_4T_M - (d_2 + a_1)T_I,$ $\frac{dT_M}{dt} = a_1T_I - (d_3 + a_4).$
Case 2 : With the presence of immune response and absence of drug
$\frac{dT_I}{dt} = 2a_4T_M - (c_1I + d_2)T_I - a_1T_I,$ $\frac{dT_M}{dt} = a_1T_I - (d_3 + a_4)T_M - c_3T_MI,$ $\frac{d_1}{dt} = f + \frac{\rho I(T_I + T_M)^n}{\alpha + (T_I + T_M)^n} - c_2IT_I - c_4T_MI - d_1I.$
Case 3 : With the presence of both immune response and drug.

$$\frac{dT_I}{dt} = 2a_4T_M - (c_1I + d_2)T_I - a_1T_I,$$

$$\frac{dT_M}{dt} = a_1T_I - (d_3 + a_4 + c_3I)T_M - f_1(1 - e^{-f_2D})T_M,$$

$$\frac{d_1}{dt} = f + \frac{\rho I(T_I + T_M)^n}{\alpha + (T_I + T_M)^n} - c_2IT_I - c_4T_MI - d_1 - f_3(1 - e^{-f_4D})I,$$

$$\frac{dD}{dt} = -yD.$$

The variables denotes as :

T_I	:	The number of tumor cells in interphase at time t.
T_M	:	The number of tumor cells during mitosis at time t.
a_1 & a_4	:	The different rates of cells cycle or reproduce.
d_2T_I, d_3T_M, , d_1I	:	Proportions of natural cell death or apoptosis.
c_i	:	Losses of immune cell or tumor cell during the event of an encounter for both cells.
$\frac{\rho I\ (TI\ +\ TM)^n}{\alpha\ +\ (TI\ +\ TM)^n}$	:	Nonlinear increase in immune cell population due to the presence of tumor cells.
(constant) : f	:	The production rate of immune cells in the absence of a tumor should be low.
(parameters):ρ,α and n	:	This depends on the tumor type and the patient's immune health, particularly its capacity to generate specific cytokines.
I	:	The number of immune cells at time t.
D	:	Amount of drug present at time t.
The kills terms $f_1(1\text{-}e^{-f2D})T_M$ and $f_3(1\text{-}e^{-f4D})I$	:	Represents the impact of drug on mitosis and immune system respectively.
Coefficient y	:	Incorporates both the elimination & absorbtion effects.

3. Methodology

3.1.1 System of ordinary differential equation

The model is built using a system of ODEs.
The Existence and Uniqueness Theorem ensures the solution is valid: If $f : R^n \rightarrow R^n$ is a differentiable function defined on the domain U and $x_0 \in U$, then there exists a unique solution x(t) for some interval around $t = 0$.

3.1.2 Stability analysis

1. A steady-state solution, or equilibrium point, is found by setting the differential equations $\frac{dx}{dt} = 0$. It represents a condition where the system remains constant over time.

2. The stability of steady states is evaluated using the Routh-Hurwitz criterion. After linearizing the system with the Jacobian matrix J, eigenvalues are obtained from the characteristic equation Det (**J** - λ**I**) = 0 and this leads to a characteristic equation of the form $\lambda^n + p_1\lambda^{n-1} + p_2\lambda^{n-2} + \dots p_n = 0$.

3.1.3 Numerical method

$$x_{i+1} = x_i + \frac{1}{6}(f_1 + 2f_2 + 2f_3 + f_4),$$

$$y_{i+1} = y_i + \frac{1}{6}(g_1 + 2g_2 + 2g_3 + g_4),$$

where

$$f_1 = hf(t_i, x_i, y_i),$$

$$f_2 = hf\left(t_i + \frac{h}{2}, x_i + \frac{f_1}{2}, y_i + \frac{g_1}{2}\right),$$

$$f_3 = hf\left(t_i + \frac{h}{2}, x_i + \frac{f_2}{2}, y_i + \frac{g_2}{2}\right),$$

$$f_4 = hf(t_i + h, x_i + f_3, y_i + g_3),$$

$$g_1 = hg(t_i, x_i, y_i),$$

$$g_2 = hg\left(t_i + \frac{h}{2}, x_i + \frac{f_1}{2}, y_i + \frac{g_1}{2}\right),$$

$$g_3 = hg\left(t_i + \frac{h}{2}, x_i + \frac{f_2}{2}, y_i + \frac{g_2}{2}\right),$$

$$g_4 = hg(t_i + h, x_i + f_3, y_i + g_3).$$

4. Result and Discussion

4.1.1 Case 1 : With the absence of both the Immune response and drug

This case examines tumor cell behavior without immune response and chemotherapy. The steady-state at (T_I,T_M) = (0,0) is analyzed by deriving the Jacobian matrix and the characteristic equation. The Routh-Hurwitz criterion is applied to determine the stability of this equilibrium. Finally, the necessary condition for tumor growth is identified based on the stability result for this cases is $d < \frac{2a4a1}{d2 + a1}$ (1)

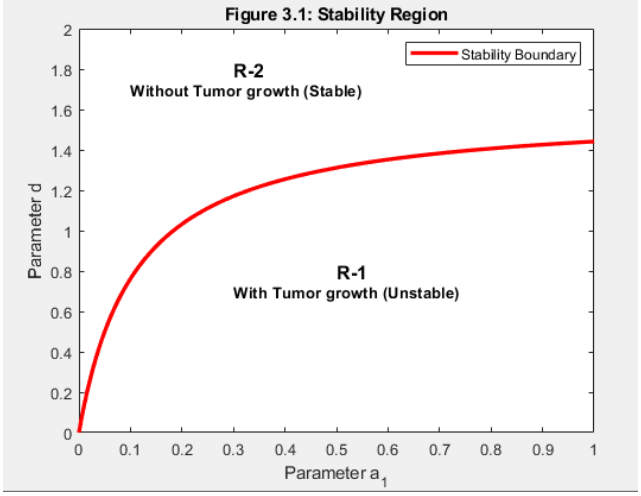

Fig. 1. Stability region for Case 1 with the absence of both immune response and drug when value of parameter a_4 = 0.8 and d_2 = 0.11

i. Without the immune system (R-1), tumors grow and (0,0) is an unstable steady state.
ii. With the immune system (R-2), tumors decay and (0,0) becomes a stable steady state.

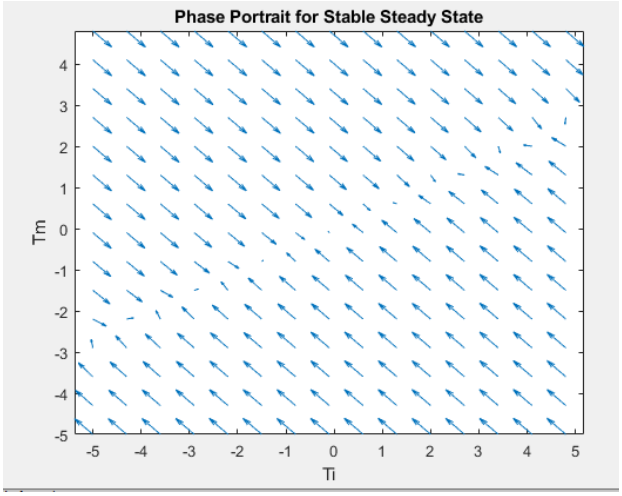

Fig. 2. (a) : Phase portrait for stable steady state (0,0) for Case 1 with the absence of both immune response and drug when value of parameter a_1 = 0.8, d = 1.6, a_4 = 0.8 and d_2 = 0.11

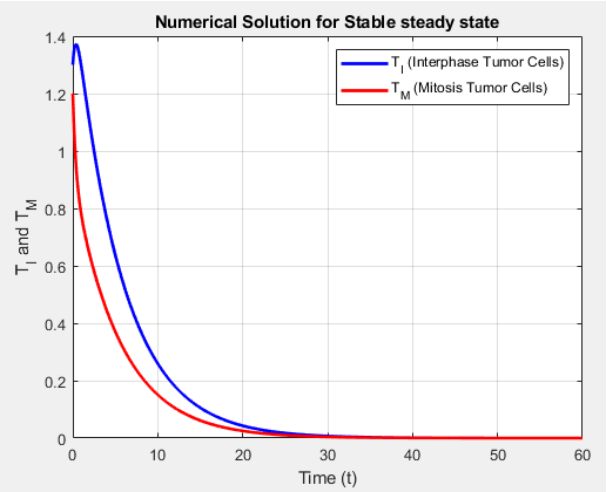

Fig. 2. (b) : Numerical Solution for stable steady state (0,0) for Case 1 with the absence of both immune response and drug when value of parameter a_1 = 1 and d = 1.2 with the initial condition T_I =1.3, T_M = 1.2

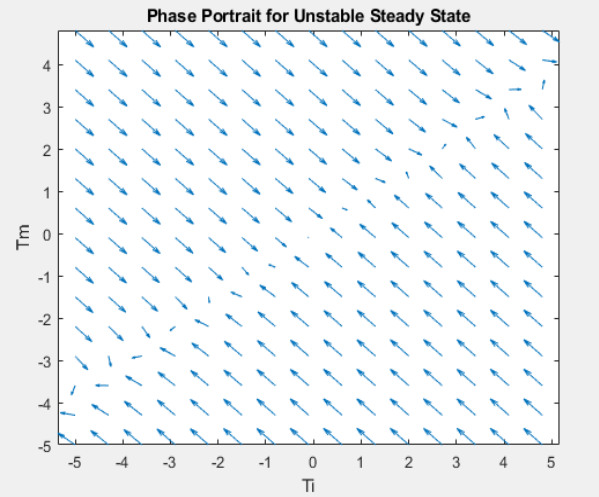

Fig. 3. (a) : Phase portrait for unstable steady state (0,0) for Case 1 with the absence of both the immune response and drug when value a_1 = 1, d = 1.2, a_4 = 0.8, d_2 = 0.11

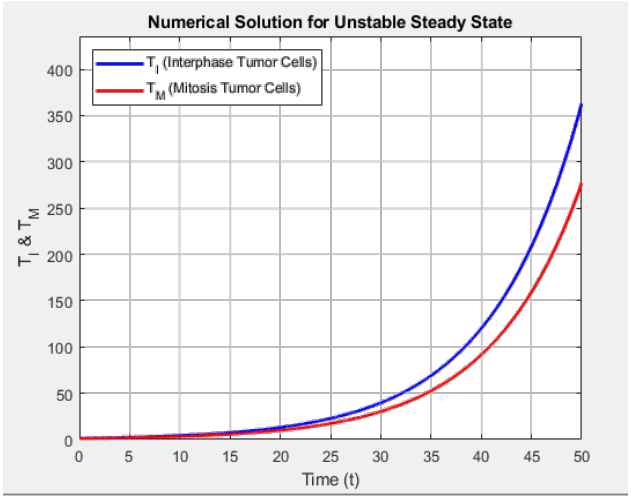

Fig. 3. (b) : Numerical solution for unstable steady state (0,0) for Case 1 with the absence of both immune response and drug when value of parameter a_1 = 1 and d = 1.2 with the initial condition T_I=1.3, T_M = 1.2

4.1.2 Case 2 : With the presence of Immune response and absence drug

This case studies tumor growth influenced by the immune response without drug intervention. The system includes immune cells *I(t)*, and the analysis focuses on their impact on tumor dynamics. The necessary condition for tumor growth is:

$$d < \frac{-(c1 + c3)\,\beta + 2a4a1}{d2 + a1} \quad (2)$$

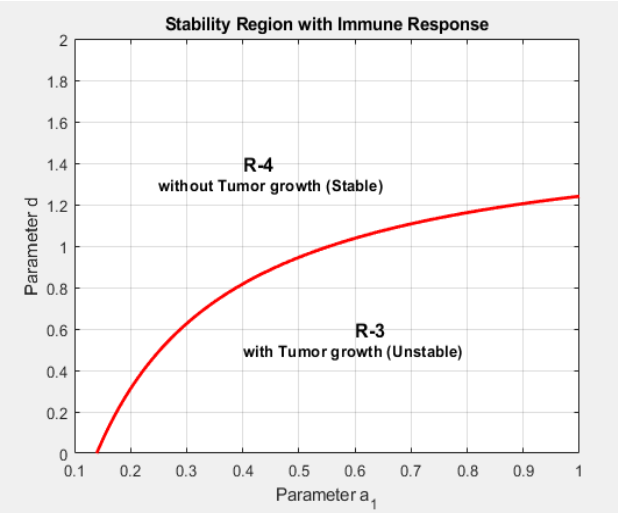

Fig. 4. The stability region for Case 2 with the presence of immune response but the absence of drug when value of parameter a_4= 0.8, c_1=c_3 = 0.9, $d_{1=}$ 0.29, d_2 = 0.11, f = 0.036 and β = 0.1241

i. With immune response, in R-3 (tumor growth), the steady state (0,0, $\frac{f}{d1}$) is unstable.
ii. With immune response, in R-4 (tumor decay), the steady state (0,0, $\frac{f}{d1}$) is stable.

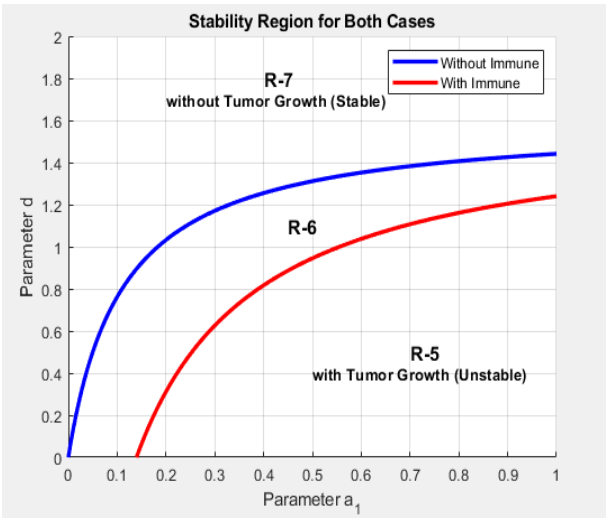

Fig. 5. The stability region with and without immune response

i. Without immune response, in R-5 and R-6 (tumor growth), the steady state (0,0) is unstable.
ii. Without immune response, in R-7 (tumor decay), the steady state (0,0) is stable.
iii. With immune response, in R-5 (tumor growth), the steady state (0,0, $\frac{f}{d1}$) is unstable.
iv. With immune response, in R-6 and R-7 (tumor decay), the steady state (0,0, $\frac{f}{d1}$) is stable.

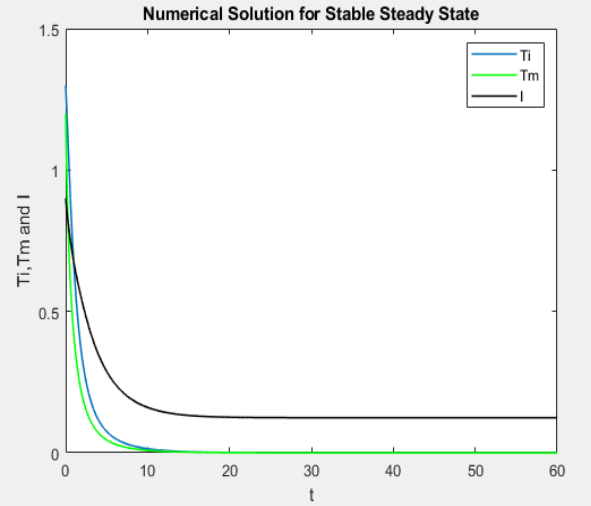

Fig. 6. Numerical solution for stable steady state (0,0,$\frac{f}{d1}$) for Case 2 with the presence of immune response but the absence of drug when value of parameter a_1 = 1, d = 1.8, a_4= 0.8 and d_2 = 0.11 with the initial condition T_I=1.3, T_M = 1.2, I = 0.9

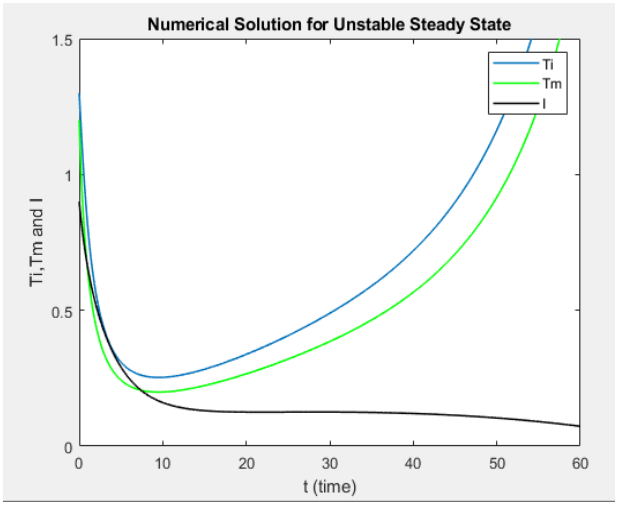

Fig. 7. Numerical solution for unstable steady state for Case 2 (0,0,$\frac{f}{d1}$) with the presence of immune response but the absence of drug when value of parameter a_1 = 1, d = 1.2, a_4= 0.8 and d_2 = 0.11 with the initial condition T_I=1.3, T_M = 1.2, I = 0.9

4.1.3 Case 3 : With the presence of both Immune response and drug

This case considers the combined effects of immune response and drug with different dosage which is D_0 = 0.07, 0.1 and 0.15.

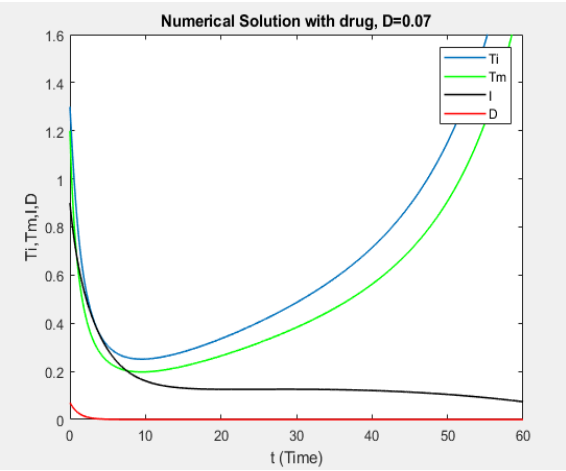

Fig. 8. (a) : In Case 3**,** the focus is on the numerical solution for the drug system in the presence of an immune responses when value of parameter a_1 =1, d =1.12 with the initial condition T_I=1.3, T_M = 1.2, I = 0.9 and the drug dosage parameter set to D_0 = 0.07

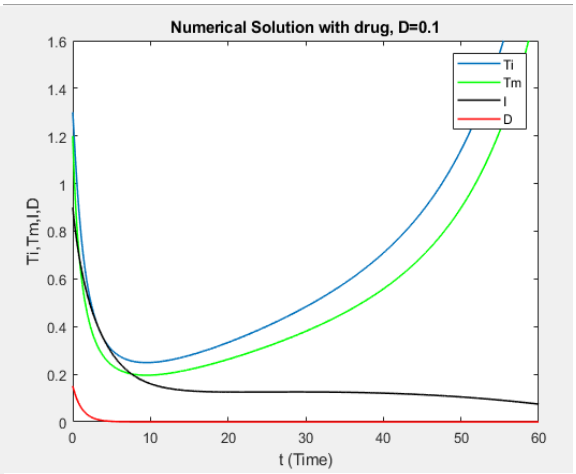

Fig. 8. (b) : In Case 3**,** the focus is on the numerical solution for the drug system in the presence of an immune responses when value of parameter a_1 =1, d =1.12 with the initial condition T_I=1.3, T_M = 1.2, I = 0.9 and the drug dosage parameter set to D_0 = 0.1

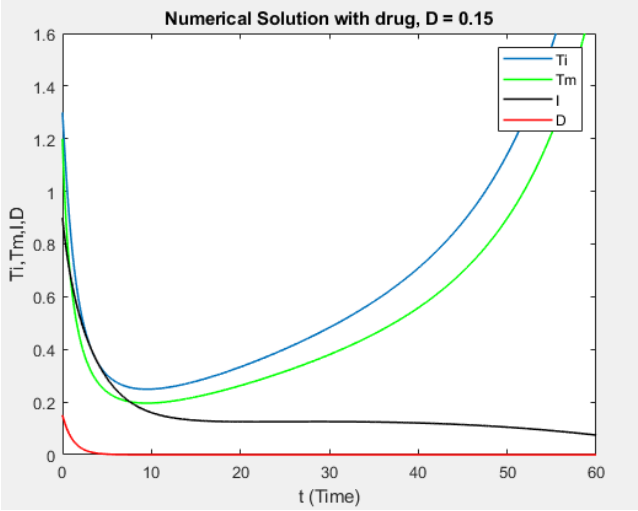

Fig. 8. (c) : In Case 3**,** the focus is on the numerical solution for the drug system in the presence of an immune responses when value of parameter a_1=1, d =1.12 with the initial condition T_I =1.3, T_M = 1.2, I = 0.9 and the drug dosage parameter set to D_0 = 0.15

Table 2
Comparison of numerical tumor values at each stage for different drug amounts

t	D_0 = 0.07		D_0 = 0.1		D_0 = 0.15	
	T_I	T_M	T_I	T_M	T_I	T_M
10	0.2513	0.1979	0.2504	0.1972	0.2491	0.1962
20	0.3357	0.2643	0.3347	0.2636	0.3332	0.2624
30	0.4861	0.3828	0.4848	0.3818	0.4828	0.3802
40	0.7142	0.5624	0.7121	0.5608	0.7087	0.5581
50	1.1525	0.9075	1.1480	0.9040	1.1407	0.8982
60	2.2900	1.8032	2.2766	1.7927	2.2551	1.7757

Table 3
Comparison of tumor values at each phase between a drug-free system and a drug- system, both involving an immune response

t	Immune is present			
	Without drug		With drug D_0 = 0.15	
	T_I	T_M	T_I	T_M
10	0.2532	0.1994	0.2491	0.1962
20	0.3379	0.2661	0.3332	0.2624
30	0.4892	0.3852	0.4828	0.3802
40	0.7193	0.5664	0.7087	0.5581
50	1.1636	0.9163	1.1407	0.8982
60	2.3228	1.8291	2.2551	1.7757

5. Conclusion and Recommendation

This study models tumor growth under varying biological conditions using differential equations. Results show that immune response alone can suppress tumors but combining it with drug therapy moderately enhances effectiveness. The stability analysis and simulations for all three cases successfully meet the research objectives: the absence of both immune response and drug, the presence of immune response without drug, and the presence of both immune response and drug.

5.1 Recommendation

1. Future models should include NK cells and cytokine interactions.
2. Optimal drug dosing and scheduling should be studied using control theory to improve treatment outcomes and minimize side effects.

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