InPrime: Indonesian Journal of Pure and Applied Mathematics,
Vol. 3, No. 1 (2021), pp. 20 – 28, doi: 10.15408/inprime.v3i1.19515
p-ISSN 2686-5335, e-ISSN: 2716-2478

Analytical Study of the Existence of a Hopf Bifurcation in the Tumor Cell Growth Model with Time Delay

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Abstract

In this paper we study a mathematical model of an immune response system consisting of a number of immune cells that work together to protect the human body from invading tumor cells. The delay differential equation is used to model the immune system caused by a natural delay in the activation process of immune cells. Analytical studies are focused on finding conditions in which the system undergoes changes in stability near a tumor-free steady-state solution. We found that the existence of a tumor-free steady-state solution was warranted when the number of activated effector cells was sufficiently high. By considering the lag of stimulation of helper cell production as the bifurcation parameter, a critical lag is obtained that determines the threshold of the stability change of the tumor-free steady state. It is also leading the system undergoes a Hopf bifurcation to periodic solutions at the tumor-free steady-state solution.

Keywords: tumor–immune system; delay differential equation; transcendental function; Hopf bifurcation.

Abstrak

Dalam makalah ini, dikaji model matematika dari sistem respon imun yang terdiri dari sejumlah sel imun yang bekerja sama untuk melindungi tubuh manusia dari invasi sel tumor. Persamaan diferensial tunda digunakan untuk memodelkan sistem kekebalan yang disebabkan oleh keterlambatan alami dalam proses aktivasi sel-sel imun. Studi analitik difokuskan untuk menemukan kondisi di mana sistem mengalami perubahan stabilitas di sekitar solusi kesetimbangan bebas tumor. Diperoleh bahwa solusi kesetimbangan bebas tumor dijamin ada ketika jumlah sel efektor yang diaktifkan cukup tinggi. Dengan mempertimbangkan tundaan stimulasi produksi sel helper sebagai parameter bifurkasi, didapatkan lag kritis yang menentukan ambang batas perubahan stabilitas dari solusi kesetimbangan bebas tumor. Parameter tersebut juga mengakibatkan sistem mengalami percabangan Hopf untuk solusi periodik pada solusi kesetimbangan bebas tumor.

Kata kunci: *sistem tumor–imun; persamaan differensial tundaan; fungsi transedental; bifurkasi Hopf.*

1. INTRODUCTION

Tumor or cancer is a kind of neoplasm that is formed due to an abnormal growth or excessive growth of tissue caused by the rapid division of body cells that have undergone some form of mutation [1] [2]. Tumors are divided into two major groups, namely benign and malignant or cancerous tumors [1]. Benign tumors do not invade surrounding systems and do not spread to other parts of the body but can grow locally to become large. Meanwhile, malignant or cancerous tumors damage other normal cell systems and spread to other organs through connective system, blood, nerves, and system supporting organs [1][2]. Naturally in the human body, tumor cells can be controlled by the immune system as antigens because of the expression of viral proteins that these cells have not previously

Submitted January 30th, 2021, Revised March 19th, 2021, Accepted for publication March 19th, 2021.

produced. However, a person's immune system is not always adequate to destroy tumor cells. So that the failure of the immune system to destroy these tumor cells causes the tumor to become metastatic to a wider tissue [3].

Immune system consists of a number of immune cells that work together to protect the human body. The part of the immune system that attacks antigens is effector cells which require the activation of helper T cells ($CD4^+$) [4][5]. To stimulate effector cell proliferation, helper T cells must secrete cytokines (signaling molecules) to activate proliferation. On the other hand, activation of helper T cells requires stimulation via antigen presentation by macrophages or dendritic cells. Both activation processes arise delays in the immune system. It plays important roles in the adaptive immune responses against tumors since the time delay describes the time lag needed in the tumor stimulated proliferation of effector cells or time lag for the antigen to stimulate helper T cell production [6]. The time delay in mathematical modeling represents the delay in the growth of the logistic equation so that it does not grow monotone (up or down). It is important to incorporate the delays in the mathematical model since it can exhibit much richer dynamics where the delay can cause the loss the steady-state stability or the opposite effect. Several previous studies have discussed the dynamics between the immune system and tumor diseases [7][8][9][10][11]. For instance, a study on the growth dynamics of effector cells and tumor cells to predict the optimal combination of approaches leads to tumor clearance [12]. Other study carried out the development of [12] which discussed the delay differential model to describe the interaction between effector cells and tumor cells [11]. The model [11] also predicted dormancy as a period of temporary growth that will result in tumor elimination or tumor shedding. The other researcher developed a mathematical model of the dynamic behavior of tumor-immune system interactions with two separate delays, namely delayed immune activation for effector cells (ECs) and delayed activation for helper T cells (HTCs) [13]. The obtained results suggested that the immune activation delay for HTCs can induce heteroclinic cycles to connect the tumor-free equilibrium and immune-control equilibrium. In this paper, we also study a mathematical model of tumor-immune system interaction by developing the mathematical model of [13]. To further study the dynamics of tumor immune system interaction, several new assumptions were applied to the model. Our new model assumes that there is maximum stimulation of effector cell production due to tumor cell invasion. This is based on the fact that in the activated phase, the effector cells have relatively short-lived [14]. We also assume that the number of effector cells decreases caused by its interaction with the tumor cells whose have the capability to evolve in different mechanisms [3] [15][16]. We believe that the development of the model closer to the real mechanism will present different theoretical results especially for the stability conditions of the system.

2. MATHEMATICAL MODEL OF TUMOR CELL GROWTH

The model is formulated following the main assumptions of [13]. We consider three compartments i.e. T represents the number of tumor cells in the body, E represents the number of effector cells in the immune system, and H represents the number of T helper cells (see Figure 1). Due to the long process for tumor cells to induce the recruitment of immune cells, two time-lags are considered in this model. The first delay affects the interaction of tumor cells and effector cells and the other delay affects the interaction of helper cell and tumor cells which influence the dynamic of the both immune cells system.

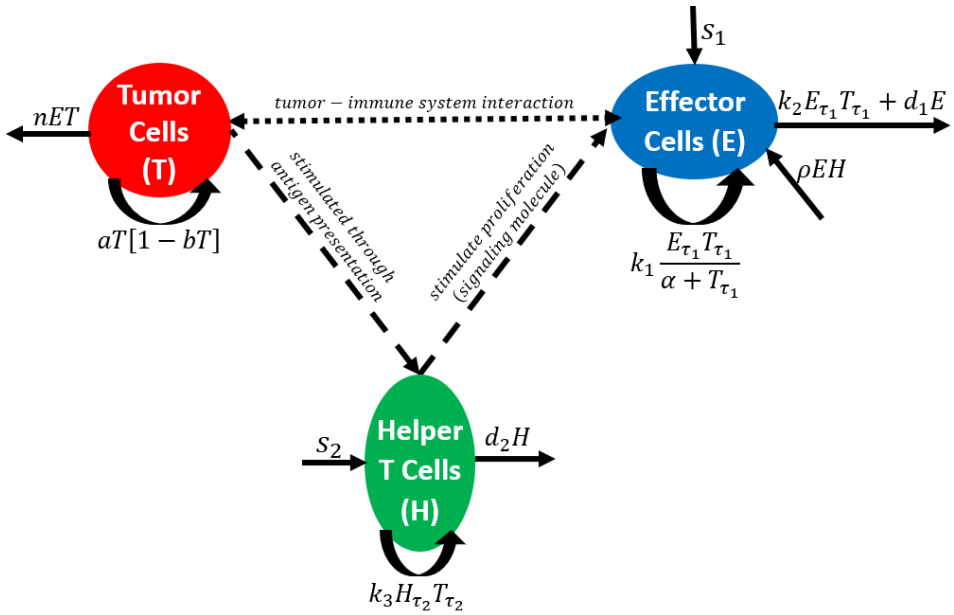

Figure 1. Schematic representation of tumor-immune system interaction model.

The dynamic of the interaction of tumor-immune system in each compartment is given as delay differential equation as follows:

$$\frac{dT(t)}{dt} = aT(t)[1 - bT(t)] - nE(t)T(t), \tag{1}$$

$$\frac{dE(t)}{dt} = s_1 + k_1\frac{E(t-\tau_1)T(t-\tau_1)}{\alpha+T(t-\tau_1)} - k_2E(t-\tau_1)T(t-\tau_1) - d_1E(t) + \rho E(t)H(t), \tag{2}$$

$$\frac{dH(t)}{dt} = s_2 + k_3H(t-\tau_2)T(t-\tau_2) - d_2H(t). \tag{3}$$

Equation (1) shows the dynamic of the tumor cells which is influenced by its logistic growth with natural growth rate a per day and carrying capacity b^{-1} cells. Reduction of the number of tumor cells is affected by the activated immune system where the effector cells travel via the blood vessels to reach the tumor, infiltrate it, recognize the tumor cells and kill them.

Equation (2) presents the dynamic of effector cells which increase due to the response immune activation by the helper cells. The helper cells trigger the body's response to infection such that the effector cells are activated with activation rate ρ per cells per day. As we have mentioned before that the effector cells are relatively short-lived activated cells with natural lifespan of an average $1/d_1$ days. The stimulation of the production of effector cells due to the invasion of tumor cells is modeled as a nonlinear function $k_1\frac{E(t-\tau_1)T(t-\tau_1)}{\alpha+T(t-\tau_1)}$ with the maximum rate k_1. Here, there exists a time delay τ_1 which influences the dynamic of effector cells due to the lag in the tumor stimulated proliferation of the effector cells. So, does for the decreasing rate of the effector cells due to its interaction with the tumor cells which also experiences a delay. We assume that there is a treatment such as gene therapy where activated effector cells are injected into the body with injection rate s_1 cells per day. Such gene therapy includes transferring genetic material into a host cell (the region of tumor localization) to increase tumor antigenicity for better recognition by the host immune system [17].

In the helper cells compartment, the dynamic is influenced by the constant production of helper cells in the bone marrow with rate production s_2 cells per day. Hence, the helper T cells also play a role in helping the formation of effector cells to fight the tumor cells. However, the helper T cells need a certain time to mature in order to function more effectively against tumor cells. Therefore, there exists the second time lag τ_2 which represents the lag time for helper T cells to be mature. The helper T cells also have an average natural lifespan $1/d_1$ days. Table 1 summarizes the definition of the parameters of model (1)-(3). The initial conditions applied to models (1) - (3) are $T(0) = T_0 > 0$, $E(0) = E_0 > 0$, $H(0) = H_0 > 0$. In the next section, variables $E(t-\tau_1)$, $T(t-\tau_1)$, $T(t-\tau_2)$, $H(t-\tau_2)$ will be written as $E_{\tau_1}, T_{\tau_1}, T_{\tau_2}$and H_{τ_2}, respectively.

Table 1. Definition of the parameters.

Par.	Definition	Unit	Par.	Definition	Unit
a	Natural growth rate of tumor cells	day^{-1}	k_1	The activation rate of effector cell by tumor cells	day^{-1}
b^{-1}	Carrying capacity of the biological environment for tumor cells	cell	k_2	Effector cell extinction rate due to interaction with tumor cells	day^{-1} cell^{-1}
α	The half of maximum immune reaction against tumor cells	cell	k_3	The helper cells stimulation rate	day^{-1} cell^{-1}
ρ	Activation rate of effector cells by helper cells	day^{-1} cell^{-1}	$1/d_1$	The natural lifespan of ECs	day
n	The loss rate of tumor cell by effector cells interaction	day^{-1} cell^{-1}	$1/d_2$	The natural lifespan of HTCs	day
s_1	Injection rate of the effector cells into the region of tumor localization	cell /day	τ_1	The time lags between helper T cells injection and the maturation of effector cells.	(1.5) days
s_2	The birth rate of cells produced in the bone marrow	cell /day	τ_2	The time lags of HTCs.	(4) days

3. ANALYTICAL RESULTS

In this section we present analytical results of the model (1)-(3) including the study of the stability and the appearance of bifurcation phenomena for the model. First of all, we determine the steady state solutions of the model. Note that the appearance of delays in the system does not affect the steady-state solution since it is unchanging in time. By taking the equations (1)-(3) equal to zero we obtain the steady-state solutions $N_0 = (T_0, E_0, H_0) = \left(0, \frac{s_1 d_2}{d_1 d_2 - \rho s_2}, \frac{s_2}{d_2}\right)$ and $N_1 = (T_1, E_1, H_1)$, where $T_1 = \frac{a - nE_1}{ab}$, $H_1 = \frac{abs_2}{d_2 - k_3(a - nE_1)}$, and E_1 is the positive roots of a fourth order polynomial equation. The first solution refers to the tumor-free solution, while the second one shows the appearance of tumor cells in the future called immune-control solution. The tumor-free solution is positive if it fulfils the condition,

$$\textbf{C1:}\quad s_2 < \frac{d_1 d_2}{\rho},$$

which indicates that tumor-free solution can be achieved when the number of activated effector cells is high enough. In order to investigate the local stability of the system, we then linearize (1)-(3) around a steady-state solution, says $N = (T, E, H)$, and we get the linearized system,

$$\dot{\boldsymbol{x}} = J_0\boldsymbol{x} + J_1\boldsymbol{x}_{\tau 1} + J_2\boldsymbol{x}_{\tau 2}, \tag{4}$$

with Jacobian matrices

$$J_0 = \begin{bmatrix} a(1-bT) - nE & -nT & 0 \\ 0 & \rho H - d_1 & \rho E \\ 0 & 0 & -d_2 \end{bmatrix}, J_1 = \begin{bmatrix} 0 & 0 & 0 \\ (k_1 - k_2)E & (k_1 - k_2)T & 0 \\ 0 & 0 & 0 \end{bmatrix},$$

$$J_2 = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ k_3 H & 0 & k_3 T \end{bmatrix}, \text{ and } \dot{\boldsymbol{x}} = \begin{bmatrix} \dot{T} \\ \dot{E} \\ \dot{H} \end{bmatrix}; \boldsymbol{x} = \begin{bmatrix} T \\ E \\ H \end{bmatrix}; \boldsymbol{x}_{\tau 1} = \begin{bmatrix} T_{\tau 1} \\ E_{\tau 1} \\ H_{\tau 1} \end{bmatrix}; \boldsymbol{x}_{\tau 2} = \begin{bmatrix} T_{\tau 2} \\ E_{\tau 2} \\ H_{\tau 2} \end{bmatrix}.$$

The characteristic equation of (4) is

$$det\left(J_0 + J_1 e^{-\lambda\tau_1} + J_2 e^{-\lambda\tau_2} - \lambda I\right) = 0,$$

or

$$det\begin{bmatrix} a(1-bT) - nE - \lambda & -nT & 0 \\ (k_1 - k_2)Ee^{-\lambda\tau_1} & \rho H - d_1 + (k_1 - k_2)Te^{-\lambda\tau_1} - \lambda & \rho E \\ k_3 H e^{-\lambda\tau_2} & 0 & k_3 T e^{-\lambda\tau_2} - d_2 - \lambda \end{bmatrix} = 0.$$

Solving the determinant, it gives a cubic polynomial,

$$\begin{aligned} f(\lambda) = \lambda^3 + \Delta_1\lambda^2 + \Delta_2\lambda + (\Delta_4\lambda + \Delta_5)e^{-\lambda(\tau_1+\tau_2)} + (\Delta_3\lambda^2 - \Delta_6\lambda + \Delta_7)e^{-\lambda\tau_2} \\ +(\Delta_8\lambda^2 + \Delta_9\lambda - \Delta_{10})e^{-\lambda\tau_1} + \Delta_{11} = 0, \end{aligned} \tag{5}$$

with

$$\Delta_1 = u + v + d_2, \Delta_2 = (u+v)d_2 - uv, \Delta_3 = k_3 T, \Delta_4 = -n\Delta_3, \Delta_5 = n\Delta_3(u + mT),$$

$$\Delta_6 = (u+v)\Delta_3, \Delta_7 = uv - n\rho EH\Delta_3, \Delta_8 = (k_1 - k_2)T, \Delta_9 = \Delta_8(d_2 - u) - nmT,$$

$$\Delta_{10} = (u + mT)\Delta_8 d_2, \Delta_{11} = -uvd_2, u = a(1-bT) - nE, v = \rho H - d_1, m = (k_1 - k_2)E\,,$$

For $N = N_0$, we have $T = 0$ such that $\Delta_i = 0,\ i = 3, \ldots 6, 8, \ldots 10$. So, equation (5) becomes

$$f(\lambda) = \lambda^3 + \Delta_1\lambda^2 + \Delta_2\lambda + \Delta_{11} + \Delta_7 e^{-\lambda\tau_2} = 0. \tag{6}$$

We can observe that the stability of N_0 is influenced by τ_2 only. It is not influenced by τ_1. If $\tau_2 = 0$, the stability of N_0 is determined by the roots of the third polynomial degree,

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0. \tag{7}$$

where $a_1 = \Delta_1, a_2 = \Delta_2, a_3 = \Delta_7 + \Delta_{11}$. Following the Routh-Hurtwitz criteria, polynomial (7) has the roots with negative real parts if it fulfills the conditions:

$$\textbf{C2:}\quad H_1 = a_1 > 0, H_2 = a_1a_2 - a_3 > 0, H_3 = a_1a_2a_3 - (a_3)^2 > 0.$$

Therefore, the steady-state N_0 is locally asymptotically stable if it fulfils the conditions C1 and C2 when $\tau_1 > 0$ and $\tau_2 = 0$.

For $N = N_1, T \neq 0$ such that there is no change in equation (5). The stability of N_1 is determined by the both time delays, τ_1 and τ_2. However, we expect the stability of N_0 rather than N_1 since we expect the extinction of the tumor cells in the future. From the practical point of view, it is interesting to know the conditions that guarantee the stability of N_0 such that we can control the system to achieve a tumor-free condition. Therefore, in the next analysis, we will investigate the stability of N_0 whether it changes as τ_2 increases from the zero. We also interested to study the possibility of the appearance a Hopf bifurcation by considering τ_2 as the bifurcation parameter.

Now consider equation (6). When the roots of (6) cross the imaginary axis to the right as τ_2 increases then τ_2 is able to destabilize N_0 and produces oscillations. To answer this hypothesis, let $\omega > 0$ and $\lambda = i\omega$ is a pure imaginary root of (6). By substituting λ into (6), we get

$$(i\omega)^3 + \Delta_1(i\omega)^2 + \Delta_2(i\omega) + \Delta_{11} + \Delta_7 e^{-i\omega\tau_2} = 0, \tag{8}$$

with $e^{-i\omega\tau_2} = cos(\omega\tau_2) - i\, sin(\omega\tau_2)$. By separating the real and imaginary part of (8), we have

$$\Delta_7 sin(\omega\tau_2) = -\omega^3 + \Delta_2\omega \quad \text{and} \quad \Delta_7\, cos(\omega\tau_2) = \Delta_1\omega^2 - \Delta_{11}. \tag{9}$$

By squaring and adding the both equations, we get the following equation

$$\omega^6 + c_1\omega^4 + c_2\omega^2 + c_3 = 0, \tag{10}$$

with $c_1 = {\Delta_1}^2 - 2\Delta_2, c_2 = {\Delta_2}^2 - 2\Delta_1\Delta_{11},\ c_3 = {\Delta_{11}}^2 - {\Delta_7}^2$. Let $z = \omega^2$, then we have

$$G(z) = z^3 + c_1z^2 + c_2z + c_3 = 0. \tag{11}$$

Next, we need to find the conditions for which $G(z)$ has at least one positive root. We can observe that as $z \to \infty$, $G(z) \to \infty$ such that $G(z)$ has at least one positive root if $c_3 < 0$. When $c_3 \geq 0$, $G(z)$ probably has or has no positive real roots. Using Lemma 2.2 in [18], we have the conditions for which $G(z)$ has at least one positive root, i.e.

a. If $c_3 < 0$ then $G(z)$ has at least one positive root
b. If $c_3 \geq 0$ and $c_1^2 - 3c_2 \leq 0$ then $G(z)$ has no positive roots
c. If $c_3 \geq 0$ and $c_1^2 - 3c_2 > 0$ then $G(z)$ has positive roots if and only if $z_1^* = \frac{1}{3}\left(-c_1 + \sqrt{c_1^2 - 3c_2}\right) > 0$ and $G(z_1^*) \leq 0$ where z_1^* is the local minimum of $G(z)$.

Now, without loss of generality, suppose that $G(z)$ has three positive roots namely z_1, z_2, and z_3. Therefore equation (10) has three positive roots, $\omega_k = \sqrt{z_k}, k = 1,2,3$. Solving equation (9) for τ_2 yields,

$$\omega_k\tau_2 = arccos\left(\frac{\Delta_1\omega^2 - \Delta_{11}}{\Delta_7}\right) \text{ if } sin(\omega_k\tau_2) > 0, \text{ that is if } \frac{-\omega^3 + \Delta_2\omega}{\Delta_7} > 0, \text{ and}$$

$$\omega_k\tau_2 = 2\pi - arccos\left(\frac{\Delta_1\omega^2 - \Delta_{11}}{\Delta_7}\right) \text{ if } \frac{-\omega^3 + \Delta_2\omega}{\Delta_7} \leq 0,\ \ k = 1,2,3.$$

If we define

$$\tau_{2,k}^{1,j} = \frac{1}{\omega_k}\left[arccos\left(\frac{\Delta_1\omega^2 - \Delta_{11}}{\Delta_7}\right) + 2j\pi\right],$$

$$\tau_{2,k}^{2,j} = \frac{1}{\omega_k}\left[2\pi - arccos\left(\frac{\Delta_1\omega^2 - \Delta_{11}}{\Delta_7}\right) + 2j\pi\right],$$

for $k = 1,2,3, j = 0,1,2,\cdots$ then $\pm\omega_k$ is a pair of pure imaginary roots of (10) with $\tau_{2,k}^{1,j}$ and $\tau_{2,k}^{2,j}$. Let $\tau_2^* = \min_{k=1,2,3}\{\tau_{2,k}^{1,0}; \tau_{2,k}^{2,0}\}$. We then derive the transversality condition for the Hopf bifurcation at $\tau_2 = \tau_2^*$. Differentiating equation (6) with respect to τ_2, we get

$$\frac{df(\lambda)}{d\lambda}\frac{d\lambda}{d\tau_2} + \frac{df(\lambda)}{d\tau_2}\frac{d\tau_2}{d\tau_2} = \left[3\lambda^2 + 2\Delta_1\lambda + \Delta_2 - \tau_2\Delta_7 e^{-\lambda\tau_2}\right]\frac{d\lambda}{d\tau_2} - \lambda\Delta_7 e^{-\lambda\tau_2} = 0.$$

From equation (6), we have

$$\Delta_7 e^{-\lambda\tau_2} = -(\lambda^3 + \Delta_1\lambda^2 + \Delta_2\lambda + \Delta_{11}),$$

such that we have

$$\frac{d\lambda}{d\tau_2} = \frac{-\lambda(\lambda^3+\Delta_1\lambda^2+\Delta_2\lambda+\Delta_{11})}{[3\lambda^2+2\Delta_1\lambda+\Delta_2]+\tau_2[\lambda^3+\Delta_1\lambda^2+\Delta_2\lambda+\Delta_{11}]},$$

or

$$\left(\frac{d\lambda}{d\tau_2}\right)^{-1} = -\frac{[3\lambda^2+2\Delta_1\lambda+\Delta_2]}{\lambda(\lambda^3+\Delta_1\lambda^2+\Delta_2\lambda+\Delta_{11})} - \frac{\tau_2}{\lambda}. \tag{12}$$

Evaluating (12) at $\tau_2 = \tau_2^*$ (corresponding to $\lambda = i\omega^*$) and taking its real part, we get

$$Re\left[\left(\frac{d\lambda}{d\tau_2}\right)^{-1}\Big|_{\tau_2=\tau_2^*}\right] = Re\left[-\frac{[3(i\omega^*)^2+2\Delta_1(i\omega^*)+\Delta_2]}{[(i\omega^*)^4+\Delta_1(i\omega^*)^3+\Delta_2(i\omega^*)^2+\Delta_{11}(i\omega^*)]} - \frac{\tau_2}{(i\omega^*)}\right],$$

$$= Re\left[\frac{[3\omega^{*2}-\Delta_2]-i2\Delta_1\omega^*}{[\omega^{*4}-\Delta_2\omega^{*2}]+i[\Delta_{11}\omega^*-\Delta_1\omega^{*3}]} + \frac{i\omega^*\tau_2}{3\omega^{*2}}\right],$$

$$= \left[\frac{3\omega^{*4}+(2\Delta_1{}^2-4\Delta_2)\omega^{*2}+(\Delta_2{}^2-2\Delta_1\Delta_{11})}{[\omega^{*3}-\Delta_2\omega^*]^2+[\Delta_{11}-\Delta_1\omega^{*2}]^2}\right].$$

From (11) we have $G'(z) = 3z^2 + (2\Delta_1{}^2 - 4\Delta_2)\mathrm{z} + (\Delta_2{}^2 - 2\Delta_1\Delta_{11})$. Thus

$$Re\left[\left(\frac{d\lambda}{d\tau_2}\right)^{-1}\Big|_{\tau_2=\tau_2^*}\right] = \left[\frac{G'(\omega^{*2})}{[\omega^{*3}-\Delta_2\omega^*]^2+[\Delta_{11}-\Delta_1\omega^{*2}]^2}\right].$$

Therefore, we get

$$sign\left\{\frac{dRe(\lambda)}{d\tau_2}\Big|_{\tau_2=\tau_2^*}\right\} = sign\left\{Re\left[\left(\frac{d\lambda}{d\tau_2}\right)^{-1}\Big|_{\tau_2=\tau_2^*}\right]\right\} = sign\{G'(\omega^{*2})\}.$$

It implies that the transversality condition for the Hopf bifurcation at $\tau_2 = \tau_2^*$ holds if $G'(\omega^{*2}) \neq 0$. Summarizing our analytical results and using the Hopf bifurcation theorem in [19], we have the following theorem.

Theorem 1. For $\tau_1, \tau_2 > 0$, suppose conditions C1 and C2 are fulfilled. If either $c_3 < 0$ or $c_3 \geq 0$, $c_1^2 - 3c_2 > 0$, $z_1^* > 0$ and $G(z_1^*) \leq 0$ then the tumor-free steady state $N_0 = \left(0, \frac{s_1 d_2}{d_1 d_2 - \rho s_2}, \frac{s_2}{d_2}\right)$ is locally asymptotically stable for $0 < \tau_2 < \tau_2^*$ where $\tau_2^* = \min_{k=1,2,3}\{\tau_{2,k}^{1,0}; \tau_{2,k}^{2,0}\}$, with

$$\tau_{2,k}^{1,0} = \frac{1}{\omega_k}\left[arccos\left(\frac{\Delta_1\omega^2-\Delta_{11}}{\Delta_7}\right)\right] \text{ and } \tau_{2,k}^{2,j} = \frac{1}{\omega_k}\left[2\pi - arccos\left(\frac{\Delta_1\omega^2-\Delta_{11}}{\Delta_7}\right)\right].$$

Furthermore, if $G'(\omega^{*2}) \neq 0$ then the system (1) − (3) undergoes a Hopf bifurcation to periodic solutions at N_0 when $\tau_2 = \tau_2^*$.

4. RESULT AND CONCLUSION

In the previous section, we have analytically investigated the possibilities of the existence of Hopf bifurcation in the tumor-immune system model. We focus to study the stability of the tumor-free steady state due to its important role in the study of the extinction of tumor cells. We found that the time delays play an important role in bringing up stability changes near the tumor-free equilibrium point. Among the two-time delays, delay in the stimulation of the production of helper cell take an important part in affecting the stability of the tumor-free steady state. There exists a critical lag for stimulation of the helper cells that can destabilize the tumor-free steady state. When the stimulation delay is lower than the critical delay, the stability of the tumor-free steady state can be preserved. It means that the helper cells will activate effector cells more quickly such that the tumor cells can be destroyed faster. However, when the delay in the stimulation of the helper cells production is high enough, even higher than the critical one, then it will worsen the body condition where the number of tumor cells will growth rapidly and probably converge to the immune-control solution. Indeed, when this condition occurs, some prevention strategies should be applied to control the growth of these tumor cells. For the gene therapy effect, we can observe from the analytical results that the constant injection of the effector cells affects the increasing of activated effector cells itself. But it is not directly affecting the stability of the system as a bifurcation parameter. That is, the stability of the tumor immune system is mainly influenced by the internal system which naturally occurs. This result can be a guidance to study the system further regarding rapidly freeing the system from tumor cell invasion. Control variable can be involved in the model to find an optimal stimulation function of proliferation of immune cells.

Author Contributions: All authors conceived and designed the study. AY conducted the literature studies, derive the analytical results, and wrote the initial draft of the paper. K brought up the ideas in the modelling development, formulate the model development, correct and examine the analytical results and revised the final draft of the manuscript. ST involved in the model development and examined the main results of the model analysis.

Funding: This research received no external funding

Conflicts of Interest: The authors declare no conflict of interest.

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