The Effects of Myeloid Cells on Tumor-Immune System Interaction in Different Time Scales

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Abstract

Despite the highly developed mechanism of the immune response, tumor cells often continue to grow uncontrollably. The recognition of tumor cells by specific immune cells is dependent on the balance between immature (ImC) and mature (MmC) myeloid cells in the body, a fact not widely used in tumor growth dynamics models. We propose a mathematical model that incorporates various stages of immune response to tumor growth. Our model includes the dynamics and interactions of tumor cells, natural killer cells, CD8+T cells, immature and mature myeloid cells. The resulting model is given by a five-dimensional non-linear system, which is reduced to a two-dimensional system using time-scale arguments and explored analytically. A discussion on the role of the ratio of immature to mature myeloid cells concludes our presentation.

1 Introduction

Cancer is a general term that encompasses a number of diseases, characterized by the uncontrollable division of cells, which is caused by accumulating mutations in the DNA. Many types of cancer are characterized by the development of a so-called solid malignant tumor - a tightly packed conglomeration of rapidly dividing cells. In this case, the tumor cells may soon invade surrounding tissues, causing the malfunction of internal organs and eventually the patient's death [1]. In the year 2000, malignant tumors were responsible for 12% of the nearly 56 million premature deaths all over the world [12].

The immune system protects the human body from tumor cells that may develop into a malignant tumor. The body's defense mechanism occurs on two levels: the innate immune response and the specific immune response [1]. Both mechanisms involve white blood cells, which, among others, consist of natural killer cells, B cells, myeloid cells, and specific cytotoxic T lymphocytes [1]. In our model, we consider three types of cells, directly involved in the destruction of the tumor cells, namely the natural killer cells, the CD8+T cells and the myeloid cells.

Natural killer (NK) cells are part of the innate immune response. They recognize the presence of a tumor cell and attempt to eliminate it. NK cells bind to the receptors on the surface of the tumor cell and release perforin, a chemical that damages its outer membrane. This creates osmotic imbalance inside the tumor cell, causing it to either shrink or swell. This also facilitates entrance of other chemicals inside the tumor cell. However, NK cells are not capable of distinguishing between specific antigens, and as a result, they neither adapt nor improve their effectiveness over time [1].

Generally, the specific immune response becomes a dominating factor in fighting the tumor some time after the organism has developed cancer, and it depends on the overall state of the patient's immune system. The CD8+T cells, which are part of the specific immune response, detect and kill specifically the tumor cells. Even if the specific immune response is able to eliminate the tumor, a certain fraction of CD8+T cells remains in the body for extended periods of time. These cells will promptly activate the immune system, should the tumor reappear [1].

The growth of CD8+T cells is stimulated by the presence of the tumor cells in the body. Every encounter with the tumor cells stimulates further production of CD8+T cells [3, 10]. They bind to the surface of tumor cells and inject chemicals, such as perforin, that destroy the tumor cell from inside [13]. Unlike NK cells, which are destroyed after each encounter with the tumor cells, each CD8+T cell is capable of killing numerous tumor cells [3, 4].

Efficiency of the specific immune response depends on the ability of CD8+T cells to recognize tumor cells. The recognition process is regulated by a class of cells, commonly referred to as mature myeloid cells (MmC). Myeloid cells are produced in the bone marrow; after a period of

maturation, which normally lasts about 5 days, they differentiate into macrophages and dendritic cells [8]. However, in the presence of the tumor cells the maturation process slows down, which results in accumulation of immature myeloid cells (ImC) at the site where tumor is present. Clinical studies have shown that inhibition of maturation of the myeloid cells is related to the production by the tumor of certain cytokines, such as vascular endothelial growth factor (VEGF) [7]. As a result, the number of antigen-presenting cells decreases, reducing the activity of the immune system and consequently allowing the tumor to grow undetected by the CD8+T cells.

Tumor cells are created in the body at all times. However, normally the immune system is capable of eliminating them before the tumor growth gets out of control. Tumor growth becomes uncontrollable in people with already weakened immune system. Understanding the mechanism of the immune response is crucial for developing an optimal treatment therapy. There are three major types of treatment therapies that strengthen the body's natural defenses: chemotherapy, immunotherapy, and vaccination [3]. Even after the tumor has been surgically removed, there are still undetectable tumor cells left in the body. In order to ensure that the tumor does not reappear, chemotherapy is administered. However, chemotherapy cannot be administered for extended periods of time as it also severely damages the healthy tissues. In order to enhance the effectiveness of chemotherapy, it is increasingly combined with other types of treatment, such as immunotherapy. One of the most promising types of immunotherapy is the adaptive cell immunotherapy (ACI). During ACI, T cells taken from the cancer patient are cultivated outside of the body and are stimulated to react to certain antigens. The cells are then infused in the patient, working to more effectively battle the tumor cells [9]. The third kind of treatment, the vaccine therapy, is still a highly experimental procedure [9]. Unlike other kinds of vaccines, cancer vaccines are injected after the disease has begun, preventing it from re-occurring [3]. They are mostly used in conjunction with other types of treatment, but early clinical trials indicate their effectiveness in strengthening the immune system response [3, 5].

In previous papers, authors have primarily looked at the interactions of the entire immune system with tumor cells, without differentiating between the two stages (innate and specific) of the immune response [13, **?**]. In cases when the distinction was taken into consideration, such as in [6, 3, 4], the authors explored the models without considering the role of myeloid cells in the dynamics of the immune response.

In this paper, we propose a mathematical model which incorporates the effect of myeloid cells on the dynamics of tumor growth. We explored the dynamics of tumor-immune system interactions at different stages of the immune response in a non-linear five-dimensional model, studied in three different time scales.

Our paper is organized as follows: the model description is given in Section 2. In Section 3, we explain the approach that we have taken in analyzing our models. In Section 4 we conduct numerical solutions and provide explanation of the results obtained. In Section 5 we summarize our results and discuss future model modifications and applications of the results.

2 Model Description

We have developed our model based on the following biological assumptions:

- In the early phase of tumor life cycle, we assume that the tumor grows exponentially in the absence of immune response.

- NK and CD8+T cells both kill tumor cells. NK cells are part of the innate immune response and have limited effectiveness. CD8+T cells are part of the adaptive immune response and are specific to tumor cells, which increases their effectiveness in battling cancer [3].

- NK cells are present in the body at all times. The growth of NK cells, however, is stimulated by the presence of tumor cells [3].

- On average it takes about 15 hours for the innate immune system to activate specific immune response [1].

- CD8+T cells are created only in the presence of tumor cells. The production of CD8+T cells is stimulated by the debris of tumor cells, previously killed both by NK cells and CD8+T cells [3].

- The effectiveness of NK cells is limited by the fact that tumor cells are not always recognized as foreign and therefore could escape destruction [13].

- NK cells die after each contact with the tumor cells, while each CD8+T cell is capable of killing numerous tumor cells [3].

- Myeloid cells are constantly being produced in the body. Their production is additionally stimulated by the presence of tumor cells [7].

- Normally, myeloid cells take about 5 days to mature and differentiate into dendritic cells and macrophages, which are antigen-presenting cells. Mature myeloid cells are crucial in helping CD8+T cells recognize tumor cells as foreign [7, 8].

- Tumor cells produce cytokines that inhibit the maturation process of the myeloid cells. Consequently, immature myeloid cells accumulate in the body in the presence of tumor and inhibit CD8+T cells responses [7].

- Both mature (MmC) and immature (ImC) myeloid cells are always present in the body. The effectiveness of interactions between tumor cells and CD8+T cells depends on the balance between ImC and MmC in the body [7].

Based on the above assumptions, we formulate the following model in terms of a system of coupled non-linear differential equations where $N(t)$: natural killer cell population, $L(t)$: CD8+T cell population, $T(t)$: tumor cell population, $M_1(t)$: immature myeloid cell population, and $M_2(t)$: mature myeloid cell population.

$$\begin{cases} \dot{N} &= \Lambda + bT - \mu_1 N - fNT, \\ \dot{L} &= -\mu_2 L + cLT(\frac{M_2}{M_1})L + b_1 \frac{NT}{h+N}, \\ \dot{T} &= aT - d\frac{NT}{h+N} - eLT\frac{M_2}{M_1}, \\ \dot{M_1} &= \Omega + rT - \mu_3 M_1 - (\theta - g\frac{T}{p+T})M_1, \\ \dot{M_2} &= (\theta - g\frac{T}{p+T})M_1 - \mu_4 M_2 \end{cases} \tag{1}$$

The rate of change of N cells depends on constant natural birth rate Λ from thymus and bone marrow, and production of N cells due to stimulation by tumor cells present in the system at the rate bT. $\mu_1 N$ is the natural death rate, and fNT describes the death of N cells after they have come in contact with tumor cells.

The change in count of L cells is by natural death rate $\mu_2 L$; the production of L cells via stimulated by the debris of tumor cells, previously killed by N cells at the rate $b_1 \frac{NT}{h+N}$, as well as by debris of tumor cells killed by L cells at the rate $cLT(\frac{M_2}{M_1})L$. Note that the last term $cLT(\frac{M_2}{M_1})L$ also shows the influence of presence of myeloid cells. As previously mentioned in the assumptions, the recognition of the tumor cells by L cells is increased by the presence of M_2 cells whereas it is decreased due to the presence of M_1 cells.

The rate of change of tumor cells depends on the natural growth rate of tumor cells at rate aT, and the killing of tumor cells by N cells and L cells at $d\frac{NT}{h+N}$ and $eLT\frac{M_2}{M_1}$, respectively. The term $\frac{M_2}{M_1}$ accounts for the balance between the mature and immature cells, which is crucial for the success rate of the interactions between tumor cells and L cells.

The count of the immature myeloid cells is changed by Ω, the constant production rate of ImC cells from thymus, $\mu_3 M_1$, their natural death rate, rT which describes the additional production rate of myeloid cells due to the release of certain cytokines by tumor cells. $g\frac{M_1 T}{p+T}$ describes the fraction of cells that cannot mature because of the presence of the tumor cells, and $(\theta - g\frac{T}{p+T})M_1$ are ImC that can mature despite the presence of tumor cells, where θ is constant.

In the $\dot{M_2}$ equation, $(\theta - g\frac{T}{p+T})M_1$ describes the ImC that have matured despite the inhibition by tumor cells, μ_4 describes the per capita natural death rate of matured cells.

If $g > \theta$, then our model is valid for $0 \leq T < \frac{\theta p}{g-\theta}$ and if $g \leq \theta$, then our model is valid for all non-negative T.

Table 1: Parameter Definitions

Parameter	Definition	Value	Units	Ref
a	Natural tumor growth rate	4.31×10^{-1}	day^{-1}	[3, 4]
f	Coefficient of successful encounter of N with T	3.42×10^{-6}	$cell^{-1}day^{-1}$	[3, 4]
d	Coefficient of successful encounter of T with N	1.245×10^{-1}	day^{-1}	[3]
e	Coefficient of successful encounter of T with L	2.02×10^{-8}	$cell^{-1}day^{-1}$	[3]
r	Production rate of ImC due to T presence	3.9×10^{-7}	day^{-1}	[4]
c	Production rate of L due to debris of T, killed by other L	2.49×10^{-2}	$(cells^2 * day)^{-1}$	[3]
b	Production rate of N due to T presence	3.9×10^{-7}	day^{-1}	[4]
b_1	Production rate of L due to debris of T, killed by N	1.245×10^{-1}	day^{-1}	[3]
h	Saturation coefficient of N	2.02×10^{7}	$cells$	[3, 7]
p	Saturation coefficient of ImC	2.02×10^{7}	$cells$	[3, 7]
g	Maturation rate of ImC with respect to T	1.25×10^{-2}	day^{-1}	[7]
θ	Maturation rate of ImC regardless of T	0.2	day^{-1}	[5]
Λ	Natural birth rate of N	1.3×10^{4}	$cell^{-1}day^{-1}$	[4]
Ω	Natural growth rate of ImC	1.3×10^{4}	$cell^{-1}day^{-1}$	[5]
μ_1	Natural death rate of N	4.12×10^{-2}	day^{-1}	[3, 4, 7]
μ_2	Natural death rate of L	2.04×10^{-1}	day^{-1}	[3]
μ_3	Natural death rate of ImC	1.1×10^{-7}	day^{-1}	[3]
μ_4	Natural death rate of MmC	4.12×10^{-2}	day^{-1}	[3]

3 Analysis

3.1 Method Description - Handling Time

We have used different time scales arguments to simplify the analysis of our model. The general approach is as follows. Consider the following non-linear system

$$x' = \widetilde{f}(x, y),$$

$$y' = \widetilde{g}(x, y),$$

where $\widetilde{f}(x, y)$ and $\widetilde{g}(x, y)$ are some functions. If we know that the dynamics of one of the equations changes faster than of the other, we can rewrite our system of equations as

$$\epsilon x' = f(x, y)$$

$$y' = g(x, y),$$

where $\epsilon > 0$, $f(x, y) = \epsilon^{-1}\widetilde{f}(x, y)$ and $g(x, y) = \widetilde{g}(x, y)$.

In this case we can classify x as a "fast" variable and y as the "slow" variable (see [2, 11, 10]). This suggests that x reaches an equilibrium value $1/\epsilon$ times faster than y (i.e. $x = \phi(y)$ where y is assumed to be constant). This equilibrium is commonly referred to as a quasi-equilibrium state. In this paper we apply this concept of different time scales in studying our models.

3.2 Model 1.A

Let us first consider a simplified model, where we do not take into account the influence of myeloid cells

$$\begin{cases} \dot{N} &= \Lambda + bT - \mu_1 N - fNT, \\ \dot{L} &= -\mu_2 L + cTL^2 + b_1 \frac{NT}{h+N}, \\ \dot{T} &= aT - d\frac{NT}{h+N} - eLT. \end{cases} \tag{2}$$

We assume that N cells cannot grow indefinitely, while the growth rate of L cells is directly proportional to the number of tumor cells present in the system.

The system has a trivial (tumor-free) equilibrium $(N^0, L^0, T^0) = (\frac{\Lambda}{\mu_1}, 0, 0)$. The eigenvalues for this system at this trivial steady state are given by $\lambda_1 = a - (\frac{d\Lambda}{h\mu_1+\Lambda})$, $\lambda_2 = -\mu_2$, and $\lambda_3 = -\mu_3$. Hence, the equilibrium is stable if

$$a - (d\frac{\frac{\Lambda}{\mu_1}}{h + \frac{\Lambda}{\mu_1}}) < 0, \tag{3}$$

and unstable otherwise $a - (d\frac{\frac{\Lambda}{\mu_1}}{h+\frac{\Lambda}{\mu_1}}) > 0$. Expression $d\frac{\frac{\Lambda}{\mu_1}}{h+\frac{\Lambda}{\mu_1}}$ can be seen as the "maximum" per capita killing rate of tumor cells by NK cells. Hence, tumor cells will be completely wiped out

from the body if the natural replication rate of tumor cells will be less than maximum killing rate of NK cells.

The nontrivial equilibria are given as follows:

$$\begin{array}{rcl} N^* & = & \alpha L - \beta, \\ T^* & = & \frac{\mu_1(\beta - \alpha L)}{\delta - f\alpha L}, \end{array} \tag{4}$$

and L^*, which is given by the following quartic polynomial

$c\alpha^2 L^4 + L^3(ch\alpha - \mu_2\gamma\alpha - 2c\alpha\beta) + L^2(\mu_2\delta\alpha + \mu_2\beta\gamma - \mu_2 h\gamma - ch\beta + c\beta^2 + b_1\alpha^2) + L(-\mu_2 h\delta_1 - \mu_2\beta\delta_1 - 2\alpha\beta b_1) + b_1\beta^2 = 0,$

where $\alpha = \frac{eh}{a-d}$, $\beta = \frac{ah}{a-d}$, $\delta = b + \beta f$, $\gamma = \frac{f\alpha}{\mu_1}$, and $\delta_1 = \frac{\delta}{\mu_1}$.

Under certain conditions, $\beta = 0$ (i.e. $h = 0$) and $a > d/2$, an expression for the unique non-trivial steady state is given by (4) and

$L^* = \frac{-\mu_2 e(g-ba) - \alpha be + \sqrt{(\alpha be - \mu_2 e(b-ba)^2) + 4dc\alpha(\mu_2 ad + ba\alpha)}}{2dc\alpha}.$

3.3 Model 1.B

We assume that at first the immune system responds only with activation of the innate immune response, the N cells, and the L cells have not yet been produced in the body. The activation of the innate immune systems occurs very rapidly, rendering N as the fast variable, which reaches the quasi-steady state

$$N^*(T) = \frac{\Lambda + bT}{\mu_1 + fT},$$

Substituting N(t) into (2), we obtain:

$$\begin{cases} \dot{T} & = & aT - d\frac{(\Lambda+bT)T}{(h\mu_1+\Lambda)+(hf+b)T} - eLT, \\ \dot{L} & = & -\mu_2 L + cL^2T + b_1\frac{(\Lambda+bT)T}{(h\mu_1+\Lambda)+(hf+b)T}. \end{cases} \tag{5}$$

We have therefore reduced our system of three equations to a system of two equations. Mathematically this reduction can be seen as using parameters values in Table 1 and then choosing $\epsilon = 10^{-4}$, as Λ is very large as compared to other parameter in $\dot{N}$, $\dot{T}$, and $\dot{L}$ equations.

Trivial equilibrium for this system is $(T^0, L^0) = (0, 0)$, which is stable if $a - (\frac{d\Lambda}{h\mu_1+\Lambda}) < 0$, $-\mu_2 < 0$, and $-\mu_3 < 0$ and unstable otherwise. Noticeably, the conditions for the trivial equilibrium are the same as for (2).

Non-trivial equilibria for this system are

$$T^* = \alpha + \beta L, \tag{6}$$

and L^*, which is given by the following quartic polynomial,

$L^4(cb_2\beta - ch\beta\beta_2) + L^3(ch\beta\alpha_2 - ch\alpha\beta_2 + c\alpha b_2 + c\beta\alpha_1) + L^2(\mu_2 h\beta_2 - \mu_2 b_2 + ch\alpha\alpha_2 + c\alpha\alpha_1 + bb_1\beta) + L(b_1 + b_2 + b_1\alpha_1\beta - \mu_2 h\alpha_2 - \mu_2\alpha_1) + b_1\alpha\alpha_1 = 0,$

where $h_1 = \Lambda + h\mu$, $h_2 = b - hf$, $\beta = \frac{e}{ah_2 - db}$, $\alpha = \frac{d\Lambda - ah_1}{ah_2 - db}$, $\alpha_1 = \Lambda + \alpha b$, $\alpha_2 = \mu - f\alpha$, $\beta_2 = b\beta$, and $\beta_2 = f\beta$.

With the values of the parameters taken from Table 1, we found a unique non-trivial equilibrium, $E^* = (155683, 5.24 \times 10^{-5})$ and it is stable.

3.4 Model 2

Now, let consider system (1). In our study of the cancer-immune system interactions we are interested in exploring the dynamics of interaction between tumor cells and CD8+T cells, which is directly influenced by the presence of myeloid cells. We assume that this occurs after the NK cells have reached a steady state. At this point we take it that NK cells have reached a constant saturation state, which allows us to eliminate the equation for NK cells and reduce our system of equations to four dimensions as follows:

$$\begin{cases} \dot{L} &= -\mu_2 L + cL^2 T\frac{M_2}{M_1} + \psi_1 T, \\ \dot{T} &= aT - \psi_2 T - eLT\frac{M_2}{M_1}, \\ \dot{M}_1 &= \Omega + rT - \mu_3 M_1 - (\theta - g\frac{T}{p+T})M_1, \\ \dot{M}_2 &= (\theta - g\frac{T}{p+T})M_1 - \mu_4 M_2, \end{cases} \tag{7}$$

where $\psi_1 = b_1\frac{N}{h+N}$ and $\psi_2 = d\frac{N}{h+N}$ are constants. Considering the order of the magnitude of parameters in Table 1, we can interpret this reduction with $\epsilon_1 = 10^{-7}$.

3.4.1 Analysis on the fast time scale

We know that the balance of immature to mature myeloid cells has to stabilize before it can affect the interaction rate between CD8+T cells and tumor cells. Hence, we can consider system of M_1 and M_2 equations as fast variables where $\epsilon_2 = 10^{-4}$, since Ω is of order 10^4.

Therefore, we can first analyze the following system, by assuming T as constant:

$$\begin{cases} \dot{M}_1 &= \Omega + rT - \mu_3 M_1 - (\theta - g\frac{T}{p+T})M_1, \\ \dot{M}_2 &= (\theta - g\frac{T}{p+T})M_1 - \mu_4 M_2 \end{cases} \tag{8}$$

If we set both equations equal to 0, we obtain that the equilibrium is

$$\begin{array}{rcl} M_1^* & = & \frac{\Omega(p+T)+rT(p+T)}{T(\theta+\mu_3-g)} + p(\theta+\mu_3) \\ M_2^* & = & \frac{M_1^*}{\mu_4}(\theta - \frac{gT}{p+T}). \end{array} \tag{9}$$

System (8) has a unique equilibrium. It is globally asymptotically stable (see Apendix for proof).

3.4.2 Analysis on the real time scale

We know from experimental data that the ratio of immature to mature myeloid cells is often used in order to measure the overall state of the immune system of the patient. Consequently, we can assume that the balance between immature and mature myeloid cells has to be established before they can affect the interactions between tumor cells and the CD8+T cells, rendering M_1 and M_2 as "fast" variables. Therefore, if we assume that M_1 and M_2 first achieve a quasi-equilibrium, which is given by (9) M_1^* and M_2^* and substitute these points into (5). We obtain a reduced system from system (5)

$$\begin{cases} \dot{T} & = & aT - \psi_2 T - eLT\frac{\theta(p+T)-gT}{\mu_4(p+T)}, \\ \dot{L} & = & -\mu_2 L + cL^2T\frac{\theta(p+T)-gT}{\mu_4(p+T)} + \psi_1 T, \end{cases} \tag{10}$$

where $\psi_1 = b_1\frac{N}{h+N}$ and $\psi_2 = d\frac{N}{h+N}$, both now taken as constants.

The major characteristics of the five-dimensional system (1) are now described by the newly obtained two-dimensional system (7).

Non-trivial equilibria for this system are

$$T^* = \frac{\alpha_1 L-\beta}{\alpha_1-\gamma L}, \tag{11}$$

and L^*, given by the following quartic polynomial,

$-cL^4 + L^3(\alpha_1 c + \gamma_1 - c\beta_1 - \gamma_4) + L^2(\gamma_3 - \alpha_1\gamma_1 - c\beta_1\alpha_1 - \gamma_2 + \beta_1\gamma_1 + 2\alpha_1\gamma_4) + L(-2\beta_1 + \alpha_1\gamma_2 + \beta_1\gamma_1\alpha_1 - \beta_1\gamma_2 - \gamma_4\alpha_1^2) + \gamma_3\beta_1^2 - \alpha_1\beta_1\gamma_2 = 0.$

where $\alpha = a(g+\theta)$, $\alpha_1 = \frac{\alpha}{\gamma}$, $\beta = a\theta p$, $\beta_1 = \frac{\beta}{\gamma}$, $\gamma = \mu_4 ep$, $\gamma_1 = \mu_2(g+\theta)$, $\gamma_2 = b\theta p$, $\gamma_3 = b(g+\theta)$, and $\gamma_4 = \mu_2\theta p$.

By appropriate rescaling of system (7), we obtain the following system.

$$\begin{cases} \dot{x} & = & x - \varphi xy\frac{1+x}{\beta+x}, \\ \dot{y} & = & -\gamma y + xy^2\frac{1+x}{\beta+x} + \delta x \end{cases} \tag{12}$$

This system has trivial equilibrium at $(0,0)$, which is always unstable.

There also exists a unique non-trivial equilibrium at (7)
$x^* = \frac{-a+\sqrt{a^2+2\gamma\varphi c}}{c}$

$y^* = \frac{1+x^*}{\varphi(\beta+x^*)}$,

where $\varphi = \frac{e(g+\theta)^2}{\theta p}, \gamma = \frac{\mu_2}{a}, \beta = \frac{p(g+\theta)}{\theta p}, \delta = cb, a = \frac{b}{\delta}$, and $c = \frac{1}{a}$.

Through numerical simulations we were able to determine that there exist two bifurcations in our system: a Hopf bifurcation and a bifurcation "from infinity", both of which are discussed in more detail in Section 4.

4 Discussion and Numerical Results

4.1 Model 1

Model 1 describes the dynamics of the tumor-immune system interactions without taking the influence of myeloid cells into consideration. As has been noted in Sections 3.2 and 3.3, the conditions for trivial equilibria for both model 1.A and model 1.B are the same. Moreover, for the selected range of parameter values, non-trivial equilibria for both systems are unstable. Therefore, we can conclude that reduction of a higher-dimensional system of equations to a lower-dimensional system using time scales does not change the overall dynamics of the system. We can therefore apply the same method to analyzing our five-dimensional system.

Moreover, Model 1 describes only one type of behavior at the non-trivial equilibrium (see Fig.1). Biologically this implies that, the growth of the tumor is always controlled by the immune system, or at least the number of tumor cells are kept at a constant value. This is inconsistent with experimental data. In order to correct our model, we introduce equations for the dynamics of immature and mature myeloid cells to our system of equations.

4.2 Model 2

In Model 2 we incorporate the dynamics of myeloid cells in an attempt to explain how the balance between ImC and MmC influences the dynamics of the immune system response.

Through variation of the parameter φ we have been able to numerically identify four distinct patterns of behavior. Parameter φ determines the effectiveness of tumor killing by CD8+T cells, influenced by the ratio of MmC to ImC (recognition of tumor cells by CD8+T cells, which allows tumor destruction).

In case of a good immune response ($\varphi > 1.528$, $\beta = 0.33$, $\delta = 0.4$, $\gamma = 1$) the system has only one equilibrium point (see Fig.2). This implies that the immune system is able to control tumor growth and keep it at a constant value. However, it is not capable of extinguishing the tumor completely.

At $\varphi = 1.528$ (all other parameters held constant), the equilibrium point loses stability with the appearance of a stable limit cycle by Hopf bifurcation (see Fig.2a). This implies that the immune system is not capable of controlling the tumor growth completely and therefore cannot keep the number of tumor cells at a constant value anymore. At this point the tumor produces a sufficient number of cytokines to inhibit maturation of ImC so that the immune system is not able to recognize and extinguish enough tumor cells. Therefore, the ImCs don't mature fast enough,

the balance between the ImC and MmC is not achieved in time, and the tumor cells grow faster than the CD8+T cells can detect and kill them.

As the value of φ decreases further, the amplitude of the stable limit cycle increases (see Fig.2d), which implies that CD8+T cells require increasingly more time to catch up with the tumor growth. As can be seen from Fig. 2e, the growth rate of the tumor remains constant. However, the immune system does not respond immediately but rather accumulates its forces and then "fires"(Fig.2f), causing the number of tumor cells to rapidly decrease for a short period of time.

The smaller the value of the parameter φ, the larger the amplitude of the cycle, the more time it takes for the immune system to respond effectively. The cycle repeats until it takes too much time for the immune system to respond adequately, which allows the tumor to grow to be too large, causing the patient's death before the immune response.

The amplitude of the limit cycle keeps increasing with the decreasing value of parameter φ (decreased recognition of tumor cells by the immune system cells, caused by decreased maturation rate of MmC), until the limit cycle collapses "at infinity", resulting in an unstable fixed point (see Fig.4). This means that at this stage the immune system is able to only slightly delay the growth of the tumor (make it grow not exponentially but in an unwinding spiral), but cannot control it.

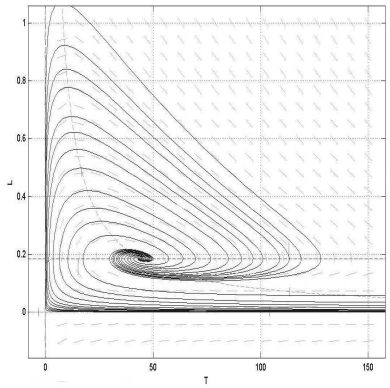


Figure 1: Model 1.B. A stable equilibrium, parameter values were taken from Table 1.

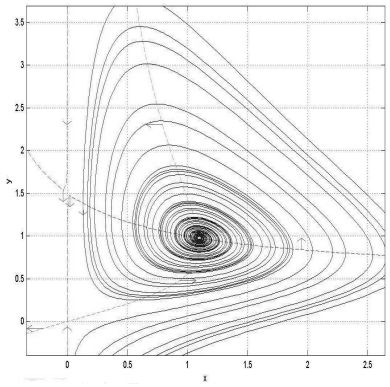
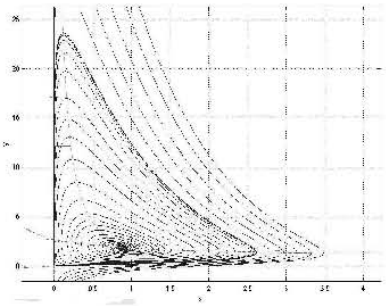
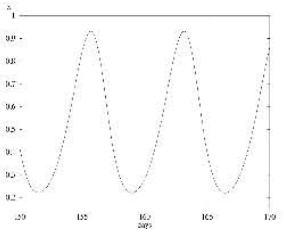


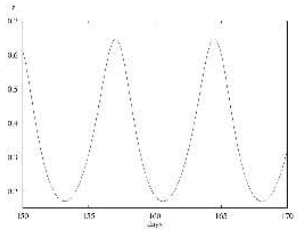
Figure 2: Model 2B. A stable equilibrium for $\varphi = 2$, $\beta = 0.33$, $\delta = 0.4$, $\gamma = 1$.



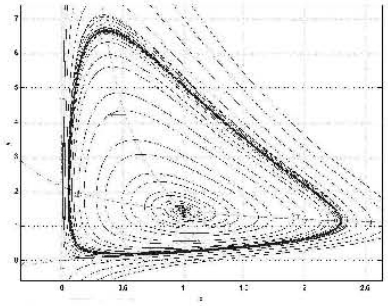
(a) Model 2B. A stable periodic orbit for $\varphi = 1.4$, $\beta = 0.33$, $\delta = 0.4$, $\gamma = 1$.



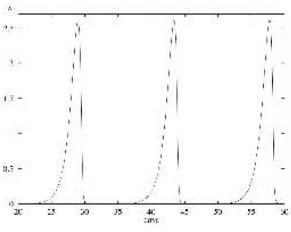
(b) Model 2B. A stable periodic orbit for $\varphi = 1.4$, $\beta = 0.33$, $\delta = 0.4$, $\gamma = 1$. "Relaxed" oscillations for T vs. time



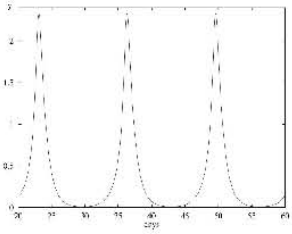
(c) Model 2B. A stable periodic orbit for $\varphi = 1.4$, $\beta = 0.33$, $\delta = 0.4$, $\gamma = 1$. "Relaxed" oscillations for L vs. time



(d) Model 2B. A stable periodic orbit for $\varphi = 1.1$, $\beta = 0.33$, $\delta = 0.4$, $\gamma = 1$.



(e) Model 2B. A stable periodic orbit for $\varphi = 1.1$, $\beta = 0.33$, $\delta = 0.4$, $\gamma = 1$. "Sinusoidal" oscillations for T vs. time



(f) Model 2B. A stable periodic orbit for $\varphi = 1.1$, $\beta = 0.33$, $\delta = 0.4$, $\gamma = 1$. "Sinusoidal" oscillations for L vs. time

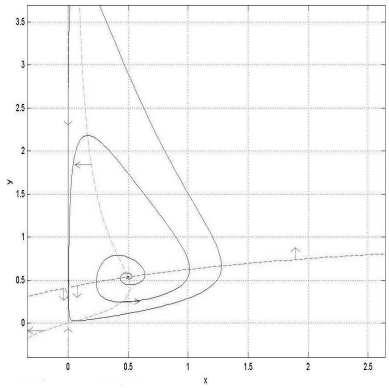


Figure 3: Model 2B. An unstable equilibrum and stable periodic orbit for $\varphi = 0.8$, $\beta = 0.33$, $\delta = 0.4$, $\gamma = 1$.

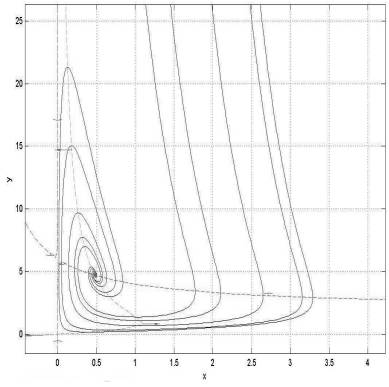


Figure 4: Model 2B. An unstable equilibrium for $\varphi = 0.5$, $\beta = 0.33$, $\delta = 0.4$, $\gamma = 1$.

5 Conclusion

In this paper for the first time we incorporate the impact of myeloid cells, which are part of the innate immune response, on the tumor-immune system interactions. In our model we consider NK cells, CD8+ cells, myeloid cells and tumor cells. We then perform analysis in different time scales.

Firstly, we study the dynamics of a simplified three-dimensional system of equations, describing the immune system-tumor interactions without taking the effect of myeloid cells into account. We study the system in two different time scales and are able to identify only one type of behavior for the given parameter range. According to this model, the tumor is always eliminated, which is inconsistent with experimental data. However, this model does demonstrate that the overall dynamics of the system does not change when the system is reduced to lower dimensions using time scale arguments.

In order to elucidate the mechanisms that influence the success of the tumor-immune system interactions and to obtain richer dynamical behavior, we incorporate two new equations, describing the dynamics of immature and mature myeloid cells, into our system. We then analyze the newly obtained system of equations in three different time scales, which allows us to a reduce a five-dimensional system to two dimensions.

The reduced system of equations, in which we have incorporated the myeloid cells, exhibits four distinct patterns of behavior. At first the immune system is able to keep the level of tumor cells at a constant level, which is represented by the existence of a stable equilibrium point. As the tumor cells release more cytokines, the recognition of the tumor cells by the CD8+T cells decreases. At some point the equilibrium point changes stability with the appearance of a stable limit cycle by Hopf bifurcation occurs. At this point the immune system is still able to control the tumor growth but not entirely anymore. As the tumor grows, the specific immune response increasingly requires more time to respond. Eventually the tumor becomes so large that the immune response is no longer capable of responding in time, and the patient dies. If the person with initially highly weakened immune response develops a tumor, the immune system is only capable of slightly delaying the tumor growth but it cannot control it, which mathematically is presented by an unstable node.

In the future work we intend to explore the effects of the vaccine therapy on the rate of maturation of myeloid cells in particular and on the effectiveness of the specific immune response in general.

6 Acknowledgments

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7 Appendix A

7.1 Applying Dulac Criterion

We can prove that there are no periodic orbits in the system (6) using Dulac criterion as follows:

Taking $\beta = \frac{1}{M_1}$, we have

$$\begin{aligned}
\beta\dot{M}_1 &= \frac{1}{M_1}(\Omega + rT - \mu_3 M_1 - g\frac{M_1 T}{p+T} - \theta M_1) \\
&= \frac{\Omega}{M_1} + \frac{rT}{M_1} - g\frac{T}{p+T} - (\theta + \mu_3), \\
\frac{\partial}{\partial M_1}(\beta\dot{M}_1) &= -\frac{1}{M_1^2}\Omega - \frac{rT}{M_1^2}, \\
\beta\dot{M}_2 &= \frac{1}{M_1}(g\frac{M_1 T}{p+T} + \theta M_1 - \mu_4\mu_2), \\
&= g\frac{T}{p+T}\theta - \frac{\mu_4\mu_2}{M_1}, \\
\frac{\partial}{\partial M_2}(\beta\dot{M}_2) &= -\frac{\mu_4}{M_1}, \\
\frac{\partial}{\partial M_1}(\beta\dot{M}_1) - \frac{\partial}{\partial M_2}(\beta\dot{M}_2) &= -\frac{\mu_4}{M_1} - \frac{\Omega}{M_1^2} - \frac{rT}{M_1^2} - \frac{\mu_4}{M_1}.
\end{aligned}$$

The obtained expression is strictly negative in $\mathbb{R}^2_+ \setminus \{(0,0)\}$. Hence, there are no periodic orbits on $\dot{M}_1$ and $\dot{M}_2$ in $\mathbb{R}^2_+ \setminus \{(0,0)\}$.

7.2 Applying Poincaré-Bendixon Theorem

Now, we find a condition such that $M_1(t) + M_2(t) \leq$constant.

Solving $\dot{M}_1 + P_1 M_1 = P_2$ and $\dot{M}_2 + K_1 M_2 = K_2$,
where $P_1 = \mu_3 + g\frac{T}{p+T} + \theta$, $P_2 = \Omega + rT$, $K_1 = \mu_4$, and $K_2 = g\frac{T}{p+T} + \theta$.

We obtain,

$$\begin{aligned}
M_1 &= \frac{P_2}{P_1} + (M_1(0) - \frac{P_1}{P_2})\exp(-P_1 t), \\
M_2 &= \frac{K_2}{K_1} + r_1\exp(-K_2 t) + r_2\exp(-K_1 t),
\end{aligned}$$

where r_1 and r_2 are constants.

Then,

$$\begin{aligned}\lim_{t\to\infty} M_1(t) &= \frac{P_2}{P_1},\\ \lim_{t\to\infty} M_2(t) &= \frac{K_2}{K_1}.\end{aligned}$$

Therefore, the system (6) is bounded. Hence, the unique steady state is globally asymptotically stable.

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