Modeling Interactions Between Various Cell Populations in a Cancerous System*

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Abstract

We create two models based on systems of ordinary differential equations (ODEs) to study how normal, benign, metastatic, and immune cell populations evolve in a patient with cancer. The first, one-patch, model is used to simulate the cell populations in a single fixed area. Using stability analysis for this model, we determine a healthy equilibrium point with no tumor cells and derive necessary and sufficient conditions for stability. This model is also used to show the effects of immunotherapy on a cancerous system. To capture the effects of metastatic cancer, a two-patch model is introduced. It looks at the cell populations in two different areas of the body. A healthy equilibrium is also found for this model and sufficient conditions for stability are provided.

Keywords: Mathematical Modeling; Interactions between Cells; Cancer; Ordinary Differential Equations; Immune System; Benign; Metastatic; Equilibrium; Immunotherapy

1 Introduction

Cancer ravages the body, killing thousands of people a year. There are two types of tumor cells present in the body: metastatic and benign. Both types are cancerous and replicate faster than the normal cells. Metastatic cells are more fatal than benign cells because they have the ability to travel and spread throughout the body. In this paper we develop systems of ODEs that allow us to model the growth of these different types of cancerous cells in cancer patients.

There are two ways the metastatic cells can travel throughout the body. One way is through the lymphatic system. The metastatic cells attach to the lymph nodes, the major sites for immune cells [6]. They replicate, replace the node with a cancerous tumor, and travel to another lymph node to repeat the process. Another way for the metastatic cells to travel is through the blood vessels.

The immune system has three lines of defense: physical, natural immune response, and adaptive immune response. Most pathogens are defeated through the first two lines of defense. Tumors are defeated through the third line of defense. The body recognizes foreign species and sends immune cells, called lymphocytes,

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to the site of infection. Once the immune cells destroy the pathogens, they go through a programmed death. A few lymphocytes remain as memory lymphocytes, so if the pathogen comes back, the body knows how to fight it off. Immune cells that destroy cancer cells do not have this memory function [4]. Thus, when the cancer comes back, the body cannot easily defeat it.

The model provided herein is based on models studied in [7] and [3]. As in these studies, we assume that tumor cells, immune cells, normal cells are in competition with each other for the resources of the body. In [7] and [3] tumor cells are modeled as a single species, however we distinguish between metastatic and benign tumor cells, by modeling them as two separate species. We construct two mathematical models based on systems of ODEs, which model the interactions between the different cell populations. In the first, simpler, model, we consider the cells in one area, and refer to it as the "one patch model". We study what conditions need to be satisfied in order for the patient to be considered healthy. We test parameters for when both types of tumor cells are present in the body. When the growth rate of the tumor cells exceeds the competition rate with the normal cells and death rate from the immune cells, the patient is no longer in a healthy equilibrium. For this unhealthy patient, we provide a preliminary study of the effects of immunotherapy treatments, which consists of extracting a few immune cells from the patient, increasing their number, and placing them back in the body.

In the second model, we consider the cells in two different areas and refer to it as the "two patch model". We assume that the metastatic and immune cells are migrating between the two patches. The normal and benign cells do not migrate. For this case, we also consider conditions on the parameters which ensure that the introduction of a small number of tumor cells will not lead to an unhealthy equilibrium, i.e., the healthy state is stable under small perturbations.

2 One Patch Model

We assume that the normal, benign, metastatic and immune cell populations are only interacting in one area of the body. Any influences outside of this area are ignored. Let $N(t)$, $B(t)$, $M(t)$, and $I(t)$ denote respectively the normal, benign, metastatic, and immune cell populations at time t. The following system of differential equations models the interactions between the four types of cells in this fixed area. The model below is an extension of the tumor model studied by dePillis and Rudinskaya in [3]. In this paper, however, we separate the tumor cell population into two kinds - benign and metastatic, while in [3] all tumor cells are modeled as a single species.

$$\frac{dN}{dt} = aN(1-bN) - cBN - dMN, \tag{1}$$

$$\frac{dB}{dt} = eB\left(1 - \frac{B}{K_1} - \frac{fM}{K_1}\right) - \frac{gBN}{K_1} - hBI, \tag{2}$$

$$\frac{dM}{dt} = jM\left(1 - \frac{M}{K_2} - \frac{lB}{K_2}\right) - \frac{mMN}{K_2} - nMI, \tag{3}$$

$$\frac{dI}{dt} = o + \frac{pIB}{q+B} + \frac{rIM}{s+M} - uIB - vIM - wI. \tag{4}$$

Here a denotes the growth rate of normal cells and b is the death rate of normal cells, while c and d represent the competition rates of the normal cells with the benign and metastatic cells respectively. In Eq. (2) e is the growth rate of the benign cells and K_1 is the carrying capacity of the tissue where the benign tumor is located. Furthermore, f and g denote the competition rates between the benign cells and the metastatic and normal cells respectively, and h is the death rate of the benign cells due to the actions of the immune cells. In Eq. (3) j is the growth rate of the metastatic cells, K_2 is the tissue's carrying capacity of the metastatic cells, l and m denote the competition between the metastatic cells and the benign and normal cells respectively, and n denotes the death rate of the metastatic cells due to the immune cells. Lastly, in Eq. (4), o is the constant supply of immune cells from the body, p and r are the growth rates of the immune cells, due to the benign and metastatic tumor cells respectively. The non-linear growth terms in the immune-cells

equation are taken to be of Michaelis-Menten type, and q and s are positive constants corresponding to the half-maximum of the rate they are used to define. In addition, u and v represent the death rates of immune cells due to fighting off the tumor cells, and w represents the immune cells dying from programmed cell death.

2.1 Nondimensionalization

For the sake of simplifying the analysis, we nondimensionalize our equations to remove artificial effects due to choice of units for measurements. This yields the following change of variables:

$$t = \frac{t^*}{a}, \quad B = B^* K_1, \quad N = \frac{N^*}{b}, \quad M = M^* K_2, \quad I = \frac{oI^*}{w},$$

where the starred quantities are nondimensional. Then, it is convenient to set

$$\hat{c} = \frac{cK_1}{a}, \quad \hat{d} = \frac{dK_2}{a}, \quad \hat{j} = \frac{j}{a}, \quad \hat{m} = \frac{m}{K_2 ba}, \quad \hat{l} = \frac{lK_1}{K_2}, \quad \hat{n} = \frac{no}{wa}, \quad \hat{e} = \frac{e}{a}, \quad \hat{g} = \frac{g}{abK_1}, \quad \hat{f} = \frac{fK_2}{K_1},$$
$$\hat{h} = \frac{ho}{aw}, \quad \hat{w} = \frac{w}{a}, \quad \hat{p} = \frac{p}{a}, \quad \hat{q} = \frac{q}{K_1}, \quad \hat{r} = \frac{r}{a}, \quad \hat{s} = \frac{s}{K_2}, \quad \hat{u} = \frac{uK_1}{a}, \quad \hat{v} = \frac{vK_2}{a}.$$

From this we arrive at the nondimensionalized equations:

$$\frac{dN^*}{dt} = N^* - (N^*)^2 - \hat{d}M^*N^* - \hat{c}B^*N^*, \tag{5}$$
$$\frac{dB^*}{dt} = \hat{e}B^*(1 - B^* - \hat{f}M^*) - \hat{g}B^*N^* - \hat{h}B^*I^*, \tag{6}$$
$$\frac{dM^*}{dt} = \hat{j}M^*(1 - M^* - \hat{l}B^*) - \hat{m}M^*N^* - \hat{n}M^*I^*, \tag{7}$$
$$\frac{dI^*}{dt} = \hat{w}(1 - I^*) + \frac{\hat{p}I^*B^*}{\hat{q} + B^*} + \frac{\hat{r}I^*M^*}{\hat{s} + M^*} - \hat{u}I^*B^* - \hat{v}I^*M^*. \tag{8}$$

Using the nondimensionalized system we proceed to determine equilibrium points. The healthy equilibrium point can be found when a healthy individual has a body containing no benign or metastatic tumor cells, that is, $M^* = 0$ and $B^* = 0$. By substituting these values back into the nondimensionalized equations and setting $dN^*/dt = 0$ and $dI^*/dt = 0$, we obtain $N^* = I^* = 1$. Thus the healthy equilibrium point is $(N^*, B^*, M^*, I^*) = (1, 0, 0, 1)$.

2.2 Analysis

2.2.1 Determining Stability of Healthy Equilibrium Point (1,0,0,1)

To determine the stability of the healthy equilibrium point for the system, we analyze the eigenvalues associated with this point. If any eigenvalue is positive, the equilibrium point is unstable, and if all of them are negative, the equilibrium point is asymptotically stable, i.e., the system will approach the healthy equilibrium after a small perturbation off of the equilibrium state.

The linearized system around $N^* = 1$, $B^* = 0$, $M^* = 0$, and $I^* = 1$

$$\frac{d\hat{N}}{dt} = -\hat{N} - \hat{c}\hat{B} - \hat{d}\hat{M}, \tag{9}$$
$$\frac{d\hat{B}}{dt} = e^*\hat{B}, \tag{10}$$
$$\frac{d\hat{M}}{dt} = j^*\hat{M}, \tag{11}$$
$$\frac{d\hat{I}}{dt} = p^*\hat{B} + r^*\hat{M} - \hat{w}\hat{I}, \tag{12}$$

where $e^* = \hat{e} - \hat{g} - \hat{h}$, $j^* = \hat{j} - \hat{m} - \hat{n}$, $p^* = \dfrac{\hat{p}}{\hat{q}} - \hat{u}$, and $r^* = \dfrac{\hat{r}}{\hat{s}} - \hat{v}$.

To find the eigenvalues associated with these equations, we solve $det(A - \lambda I) = 0$ for λ, where A is the matrix associated with equations (9)$\sim$(12) and I is the corresponding identity matrix:

$$\det \begin{bmatrix} -1-\lambda & -\hat{c} & -\hat{d} & 0 \\ 0 & e^*-\lambda & 0 & 0 \\ 0 & 0 & j^*-\lambda & 0 \\ 0 & p^* & r^* & -\hat{w}-\lambda \end{bmatrix} = 0.$$

As a result, we arrive at the following four eigenvalues $\lambda_1 = -1$, $\lambda_2 = e^*$, $\lambda_3 = j^*$, and $\lambda_4 = -\hat{w}$. Recall that in order for a point to be considered a stable equilibrium point, all of the eigenvalues must be negative. Since $\hat{w}$ is the death rate of the immune cells, it is assumed to be positive. Hence, $-\hat{w}$ is always negative. The values e^* and j^* can be positive or negative. Since, $e^* = \hat{e} - (\hat{g} + \hat{h})$, in order for e^* to be negative, we need $\hat{e} < \hat{g} + \hat{h}$. This means that the growth rate of the benign cells must be less than the sum of the rate of competition between the benign and normal cells and the death rate of the benign cells from the immune cells. In other words, the growth rate of the benign cells must be less than their total death rate. Similarly, since $j^* = \hat{j} - (\hat{m} + \hat{n})$, the eigenvalue j^* is negative when $\hat{j} < \hat{m} + \hat{n}$. This implies that stability of the equilibrium point requires the growth rate of the metastatic cells be less than the rate of competition between the metastatic and normal cells and the death rate of the metastatic cells from the immune cells.

To summarize, the healthy equilibrium point $(1, 0, 0, 1)$ is asymptotically stable if and only if

$$\hat{e} < \hat{g} + \hat{h} \text{ and } \hat{j} < \hat{m} + \hat{n}. \tag{13}$$

2.2.2 Numerical Experiments

Numerical experiments are run to test the stability of the equilibrium point under the parameters that were found to yield stable or unstable conditions. Figure 1a corresponds to the initial conditions $N^*(0) = 1$, $M^*(0) = 0.1$, $B^*(0) = 0.1$, $I^*(0) = 1$ and a parameter set satisfying the conditions that $\hat{j} < \hat{m} + \hat{n}$, and $\hat{e} < \hat{g} + \hat{h}$. Recall, that these conditions yield a stable equilibrium where the normal and immune cell populations converge to 1 and benign and metastatic cell populations converge to zero.

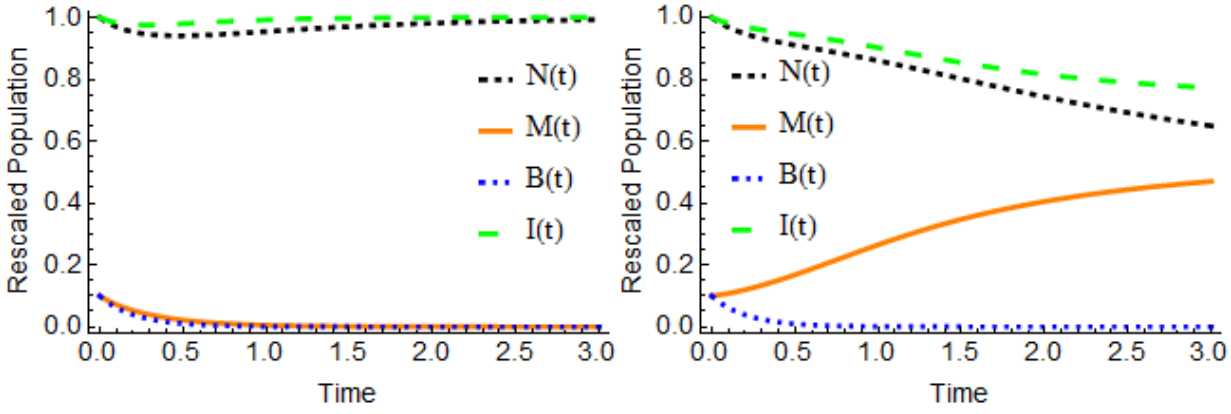
Figure 1b corresponds to the same parameters as Figure 1a except the value of $\hat{j}$ has been increased to surpass $\hat{m}+\hat{n}$. (Note that $\hat{j}$ is related to the growth rate of the meastatic cells.) This shows the instability of the equilibrium point when the necessary conditions are not met. The normal and immune cell populations no longer converge to 1, and the metastatic cell population has increased as shown.

2.3 Effects of Immunotherapy for the One Patch Model

According to [1], immunotherapy is a form of cancer treatment that uses a person's immune system to combat cancer. Immunotherapy can be implemented in a couple of different ways. Some examples include inserting man-made proteins into a patient's immune system to increase performance or simply injecting more immune cells into the body. In the following discussion, the one patch model is used to analyze the outcomes of adding more immune cells to a cancerous system. Figures 2a and 2b represent a person with a stable immune system (i.e. the healthy equilibrium is a stable point). Figures 3a and 3b represent a person with an unstable immune system (i.e. the healthy equilibrium is an unstable point).

Figure 2a represents a cancerous system where the metastatic cells level off at a significant number, indicating an unhealthy state. The normal cell population is decreasing because of their competition with the metastatic cells. The immune cell population is decreasing because they are dying from fighting the growing population of metastatic cells. The benign cells die out because of the competition with the metastatic cells.

Figure 2b considers the case when immunotherapy is added to a cancerous system. In order to try to drive the system to a healthy state we interrupt system 2a at time $t = 1$ and start it with initial conditions

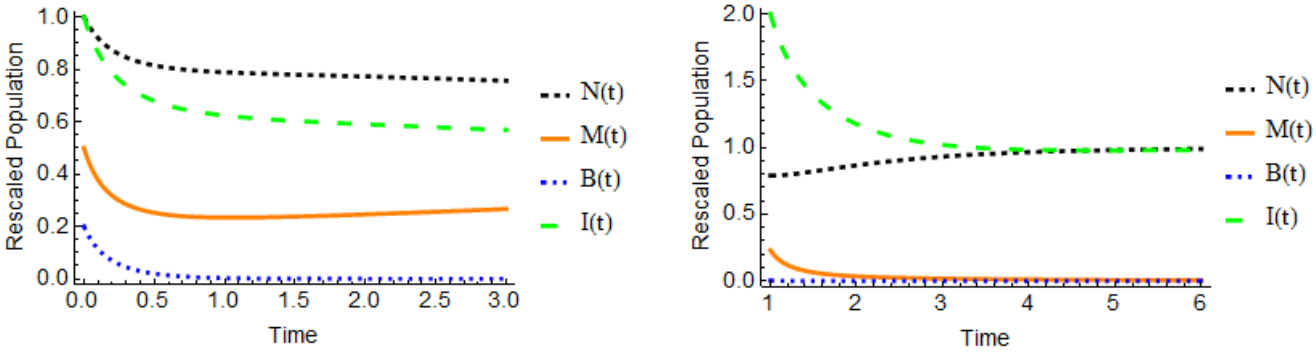


(a) (Stable Equilibrium) $\hat{j} = 2 < 5 = \hat{m} + \hat{n}$.

(b) (Unstable Equilibrium) $\hat{j} = 7 > 5 = \hat{m} + \hat{n}$.

Figure 1: Common parameters for (a) and (b): $\hat{c} = 3$, $\hat{d} = 1$, $\hat{e} = 1$, $\hat{f} = 3$, $\hat{g} = 3$, $\hat{h} = 2.5$, $\hat{l} = 1$, $\hat{m} = 2$, $\hat{n} = 3$, $\hat{w} = 3$, $\hat{p} = 2$, $\hat{q} = 1$, $\hat{s} = 1$, $\hat{r} = 3$, $\hat{u} = 3$, $\hat{v} = 4$.

such that the natural, metastatic and benign cells have the same values as at time $t = 1$ in system 2a, but the number of immune cells is much larger (in this case I(1)=2). The addition of more immune cells will cause the population of the metastatic cells to decrease and cause the normal cell population to grow. In this figure the initial value of immune cells is increased so that they can fight the metastatic cells in a more aggressive manner. We can see that as time progresses, the metastatic cell population does not return; thus, this patient is cancer free. We also observe that the normal and immune cell populations reach a healthy equilibrium.



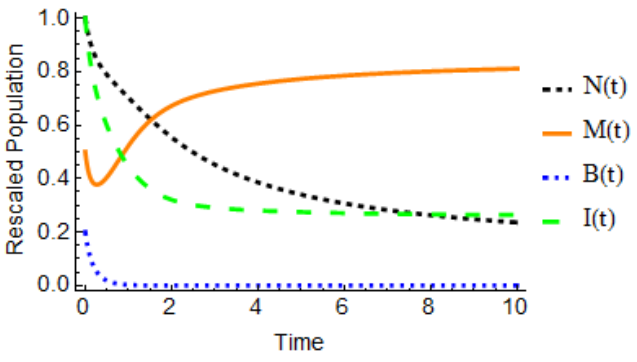
(a) (Stable System without Immunotherapy) Initial conditions are $N(0) = 1$, $I(0) = 1$, $M(0) = 0.5$, and $B(0) = 0.5$.

(b) (Stable System with Immunotherapy) Initial conditions are $N(1) = 0.79$, $I(1) = 2$, $M(1) = 0.23$, and $B(1) = 0.003$.

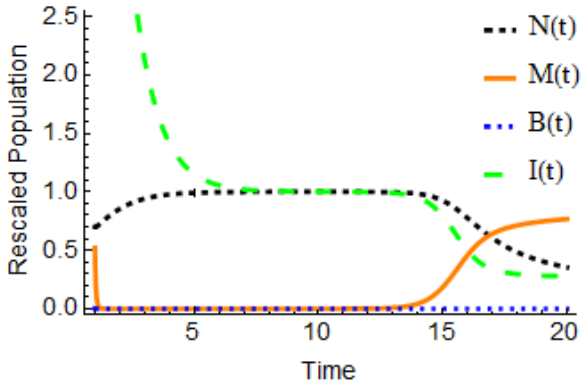
Figure 2: Common parameters for (a) and (b): $\hat{c} = 3$, $\hat{d} = 1$, $\hat{e} = 2$, $\hat{f} = 3$, $\hat{g} = 3$, $\hat{l} = 1$, $\hat{p} = 2$, $\hat{r} = 1.27$, $\hat{q} = 1$, $\hat{s} = 1$, $\hat{n} = 3$, $\hat{v} = 4$, $\hat{h} = 2.5$, $\hat{j} = 4.5$, $\hat{m} = 2$, $\hat{n} = 3$, $\hat{w} = 1$, $\hat{u} = 3$.

Similarly to Figure 2a, Figure 3a represents a cancerous system where the metastatic cell population surpasses the populations of normal and immune cells. However, in this case, the parameters do not satisfy conditions (13), i.e., the healthy equilibrium is unstable.

Figure 3b represents immunotherapy where more immune cells are added to our initial immune cell population. Initially, the metastatic cell population looks like it is approaching zero and the population of normal cells decreases then levels off. Eventually, however, the metastatic cell population returns. Even



(a) (Unstable System without Immunotherapy) Initial conditions are $N(0) = 1$, $I(0) = 1$, $M(0) = 0.5$, and $B(0) = 0.2$.



(b) (Unstable System with Immunotherapy) Initial conditions are $N(1) = 0.7$, $I(1) = 10$, $M(1) = 0.52$, and $B(1) = 0.002$.

Figure 3: Common parameters for (a) and (b): $\hat{c} = 3$, $\hat{d} = 1$, $\hat{e} = 2$, $\hat{f} = 3$, $\hat{g} = 3$, $\hat{l} = 1$, $\hat{p} = 2$, $\hat{r} = 1$, $\hat{q} = 1$, $\hat{s} = 1$, $\hat{n} = 3$, $\hat{v} = 4$, $\hat{h} = 2.5$, $\hat{j} = 6.7$, $\hat{m} = 2$, $\hat{w} = 1$, $\hat{w} = 3$.

with the help of immunotherapy, eventually the normal cells will die out, implying that the person has died.

According to [2], for 2 women out of 9 with cervical cancer, the cancer went away and for the remaining 7 it either came back or never went away. While exploring how effective immunotherapy would be with our models, we can conclude that it depends on the person's immune system and whether the healthy equilibrium is stable or unstable (i.e., whether conditions (13) are satisfied or not). We believe that this could help explain why immunotherapy works for some individuals and not for others. Hopefully immunotherapy in addition to other methods of fighting cancer, such as chemotherapy, could possibly help an unstable immune system eradicate cancer. This is something we intend to study further in the future.

3 Two Patch Model

For our two patch model, we assume that metastatic cells and immune cells are mobile. To account for this we have added migration terms μ_i and γ_i, where $i = 1, 2$ represent the two patches. Without loss of generality, we assume that μ_i and γ_i are positive constants. For example, in the equation for the rate of change of M_1, the term $-\mu_1 M1$ represents migration rate out of patch 1, and $+\mu_2 M_2$ represents rate of migration from patch 2 into patch 1. There is one equation for each type of cell and each patch contains all four cell types; so, there are eight equations altogether. The following is the ODE system for two patches:

$$
\begin{aligned}
\frac{dN_1}{dt} &= a_1 N_1 - b_1 a_1 N_1^2 - c_1 B_1 N_1 - d_1 M_1 N_1, \\
\frac{dN_2}{dt} &= a_2 N_2 - b_2 a_2 N_2^2 - c_2 B_2 N_2 - d_2 M_2 N_2, \\
\frac{dB_1}{dt} &= e_1 B_1 (1 - \frac{B_1}{K_1} - \frac{f_1 M_1}{K_1}) - \frac{g_1 B_1 N_1}{K_1} - h_1 B_1 I_1, \\
\frac{dB_2}{dt} &= e_2 B_2 (1 - \frac{B_2}{K_2} - \frac{f_2 M_2}{K_2}) - \frac{g_2 B_2 N_2}{K_2} - h_2 B_2 I_2, \\
\frac{dM_1}{dt} &= j_1 M_1 (1 - \frac{M_1}{K_3} - \frac{l_1 B_1}{K_3}) - \frac{m_1 M_1 N_1}{K_3} - n_1 M_1 I_1 - \mu_1 M_1 + \mu_2 M_2, \\
\frac{dM_2}{dt} &= j_2 M_2 (1 - \frac{M_2}{K_4} - \frac{l_2 B_2}{K_4}) - \frac{m_2 M_2 N_2}{K_4} - n_2 M_2 I_2 - \mu_2 M_2 + \mu_1 M_1,
\end{aligned}
$$

$$\begin{aligned}
\frac{dI_1}{dt} &= o + \frac{p_1 I_1 B_1}{q_1 + B_1} + \frac{r_1 I_1 M_1}{s_1 + M_1} - u_1 I_1 B_1 - v_1 I_1 M_1 - w_1 I_1 - \gamma_1 I_1 + \gamma_2 I_2, \\
\frac{dI_2}{dt} &= o + \frac{p_2 I_2 B_2}{q_2 + B_2} + \frac{r_2 I_2 M_2}{s_2 + M_2} - u_2 I_2 B_2 - v_2 I_2 M_2 - w_2 I_2 - \gamma_2 I_2 + \gamma_1 I_1, .
\end{aligned}$$

The equations in the two patch model are very similar to those used in the one patch model. New additions to the two patch model include the subscripts 1 and 2 to denote which patch each variable is referring to and migration rates represented by terms at the end of the metastatic and immune cell equations to account for the cells' ability to move between the two patches.

3.1 Nondimensionalization

Similarly to the one patch model, we nondimensionalized the equations for the two patch model. This resulted in the following change of variables

$$\begin{aligned}
&N_1 = \frac{N_1^*}{b_1}, \quad B_1 = B_1^* K_1, \quad M_1 = M_1^* K_3, \quad I_1 = \frac{I_1^* o}{w_1}, \quad N_2 = \frac{N_2^*}{b_2}, \\
&B_2 = B_2^* K_2, \quad M_2 = M_2^* K_4, \quad I_2 = \frac{I_2^* o}{w_2}, \quad t = \frac{t^*}{a_1},
\end{aligned}$$

where the starred quantities are nondimensional. For convenience, we set

$$\begin{array}{lllllll}
\hat{c_1} = \frac{c_1 K_1}{a_1}, & \hat{d_1} = \frac{d_1 K_3}{a_1}, & \hat{a_2} = \frac{a_2}{a_1}, & \hat{c_2} = \frac{c_2 K_2}{a_1}, & \hat{d_2} = \frac{d_2 K_4}{a_1}, & \hat{e_1} = \frac{e_1}{a_1}, & \\
\hat{f_1} = \frac{f_1 K_3}{K_1}, & \hat{g_1} = \frac{g_1}{a_1 b_1 K_1}, & \hat{h_1} = \frac{h_1 o}{w_1 a_1}, & \hat{e_2} = \frac{e_2}{a_1}, & \hat{f_2} = \frac{f_2 K_4}{K_2}, & \hat{g_2} = \frac{g_2}{b_2 K_2 a_1}, & \\
\hat{h_2} = \frac{h_2 o}{w_2 a_1}, & \hat{j_1} = \frac{j_1}{a_1}, & \hat{l_1} = \frac{l_1 K_1}{K_3}, & \hat{m_1} = \frac{m_1}{a_1 b_1 K_3}, & \hat{n_1} = \frac{n_1 o}{w_1 a_1}, & \hat{\mu_1} = \frac{\mu_1}{a_1}, & \\
\hat{\mu_2} = \frac{\mu_2}{a_1}, & \hat{\alpha} = \frac{K_4}{K_3}, & \hat{j_2} = \frac{j_2}{a_1}, & \hat{l_2} = \frac{l_2 K_2}{K_4}, & \hat{m_2} = \frac{m_2}{a_1 K_4 b_2}, & \hat{n_2} = \frac{n_2 o}{w_2 a_1}, & \\
\hat{w_1} = \frac{w_1}{a_1}, & \hat{p_1} = \frac{p_1}{a_1}, & \hat{q_1} = \frac{q_1}{K_1}, & \hat{r_1} = \frac{r_1}{a_1}, & \hat{s_1} = \frac{s_1}{K_3}, & \hat{u_1} = \frac{u_1 K_1}{a_1}, & \\
\hat{v_1} = \frac{v_1 K_3}{a_1}, & \hat{\gamma_1} = \frac{\gamma_1}{a_1}, & \hat{\gamma_2} = \frac{\gamma_2}{a_1}, & \hat{\beta} = \frac{w_1}{w_2}, & \hat{w_2} = \frac{w_2}{a_1}, & \hat{p_2} = \frac{p_2}{a_1}, & \\
\hat{q_2} = \frac{q_2}{K_2}, & \hat{r_2} = \frac{r_2}{a_1}, & \hat{s_2} = \frac{s_2}{K_4}, & \hat{u_2} = \frac{u_2 K_2}{a_1}, & \hat{v_2} = \frac{v_2 K_4}{a_1}. &&
\end{array}$$

Thus, the ODE system of nondimensionalized equations takes the following form:

$$\frac{dN_1^*}{dt^*} = N_1^* - (N_1^*)^2 - \hat{c_1} B_1^* N_1^* - \hat{d_1} M_1^* N_1^*, \tag{14}$$

$$\frac{dN_2^*}{dt^*} = \hat{a_2} N_2^* - \hat{a_2} (N_2^*)^2 - \hat{c_2} B_2^* N_2^* - \hat{d_2} M_2^* N_2^*, \tag{15}$$

$$\frac{dB_1^*}{dt^*} = \hat{e_1} B_1^* (1 - B_1^* - \hat{f_1} M_1^*) - \hat{g_1} B_1^* N_1^* - \hat{h_1} B_1^* I_1^*, \tag{16}$$

$$\frac{dB_2^*}{dt^*} = \hat{e_2} B_2^* (1 - B_2^* - \hat{f_2} M_2^*) - \hat{g_2} B_2^* N_2^* - \hat{h_2} B_2^* I_2^*, \tag{17}$$

$$\frac{dM_1^*}{dt^*} = \hat{j_1} M_1^* (1 - M_1^* - \hat{l_1} B_1^*) - \hat{m_1} M_1^* N_1^* - \hat{n_1} M_1^* I_1^* - \hat{\mu_1} M_1^* + \hat{\mu_2} \hat{\alpha} M_2^*, \tag{18}$$

$$\frac{dM_2^*}{dt^*} = \hat{j_2} M_2^* (1 - M_2^* - \hat{l_2} B_2^*) - \hat{m_2} M_2^* N_2^* - \hat{n_2} M_2^* I_2^* - \hat{\mu_2} M_2^* + \frac{\hat{\mu_1}}{\hat{\alpha}} M_1^*, \tag{19}$$

$$\frac{dI_1^*}{dt^*} = \hat{w_1} + \frac{\hat{p_1} I_1^* B_1^*}{\hat{q_1} + B_1^*} + \frac{\hat{r_1} I_1^* M_1^*}{\hat{s_1} + M_1^*} - \hat{u_1} I_1^* B_1^* - \hat{v_1} I_1^* M_1^* - \hat{w_1} I_1^* - \hat{\gamma_1} I_1^* + \hat{\gamma_2} \hat{\beta} I_2^*, \tag{20}$$

$$\frac{dI_2^*}{dt^*} = \hat{w_2} + \frac{\hat{p_2} I_2^* B_2^*}{\hat{q_2} + B_2^*} + \frac{\hat{r_2} I_2^* M_2^*}{\hat{s_2} + M_2^*} - \hat{u_2} I_2^* B_2^* - \hat{v_2} I_2^* M_2^* - \hat{w_2} I_2^* - \hat{\gamma_2} I_2^* + \frac{\hat{\gamma_1}}{\hat{\beta}} I_1^*. \tag{21}$$

The above system of equations is used to find a healthy equilibrium point for the two patch model. A healthy equilibrium is again defined as having some normal and immune cells in each patch and no tumor cells. So, B_1^*, B_2^*, M_1^*, and M_2^* all equal zero. This makes equations (16), (17), (18), and (19) trivially satisfied. The remaining equations are set equal to zero and we solve for N_1^*, N_2^*, I_1^*, and I_2^*. Equations (14) and (15) are simple and result in $N_1^* = 1$ and $N_2^* = 1$. Equations (20) and (21) are more complicated and simplify in the following manner

$$I_1^* = \frac{\hat{w}_1 + \hat{\gamma}_2\hat{\beta}I_2^*}{\hat{w}_1 + \hat{\gamma}_1}, \qquad I_2^* = \frac{\hat{w}_2 + \frac{\hat{\gamma}_1}{\hat{\beta}}I_1^*}{\hat{w}_2 + \hat{\gamma}_2}.$$

After substitution we obtained

$$I_1^* = \frac{\hat{w}_1\hat{w}_2 + \hat{w}_1\hat{\gamma}_2 + \hat{\gamma}_2\hat{\beta}\hat{w}_2}{\hat{w}_1\hat{w}_2 + \hat{w}_2\hat{\gamma}_1 + \hat{w}_1\hat{\gamma}_2}, \qquad I_2^* = \frac{\hat{w}_1\hat{w}_2\hat{\beta} + \hat{w}_2\hat{\gamma}_1\hat{\beta} + \hat{w}_1\hat{\gamma}_1}{\hat{\beta}(\hat{w}_1\hat{w}_2 + \hat{w}_1\hat{\gamma}_2 + \hat{w}_2\hat{\gamma}_1)}.$$

From now we will denote these values I_1^* and I_2^* by w_1^* and w_2^* respectively. Thus, the healthy equilibrium point for the two patch model is $(N_1^*N_2^*, B_1^*, B_2^*, M_1^*, M_2^*, I_1^*, I_2^*) = (1, 1, 0, 0, 0, 0, w_1^*, w_2^*)$.

3.2 Determining Stability of Healthy Equilibrium Point $(1, 1, 0, 0, 0, 0, w_1^*, w_2^*)$

We use methods very similar to those used in our analysis of the healthy equilibrium point for the one patch model to determine the stability of this equilibrium point. After linearizing the system of equations (14-21) about the point $(N_1^*N_2^*, B_1^*, B_2^*, M_1^*, M_2^*, I_1^*, I_2^*) = (1, 1, 0, 0, 0, 0, w_1^*, w_2^*)$, we arrive at

$$\begin{aligned}
\hat{N_1}' &= -\hat{N_1} - \hat{c_1}\hat{B} - \hat{d_1}\hat{M_1}, \\
\hat{N_2}' &= -\hat{a_2}\hat{N_2} - \hat{c_2}\hat{B_2} - \hat{d_2}\hat{M_2}, \\
\hat{B_1}' &= e_1^*\hat{B_1}, \\
\hat{B_2}' &= e_2^*\hat{B_2}, \\
\hat{M_1}' &= j_1^*\hat{M_1} + \hat{\mu_2^*}\hat{M_2}, \\
\hat{M_2}' &= \mu_1^*\hat{M_1} + j_2^*\hat{M_2}, \\
\hat{I_1}' &= p_1^*\hat{B_1} + r_1^*\hat{M_1} - \gamma_1^*\hat{I_1} + \gamma_2^*\hat{I_2}, \\
\hat{I_2}' &= p_2^*\hat{B_2} + r_2^*\hat{M_2} + \phi_1^*\hat{I_1} - \phi_2^*\hat{I_2},
\end{aligned}$$

where $e_1^* = \hat{e_1} - \hat{g_1} - \hat{h_1}w_1^*$, $e_2^* = \hat{e_2} - \hat{g_2} - \hat{h_2}w_2^*$, $j_1^* = \hat{j_1} - \hat{m_1} - \hat{n_1}w_1^* - \hat{\mu_1}$, $\mu_2^* = \hat{\mu_2}\hat{\alpha}$, $j_2^* = \hat{j_2} - \hat{m_2} - \hat{n_2}w_2^* - \hat{\mu_2}$, $\mu_1^* = \frac{\hat{\mu_1}}{\hat{\alpha}}$, $p_1^* = \frac{\hat{p_1}w_1^*}{\hat{q_1}} - \hat{u_1}w_1^*$, $r_1^* = \frac{\hat{r_1}w_1^*}{\hat{s_1}} - \hat{v_1}w_1^*$, $\gamma_1^* = \hat{w_1} + \hat{\gamma_1}$, $\gamma_2^* = \hat{\gamma_2}\hat{\beta}$, $p_2^* = \frac{\hat{p_2}w_2^*}{\hat{q_2}} - \hat{u_2}w_2^*$, $r_2^* = \frac{\hat{r_2}w_2^*}{\hat{s_2}} - \hat{v_2}w_2^*$, $\phi_1^* = \frac{\hat{\gamma_1}}{\hat{\beta}}$, and $\phi_2^* = \hat{w_2} + \hat{\gamma_2}$.

One can easily show that the eigenvalues associated with the above system of equations are given by

$$\begin{aligned}
&\lambda_1 = -1,\ \lambda_2 = -\hat{a}_2,\ \lambda_3 = e_1^*,\ \lambda_4 = e_2^*, \\
\lambda_5 &= \frac{1}{2}\left(-\gamma_1^* - \phi_2^* - \sqrt{(\gamma_1^*)^2 - 2\gamma_1^*\phi_2^* + (\phi_2^*)^2 + 4\gamma_2^*\phi_1^*}\right), \\
\lambda_6 &= \frac{1}{2}\left(-\gamma_1^* - \phi_2^* + \sqrt{(\gamma_1^*)^2 - 2\gamma_1^*\phi_2^* + (\phi_2^*)^2 + 4\gamma_2^*\phi_1^*}\right), \\
\lambda_7 &= \frac{1}{2}\left(j_1^* + j_2^* - \sqrt{(j_1^*)^2 - 2j_1^*j_2^* + (j_2^*)^2 + 4\mu_1^*\mu_2^*}\right), \\
\lambda_8 &= \frac{1}{2}\left(j_1^* + j_2^* + \sqrt{(j_1^*)^2 - 2j_1^*j_2^* + (j_2^*)^2 + 4\mu_1^*\mu_2^*}\right).
\end{aligned}$$

As discussed above, the healthy equilibrium point is asymptotically stable if and only if $\lambda_i < 0$ for all $i = 1, \ldots 8$. Similarly to the one patch model, the stability of the healthy equilibrium point depends on the

birth rate of the benign and metastatic cells and the rate at which they compete with normal cells and are killed by immune cells.

In particular, note that to ensure that $\lambda_5 < 0$ and $\lambda_6 < 0$ is equivalent to $\lambda_5 + \lambda_6 < 0$ and $\lambda_5\lambda_6 > 0$. After some algebraic manipulations one can check that this is satisfied for all physical values of the parameters (as we are assuming that $\hat{\gamma}_i$ and $\hat{w}_i$ are non-negative).

On the other hand, having $\lambda_7 < 0$ and $\lambda_8 < 0$ is equivalent to $j_1^* + j_2^* < 0$ and $\hat{\mu_1}\hat{\mu_2} < j_1^* j_2^*$. Keeping everything else fixed, these conditions, together with $\lambda_3 < 0$ and $\lambda_4 < 0$, can be satisfied by making ω_1^* and ω_2^* sufficiently large. In other words, if the number of immune cells in each patch is sufficiently large, the healthy equilibrium is stable. This analysis lends support for the effectiveness of immunotherapy.

4 Discussion

We based our analysis on mathematical models of cancer introduced in [3], where three types of cells were considered: normal, tumor, and immune cells. In our model, however, the tumor cell population is split into two different types of cells - metastatic and benign, thus arriving to what we refer to as the "one patch model". Necessary and sufficient conditions for the stability of the healthy equilibrium point were derived analytically and studied numerically. Further, the effects of immunotherapy were studied, both in the case of a stable healthy equilibrium and in the case of an unstable one. In the former case, a person's tumor cell population can be eradicated using immunotherapy, while in the latter case, after an initial decline in the tumor population, the metastatic tumor cells can come back. Furthermore, in order to capture the effects of cell migration, the two patch model was created and necessary and sufficient conditions for stability of the healthy equilibrium point were derived.

For future investigations, a more in depth biological background could help with a more accurate choice of the parameters for the numerical experiments. An understanding of how cancer moves in the body can assist in finding ways to control aspects, such as metastatic cell mobility and the rapid growth rates of the benign and metastatic cell populations, which make cancer such a lethal disease.

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