ANALYSIS OF TUMOR GROWTH AND IMMUNE SYSTEM INTERACTION MODEL

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Abstract. Immune system plays a vital role in controlling the tumor growth. Therefore, this paper proposes a new mathematical model that describes tumor-immune interaction, focusing on the role of natural killer (NK) cell and $CD8^+$ T cell. The tumor population is subdivided into two different phases, namely interphase and mitosis. This model used Ordinary Differential Equations (ODEs) and the functions involved in the model represents tumor-immune growth, responses and interaction between the cells. The stability and analysis of the model are carried out. From the analysis, it shown that the stability curve limits tumor growth region. The curve from the model lie below the curve of the model with single immune response ($CD8^+$ T cell). This result concluded that the proposed model with involvement of NK cell suppression will lower the tumor growth region.

Keywords: tumor growth; natural killer (NK); $CD8^+$ T cell.
PACS: Replace this text with PACS numbers; choose from this list: http://www.aip.org/pacs/index.html

INTRODUCTION

Tumor represents a real crisis for public health system worldwide. Primary tumor growth is a complex process, involving many interaction between the tumor and surrounding tissues. Treatments traditionally used to fight against tumor are surgery, radiotherapy and chemotherapy. Unfortunately, these treatments kill normal cells as well as tumor cells. Then, immunotherapy is introduced [1-6]. It is based on the generally-accepted hypothesis that the immune system is the best tool humans have for fighting disease [3,10-13].

In recent years, there is evidence that immune system is capable of recognizing and eliminating tumor cells. Therefore, some researchers intensively continue to develop and investigate the interaction between growing tumor and immune system [1-13]. Majority of the research on immune cells focused on NK cell, T cell and macrophages [3,5-7,10]. The experimental result have shown that these immune cells are associated with good tumor prognosis and also being involved in the lysis of tumor cells [10]. Each of them uses a different mechanism and plays a different role in cell lysis. NK cells are lymphocytes in innate immunity that have ability to kill tumor cells directly without activation [14-16]. It also play key role by destroying abnormal cells before they replicate and grow [10]. By contrast, T cells are part of the adoptive immune system and also have capability to fight the tumor cells. Both innate and adoptive immune cells actively prevent neoplastic development in a process called 'cancer immunesurveillance'. So, the effectors of the adaptive and innate immunity need to actively cooperate in order to reject tumor cells [7].

Early 1990s, Kuznetsor [17] proposed a mathematical model of the cytotoxic T lymphocyte response to the tumor growth. The model described the kinetic growth and regression of lymphoma. They found that the cytotoxic effector cells are responsible for the lysis of tumor cells. In 1998, Kirschner and Panetta define an ODE model for three main population: effector cell, tumor cell and concentration IL-2. Effector cell or also called as immune-system cell are stimulated to grow based on two terms: recruitment term and proliferation term. Logistic growth function is used as the growth term in this model. de Pillis [10] found that the combination effect of the NK cells and T cells can eliminate larger tumors compared to individual effect of immune cell (the depletion of NK cells have different impact to depletion of T cell). Most of the tumor-immune models are using logistic function, gompertz and exponential function as the growth term [10,17-18]. Gompertz have a serious limitation which is not appropriate in describing the dynamics of very small tumors [19-20] while exponential function only fixed for small population of tumor cells [17].

Then, Villasana [11] come out with the mitosis as the growth term in tumor population. She introduced tumor-immune system model which involved cell-cycle. The population of tumor take placed during interphase and mitosis (M phase). However, Villasana only consider T cell as the immune cell that can fight tumor cells. The system is simple and does not contain many importance interactions. A followed up study of Villasana's model was recently conducted by Liu [12].

[1] Sila gariskan nama pembentang.

The author modified the model by adding quiescent phase into the model. The result showed the resting phase (quiescent phase) is the most importance compartment for tumor treatment.

Our concern is to use Villasana's model by adding another immune response (NK cell) since the combination of T cell and NK cell will give a great impact to tumor growth. However, this work will only discuss on Ordinary Differential Equations (ODE). The model involves cell-cycle which population of tumor will based on interphase and mitosis without considering quiescent phase.

MODEL

Cell cycle is the alternating growth and division activities of the cell. Cell must accomplish two basic things during the cell-cycle which are copying cellular components and dividing the cell so that components are distributed evenly to the daughter cells.

The cycle can be divided into two phases: Interphase and M phase (Mitosis phase). The division activity corresponds to M phase while growth activity corresponds to interphase. The interphase is divided into three further phases: G1 phase (Gap 1 phase) is a resting phase called pre-synthetic phase. G1 corresponds to the interval between mitosis and initiation of DNA replication. This phase may last up to 48 hours and it is the longest phase of the cycle. The next phase is the S phase or synthesis period. This is the phase when DNA replication occurs. S phase could last between 8 and 20 hours. The cell will enter another gap period G2 called as post-synthetic phase after completing the DNA replication. G2 and late S are preparing phase for mitosis. M phase (Mitosis phase) is the last phase where the actual division of the cell occur. This is the shortest phase of the cycle, lasting up to one hour. It is significant to note that in the 24 hours average duration of cell cycle of the human cell, cell division proper lasts for only one hour. The interphase lasts more than 95% of the duration of the cell cycle.

The division to proceed from one part of the cell cycle to another depends on the variety of factors. There are growth, DNA replication, DNA integrity and cellular integrity. If the cell cycle detect the abnormality activities, then it will prevent the cell from completing the cycle. This situation is called cell cycle checkpoints. When checkpoints are activated, signals are relayed to the cell-cycle progression machinery. These signals cause a delay in cycle progression until the danger of mutation has been averted.

Currently, there are three known checkpoints: G1 checkpoint, also known as the restriction or start checkpoint. At this point, the cells have options either to divide, delay division or exist the cell cycle. Then followed by G2 checkpoint (end of G2) and metaphase checkpoint. The cell will not proceed with mitosis if DNA replication is not complete at the G2 end point. The inability of the cell to complete the cycle can cause cancer. Cancer is a disease where regulation of the cell cycle goes wrong and normal cell growth is lost.

In this section, a new mathematical model is proposed based on Villasana [11] and de Pillis's [10] model to provide a description of the interaction between growing tumor and immune system. The model will focused on tumor growth at different stages of cell cycle which is interphase and mitosis phases. NK cells and $CD8^+$ T cells are included in the mathematical model because both of these cell can lyse tumor cells. To describe this interaction, the model is comprised by four ordinary differential equations of tumor population during interphase and mitosis and NK and $CD8^+$ T cell populations, where

- $T_I(t)$, population of tumor cells during interphase (G1+S+G2)
- $T_I(t)$, tumor population during mitosis
- $I_{NK}(t)$, population of NK cells
- $I_{TC}(t)$, population of $CD8^+$ T cells.

To construct the initial mathematical, the assumptions based on knowledge of the immune system and some assumptions state in [10-12]. These assumptions are listed as follows.

1. Both NK cell and $CD8^+$ T Cell can kill the tumor
2. NK cell- Innate immunity, NK cells are always present and active in the system, even in the absence of tumor cells
3. Each NK cell and $CD8^+$ T cell will eventually become inactivated after some number of encounters with tumor cell
4. As part of specific immunity, tumor-specific $CD8^+$ T cell are recruited once tumor cells are present

Using these assumptions, the model takes the form

$$T_I^{'}(t) = \underbrace{2a_4T_M}_{\text{from mitosis}} - \underbrace{c_1T_I I_{TC}}_{\text{destroyed by T cell}} - \underbrace{d_2T_I}_{\text{natural death}} - \underbrace{a_1T_I}_{\text{releasing to mitosis}} - \underbrace{c_7T_I I_{NK}}_{\text{destroyed by NK cell}}$$

$$T_M^{'}(t) = \underbrace{a_1T_I}_{\text{from interphase}} - \underbrace{d_3T_M}_{\text{natural death}} - \underbrace{a_4T_M}_{\text{releasing to mitosis}} - \underbrace{c_3T_M I_{TC}}_{\text{destroyed by T cell}} - \underbrace{c_8T_M I_{NK}}_{\text{destroyed by NK cell}}$$

$$I_{TC}^{'}(t) = \underbrace{k}_{\text{constant growth source}} + \underbrace{\frac{\rho I_{TC}(T_I+T_M)^n}{\alpha+(T_I+T_M)^n}}_{\text{growth due to stimulus}} - \underbrace{c_2T_I I_{TC}}_{\text{destroyed with tumor in interphase}} - \underbrace{c_4T_M I_{TC}}_{\text{destroyed with tumor in mitosis}} - \underbrace{d_1I_{TC}}_{\text{natural death}} + \underbrace{rI_{NK}(T_I+T_M)}_{\text{NK simulation}}$$

$$I_{NK}^{'}(t) = \underbrace{s}_{\text{constant growth source}} + \underbrace{\frac{\rho I_{NK}(T_I+T_M)^n}{\alpha+(T_I+T_M)^n}}_{\text{growth due to stimulus}} - \underbrace{c_5T_I I_{NK}}_{\text{destroyed with tumor in interphase}} - \underbrace{c_6T_M I_{NK}}_{\text{destroyed with tumor in mitosis}} - \underbrace{d_4I_{NK}}_{\text{natural death}}$$

Terms a_1 and a_4 represent the different rates at which cells cycle or reproduce and the c_i terms represent losses from encounters of tumor cells within cells. The terms d_2T_I, d_3T_M, d_1T_{TC} and d_4T_{NK} in the model represent proportions of natural cells death and the terms $\frac{\rho I_{TC}(T_I+T_M)^n}{\alpha+(T_I+T_M)^n}$ and $\frac{\rho I_{NK}(T_I+T_M)^n}{\alpha+(T_I+T_M)^n}$ represent the nonlinear growth of the immune population due to stimulus by the tumor cells. Michaelis-Menten form have been chosen for this term following other in literature. This form is reasonable, because proliferation of cancer-specific effector cells is stimulated by the presence of cancer cells but reaches a saturation level at cancer population. The saturation level depends on the health of the immune system, specifically on its ability to produce certain cytokines. In the absence of cancer cells $(T_1 = T_M = 0)$, the immune cells grow at constant sources rate k and s. Hence, the recruitment function should be zero when there is no tumor cells, and should increase monotonically towards a horizontal asymptote. In the case of the $CD8^+$ T cells, in addition to being recruited by interactions with T cell processed tumor cells through a Michaelis-Menten dynamics, additional $CD8^+$ T cells are stimulated by the interaction of NK cells with tumor cells. This NK simulation is represented by the term $rI_{NK}(T_I+T_M)$. This term represents interaction of NK cells with tumor cells.

The parameters α, ρ and n depend on the type of tumor and the health of the patient's immune system; more specifically their ability to produce certain kind of cytokines. The term ρ represents the increase of immune cells due to a stimulus and parameter α represents the half value for the immune response. When the tumor level is equal to α the immune response is half way to its maximum value ρ. Larger values of n mean that it takes the immune system a longer time to recognize the tumor. The growth of tumor cell population is obtained through mitosis and is given by the constants a_1 and a_4. The term $T_I I_{TC}$, $T_I I_{NK}$, $T_M I_{TC}$ and $T_M I_{NK}$ are standard competition that in our model will represent losses due to encounters among the different cell types.

In reality, all parameters depend on the tumor type and the health of the person. Table (1) summarizes parameter values by Villasana [11] and Table (2) summarized estimated parameters by de Pillis [10].

TABLE (1). Estimated parameters

Parameter	Estimated value
a_1	0.8470 day^{-1}
a_4	0.9159 day^{-1}
d_2	0.1145 day^{-1}
d_3	0.6641 day^{-1}
d_1	0.04 day^{-1}
$c_1 = c_3$	2.16 x 10^{-7} cell^{-1} day^{-1}
$c_2 = c_4$	3.422 x 10^{-10} cell^{-1} day^{-1}
k	1.3 x 10^4 cell day^{-1}
n	3
ρ	0.2 day-1
α	(0.3 x 10^6 cell)^3

TABLE (2). Estimated parameter

Parameter	Estimated value
d_4	0.0412 day^{-1}
$c_5 = c_6$	1.0 x 10^{-7} cell^{-1} day^{-1}
$c_7 = c_8$	3.23 x 10^{-7} cell^{-1} day^{-1}
s	1.3 x 10^4 cell day^{-1}
r	1.1 x 10^{-7} cell^{-1} day^{-1}

STABILITY ANALYSIS

We first determine the dynamics of the system in order to understand the behavior of the model. We begin by analyzing the tumor model without immune responses.

Tumor-Model in the Absence of Immune Response

In this subsection, we shall study the tumor model case without immune response. Necessary and sufficient conditions that guarantee the stability of the cancer-free equilibrium are obtained. In this case the equations are a simple set of ordinary differential equations:

$$\begin{aligned} T_I^{'} &= 2a_4 T_M - d_2 T_I - a_1 T_I \\ T_M^{'} &= a_1 T_I - d_3 T_M - a_4 T_M \end{aligned} \tag{1}$$

with initial values

$$\begin{aligned} T_1 &= 0 \\ T_M &= 0. \end{aligned}$$

The only fixed point for this linear system (1) is $E_0(T_I, T_M) = (0,0)$. The Jacobian matrix of the system is

$$J(T_I, T_M) = \begin{bmatrix} -(d_2 + a_1) & 2a_4 \\ a_1 & -(d_3 + a_4) \end{bmatrix}$$

and the characteristic equation is

$$\lambda^2 - (-d_2 + a_1 + d_3 + a_4)\lambda + (d_3 + a_4)(d_2 + a_1) - 2a_1a_4 = 0 .$$

The eigenvalues associated with the matrix are given by

$$\lambda\pm = \frac{tr + \sqrt{tr^2 - 4\Delta}}{2} .$$

The trace of the corresponding matrix representation of the system is $tr = -(d_2 + a_1 + d_3 + a_4)$ and the determinant Δ, is given by $\Delta = (d_3 + a_4)(d_2 + a_1) - 2a_1a_4$. Clearly, the trace, tr will always negative values, $tr = -(d_2 + a_1 + d_3 + a_4) < 0$. If $\Delta < 0$, then $tr^2 - 4\Delta > 0$ and the fixed point result in a saddle which will result in unstable fixed point. If $\Delta > 0$, then we are in the present of a stable fixed point. We will have a stable spiral $(tr^2 - 4\Delta < 0)$ and a stable node $(tr^2 - 4\Delta > 0)$.

Then, the necessary condition for tumor to grow is $\Delta < 0$, such that

$$(d_3 + a_4)(d_2 + a_1) < 2a_1a_4$$

which means that the growth rate dominate the death rate. Otherwise, the tumor will not grow.

As the result, we have the following proposition.

PROPOSITION 1.1 *The tumor-free equilibrium* E_0 *of the system (1) is locally asymptotically stable if and only if* $\Delta > 0$.

Biomedical Interpretation

Note that M phase acts as a control center to determine the rate of proliferation. a_4 represents the rate of cell reproduce from the mitosis into the interphase and a_1 represents the rate of cell release from interphase enter into mitosis (M phase). The natural cell death for each phases (interphase and M phase) represent by d_2 and d_3.

Assume $\Delta < 0$ such that a tumor is growing. We consider the parameters are beneficial for tumor elimination. In Proposition 2.1, the only condition for cancer decay is $\Delta > 0$. Hence for tumor to grow, the necessary condition is $(d_3 + a_4)(d_2 + a_1) < 2a_1a_4$, which means that the rate of cell growth is dominate the rate of natural cell death. If $(d_3 + a_4)(d_2 + a_1) > 2a_1a_4$, the tumor will not grow.

Tumor-Model in the Present of Immune Response

Now we will add the effect of immune suppression to study how $CD8^+$ T cell and NK cell will change the dynamical behavior of tumor cells. New conditions for tumor growth or extinction that involve the immune suppression parameter terms will be obtained.

Tumor-model in the present of single immune response

Firstly, we study the interaction between tumor growths with a single immune response, which is $CD8^+$ T cell. So, the system will be

$$\begin{aligned} T_I^{'}(t) &= 2a_4T_M - c_1T_II_{TC} - d_2T_I - a_1T_I \\ T_M^{'}(t) &= a_1T_I - d_3T_M - a_4T_M - c_3T_MI_{TC} \\ I_{TC}^{'}(t) &= k + \frac{\rho I_{TC}\left(T_I+T_M\right)^n}{\alpha+\left(T_I+T_M\right)^n} - c_2T_II_{TC} - c_4T_MI_{TC} - d_1I_{TC} \end{aligned} \tag{2}$$

$E_1\left(T_I,T_M,I_{TC}\right) = E_1\left(0,0,\frac{k}{d_1}\right)$ is the fixed point of the system which represent a tumor-free state with positive immune level. The Jacobian matrix about the system is

$$J\left(T_I,T_M,I_{TC}\right) = \begin{bmatrix} -d_2 - a_1 - c_1\frac{k}{d_1} & 2a_4 & 0 \\ a_1 & -d_3 - a_4 - c_3\frac{k}{d_1} & 0 \\ -c_2\frac{k}{d_1} & -c_4\frac{k}{d_1} & -d_1 \end{bmatrix}$$

Clearly, we have $\lambda = -d_1$ is an eigenvalue and the remaining eigenvalues are given by the solution to the characteristic equation

$$\left(\lambda + d_2 + a_1 + c_1\frac{k}{d_1}\right)\left(\lambda + d_3 + a_4 - c_3\frac{k}{d_1}\right) - 2a_1a_4 = 0\,.$$

Solve the equation. Then, we will have

$$\lambda^2 + \alpha_1\lambda + \alpha_0 = 0$$

where

$$\begin{aligned} \alpha_1 &= d_2 + a_1 + \left(c_1 + c_3\right)\frac{k}{d_1} + d_3 + a_4 \\ \alpha_0 &= \left(d_2 + a_1 + c_1\frac{k}{d_1}\right)\left(d_3 + a_4 + c_3\frac{k}{d_1}\right) - 2a_1a_4. \end{aligned}$$

α_1 is always positive. By Routh-Hurwitz criteria, sufficient and necessary conditions for λ to become negative real part is $\alpha_0 > 0$ such that

$$\left(d_2 + a_1 + c_1\frac{k}{d_1}\right)\left(d_3 + a_4 + c_3\frac{k}{d_1}\right) > 2a_1a_4.$$

As the result, we have the following.

PROPOSITION 1.2 *For system (2), the equilibrium* E_1 *is locally asymptotically stable if and only if* $\alpha_0 > 0$.

Biomedical Interpretation

Note that $\alpha_0 \geq \Delta$. An immune response can control tumor growth. In this model it occurs when $\left(d_2 + a_1 + c_1\frac{k}{d_1}\right)\left(d_3 + a_4 + c_3\frac{k}{d_1}\right) > 2a_1a_4$. The parameter k represents the growth of T cell (CD8$^+$ T cell), c_1 and c_3 represent the rate at which the immune cell destroyed the tumor cell at interphase and mitosis, and d_1, d_2 and d_3 represent the natural death of T cell at every phase.

However if $\alpha_0 \leq 0$, the chance for tumor cell to grows is increased. This occurs because the reproduction of tumor cell is higher than natural death cell and immune response, $\left(d_2 + a_1 + c_1\frac{k}{d_1}\right)\left(d_3 + a_4 + c_3\frac{k}{d_1}\right) \leq 2a_1a_4$.

Tumor-model in the present of double immune response

Now, we proceed with the interaction between tumor growth with two immune response that is CD8$^+$ T cell and NK cell. The system is

$$\begin{aligned}
T_I^{'}(t) &= 2a_4T_M - c_1T_II_{TC} - d_2T_I - a_1T_I - c_7T_II_{NK}\\
T_M^{'}(t) &= a_1T_I - d_3T_M - a_4T_M - c_3T_MI_{TC} - c_8T_MI_{NK}\\
I_{TC}^{'}(t) &= k + \frac{\rho I_{TC}\left(T_I+T_M\right)^n}{\alpha+\left(T_I+T_M\right)^n} - c_2T_II_{TC} - c_4T_MI_{TC} - d_1I_{TC} + rI_{NK}\left(T_I+T_M\right)\\
I_{NK}^{'}(t) &= s + \frac{\rho I_{NK}\left(T_I+T_M\right)^n}{\alpha+\left(T_I+T_M\right)^n} - c_5T_II_{NK} - c_6T_MI_{NK} - d_4I_{NK}
\end{aligned} \tag{3}$$

Again the system is assumed in tumor-free state point with positive immune level.

$$J\left(T_I,T_M,I_{TC},I_{NK}\right) = \begin{bmatrix}
-d_2 - a_1 - c_1\frac{k}{d_1} - c_7\frac{s}{d_4} & 2a_4 & 0 & 0\\
a_1 & -d_3 - a_4 - c_3\frac{k}{d_1} - c_8\frac{s}{d_4} & 0 & 0\\
-c_2\frac{k}{d_1} & -c_4\frac{k}{d_1} & -d_1 & 0\\
-c_5\frac{s}{d_4} & -c_6\frac{s}{d_4} & 0 & -d_4
\end{bmatrix}$$

Clearly, $\lambda = -d_1$, $\lambda = -d_4$ are two eigenvalues. The remaining eigenvalues are the same as the solution to characteristic equation, that is

$$\lambda^2 + \beta_1\lambda + \beta_0 = 0$$

where

$$\beta_1 = d_2 + a_1 + (c_1 + c_3)\frac{k}{d_1} + (c_7 + c_8)\frac{s}{d_4} + d_3 + a_4$$

$$\beta_0 = \left(d_2 + a_1 + c_1\frac{k}{d_1} + c_7\frac{s}{d_4}\right)\left(d_3 + a_4 + c_3\frac{k}{d_1} + c_8\frac{s}{d_4}\right) - 2a_1a_4.$$

Obviously, β_1 will always positive. By Routh –Hurwitz criteria, the necessary and sufficient conditions for λ to become negative real part are $\beta_1 > 0$ and $\beta_0 > 0$. Then

$$\left(d_2 + a_1 + c_1\frac{k}{d_1} + c_7\frac{s}{d_4}\right)\left(d_3 + a_4 + c_3\frac{k}{d_1} + c_8\frac{s}{d_4}\right) > 2a_1a_4 .$$

As the result, we have the following.

PROPOSITION 1.3 *For system (3), the equilibrium E_2 is locally asymptotically stable if and only if $\beta_0 > 0$.*

Biomedical Interpretation

Note that $\beta_0 \geq \alpha_0 \geq \Delta$. As the result before by including immune response in the model, the survival of tumor growth is decreased, $\left(d_2 + a_1 + c_1\frac{k}{d_1} + c_7\frac{s}{d_4}\right)\left(d_3 + a_4 + c_3\frac{k}{d_1} + c_8\frac{s}{d_4}\right) > 2a_1a_4$.

Figure 1 showed the region of tumor growth with and without immune responses. From the graph, we can see that the size of tumor growth is reduced when immune response is included. The region become smaller compared to the case without immune response.

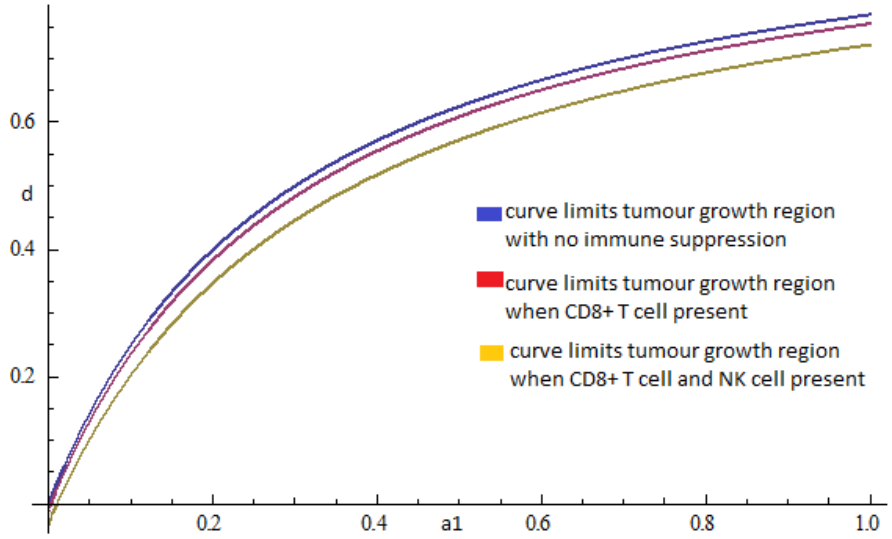

FIGURE 1. Setting our parameter to $a_4 = 0.5$, $d_2 = 0.3$, $k = 0.1$, $d_1 = 0.6$, $c_1 = c_2 = 0.05$, $s = 0.1$, $c_8 = c_9 = 0.1$ and $d_4 = 0.412$, we obtain a stability map in a_1 and d plane. The region of tumor growth with no immune suppression is limited by the upper curve. Below this curve, there is tumor growth and above this curve there is tumor decay. The corresponding curve when immune suppression is added is shown to lie consistently below the first.

CONCLUSION

The model presented represent the basic interaction between tumor cells and immune responses. The model started with the tumor population without immune suppression. The tumor population is divided into two phases related to the cell cycle, interphase and mitosis (M phase). From Proposition 1.1, the tumor growth mainly depend on the natural death rate and the production rate of the cell in the cell cycle. The tumor will grow if the reproduction rate of the cell is dominate the natural death rate. In that case, the tumor will keep growing and eventually become malignant to the body.

By adding immune suppression in the model, NK cell and $CD8^{+}$T cell, it greatly helps to stabilize the system and inhibit the further growth of tumor cells (Proposition 1.2). This is reasonable because some tumor cells are destroyed by T cell and NK cells. In our body, NK cell and T cell are innate and adaptive immunity in immune system. The comparison of tumor region between immune response and without immune responses showed that the involvement of immune responses have lower the tumor growth region.

Immune system will react naturally to fight the tumor cells. So, there is important to make sure that the immune cells in our body have ability and capability to kill tumor cells. NK cell is exhibit spontaneous killing against a variety of tumor cell without the need for antigen specific activation as required by T cell ($CD8^{+}$ T cell).The contribution from both NK cell and T cell are effective defense against tumor growth. T cell are particularly efficient at killing tumor cells. However, T cell will take several days to recognize tumor cells, whereas NK cells are spontaneously active against infected cells. So, NK cell is helped T cell in minimizing the tumor growth. Therefore, the probability for tumor cells to reach maturity become lower.

This is ongoing research. There are a few significant features that have not been included in this paper. For example, the resting phase (quiescent phase) is used to be an important phase for tumor growth [12]. Tumor cells will escape the cell cycle and enter the quiescent phase if they can escaping the immune cells attacked. The surviving quiescent cells can contribute to further tumor growth. Besides, the inclusion delay term in the model will represent the real situation of tumor growth in the body. The delay term appear naturally when one consider the cell cycle. These features will be included in future research.

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