

MODELLING TUMOR GROWTH WITH IMMUNE RESPONSE AND DRUG USING ORDINARY DIFFERENTIAL EQUATIONS

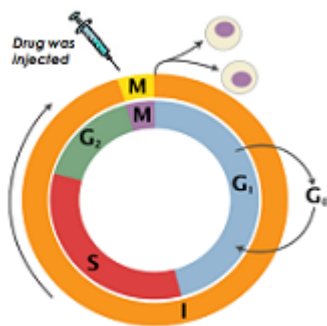
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Graphical abstract



Abstract

This is a mathematical study about tumor growth from a different perspective, with the aim of predicting and/or controlling the disease. The focus is on the effect and interaction of tumor cell with immune and drug. This paper presents a mathematical model of immune response and a cycle phase specific drug using a system of ordinary differential equations. Stability analysis is used to produce stability regions for various values of certain parameters during mitosis. The stability region of the graph shows that the curve splits the tumor decay and growth regions in the absence of immune response. However, when immune response is present, the tumor growth region is decreased. When drugs are considered in the system, the stability region remains unchanged as the system with the presence of immune response but the population of tumor cells at interphase and metaphase is reduced with percentage differences of 1.27 and 1.53 respectively. The combination of immunity and drug to fight cancer provides a better method to reduce tumor population compared to immunity alone.

Keywords: Tumor growth, immune response, cycle phase specific drug, cell cycle, stability region

Abstrak

Kajian ini adalah berkenaan dengan pertumbuhan tumor daripada sudut perspektif yang berbeza, bertujuan untuk meramal atau mengawal penyakit tersebut. Fokus perspektif tersebut adalah kesan dan interaksi antara sel tumor dengan sistem imunisasi dan ubat. Kajian ini menerangkan sistem persamaan terbitan yang melibatkan pertumbuhan tumor bersama tindak balas imunisasi dan ubat yang bertindak mengikut fasa spesifik dalam kitaran sel. Kaedah analisis kestabilan digunakan untuk menghasilkan kawasan kestabilan bagi nilai-nilai parameter tertentu dalam fasa mitosis. Kawasan kestabilan untuk ketidakhadiran tindak balas imunisasi menunjukkan kawasan pertumbuhan tumor dan kawasan pereputan tumor dipisahkan oleh garis lengkung. Dengan kehadiran tindak balas imunisasi, kawasan pertumbuhan tumor didapati berkurang. Apabila ubat untuk kitaran spesifik diambil kira dalam sistem, kawasan kestabilan tidak mengalami sebarang perubahan tetapi pertumbuhan sel-sel tumor pada kedua-dua fasa berkurang dengan perbezaan peratus masing-masing 1.27 dan 1.53. Ini menunjukkan bahawa gabungan antara imunisasi dan ubat adalah cara yang lebih baik untuk mengurangkan populasi sel tumor berbanding dengan hanya bergantung pada tindak balas imunisasi sahaja.

Kata kunci: Pertumbuhan tumor, tindak balas imunisasi, ubat untuk kitaran fasa spesifik, kitaran sel, kawasan kestabilan

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1.0 INTRODUCTION

Every year more than 8.2 million people die from cancer worldwide [1]. World Health organization [2] reports that the majority of death caused by cancer occurs in countries that are economically well developed. This scenario forces scientists all over the world to develop theory and practical strategies to address the threat from cancer. On the whole, most researchers focused on particular issues since the interaction between tumor cells and other type of cells are very complex. Immune system plays an important role in human body to fight tumor. However there are limits for ability of immune system due to unpredictable tumor behaviour [3]. In medical treatment, chemotherapy offers a powerful mechanism among other tools to kill cancer cell, but it also kill the normal cells [4, 5, 6].

The problem of modelling tumor growth is a vast study by researchers, with each focussing on different aspects on cancer development [7]. This includes the importance of the immune systems in fighting tumor that has been summarized by Adam and Bellomo [8]. Kuznetsov *et al.* [9] proposed an ordinary differential equation model of the cytotoxic T lymphocyte (CTL) response with population of tumor cells. They found that CTL and tumor cells competed like “predator-prey” interaction in which CTL in the role of predator while tumor cell act as prey. Adam [10] then formulated the cell populations of a solid tumor and reactive lymphocyte and found that if the immune system is stimulated, the survival chance for tumor increases. In addition, whether growth rate and death rate increase or decrease, this condition will probably lead to an uncontrolled tumor growth. De Pillis *et al.* [11] proceeded to develop and analyze a mathematical model in order to understand the dynamics between tumor and immune system. The model concluded out that the combination effect of natural killer (NK) and CD8+ T cells could eliminate larger tumors compared to the effect of individual immune cell. This is due to the depletion of NK cells having different impact to CD8+ T cells.

Chemotherapy is usually the first treatment for cancer [4, 5, 6, 12, 13]. Pastorino *et al.* [14] reported that chemotherapy treatments are in the process of improvement for better distribution mechanism that will reduce the toxicity of anticancer drugs. Besides, most of the drug used are cycle phase specific drugs such as vincristine and paclitaxel which interfere with certain phases in cell cycle [15]. It may prevent the cell from continuing the cycle, causing the proliferation to be stopped. Immune system then target and kill the cancerous cell by their natural mechanism. By taking this advantage, it will minimized the loss of normal cells. The use of cycle phase specific drugs have been included in the model proposed by Villasana M. and Radunskaya [16]. However, they did not present results of analysis and numerical computation had not been shown in their paper.

A different approach was adopted by Villasana M. and Radunskaya [16]. They presented a system of

differential equations without considering any delay terms. Numerical results were done as a contribution to investigate the stability of the presented model. The model takes the form of ordinary differential equation (ODE) which includes tumor cell population during interphase, tumor population during metaphase, immune response and cycle phase with specific drugs. Three different systems were discussed by analysing its stability and numerical examples using Fourth Order Runge Kutta Method.

2.0 METHODOLOGY

The tumor growth model considered in this paper is a system of first order differential equations with n^{th} dimensional system.

$$\begin{aligned} \frac{dx_1}{dt} &= f_1(x_1, x_2, \dots, x_n) \\ \frac{dx_2}{dt} &= f_2(x_1, x_2, \dots, x_n) \\ &\vdots \\ \frac{dx_n}{dt} &= f_n(x_1, x_2, \dots, x_n) \end{aligned} \quad (1)$$

where x_1, x_2, \dots, x_n are the variables, f_1, f_2, \dots, f_n can be linear or nonlinear functions and the right hand side of the ODEs may depend only on the independent variable t [17]. The first step is to find the steady state solution of the system

2.1 Steady State Solution

A steady state or equilibrium point, $\bar{X} = (\bar{x}_1, \bar{x}_2, \dots, \bar{x}_n)$ is a situation in which the system does not appear to undergo any change [18]. To find the steady state of a system, set the derivatives equal to zero:

$$\begin{aligned} \frac{dx_1}{dt} &= 0 \\ \frac{dx_2}{dt} &= 0 \\ &\vdots \\ \frac{dx_n}{dt} &= 0 \end{aligned} \quad (2)$$

There may exist one or several steady state points.

2.2 Stability of Steady State

The stability of steady state can be investigated by using Routh-Hurwitz condition/criteria [18, 19, 20]. System (1) is linearized using Jacobian Matrix

$$J(\bar{x}_1, \bar{x}_2, \dots, \bar{x}_n) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \dots & \frac{\partial f_1}{\partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \dots & \frac{\partial f_n}{\partial x_n} \end{pmatrix} \quad (3)$$

The next step is to find the eigenvalues, λ satisfying

$$\det(J - \lambda I) = 0 \tag{4}$$

This will yield a characteristic equation of the form

$$\lambda^n + p_1\lambda^{n-1} + p_2\lambda^{n-2} + \dots + p_n = 0 \tag{5}$$

where p_i 's will be functions of the elements of the $n \times n$ matrix.

The Hurwitz matrix is defined as follows:

$$\begin{aligned} H_1 &= (p_1), \\ H_2 &= \begin{pmatrix} p_1 & 1 \\ p_3 & p_2 \end{pmatrix}, \\ H_3 &= \begin{pmatrix} p_1 & 1 & 0 \\ p_3 & p_2 & p_1 \\ p_5 & p_4 & p_3 \end{pmatrix}, \dots \\ H_j &= \begin{pmatrix} p_1 & 1 & 0 & \dots & 0 \\ p_3 & p_2 & p_1 & \dots & 0 \\ p_5 & p_4 & p_3 & \dots & 0 \\ \dots & \dots & \dots & \ddots & \dots \\ p_{2j-1} & p_{2j-2} & p_{2j-3} & \dots & p_j \end{pmatrix}, \dots \\ H_n &= \begin{pmatrix} p_1 & 1 & 0 & \dots & 0 \\ p_3 & p_2 & p_1 & \dots & 0 \\ p_5 & p_4 & p_3 & \dots & 0 \\ \dots & \dots & \dots & \ddots & \dots \\ 0 & 0 & 0 & \dots & p_n \end{pmatrix} \end{aligned} \tag{6}$$

where the (l, m) element in the matrix H_j is

$$\begin{aligned} p_{2l-m} & \text{ for } 0 < 2l - m < k \\ 1 & \text{ for } 2l = m \\ 2 & \text{ for } 2l < m \text{ or } 2l > k + m \end{aligned}$$

Hence, all eigenvalues have negative real parts (steady state stable) if and only if the determinants of the Hurwitz matrix are positive:

$$\det(H_j) > 0, \quad (j = 1, 2, \dots, k) \tag{7}$$

2.3 Numerical Method

Runge Kutta (RK4) method is applied to present several graphical results using MATLAB software. Tay *et al.* [21] considered an initial value problem of the first order differential equation given below:

$$\begin{aligned} \frac{dx}{dt} &= F(t, x, y) \\ \frac{dy}{dt} &= G(t, x, y) \end{aligned} \tag{8}$$

with $x(t_0) = x_0, y(t_0) = y_0$ and $t_0 \leq t \leq t_n$. This problem is a system of ODEs, which consists of a single pair of ordinary differential equations. The solution domain is discretized such that $t_0, t_1 = t_0 + h, t_n = t_0 + nh$, where h is the step size of t . The solution that is obtained by the RK4 method is given as

$$\begin{aligned} x_{i+1} &= x_i + \frac{1}{6}(f_1 + 2f_2 + 2f_3 + f_4), \\ y_{i+1} &= y_i + \frac{1}{6}(g_1 + 2g_2 + 2g_3 + g_4), \end{aligned} \tag{9}$$

where

$$\begin{aligned} f_1 &= hf(t_i, x_i, y_i) \\ f_2 &= hf\left(t_i + \frac{h}{2}, x_i + \frac{f_1}{2}, y_i + \frac{g_1}{2}\right) \\ f_3 &= hf\left(t_i + \frac{h}{2}, x_i + \frac{f_2}{2}, y_i + \frac{g_2}{2}\right) \\ f_4 &= hf(t_i + h, x_i + f_3, y_i + g_3) \\ g_1 &= hg(t_i, x_i, y_i) \\ g_2 &= hg\left(t_i + \frac{h}{2}, x_i + \frac{f_1}{2}, y_i + \frac{g_1}{2}\right) \\ g_3 &= hg\left(t_i + \frac{h}{2}, x_i + \frac{f_2}{2}, y_i + \frac{g_2}{2}\right) \\ g_4 &= hg(t_i + h, x_i + f_3, y_i + g_3) \end{aligned}$$

3.0 RESULTS AND DISCUSSION

The system considers three population which are population of tumor cells during interphase ($G_1 + S + G_2$) denoted by T_I , population of tumor cells during mitosis denoted by T_M and population of immune response denoted by I . In this research, Cytotoxic T Lymphocytes (CTL) is assume to be main representative of the immune system in fight cancer. A certain amount of cycle phase specific drug is included to analyze the effect on the system. The model takes form

$$\begin{aligned} \frac{dT_I}{dt} &= 2a_4T_M - (c_1I + d_2)T_I - a_1T_I \\ \frac{dT_M}{dt} &= a_1T_I - d_3T_M - a_4T_M - c_3T_MI \\ &\quad - k_1(-e^{-k_2u})T_M \\ \frac{dI}{dt} &= k + \frac{\rho I(T_I + T_M)^n}{\alpha + (T_I + T_M)^n} - c_2IT_I - c_4T_MI - d_1I \\ &\quad - k_3(1 - e^{-k_4u})I \\ \frac{du}{dt} &= -\gamma u \end{aligned} \tag{10}$$

where parameter a_1 and a_4 represent the rates of cell cyle and rates of cell reproduction respectively. Besides, the proportion for cell deaths are represent by the term d_2T_I, d_3T_M and d_1I . Note that the term $2a_4T_M$ present in the equation because in fact, one parent cell will split into two new daughter cells during mitosis. The parameter c_i then represent the losses of immune cell or tumor cell during the event of an encounter for both cell. Due to the presence of tumor, the growth for immune population is assumed to be nonlinear which indicated by the term $\frac{\rho I(T_I + T_M)^n}{\alpha + (T_I + T_M)^n}$. Another parameter which are ρ, α , and n in the equations are influence by the type of tumor itself together with the healthiness of patient's immune system.

The impact of drug towards tumor population in mitosis and immune are modeled by the killing terms

$k_1(1 - e^{-k_2u})T_M$ and $k_3(1 - e^{-k_4u})I$ respectively. Since the drug is decay over time, it assumed to be exponential while parameter γ acts as both elimination and absorption effects. This paper highlights only an application of single drug dose treatment, otherwise it is beyond the scope of this paper.

It is important to know that the parameter values are vary for any model presented since patients have different types of tumor. Thus, it is allowed to vary the parameter values in order to understand better of tumor problem. This research will used the non dimensionalized parameter that have been set by Villasana and Ochoa [21].

$$\begin{aligned}
 a_1 &= 0.98; a_4 = 0.8; d_1 = 0.29; d_2 = 0.11; d_3 = 0.4 \\
 c_1 = c_3 &= 0.9; c_2 = c_4 = 0.085; k = 0.029 \\
 k_1 &= 0.47; k_2 = 0.57; k_3 = 0.49; k_4 = 0.061 \\
 \alpha &= 0.2; \rho = 0.1; n = 3; \gamma = 0.85
 \end{aligned}$$

The analysis is divide into three cases which are tumor system without immune response, tumor system with the presence of immune response and tumor system with single drug. The behavior of these system are depended on fixed point and its stability. Numerical examples for certain chosen parameters in stability region are then computed using Fourth Order Runge Kutta Method.

3.1 Tumor System without Immune Response

Consider a system of ordinary differential equations:

$$\begin{aligned}
 \frac{dT_I}{dt} &= 2a_4T_M - (d_2 + a_1)T_I \\
 \frac{dT_M}{dt} &= a_1T_I - d_3T_M - a_4T_M
 \end{aligned} \tag{11}$$

The auxiliary equation at tumor free point $(T_I, T_M) = (0,0)$ is

$$\lambda^2 + (a_1 + d + d_2)\lambda + d(a_1 + d_2) - 2a_1a_4 = 0 \tag{12}$$

$$\lambda^2 + p_1\lambda + p_2 = 0 \tag{13}$$

where

$$\therefore p_1 = a_1 + d + d_2 \tag{14}$$

$$p_2 = d(a_1 + d_2) - 2a_1a_4 \tag{15}$$

The value of p_1 from Eq. (14) is always positive [15, 16, 22]. The value of p_2 can be negative or positive. According to the Routh-Hurwitz stability criteria, the tumor free point will be stable if $p_1 > 0$ and $p_2 > 0$. Thus, the necessary condition for the tumor growth is given by Eq. (16).

$$d < \frac{2a_1a_4}{a_1 + d_2} \tag{16}$$

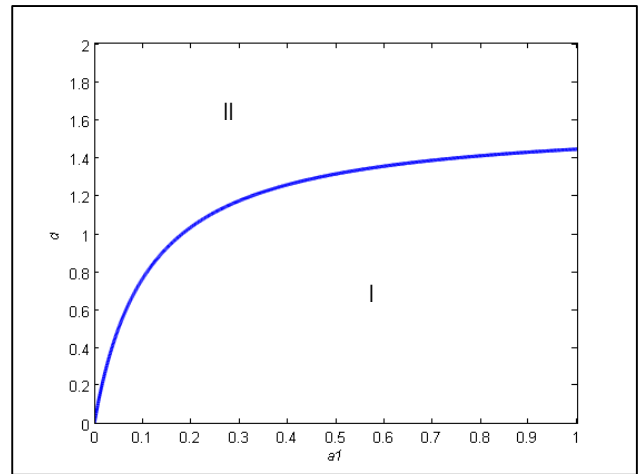


Figure 1 Stability region for the case without immune response when $a_4 = 0.8$ and $d_2 = 0.11$

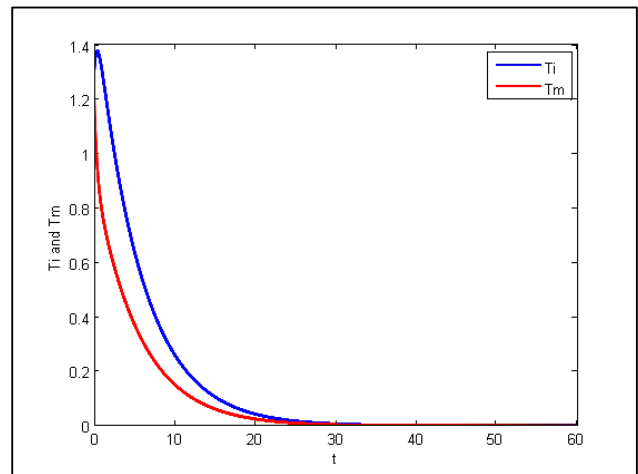


Figure 2 Numerical example for stable fixed point $(0,0)$ when $a_1 = 1$ and $d = 1.9$ with initial condition $T_I(0) = 1.3$ and $T_M(0) = 1.2$

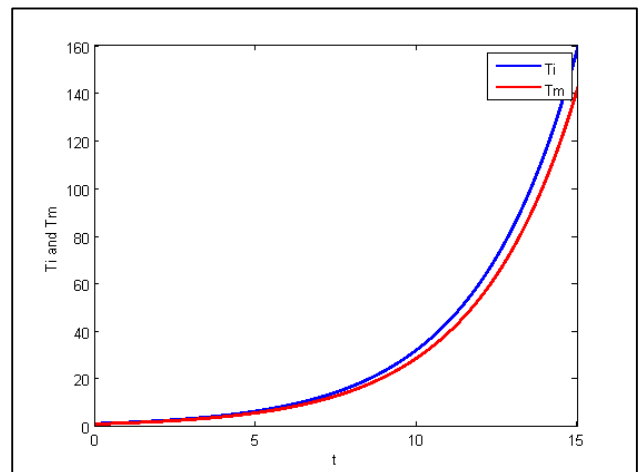


Figure 3 Numerical example for unstable fixed point $(0,0)$ when $a_1 = 1$ and $d = 0.8$ with initial condition $T_I(0) = 1.3$ and $T_M(0) = 1.2$

From Figure 1, the region for tumor growth where (0,0) unstable is given by I and the region for tumor decay where (0,0) stable is given by the complement II. The values were chosen from different regions to observe the solution of the system as presented in Figure 2 and Figure 3.

3.2 Tumor System with the presence of Immune Response

In this case, the effect of immune response is added to the model. The system of equations now becomes

$$\begin{aligned} \frac{dT_I}{dt} &= 2a_4T_M - (c_1I + d_2)T_I - a_1T_I \\ \frac{dT_M}{dt} &= a_1T_I - d_3T_M - a_4T_M - c_3T_MI \quad (17) \\ \frac{dI}{dt} &= k + \frac{\rho I(T_I + T_M)^n}{\alpha + (T_I + T_M)^n} - c_2IT_I - c_4T_MI - d_1I \end{aligned}$$

One of the tumor free point is $(T_I, T_M, I) = (0, 0, \frac{k}{d_1})$ with zero tumor population. This is our starting point since it represents a tumor free condition. The factorization form of the auxiliary equation at this steady state yields Eq. (18).

$$(-d_1 - \lambda)[(-c_1\bar{d}_1 - d_2 - a_1 - \lambda)(-d - c_3\bar{d}_1 - \lambda) - 2a_1a_4] = 0 \quad (18)$$

where $\bar{d}_1 = \frac{k}{d_1}$. Clearly, one of the eigenvalue is $\lambda = -d_1$. The remaining eigenvalues are given as the solution to the auxiliary equation

$$\begin{aligned} \lambda^2 + [a_1 + d_2 + (c_1 + c_3)\bar{d}_1 + d]\lambda + (a_1 + d_2 + c_1\bar{d}_1)(d + c_3\bar{d}_1) - 2a_1a_4 &= 0 \quad (19) \\ \lambda^2 + p_1^*\lambda + p_2^* &= 0 \quad (20) \end{aligned}$$

where

$$p_1^* = a_1 + d_2 + (c_1 + c_3)\bar{d}_1 + d \quad (21)$$

$$p_2^* = (a_1 + d_2 + c_1\bar{d}_1)(d + c_3\bar{d}_1) - 2a_1a_4 \quad (22)$$

The value of p_1^* is always positive [15, 16, 22]. The value of p_2^* can be negative or positive. According to the Routh-Hurwitz stability criteria the fixed point $(0, 0, \frac{k}{d_1})$ will stable if $p_1^* > 0$ and $p_2^* > 0$. Thus, the necessary condition for the tumor growth is given by Eq. (23).

$$d < \frac{-(c_1 + c_3)\bar{d}_1 + 2a_1a_4}{d_2 + a_1} \quad (23)$$

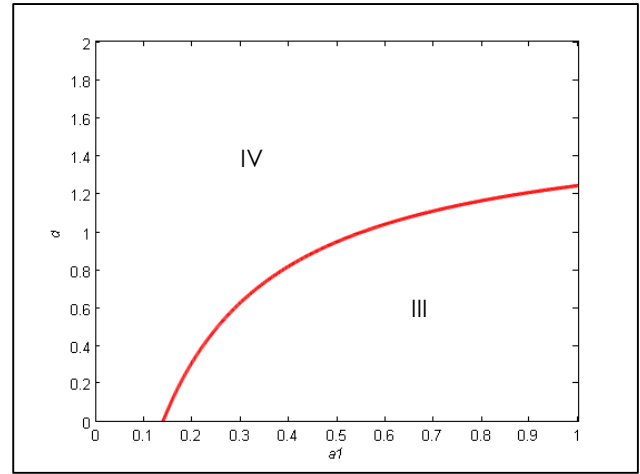


Figure 4 Stability region for the case with the presence of immune response when $a_4 = 0.8, c_1 = c_3 = 0.9, d_2 = 0.11$ and $\bar{d}_1 = 0.1241$

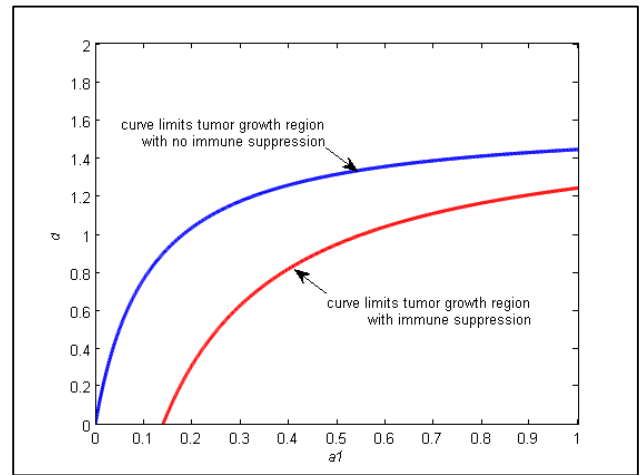


Figure 5 Stability region for both cases

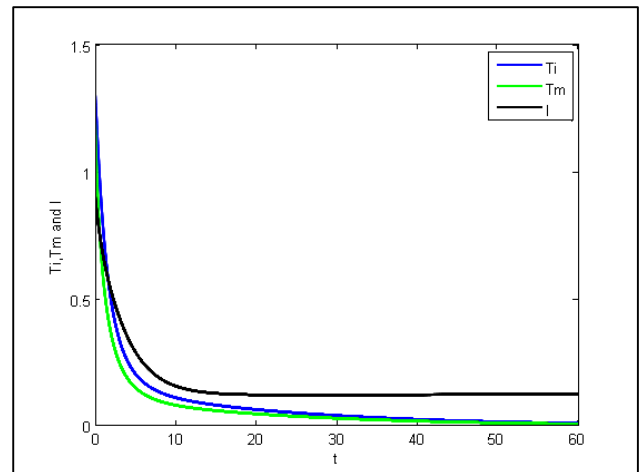


Figure 6 Numerical example for stable fixed point $(0, 0, \frac{k}{d_1})$ when $a_1 = 1$ and $d = 1.3$ with initial condition $T_I = 1.3, T_M = 1.2$ and $I = 0.9$

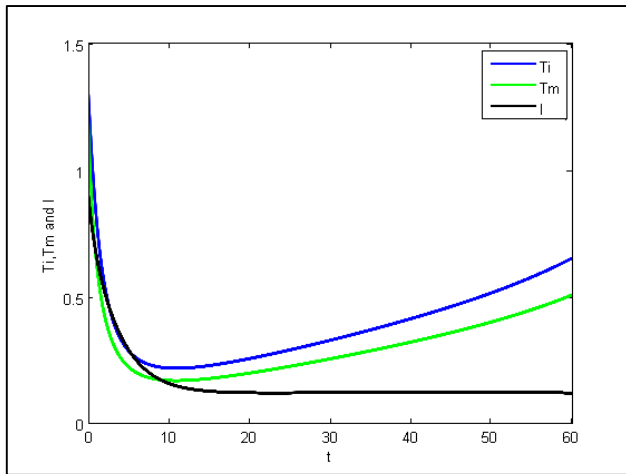


Figure 7 Numerical example for unstable fixed point $(0,0, \frac{k}{a_1})$ when $a_1 = 1$ and $d = 1.15$ with initial condition $T_I = 1.3, T_M = 1.2$ and $I = 0.9$

From Figure 4, the region for tumor growth, where $(0,0, \frac{k}{a_1})$ is unstable is given by III and the region for tumor decay where $(0,0, \frac{k}{a_1})$ is stable is given by the complement IV. It can be seen in Figure 5 that the region of tumor growth without immune response for system (11) is larger than the region of tumor growth with the presence of immune response for system (17). Thus, system (17) is more stable compared to system (11). Various values were chosen from different regions to observe the solution of the system as presented in Figure 6 and Figure 7.

3.3 Tumor System with Single Drug

Now, consider the effect of single drug to the system

$$\begin{aligned} \frac{dT_I}{dt} &= 2a_4T_M - (c_1I + d_2)T_I - a_1T_I \\ \frac{dT_M}{dt} &= a_1T_I - d_3T_M - a_4T_M - c_3T_M I \\ &\quad - k_1(1 - e^{-k_2u})T_M \\ \frac{dI}{dt} &= k + \frac{\rho I(T_I + T_M)^n}{\alpha + (T_I + T_M)^n} - c_2IT_I - c_4T_M I - d_1I \\ &\quad - k_3(1 - e^{-k_4u})I \\ \frac{du}{dt} &= -\gamma u \end{aligned} \tag{24}$$

One of the tumor free point for this system is $(T_I, T_M, I, u) = (0,0, \frac{k}{a_1}, 0)$ with zero tumor and drug level. This represents a tumor and drug free condition and serves as the base for reference. The factorization form of the auxiliary equation at this steady state yields Eq. (24)

$$(-\gamma - \lambda)(-d_1 - \lambda)[(-c_1\bar{d}_1 - d_2 - a_1 - \lambda)(-d - c_3\bar{d}_1 - \lambda) - 2a_1a_4] = 0 \tag{25}$$

where $\bar{d}_1 = \frac{k}{a_1}$. Clearly, two of the eigenvalues are $\lambda = -\gamma$ and $\lambda = -d_1$. The other eigenvalues are given as the solutions to the auxiliary equation

$$\begin{aligned} \lambda^2 + [a_1 + d_2 + (c_1 + c_3)\bar{d}_1 + d]\lambda & \tag{26} \\ + (a_1 + d_2 + c_1\bar{d}_1)(d & \\ + c_3\bar{d}_1) - 2a_1a_4 = 0 & \\ \lambda^2 + p_1^{**}\lambda + p_2^{**} = 0 & \tag{27} \end{aligned}$$

where

$$\begin{aligned} \therefore p_1^{**} &= a_1 + d_2 + (c_1 + c_3)\bar{d}_1 + d & \tag{28} \\ p_2^{**} &= (a_1 + d_2 + c_1\bar{d}_1)(d + c_3\bar{d}_1) - 2a_1a_4 & \tag{29} \end{aligned}$$

The value of p_1^{**} is always positive [15, 16, 22]. The value of p_2^{**} can be negative or positive. According to the Routh-Hurwitz stability criteria the fixed point $(0,0, \frac{k}{a_1}, 0)$ will be stable if $p_1^{**} > 0$ and $p_2^{**} > 0$. Thus the necessary condition for the tumor growth is given by Eq. (30)

$$d < \frac{-(c_1 + c_3)\bar{d}_1 + 2a_1a_4}{d_2 + a_1} \tag{30}$$

Notice that Eq. (30) is the same as Eq. (23). Hence, it has the same stability region as the previous system. It can be concluded that this system has the same stability characteristics as the tumor system without the application of drug.

To observe the effect of the drug towards the tumor population, numerical calculations were carried out, with results plotted using three different amounts of drug or initial value, u_0 which are $u_0 = 0.05, u_0 = 0.1$, and $u_0 = 0.15$. These values are chosen from the range $0 \leq u_0 \leq 0.15$ founded in [23].

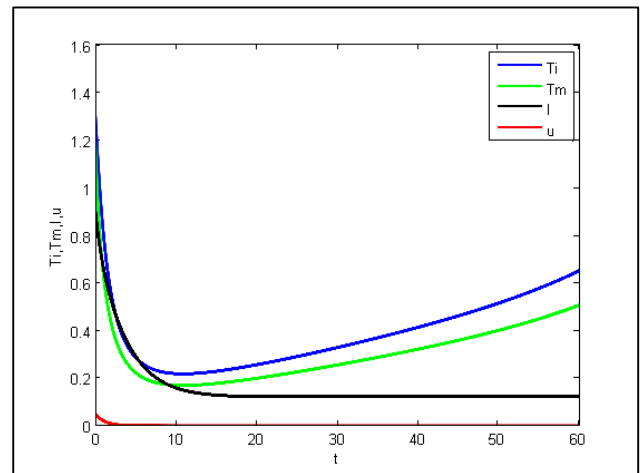


Figure 8 Numerical example for tumor system with the presence of immune response and drug when $a_1 = 1$ and $d = 1.15$ with initial condition $T_I = 1.3, T_M = 1.2, I = 0.9$ and $u = 0.05$

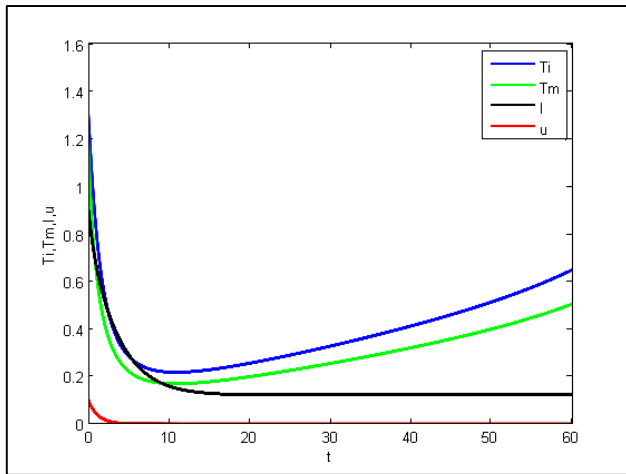


Figure 9 Numerical example for tumor system with the presence of immune response and drug when $a_1 = 1$ and $d = 1.15$ with initial condition $T_i = 1.3, T_M = 1.2, I = 0.9$ and $u = 0.1$

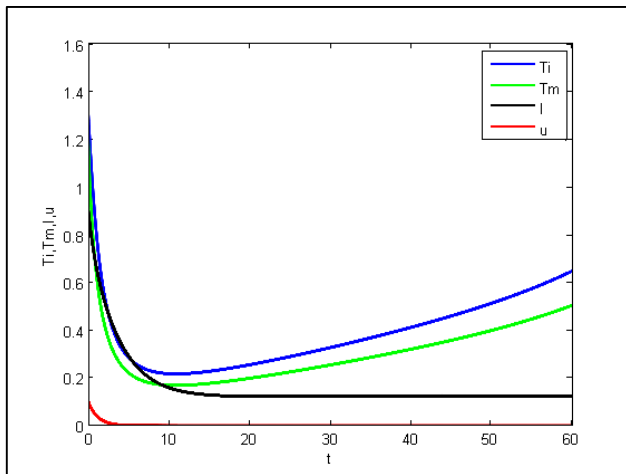


Figure 10 Numerical example for tumor system with the presence of immune response and drug when $a_1 = 1$ and $d = 1.15$ with initial condition $T_i = 1.3, T_M = 1.2, I = 0.9$ and $u = 0.15$

In Figure 8, the graph of the solution shows that the tumor population is growing when the amount of drug is $u_0 = 0.05$. Next, the initial amount of drug is increased to $u_0 = 0.1$, and the graph of the solution is shown in Figure 9.

From Figure 9, the tumor population is still growing even when the amount of drug have been increased. According to [23], the upper limit of reasonable drug is 0.15. By taking this highest amount of drug as a final selection, the graph of solution is then produced in Figure 10 to see whether the population of tumor grow or decay as time progresses.

It is obvious that the population of tumor still does not display any change with time. It can be concluded that the system maintains stability even though the maximum amount of drug have been delivered. However, the numerical values explain the differences between these figures.

These value were presented in the Table 1 while another comparison of numerical values between tumor system with immune response and drug system with $u_0 = 0.15$ have been tabulated in Table 2.

Table 1 Comparison of numerical values for tumor on each phase with respect to different amount of drug

t	$u_0 = 0.05$		$u_0 = 0.1$		$u_0 = 0.15$	
	T_I	T_M	T_I	T_M	T_I	T_M
10	0.2185	0.1700	0.2173	0.1691	0.2162	0.1683
20	0.2562	0.1994	0.2550	0.1984	0.2539	0.1976
30	0.3282	0.2554	0.3269	0.2543	0.3255	0.2533
40	0.4131	0.3214	0.4115	0.3202	0.4100	0.3190
50	0.5147	0.4005	0.5127	0.3990	0.5108	0.3975
60	0.6511	0.5067	0.6483	0.5045	0.6456	0.5024

Table 2 Comparison of numerical values for tumor on each phase for tumor system in the presence of immune response and tumor system with the presence of immune response and drug

t	without drug, immune is present		with drug $u_0 = 0.15$, immune is present	
	T_I	T_M	T_I	T_M
10	0.2197	0.1710	0.2162	0.1683
20	0.2574	0.2003	0.2539	0.1976
30	0.3296	0.2565	0.3255	0.2533
40	0.4147	0.3277	0.4100	0.3190
50	0.5168	0.4021	0.5108	0.3975
60	0.6541	0.5090	0.6456	0.5024

From Table 2 above, the population of tumor cells at interphase and metaphase decrease at 1.27% and 1.53% respectively. This shows that the system with implementation of drug provide a better way for treatment in patients.

4.0 CONCLUSION

This research considers three cases which are tumor system without immune response, tumor system with the presence of immune response and tumor system with single drug. Same procedure of stability analysis were done on each cases. For tumor system without immune response, the only steady state obtained is at origin. In this steady state, two regions of stability can be produced by fixing all parameters except for parameter a_1 and d . The regions are tumor growth region and tumor decay region, denoted by I and II respectively. By choosing a specific pair specific pair of value for parameter a_1 and d in each region, the system is solved numerically using Fourth Order Runge Kutta Method. The result shows the population of tumor at interphase and metaphase increases when the values of parameter a_1 and d are fixed at the tumor growth region I. While the population of tumor decreases when the value of parameter a_1 and d are fixed at the tumor decay region II. This implies that different values of parameter a_1 and d affect the

stability of the system. It is important to maintain the value of a_1 and d so the system will maintain at tumor decay region.

Previous models were not realistic since the system did not include immune response. By adding the immune response, the model now involves the competition of three populations. This system has more than one steady states. However, this study only analyse the steady state in which tumor populations on both phases are zero. The stability region a_1 and d again is produced and then compared to the previous systems. From the stability region, the curve built in this system shows reduction in the tumor growth region compared to the previous system. It shows that this system is more stable since immune system naturally fights infections, including tumor. With the presence of immune system, numerical examples show that the population of tumor is decreased compared to the previous system. It can also be seen that the immune population maintain at a constant rate as time progresses. However, drug is needed to fight tumor since tumor growth persists even with the presence of immune response.

The drug effect is added into the tumor system with immune response. There exists another steady states but this research only looks at the steady state with zero tumor population and drug with positive immune level. From the stability analysis, the steady states have the same stability characteristics as tumor system with immune response. This means that if a certain amount of drug is given to the patient, this system will exhibit the same behaviour as the previous system. However, the population of tumor is decreased by 1.27% at interphase and 1.53% at metaphase. This implies that combination of immune and drug provide a better way to kill tumor cells.

Several recommendations are presented as guides for future study. These include the effect of delay in the cell cycle may improve our findings. It seems more realistic since the tumor are trapped for a certain time in the mitosis for immune cells to kill it after being affected by drug. Besides, including quiescent phase could help us to understand either this phase will contribute or delay the progression of the population of tumor. A more detailed modelling involving immune systems also may provide many ideas. One such possibility is to include more types of immune cells to the model for analysis.

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