Stability analysis of a mathematical model of tumor with chemotherapy

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Abstract. The purposes of this research are to analyze a mathematical model of tumor with chemotherapy and to present numerical verification of the derived result. There are four classes in the model, namely tumor cells, immune cells which is divided by active CTL cells and helper T cells, and chemotherapy drug. There are three kinds equilibrium point: tumor free, tumor persistent, and coexisting equilibrium. The dynamical behaviour of our system by analysing the existence and stability of the system at each equilibrium is discussed. The dynamical behaviour of the model is also numerically verified.

1. Introduction

Based on WHO [1], cancer occupies the second mortality rate globally. Normally, the cells in the body will die and are replaced by new cells but tumor and cancer cells can disturb this cycle. Tumor cells grow and unlike normal cells, they don't die, even though the body does not need them. As this process continues, the tumor growth is bigger and bigger and it is added to the mass. Many causes of cancer such as smoking habits, alcohol use, lack of fruits and vegetables. But cancer can be prevented by living a healthy life [2].

Mathematical researches which are discussed neither modern or basic treatment of tumor are always developed. Mathematical model using modern treatment to fight tumor such as virotherapy [3], gene therapy [4], biochemotherapy [5], immunotherapy [6], radiotherapy [7], adjuvant therapy [8] had been discussed. But current standard tumor treatments are surgery, radiation therapy, and chemotherapy. Chemotherapy is a tumor treatment using special drugs to destroy tumor cells that grow and spread rapidly than normal cells (immune cells).

In this article, we propose stability analysis of a (modified) mathematical model of tumor with chemotherapy treatment. At first, the development of tumor begins as the result of a genetic alteration leading to abnormal proliferation of a single cell. Cell proliferation then ends up in the outgrowth of a population of clonally derived tumor cells. Normally, our body produces immune cells to fight tumor. The immune components of our model are active CTL (Cells T Lymphocyt) cells and helper T cells. Helper T cells produce T cell cytokine in the activity to form immunity. They help to stimulate on maturation of B cells and memory B cells which with active CTL cells destroy tumor cells. In other word, helper T cells can attack tumor cells indirect. We use chemotherapy as the treatment of tumor to help immune cells. Particularly, interaction of each cell can be formulated as differential equation system. We also use Michaelis-Menten equation to describe the interaction. Here, we ignore the role of...
interleukin-2 and interferon alpha, but we hope can allow us to give clear insight and have some applicable results.

The next section, we propose how the mathematical model is formed. In section 3, discussing the stability analysis of the equilibrium points derived from model. Moreover, numerical simulation is given in the section 4.

2. Mathematical Model

The cells population is divided into four parts i.e. the tumor cells ($T$), the active CTL cells ($C$), the helper T cells ($R$) and chemotherapy drug ($M$). We use similar assumptions with the ones in Sharma [9], i.e., the tumor cells and helper T cells population have logistic growth, chemotherapy drug have negative effect not only on tumor cells but also active CTL cells and helper T cells, natural death rate only occurred on active CTL cells. Moreover, we add the assumption that the interaction between $T$ and $C$ follows the Michaelis-Menten equation.

Equation (1) describes the rate of change for tumor cells population. If $x_1$ to denote per capita growth rates of tumor cells, and $y_1$ to denote reciprocal carrying capacity of tumor cells, since from the assumption that tumor cells population follows logistic growth, then we have the first term of Equation (1). If $z_1$ defines response coefficient of tumor cells to the chemotherapy drug and we use $\alpha_1$ to denote the rate at which tumor cells getting loss because of run into with active CTL cells, then it has negative sign at the second and third term of Equation (1). Following Kirschner’s idea [10], the population of tumor also decreases because of $\theta$ as the clearance tumor cell rate as shown in fourth term in Equation (1). It is modeled by Michaelis-Menten kinetics to indicate the limited immune response to the tumor

$$\frac{dT}{dt} = x_1T(1-y_1T) - z_1MT - \alpha_1TC - \frac{\theta TR}{f + T}. \tag{1}$$

Equation (2) describes the rate of change for active CTL cells population. If $\beta$ denotes the rate of direct contact or cytokine produced by helper T cells, then we have the first term of Equation (2). Using $\mu$ to denote per capita decay rate of active CTL cells, as our assumption, then we have second term of Equation (2). We use $z_2$ to denote response coefficient of active CTL cells to the chemotherapy drug, then the population of active CTL cells decrease as shown in the third term of (2). Active CTL cells which become getting loss because of run into with tumor cells at a rate $\alpha_2$ make the population decrease as shown in the fourth term (2). If $k$ as proliferation rate and $g$ as the half saturation for proliferation term, then following Michaelis-Menten Equation, we have fifth term of Equation (2).

$$\frac{dC}{dt} = \beta CR - \mu C - z_2MC - \alpha_2TC + \frac{kTC}{g + T}. \tag{2}$$

We assume helper T cells population growth logistically in the absence of active CTL cells and chemotherapy drug. Here we use $x_2$ as per capita growth rates of helper T cells and $y_2$ as reciprocal carrying capacity of helper T cells then we have the first term of (3). The population of helper T cells decreases because of response coefficient of helper T cells to the chemotherapy drug $z_3$, and helper T cells become active CTL cells at rate $\beta$, then we obtain second and third term of (3)

$$\frac{dR}{dt} = x_2R(1-y_2R) - \beta CR - z_3MR. \tag{3}$$

There are $a$ as the dose given, and it decreases at $\gamma$ as decay rate of the chemotherapy drug, then the rate of chemotherapy drug changes over time is

$$\frac{dM}{dt} = a - \gamma M. \tag{4}$$
Now, we have equation (1)-(4) as mathematical model of tumor cells-active CTL cells-helper T cells-chemotherapy drug whose 

\[ T(0) \geq 0, C(0) \geq 0, R(0) \geq 0, M(0) \geq 0 \]

as initial conditions. All parameters value is positive constants.

3. Stability Analysis

In this section, we determine the equilibrium points of System (1) and analysis its stability. The equilibrium is obtained when

\[ \frac{dT}{dt} = \frac{dC}{dt} = \frac{dR}{dt} = \frac{dM}{dt} = 0 \]

If \( T = R = 0 \), it means no tumor cells and active CTL cells exist in the blood, then System (1) has trivial equilibrium \( E_0 \left( 0, 0, 0, \frac{a}{\gamma} \right) \). It can be explained as follow. Based on Equation (4) and let \( \frac{dM}{dt} = 0 \), then we obtain \( \frac{a}{\gamma} = \frac{x_i y_i - z_i a}{x_i y_i} \). Because \( T = R = 0 \), Equation (2) and \( \frac{dC}{dt} = 0 \), we obtain \( C = 0 \). In other words, it is proven the trivial equilibrium is 

\[ E_0 \left( 0, 0, 0, \frac{a}{\gamma} \right) . \]

If \( T = C = 0 \) and \( R \neq 0 \), then System (1) has tumor free equilibrium. From Equation (3) and \( \frac{dR}{dt} = 0 \), we have \( R = \frac{x_i y_i - z_i a}{x_i y_i} \). So, we obtain \( E_i \left( 0, 0, \hat{R}, \hat{M} \right) \) where \( \hat{R} = \frac{x_i y_i - z_i a}{x_i y_i}, \hat{M} = \frac{a}{\gamma} \).

If \( T \neq 0 \) and \( C = R = 0 \), then System (1) has tumor persistent equilibrium. From Equation (1) and 

\[ \frac{dT}{dt} = 0 \]

, we have \( T = \frac{x_i y_i - z_i a}{x_i y_i} \). It means we get \( E_2 \left( \hat{T}, 0, 0, \hat{M} \right) \) where \( \hat{T} = \frac{x_i y_i - z_i a}{x_i y_i}, \hat{M} = \frac{a}{\gamma} \).

Now, we determine the Jacobian matrix of System (1) as the first step to analyze the stability. It is given by

\[
J = \begin{bmatrix}
x_i (1 - y_i T) - x_i y_i - z_i M - a_i C - \frac{\beta R (f + T) - \theta T}{(f + T)^2} & -a_i T & -\theta T & -z_i T \\
\frac{kC(y + T) - kTC}{(y + T)^2} & -a_i C & \beta R - \mu z_i M + \frac{kT}{g + T} a_i T & -\beta R \\
0 & 0 & \frac{x_i (1 - y_i R) - x_i y_i - \beta C - z_i M}{x_i y_i} - z_i R & -\gamma \\
0 & 0 & 0 & -\gamma 
\end{bmatrix}
\]

(5)

The analysis of stability at equilibrium points will be discussed in Theorem 1.

Theorem 1

(i) If \( a > \frac{x_i y_i}{z_i} \) and \( a > \frac{x_i y_i}{z_i} \), then the trivial equilibrium \( E_0 \left( 0, 0, 0, \frac{a}{\gamma} \right) \) exists and is locally asymptotically stable.

(ii) If \( \frac{1 - 2z_i R_i}{z_i} < a < \frac{x_i y_i}{z_i}, a > \frac{x_i y_i}{z_i}, \) and \( \beta < \frac{\mu y + z_i a}{R_i} \), then the tumor free equilibrium \( E_i \left( 0, 0, \hat{R}, \hat{M} \right) \) exists and is locally asymptotically stable.

(iii) If \( \frac{1 - 2z_i \hat{T}_i}{z_i} < a < \frac{x_i y_i}{z_i}, a > \frac{x_i y_i}{z_i}, a > \frac{\mu + \frac{kT}{g + T} - \alpha z_i \hat{T}}{z_i} \), then the tumor persistent equilibrium \( E_2 \left( \hat{T}, 0, 0, \hat{M} \right) \) exists and is locally asymptotically stable.
Proof

(i) If $E_0$ is substituted in $J$ in Equation (5), then the eigenvalues of $J(E_0)$ are 
\[ \lambda_1 = x_1 - z_1 \frac{a}{\gamma}, \lambda_2 = -\mu - z_2 \frac{a}{\gamma}, \lambda_3 = x_2 - z_3 \frac{a}{\gamma}, \lambda_4 = -\gamma. \]
Because $a > \frac{x_1 \gamma}{z_1}$ and $a > \frac{x_2 \gamma}{z_3}$, then $\lambda_1, \lambda_2, \lambda_3, \lambda_4 < 0$
which implies $E_0 \left(0, 0, 0, \frac{a}{\gamma}\right)$ is locally asymptotically stable.

(ii) Tumor free equilibrium $E_1 \left(0, 0, \hat{R}, \hat{M}\right)$ exists for $a < \frac{x_1 \gamma}{z_1}$. If $E_1$ is substituted in $J$ in Equation (5), then the eigenvalues of $J(E_1)$ are 
\[ \lambda_1 = x_1 - z_1 \hat{M}, \lambda_2 = \beta \hat{R} - \mu - z_2 \hat{M}, \lambda_3 = x_3 \left(1 - y_2 \hat{R}\right) - x_2 \hat{R} y_2 - z_3 \hat{M}, \lambda_4 = -\gamma. \]
It is clear $\lambda_4 < 0$. Because $a > \frac{x_1 \gamma}{z_1}$ then $\lambda_1 < 0$. Since $\beta < \frac{\mu \gamma + z_2 a}{\hat{R} \gamma}$ so $\lambda_2 < 0$. Because $a > \frac{\left(1 - 2 \hat{R} y_2\right) x_2 \gamma}{z_3}$
$\Rightarrow z_1 \frac{a}{\gamma} > x_2 - 2 x_2 \hat{R} y_2 \Leftrightarrow x_2 - 2 x_2 \hat{R} y_2 - z_1 \frac{a}{\gamma} < 0 \Leftrightarrow x_3 \left(1 - y_2 \hat{R}\right) - x_2 \hat{R} y_2 - z_3 \hat{M} < 0$, then it comes to the result $\lambda_3 < 0$.

(iii) Tumor persistent equilibrium $E_2 \left(\hat{R}, 0, 0, \hat{M}\right)$ exists for $a < \frac{x_1 \gamma}{z_1}$. If $E_2$ is substituted in $J$ in (5), then the eigenvalues of $J(E_2)$ are 
\[ \lambda_1 = x_1 \left(1 - y_1 \hat{R}\right) - x_1 \hat{R} y_1 - z_1 \hat{M}, \lambda_2 = -\mu - z_2 \hat{M} + \frac{k \hat{R}}{g + T} - \alpha_2 \hat{R}, \lambda_3 = x_3 - z_3 \hat{M}, \lambda_4 = -\gamma. \]
It is clear that $\lambda_4 < 0$. Because $a > \frac{x_1 \gamma}{z_1}$, then $\lambda_1 < 0$. It is known that $a > \frac{x_1 \gamma \left(1 - 2 y_1 \hat{R}\right)}{z_1}$, so $\lambda_1 < 0$. Here $a > \frac{\left(-\mu + \frac{k \hat{R}}{g + T} - \alpha_2 \hat{R}\right) \gamma}{z_2}$, then $\lambda_2 < 0$.

Now, we discuss coexisting equilibrium. It is occurred when tumor and active CTL cells exist. We assume $T \neq C \neq 0$ and $R = 0$. Using this condition and based on (2), we obtain
\[ a_1 T^2 + a_2 T + a_3 = 0, \tag{6} \]
where $a_1 = \alpha_2 \gamma, a_2 = \left(\alpha_2 \gamma g + z_2 a + \mu \gamma - k \gamma\right), a_3 = \mu g \gamma + z_2 \gamma a_1.$ Solving quadratic equation (6), we have
\[ T_{1,2} = \frac{-a_2 \pm \sqrt{a_1^2 - 4a_2 a_3}}{2a_1}. \tag{7} \]
On the other hand, based on (1) we get
\[ C = \frac{x_1 \gamma \left(1 - y_1 T\right) - z_1 a}{\alpha_1 \gamma}, \tag{8} \]
where $T$ in (8) as shown in (7). Equation (8) exists if $0 < T < \frac{x_1 \gamma - z_1 a}{x_1 y_1 \gamma}$ and $x_1 \gamma - z_1 a > 0$. Now, we conclude this in the following Theorem to give the existence conditions of the equilibrium point.
Theorem 2.
If \( a_2^2 - 4a_1a_3 > 0, \ a_2 < 0, \ 0 < T < \frac{-\gamma y - z a}{y x} \) and \( x_1 \gamma - z \gamma > 0, \), then the equilibrium point of (1) is

\[
E_1 \left( T_1^*, C_1^*, 0, \frac{a}{\gamma} \right) \quad \text{and} \quad E_4 \left( \frac{T_2^*}{\alpha}, C_2^*, 0, \frac{a}{\gamma} \right),
\]

where \( T_1^* = \frac{-a_2 - \sqrt{a_2^2 - 4a_1a_3}}{2a_1}, \ T_2^* = \frac{-a_2 + \sqrt{a_2^2 - 4a_1a_3}}{2a_1} \),

\[
C_1^* = \frac{x_1 \gamma (1 - y_1 T_1^*) - z_1 a}{\alpha_1 \gamma} \quad \text{and} \quad C_2^* = \frac{x_1 \gamma (1 - y_1 T_2^*) - z_1 a}{\alpha_1 \gamma}.
\]

4. Numerical Simulation
Using parameter value as shown in Table 1, we obtain Figure 1, Figure 2, Figure 3 and Figure 4.

| Parameter | Estimated value | Reference |
|-----------|----------------|-----------|
| \( x_2 \) | 0.0245 (1/time) | [9] |
| \( y_1 \) | \( 1 \times 10^{-9} \) (1/cells) | [10] |
| \( y_2 \) | \( 1 \times 10^{-10} \) (1/cells) | [9] |
| \( z_1 \) | 0.08 (1/time) | [9] |
| \( z_2 \) | \( 2 \times 10^{-11} \) (1/time) | [9] |
| \( z_3 \) | \( 1 \times 10^{-5} \) (1/time) | [9] |
| \( \alpha_1 \) | \( 1.101 \times 10^{-7} \) (1/cells/time) | [9] |
| \( \alpha_2 \) | \( 3.422 \times 10^{-10} \) (1/cells/time) | [9] |
| \( k \) | 0.1245 (1/time) | [10] |
| \( g \) | \( 10^{-3} \) (cells) | [4] |
| \( \beta \) | \( 6.2 \times 10^{-9} \) (1/cells/time) | [9] |
| \( \mu \) | 0.0412 (1/time) | [9] |
| \( \theta \) | 1 (1/time) | [4] |
| \( f \) | \( 10^5 \) (cells) | [4] |

It can be seen from Fig.1, tumor cells population growth uncontrolled. While in Figure 2, the tumor population first rises then around \( t = 100 \) goes down to a certain point and stays there. When the value of \( a \) increases, the tumor population rises longer and then falls lower than in Figure 2. In Figure 4 it appears that the tumor population actually tends to zero. It is reasonable since \( a \) denotes the drugs dose, the higher the dose of the drug is given, the faster the tumor cell population decreases.
5. Conclusion
Based on the discussion, it can be concluded that mathematical model of tumor using chemotherapy has been derived as shown in System (1). Equilibrium point of System (1) has been discussed. Stability analysis is also presented. Using the value of each parameter shown in Table 1, it can be seen the changes of behavior the system if parameter values change. In this paper, we only discuss local stability analysis. Therefore, for further research is recommended to discuss global stability analysis.

References
[1] WHO 2018 World Health Organization. [Online]. http://www.who.int/news-room/fact-sheets/detail/cancer
[2] White M C, Peipins L A, Watson M, Trivers K F, Holman D M and Rodriguez J L 2013 J. Adolesc Health 52 S1
[3] Joseph M, Precious S and Hermene M M 2015 Math. Biosci 263 102
[4] Tsygvintsev A, Marino S and Kirshner D E 2013 In Math. Methods Models Biomed (New York, NY: Springer)
[5] Mustafa M, Subiyanto and Agus K 2013 Appl. Math. Sci 7 247
[6] Ami R, Ruby K and Timothy W II 2018 Spora: J. Biomath 4 25
[7] Zijian L and Chenxue Y 2014 Comput. Math. Methods Med 2014 1
[8] Gregory W M, Twelves C J, Bell R, Smye S W, Howard D R, Coleman R E and Cameron D A 2016 Breast Cancer Res. Treat. 155 303
[9] Swarnali S and Samanta G P 2013 J. Nonlinear Dyn 2013 1
[10] Caravagna G, Barbuti R and d'Onofrio A 2012 BMC Bioinformatics 13 S8