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Dynamical Analysis of Tumor Growth Model with Immunotherapy

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Abstract: In this paper, the analysis of tumor growth model with immunotherapy involving dendritic cells is discussed. The model consists of four compartments namely the tumor cells, the active CTLs, the T-helper cells, and the dendritic cells. The growth rate of the tumor cells in this model follows the logistic model. The dendritic cell therapy functions as an inhibitor of tumor growth without causing side effects on the other cells so that the spread of tumor cells can be minimized. Next, dynamical analysis is performed by determining the stability analysis of the equilibrium point. It shows that the model has six equilibria consisting of three tumor-free equilibria namely E_0, E_1, E_2 and three tumor equilibria namely E_3, E_4, E_5. The equilibria points E_0 and E_3 are not stable since there are positive eigenvalues while other equilibria will be stable if those meet certain conditions. Furthermore, the simulation results support the analysis result.

MSC: 34D20, 92D25, 92B05

Keywords: Dynamical system, Tumor, Immunotherapy.

1. Introduction

Cancer is a term for a group of diseases spreading to parts of the body. Hence, people are afraid of cancer since the patients are most likely to die of it. Cancer is the abnormal cells growing quickly beyond the normal limit and invading parts of the body [13]. One of the factors causing cancer is a tumor. A tumor is generally divided into two types namely the benign tumor which is not cancerous and the malignant tumor which can grow uncontrollably and spread into the surrounding tissue. Cancer is a group of the abnormal cells spreading into the bloodstream, the circulatory system, and the lymphatic system [2]. Cancer is caused by transformation of normal cells into tumor cells in a multistage process that generally develops from the pre-cancerous stage into a malignant tumor. It occurs as a result of the interaction between human's genetic factors and external factors such as ultraviolet radiation and ionizing, tobacco smoke, food and water contamination and infections from certain viruses, bacteria or parasites [13].

There are some treatments to inhibit tumor growth namely radiation, chemotherapy and immunotherapy using dendritic cells (DCs) called dendritic cell vaccination. One of the new strategies in the form of immunotherapy used to treat cancer is dendritic cell vaccine [9]. The dendritic cell is the most effective APC (Antigen Presenting Cells) since it places in the strategic locations where foreign microbes and antigens enter the body. It is also around the organs targeted by bacteria and the area where the abnormal cells usually developed [1]. There are two types of dendritic cells namely conventional dendritic cells (cDCs) and plasmacytoid dendritic cells (pDCs). cDCs recognizes the antigens that presented by T cells ($CD4^+T$) and

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secretes several important molecules, meanwhile pDCs generate interferon and antivirus. $CD4^+$T function to regulate the body's immune response using cytokines as a signal to stimulate the immune system and respond to the tumor [8].

Some papers discussing the analysis of the tumor growth model have been written. Kirschner dan Panetta [6] constructed the mathematical model of a growing tumor and its response to immunotherapy. It described the dynamical interaction between tumor, immune cells, and IL-2. The result shows that the immunotherapy with cytokine interleukin-2 (IL-2) could increase the body immunity. DePillis et al. [3] studied a model of tumor metastasis using ordinary differential equations with chemotherapy as the optimal control to inhibit tumor growth. The model consisted of four subpopulations namely tumor cells, host cells, immune cells, and chemotherapy. The stability analysis was carried out without including the control. DePillis et al.[4] developed the tumor growth model with immunotherapy and chemotherapy. The simulation result showed that using chemotherapy or immunotherapy alone is not efficient. So it is assumed that by combining these two types of therapy, all the tumors can be eliminated.

DePillis et al. [5] studied the mathematical model of melanoma with dendritic cell therapy. DePillis et al. [5] reconstructed the model by Ludewig et al. [7] by describing the interaction between dendritic cells and tumor cells. Trisilowati et al.[12] discussed the optimal control of the dendritic cell therapy on tumor growth where the dendritic cell is the natural killer of the tumor. Sharma dan Samanta [11] developed the model of tumor growth and its interaction with immune cells and chemotherapy. The system consists of (i) T cell which can't eliminate the tumor directly yet release the cytokine interleukin-2 activating CTLs, (ii) the active CTLs which can eliminate the tumor cells, (iii) tumor cells, and (iv) chemotherapy. Next, Rangel et al. [10] studied the effectiveness of the dendritic cell of the murine model and optimal control. The model consists of tumor cell, $CD4^+$T cell, $CD8^+$T cell or CTLs, antigen containing the dendritic cell, IL-2, TGF-β^+T as the inhibitory cell, IFN-γ increasing the regulation of MHC 1, and M_l which defines the number of MHC 1 for every melanoma cell.

In this paper, the constructed model is based on the model by Sharma and Shamanta [11]. It is reconstructed by adding dendritic cell as an immunotherapy compartment. Next, the stability of the equilibria is also investigated. Finally, the numerical results are given to support the analysis result.

2. Mathematical Model

Based on the modification of Sharma and Shamanta's model [11], the system of nonlinear differential equations obtained can be written as

$$\frac{dT}{dt} = r_1 T(1 - p_1 T) - a_1 T I_H - q_1 C T, \tag{1}$$

$$\frac{dI_H}{dt} = \beta I_H I_R - \alpha_2 T I_H - d I_H, \tag{2}$$

$$\frac{dI_R}{dt} = r_2 I_R(1 - p_2 I_R) - \beta I_H I_R + q_2 C I_R, \tag{3}$$

$$\frac{dC}{dt} = u_0 - \gamma C, \tag{4}$$

where T, I_H, I_R, C stand for the number of tumor cells, CTLs cells, T-helper cells, and dendritic cells respectively. The first term in equation (1) explains the tumor growth follows the logistic model. Next, the parameter α_1 defines the elimination process of the tumor by CTLs and q_1 stands for the kill rate of the dendritic cell. In equation 2, β is the production rate of CTLs by $I_H I_R$. The second term explains the death rate of the CTLs because of the tumor while d is the natural death rate of the CTLs. Term $r_2 I_R(1 - p_2 I_R)$ in equation (3) defines the logistic growth rate of T helper cells while β and q_2 is the activation rate of T-helper cell by dendritic cell. In equation (4), u_0 is the secretion rate of dendritic cell and γ stands for the natural death of the dendritic cell.

3. The Equilibria Points

The equilibria points of the model are obtained by solving $\frac{dT}{dt} = \frac{dI_H}{dt} = \frac{dI_R}{dt} = \frac{dC}{dt} = 0$. The model has six equilibria consist of three free-tumor equilibria and three tumor equlibria. The free-tumor equilibria $E_0 = (0, 0, 0, \frac{u_0}{\gamma}), E_1 = (0, 0, \frac{q_2u_0+\gamma r_2}{\gamma r_2 p_2}, \frac{u_0}{\gamma}), E_2 = (0, \frac{q_2u_0\beta+r_2\beta\gamma-r_2p_2d\gamma}{\beta^2\gamma}, \frac{d}{\beta}, \frac{u_0}{\gamma})$ shows that the population are free from tumor. Meanwhile, the tumor equilibria obtained are $E_3 = (\frac{\gamma r_1-q_1u_0}{\gamma r_1 p_1}, 0, 0, \frac{u_0}{\gamma}), E_4 = (\frac{\gamma r_1-q_1u_0}{\gamma r_1 p_1}, 0, \frac{q_2u_0+\gamma r_2}{\gamma r_2 p_2}, \frac{u_0}{\gamma})$, and $E_5 = (T^*, I_H^*, I_R^*, C^*)$ with $T^* = \frac{r_1\gamma-(\gamma\alpha_1 I_H^*+q_1u_0)}{r_1\gamma p_1}, I_R^* = \alpha_2\frac{r_1\gamma-\gamma\alpha_1 I_H^*-q_1u_0}{r_1\gamma p_1} + \frac{d}{\beta}, I_H^* = \frac{L}{\alpha_1\alpha_2 p_1 p_2 r_1 r_2\gamma\beta^2}, I_R^* = \frac{\xi_1+\xi_2-N-\xi_3}{\xi_4}$,
where

$$
\begin{aligned}
L =& \alpha_2 p_2 r_1^2 r_2\gamma\beta^2 p_1 - \alpha_2^2 p_2^2 r_1 r_2^2\gamma\alpha_1 + p_1^2 p_2 r_1^2 r_2\gamma d\beta^2 - p_1 p_2^2 r_1 r_2^2\gamma d\alpha_1 - \alpha_2 - p_1^2 r_1^2 r_2\gamma\beta^3 + p_1 r_1 r_2^2\gamma\beta p_2\alpha_1\alpha_2 - \alpha_2 p_2 r_2\beta^2 p_1 r_1 q_1 u_0 \\
&+ \alpha_2^2 p_2^2 r_2^2 q_1 u_0\alpha_1 - p_1^2 r_1^2\beta^3 q_2 u_0 + p_1 r_1\beta q_2 u_0 r_2 p_1\alpha_1\alpha_2, \\
N =& \alpha_2 p_2 r_1^2 r_2\gamma\beta^2 p_1 - \alpha_2^2 p_2^2 r_1 r_2^2\gamma\alpha_1 + p_1^2 p_2 r_1^2 r_2\gamma d\beta^2 - p_1 p_2^2 r_1 r_2^2\gamma d\alpha_1\alpha_2 - p_1^2 r_1^2 r_2\gamma\beta^3 + p_1 r_1 r_2^2\gamma\beta p_2\alpha_1\alpha_2 - \alpha_2 p_2 r_2\beta^2 p_1 r_1 q_1 u_0 + \\
&\alpha_2^2 p_2^2 r_2^2 q_1 u_0\alpha_1 - p_1^2 r_1^2\beta^3 q_2 u_0 + p_1^2 r_1\beta q_2 u_0 r_2\alpha_1\alpha_2, \\
\xi_1 =& \alpha_2(p_1 p_2 r_1^2 r_2\gamma\beta^2), \\
\xi_2 =& d(p_1^2 p_2 r_1^2 r_2\gamma\beta^2), \\
\xi_3 =& \alpha_2 q_1 u_0(p_1 p_2 r_1 r_2\beta^2), \\
\xi_4 =& (p_1 p_2 r_1 r_2\gamma\beta^2)(\beta r_1 p_1).
\end{aligned}
$$

4. The Stability of the Equilibria Points

In order to analyze the stability of the system, the Jacobian matrix at E^* is given as

$$
J = \begin{bmatrix}
r_1 - 2r_1 p_1 T^* - \alpha_1 I_H^* - q_1 C^* & -\alpha_1 T^* & 0 & -q_1 T^* \\
-\alpha_2 I_H^* & \beta I_R^* - \alpha_2 T^* - d & \beta I_H^* & 0 \\
0 & -\beta I_R^* & r_2 - 2r_2 p_2 I_R^* - \beta I_H^* + q_2 C^* & q_2 I_R^* \\
0 & 0 & 0 & -\gamma
\end{bmatrix}. \tag{5}
$$

The Jacobian matrix of the equilibria are obtained by substituting each equilibrium point to (5)

Theorem 4.1. *The first free-tumor equilibrium point E_0 is unstable*

Proof. Substituting $E_0 = (0, 0, 0, u_0/\gamma)$ to (5), the Jacobian matrix for E_0 can be written as

$$
J(E_0) = \begin{pmatrix}
r_1 - \frac{q_1u_0}{\gamma} & 0 & 0 & 0 \\
0 & -d & \beta I_H & 0 \\
0 & 0 & r_2 + \frac{q_2u_0}{\gamma} & 0 \\
0 & 0 & 0 & -\gamma
\end{pmatrix}. \tag{6}
$$

By solving $|J(E_0) - \lambda I| = 0$, it is obtained the eigen values $\lambda_1 = r_1 - \frac{q_1u_0}{\gamma}, \lambda_2 = -d, \lambda_3 = r_2 + \frac{q_2u_0}{\gamma}, \lambda_4 = -\gamma$. Therefore, Theorem 4.1. is proved. □

Theorem 4.2. *The second free-tumor equilibrium point E_1 is stable if $r_1 < \frac{q_1u_0}{\gamma}$ and $\frac{\beta q_2u_0+\beta\gamma r_2}{\gamma r_2 p_2} < d$.*

Proof. Substitute $E_1 = (0, 0, \frac{q_2u_0+\gamma r_2}{\gamma r_2 p_2}, \frac{u_0}{\gamma})$ to (5) so that the Jacobian matrix of E_1 can be written as

$$J(E_1) = \begin{pmatrix} r_1 - \frac{q_1u_0}{\gamma} & 0 & 0 & 0 \\ 0 & \frac{\beta q_2u_0+\beta\gamma r_2}{\gamma r_2 p_2} - d & 0 & 0 \\ 0 & \frac{-\beta q_2u_0-\beta\gamma r_2}{\gamma r_2 p_2} & -r_2 - \frac{q_2u_0}{\gamma} & \frac{q_2^2u_0+q_2\gamma r_2}{\gamma r_2 p_2} \\ 0 & 0 & 0 & -\gamma \end{pmatrix}. \tag{7}$$

The eigenvalues of matrix $J(E_1)$ are determined by solving $|J(E_1) - \lambda I|$. The eigenvalues obtained are $\lambda_1 = \gamma, \lambda_2 = -r_2 - \frac{q_2u_0}{\gamma}, \lambda_3 = r_1 - \frac{q_1u_0}{\gamma}, \lambda_4 = \frac{\beta q_2u_0+\beta\gamma r_2}{\gamma r_2 p_2} - d$. It is proved that E_1 will be stable if $r_1 < \frac{q_1u_0}{\gamma}$ and $\frac{\beta q_2u_0+\beta\gamma r_2}{\gamma r_2 p_2} < d$. □

Theorem 4.3. *The third free-tumor equilibrium point E_2 is stable if $r_1 + \frac{\alpha_1 r_2 p_2 d}{\beta^2} < \frac{\alpha_1 q_2 u_0}{\beta\gamma} + \frac{\alpha_1 r_2}{\beta} + \frac{q_1 u_0}{\gamma}$.*

Proof. The Jacobian matrix of $E(2) = (0, \frac{q_2u_0\beta+r_2\beta\gamma-r_2p_2e\gamma}{\beta^2\gamma}, \frac{e}{\beta}, \frac{u_0}{\gamma})$ can be written as

$$J(E_2) = \begin{pmatrix} r_1 - \alpha_1(\frac{q_2u_0\beta+r_2\beta\gamma-r_2p_2d\gamma}{\beta^2\gamma}) - \frac{q_1u_0}{\gamma} & 0 & 0 & 0 \\ -\alpha_2(\frac{q_2u_0\beta+r_2\beta\gamma-r_2p_2d\gamma}{\beta^2\gamma}) & 0 & \frac{q_2u_0\beta+r_2\beta\gamma-r_2p_2d\gamma}{\beta\gamma} & 0 \\ 0 & -d & -\frac{3r_2p_2d}{\beta} & \frac{q_2d}{\beta} \\ 0 & 0 & 0 & -\gamma \end{pmatrix}. \tag{8}$$

The eigenvalues of $J(E_2)$ are $\lambda_1 = -\gamma, \lambda_2 = r_1 - \alpha_1(\frac{q_2u_0\beta+r_2\beta\gamma-r_2p_2d\gamma}{\beta^2\gamma}) - \frac{q_1u_0}{\gamma}$ while the eigenvalues $\lambda_{3,4}$ are determined by solving submatrix

$$X = \begin{vmatrix} 0 & \frac{q_2u_0\beta+r_2\beta\gamma-r_2p_2d\gamma}{\beta\gamma} \\ -d & -\frac{3r_2p_2d}{\beta} \end{vmatrix}. \tag{9}$$

The trace(X) is $-\frac{3r_2p_2d}{\beta} < 0$ and determinat(X) is $\frac{q_2u_0+r_2\gamma}{\gamma} > \frac{r_2p_2d}{\beta}$. If E_2 exists then determinant(X) > 0. Hence, $\lambda_{3,4}$ will be negative. Thus, it is proved that E_2 will be stable if $r_1 + \frac{\alpha_1 r_2 p_2 d}{\beta^2} < \frac{\alpha_1 q_2 u_0}{\beta\gamma} + \frac{\alpha_1 r_2}{\beta} + \frac{q_1 u_0}{\gamma}$. □

Theorem 4.4. *The first tumor equilibrium point E_3 is unstable.*

Proof. By substituting $E_3 = (\frac{\gamma r_1 - q_1u_0}{\gamma r_1 p_1}, 0, 0, \frac{u_0}{\gamma})$ to (5), it is obtained

$$J(E_3) = \begin{pmatrix} r_1 - 2r_1p_1(\frac{\gamma r_1-q_1u_0}{\gamma p_1 r_1}) - \frac{q_1u_0}{\gamma} & -\alpha_1(\frac{\gamma r_1-q_1u_0}{\gamma p_1 r_1}) & 0 & -q_1(\frac{\gamma r_1-q_1u_0}{\gamma p_1 r_1}) \\ 0 & -\alpha_2(\frac{\gamma r_1-q_1u_0}{\gamma p_1 r_1}) - d & 0 & 0 \\ 0 & 0 & r_2 + \frac{q_2u_0}{\gamma} & 0 \\ 0 & 0 & 0 & -\gamma \end{pmatrix}. \tag{10}$$

The eigenvalues of $J(E_3)$ can be obtained $|J(E_3) - \lambda I| = 0$. The eigenvalues obtained are $\lambda_1 = r_1 - 2r_1p_1(\frac{\gamma r_1-q_1u_0}{\gamma p_1 r_1}) - \frac{q_1u_0}{\gamma}, \lambda_2 = -\alpha_2(\frac{\gamma r_1-q_1u_0}{\gamma p_1 r_1}) - d, \lambda_3 = r_2 + \frac{q_2u_0}{\gamma}$ and $\lambda_4 = -\gamma$. Hence, the equilibrium point of E_3 is unstable since $\lambda_3 > 0$. □

Theorem 4.5. *The second tumor equilibrium point E_4 is stable if $\frac{q_1u_0}{\gamma} < r_1$ and $\beta(\frac{q_2u_0+\gamma r_2}{\gamma r_2 p_2}) + \frac{\alpha_2 q_1 u_0}{\gamma r_1 p_1} < \frac{\alpha_2}{p_1} + d$.*

Proof. By substituting $E_4 = (\frac{\gamma r_1 - q_1u_0}{\gamma r_1 p_1}, 0, \frac{q_2u_0+\gamma r_2}{\gamma r_2 p_2}, \frac{u_0}{\gamma})$, it is obtained the Jacobian matrix of E_4 as below

$$J(E_4) = \begin{pmatrix} -r_1 + \frac{q_1u_0}{\gamma} & -\alpha_1(\frac{\gamma r_1-q_1u_0}{\gamma p_1 r_1}) & 0 & -q_1(\frac{\gamma r_1-q_1u_0}{\gamma p_1 r_1}) \\ 0 & \beta(\frac{q_2u_0+\gamma r_2}{\gamma r_2 p_2}) - \alpha_2(\frac{\gamma r_1-q_1u_0}{\gamma p_1 r_1}) - d & 0 & 0 \\ 0 & -\beta(\frac{q_2u_0+\gamma r_2}{\gamma r_2 p_2}) & -r_2 - \frac{q_2u_0}{\gamma} & q_2(\frac{q_2u_0+\gamma r_2}{\gamma r_2 p_2}) \\ 0 & 0 & 0 & -\gamma \end{pmatrix}. \tag{11}$$

The eigenvalues of $J(E_4)$ are $\lambda_1 = \frac{q_1u_0}{\gamma} - r_1, \lambda_2 = \beta(\frac{q_2u_0+\gamma r_2}{\gamma r_2p_2}) + \frac{\alpha_2q_1u_0}{\gamma r_1p_1} - \frac{\alpha_2}{p_1} - d$ while $\lambda_{3,4}$ are determined by solving submatrix

$$Y = \begin{vmatrix} -r_2 - \frac{q_2u_0}{\gamma} & q_2(\frac{q_2u_0+\gamma r_2}{\gamma r_2p_2}) \\ 0 & -\gamma \end{vmatrix}. \tag{12}$$

The trace and determinant of the matrix are $-r_2 - \frac{q_2u_0}{\gamma} - \gamma < 0$ and $r_2\gamma + q_2u_0 > 0$ respectively. The condition indicates that $\lambda_{3,4}$ is negative so that the equilibrium point E_4 is proved to be stable if $\frac{q_1u_0}{\gamma} < r_1$ dan $(\frac{q_2u_0+\gamma r_2}{\gamma r_2p_2}) + \frac{\alpha_2q_1u_0}{\gamma r_1p_1} < \frac{\alpha_2}{p_1} + d$. □

Theorem 4.6. *The third tumor equilibrium point E_5 is stable if $a_3 > 0$ and $a_1a_2 - a_3 > 0$.*

Proof. The Jacobian matrix of $E_5 = (T^*, I_H^*, I_R^*, C^*)$ is

$$J(E_5) = \begin{pmatrix} r_1 - 2r_1p_1T^* - \alpha_1I_H^* - q_1C^* & -\alpha_1T^* & 0 & -q_1T^* \\ -\alpha_2I_H^* & \beta I_R^* - \alpha_2T^* - d & \beta I_H^* & 0 \\ 0 & -\beta I_R^* & r_2 - 2r_2p_2I_R^* - \beta I_H^* + q_2C^* & q_2I_R^* \\ 0 & 0 & 0 & -\gamma \end{pmatrix}. \tag{13}$$

The eigenvalues of matrix $J(E_5)$ are obtained by solving $|J(E_5) - \lambda I| = 0$,. Therefore, $\lambda_1 = -\gamma$ and $\lambda_{2,3,4}$ are determined by solving submatrices $J(E_5)$

$$\begin{vmatrix} r_1 - 2r_1p_1T^* - \alpha_1I_H^* - q_1C^* & -\alpha_1T^* & 0 \\ -\alpha_2I_H^* & \beta I_R^* - \alpha_2T^* - d & \beta I_H^* \\ 0 & -\beta I_R^* & r_2 - 2r_2p_2I_R^* - \beta I_H^* + q_2C^* \end{vmatrix} = 0. \tag{14}$$

Next, the eigenvalues of the submatrix are determined by using cofactor expansion so that it can be obtained

$$\begin{aligned} &(-\gamma - \lambda)[(r_1 - 2r_1p_1T^* - \alpha_1I_H^* - q_1C^* - \lambda)\begin{vmatrix} \beta I_R^* - \alpha_2T^* - d - \lambda & \beta I_H^* \\ -\beta I_R^* & r_2 - 2r_2p_2I_R^* - \beta I_H^* + q_2C^* - \lambda \end{vmatrix}] \\ &+ (\alpha_2I_H^*)\begin{vmatrix} -\alpha_1T^* & 0 \\ -\beta I_R^* & r_2 - 2r_2p_2I_R^* - \beta I_H^* + q_2C^* - \lambda \end{vmatrix} = 0, \end{aligned} \tag{15}$$

so that values $\lambda^3, \lambda^2, \lambda^1$ and λ^0 are obtained with coefficients

$$\begin{aligned} a =& r_1 + \beta I_R^* + r_2 + q_2C^*, \\ b =& 2r_1p_1T^* + \alpha_1I_H^* + q_1C^* + d + 2r_2p_2I_R^* + \beta I_H^* + \alpha_2T^*, \\ c =& r_1\alpha_2T^* + r_1d + 3r_2p_2I_R^* + r_1\beta I_H^* + 2r_1p_1T^*\beta I_R^* + 2r_1p_1T^*I_R^* + 2r_1p_1T^*r_2 + 2r_1p_1T^*q_2C^* + \alpha_1I_H^*\beta I_R^* \\ &+ \alpha_1I_H^*r_2 + \alpha_1I_H^*q_2C^* + q_1C^*\beta I_R^* + q_1C^*r_2 + q_1{C^*}^2q_2 + 2\beta {I_R^*}^2r_2p_2 + \alpha_2T^*r^2 + \alpha_2T^*q_2C^* + dr_2 \\ &+ dq_2C^* + \alpha_2I_H^*\alpha_1T^*, \\ d_1 =& r_1\beta I_R^* + r_1r_2 + r_1q_2C^* + 2r_1p_1{T^*}^2\alpha_2 + 2r_1p_1T^*d + 4r_1p_1T^*r_2p_2I_R^* + 2r_1p_1T^*\beta I_H^* + \alpha_1I_H^*\alpha_2T^* + \alpha_1I_H^*d \\ &+ \alpha_1I_H^*2r_2p_2I_R^* + \alpha_1{I_H^*}^2\beta + q_1C^*\alpha_2T^* + q_1C^*d + q_1C^*2r_2p_2I_R^* + q_1C^*\beta I_H^* + \beta I_R^*r_2 + \beta I_R^*q_2C^* + 2\alpha_2T^*r_2p_2I_R^* \\ &+ \alpha_2T^*\beta I_H^* + 2dr_2p_2I_R^* + d\beta I_H^*, \\ e =& r_1\beta I_R^*r_2 + r_1\beta I_R^*q_2C^* + 2r_1\alpha_2T^*r_2p_2I_R^* + r_1\alpha_2T^*\beta I_H^* + r_12dr_2p_2I_R^* + r_1d\beta I_H^* + 4r_1p_1T^*\beta I_R^*r_2p_2 + 2r_1p_1{T^*}^2\alpha_2r_2 \\ &+ 2r_1p_1{T^*}^2\alpha_2q_2C^* + 2r_1p_1T^*dr_2 + 2r_1p_1T^*dq_2C^* + \alpha_1I_H^*2\beta {I_R^*}^2r_2p_2 + \alpha_1I_H^*\alpha_2T^*r_2 + \alpha_1I_H^*\alpha_2T^*q_2C^* + \alpha_1I_H^*dr_2 \\ &+ q_1{C^*}^2dq_2 + q_1C^*2\beta {I_R^*}^2r_2p_2 + q_1C^*\alpha_2T^*r_2 + q_1{C^*}^2\alpha_2T^*q_2 + q_1C^*dr_2 + q_1{C^*}^2dq_2 \end{aligned}$$

$$
\begin{aligned}
&+ \alpha_2 I_H^* \alpha_1 T^* 2 r_2 p_2 I_R^* + \alpha_2 {I_H^*}^2 \alpha_1 T^* \beta, \\
f =& r_1 \beta {I_R^*}^2 r_2 p_2 + r_1 \alpha_2 T^* r_2 + r_1 \alpha_2 T^* q_2 C^* + r_1 d r_2 + r_1 d q_2 C^* + 2 r_1 p_1 T^* \beta I_R^* r_2 + 2 r_1 p_1 T^* \beta I_R^* q_2 C^* \\
&+ 4 r_1 p_1 {T^*}^2 \alpha_2 r_2 p_2 I_R^* + 2 r_1 p_1 T^* \alpha_2 \beta I_H^* + 4 r_1 p_1 T^* d r_2 p_2 I_R^* + 2 r_1 p_1 T^* d \beta I_H^* + \alpha_1 I_H^* \beta I_R^* r_2 + \alpha_1 I_H^* \beta I_R^* q_2 C^* \\
&+ \alpha_1 I_H^* 2 \alpha_2 T^* r_2 p_2 I_R^* + \alpha_1 I_H^* \alpha_2 T^* \beta I_H^* + \alpha_1 I_H^* 2 d r_2 p_2 I_R^* + \alpha_1 {I_H^*}^2 d \beta + q_1 C^* \beta I_R^* r_2 + q_1 {C^*}^2 \beta I_R^2 q_2 + q_1 C^2 2 \alpha_2 T^* r_2 p_2 I_R^* \\
&+ q_1 C^* \alpha_2 T^* \beta I_H^* + q_1 C^* 2 d r_2 p_2 I_R^* + q_1 C^* d \beta I_H^* + \alpha_2 I_H^* \alpha_1 T^* r_2 + \alpha_2 I_H^* \alpha_1 T^* q_2 C^*.
\end{aligned}
$$

Let $a_1 = b - a$, $a_2 = d_1 - c$, $a_3 = f - e$. Hence, it can be written as

$$\lambda^3 + a_1 \lambda^2 + a_2 \lambda^1 + a_3 = 0, \tag{16}$$

with $a_i, \forall_i = 1, 2, 3$ is real number. The equilibrium point E_5 is locally asimptotically stable if it meets Routh-Hurwitz criterion where $a_3 > 0$ and $a_1 a_2 - a_3 > 0$. □

5. Numerical Simulation

The numerical analysis of tumor growth model with immunotherapy is done by using MATLAB. Here, we run numerical simulation with parameter values satisfied the tumor-free stability and the tumor condition. For the first simulation by using initial condition $(150, 50, 75, 35)$ and the parameter values $r_1 = 0.005, r_2 = 0.0055, p_1 = 0.0008, p_2 = 0.004, \alpha_1 = 0.0001, \alpha_2 = 0.0005, q_1 = 0.003, q_2 = 0.0006, \beta = 0.00005, d = 0.00065, \gamma = 0.0065, u_0 = 1$, it is obtained E_2 which exists since the condition $q_2 u_0 \beta + r_2 \beta \gamma > r_2 p_2 d \gamma$ is fulfilled. These parameters also meet the stability condition. It can be seen in Figure 1 that the solution converges to $E_2 = (0, 1950.43, 13, 153.8461)$. This indicates the simulation result supports the analysis result.

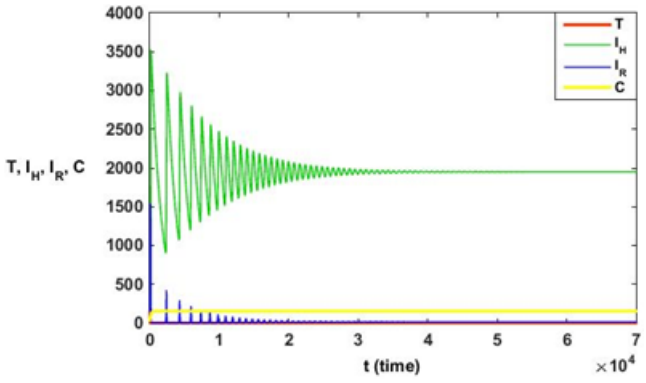

Figure 1: The graphic solution of the stability of equilibrium point E_2

The parameter values used to simulate the equilibrium point E_4 are $r_1 = 100, r_2 = 0.8, p_1 = 0.2, p_2 = 0.004, \alpha_1 = 0.1, \alpha_2 = 0.0005, q_1 = 0.003, q_2 = 0.0006, \beta = 0.00001, d = 0.002, \gamma = 0.0045, u_0 = 1$. The numerical solution is done with the initial value $(150, 50, 75, 35)$. In figure 2, it is shown that the solution converges to the equilibrium point $E_4 = (49.71, 0, 291.7, 222.2)$. This means that the numerical simulation meets the analysis result.

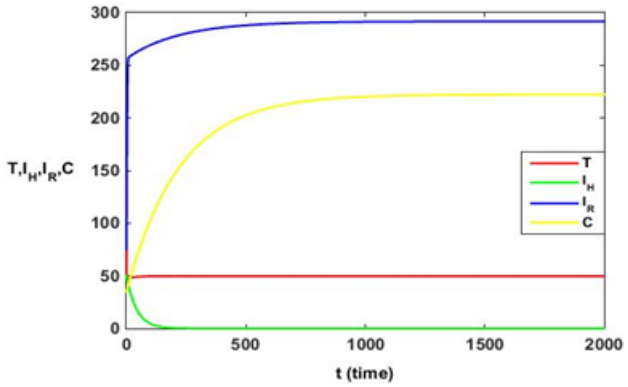

Figure 2: The graphic solution of the stability of equilibrium point E_4

By using parameter values $r_1 = 100, r_2 = 0.004, p_1 = 0.002, p_2 = 0.004, \alpha_1 = 0.001, \alpha_2 = 0.005, q_1 = 0.003, q_2 = 0.006, \beta = 0.0004, d = 0.001, \gamma = 0.0045, u_0 = 1$ and initial condition $(150, 50, 75, 35)$ the equilibrium point E_5 is obtained. The numerical simulation in Figure 3 shows that the solution converges to $E_5 = (481.153, 3102.66, 6017, 222.222)$.

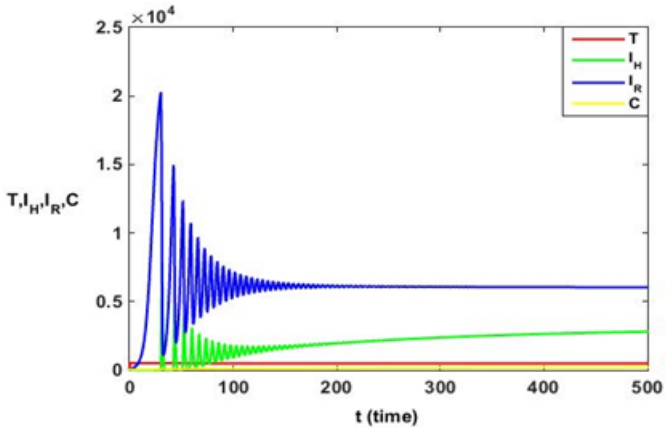

Figure 3: The graphic solution of the stability of equilibrium point E_5

6. Conclusion

In this paper, the tumor growth model is a nonlinear autonomous system consisting of four populations namely tumor cells (T), CTLs cells (I_H), T helper cells(I_R), and dendritic cells (C) with twelve parameters namely $r_1, r_2, p_1, p_2, \alpha_1, \alpha_2, q_1, q_2, \beta, d, \gamma,$ and u. The tumor growth model with immunotherapy has six equilbria consisting of three tumor-free equilibria and three tumor equilibria. The tumor-free equilibria state that the population is free of tumor cells so that the spread of the tumor does not occur. Otherwise, the tumor equilbria state that the spread of tumor occurs. The analysis result shows the tumor-free equilibria E_0 and E_1 exist unconditionally while E_2 exists with certain conditions. Next, the tumor equilibria E_3, E_4 and E_5 exist conditionally. The stability analysis of free-tumor equilbria explain that E_0 is unstable while E_1 and E_2 are conditionally stable. Meanwhile, the tumor equilibrium E_3 is unstable and E_4, E_5 are stable with certain conditions. Numerical simulations are done for E_2, E_4, E_5, where the numerical results support the analysis result.

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