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MATHEMATICAL MODEL OF IMMUNOTHERAPY RESPONSE TO ANTIBODIES AS A TREATMENT FOR CANCER

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Abstract. Immunotherapy is a significant cancer treatment as it uses the body's natural immune system to fight cancer. To help boost the immune system, monoclonal antibodies (MABs) are used as they bind to cancer cells helping the immune system recognize these cells. In this paper, we present a mathematical model of nonlinear partial differential equations describing the interaction between the immune cells, MABs, and cancer cells. After nondimensionalizing the model, we analyzed the long-term behavior and found later that it is consistent with the numerical results. Then, we calculated the numerical solutions of the model with different values of the parameters (relative growth rate of cancer cells and the number of immune cells that are removed after killing a cancer cell) to determine the values that help increase the effectiveness of the treatment. We have considered the continuous delivery of antibodies over a certain period of time. These simulations showed that immune cells will eradicate cancer if the number of immune cells that are removed after killing a cancer cell is less than one. However, if each immune cell kills only one cancer cell, then the treatment reduces the cancer to a steady state or almost a steady state. On the other hand, if the relative growth rate of cancer cells is very small and each cancer cell needs more than one immune cell to kill it, then again, we get a steady state for cancer. However, if the relative growth rate is

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not small, then the cancer will grow after an initial decrease. This study could be implemented into a clinical trial with different delivery protocols of the drug to improve cancer treatment.

Keywords: antibodies; cancer; drug delivery; immunotherapy; mathematical modeling.

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1. INTRODUCTION

The immune system is a network of different cell types and proteins cooperating together to maintain the safety of an organism by constantly protecting it from invading pathogens, such as viruses, bacteria, and mutated cells. Lymphocytes, neutrophils, and monocytes/macrophages are able to detect the presence of a foreign body and can then mount an efficient response aimed at their elimination in a short period. A robust defending system consists of a rapid nonspecific immunity of two types: innate immunity and specific adaptive immunity. The innate immune system, a naturally existing shield, is usually enough to eliminate foreign molecules without the activation of a more advanced targeted immunity. The adaptive immune system consumes more time to respond, however, it is important since it specifically targets the foreign antigen and has a permanent memory for any future attack [1, 2].

Cancer starts to form when a series of mutations take place in normal cells which lead the cells to outgrow and divide uncontrollably. These genetic mutations cause the cancer cell to have a different protein signature than normal cells. Different types of cancer treatments include: monoclonal antibodies, cancer growth blockers, and anti angiogenics (drugs that block cancer blood vessel growth). In monoclonal antibodies (MABs), the word "monoclonal" indicates that a single antibody clone, with identical properties and specifications, is produced [3]. MABs can attach to cancer cells stimulating the immune system to recognize and eliminate them [4]. In particular, MABs bind antigens on the surface of the cancer cells and this activates specific immune cells, for example natural killer (NK) cells, and the latter release cytotoxic factors, which in turn kill cancer cells. This mechanism is called antibody-dependent cell-mediated cytotoxicity (ADCC) [5]. Moreover, the antibody could itself exert an antitumor effect by blocking a specific protein, which keeps the immune cells from attacking cancer cells [6]. The

benefit of using MABs in cancer treatment is that they are less likely to have serious side effects than conventional treatments [7]. They have also shown success in clinical trials [8–10].

Mathematical modeling is a useful tool in understanding the role of the immune system in killing cancer alone or in conjunction with other treatments, which stimulate it. Hoffman et al. [11], formulated a system of ordinary differential equations (ODEs) to model how the rate, at which NK cells kill cancer cells depends on how much antibody is bound to the cancer cells . The parameters were estimated from experiments; and the numerical results showed that the ADCC processes depended on the initial concentration of antibody and NK-cancer cell ratio [11]. Another system of ODEs, describing the tumor and immune interaction by focusing on the role of NK and CD8+T cells in killing cancer cells directly, was presented by [12]. CD8+T cells are a type of T-lymphocytes, which can be cytotoxic to tumor cells. The results of the experiments and the simulation showed the importance of increasing the CD8+T-cell activation to promote tumor killing [12]. Moreover, the sensitivity analysis indicated which variable makes the model most sensitive; and that it is patient specific [12]. We therefore know which patient is likely to have a successful treatment according to the prediction of the model. Another mathematical model consisting of a system of ODEs and based on the clinical evidence that antibodies can kill cancer cells directly was presented by [13]. The antibodies were produced by B cells and plasma cells. The results showed that the growth of cancer cells could be controlled by the value of the rate at which antibodies kill cancer cells directly [13]. In particular, as this rate crosses a critical value, antibodies are able to eradicate cancer for any initial size [13]. Kirschner and Panetta [14] introduced a mathematical model for the interaction between cancer cells and the activated immune cells (for example, T and NK cells) with the presence of interleukin-2 (IL-2). They found that if the administration of antitumor immune cells (adoptive cellular immunotherapy ACI) has a concentration above a critical value, then cancer is eradicated. On the other hand, a low amount of IL-2 does not boost the immune system enough to get rid of cancer, and high amounts make the immune system grow without a bound, and the combination of ACI and IL-2 gave the best results [14].

In this paper, we investigate the role of the monoclonal antibodies in cancer immunotherapy by using a mathematical model, which is an extension to the chemotherapy models in [15, 16].

Our hypothesis is based on stimulating the immune system so it can attack and kill cancer. This is done by using MABs, which bind to the cancer cells, thus, helping the immune system recognize and attack them (ADCC). The main goal of the model is to study the interaction between cancer cells, antibodies, and immune cells and find the prameter values which help erradicate cance. After introducing the model, we analyze it and solve it numerically to find the parameters that help reduce the cancer. We assume that the antibodies are given to the patient in a continuous manner over a certain period of time. First, we introduce the formulation of the model in section 2, then we nondimensionalize it (section 2), and discuss the long-term response in section 3. Then we perform a numerical simulation of the model for different values of the parameters (section 3). Finally, we present the discussion and conclusion in section 4.

2. MATHEMATICAL MODEL

The main goal of our mathematical model is to investigate how the immune system can eradicate cancer with the help of antibodies. Therefore we have a system of three coupled partial differentia equations (PDEs), which describes the space and time evolution of three types of densities: $\sigma(\mathbf{x},t)$, the density of antibodies; $\rho(\mathbf{x},t)$, the density of cancer cells, and $\psi(\mathbf{x},t)$, the density of immune cells. The first equation describes the diffusion of antibodies and the uptake by cancer cells. The second equation describes the death rate of cancer cells by immune cells due to the history of uptake of antibodies. Also, in the absence of immune cells (the first term on the right hand side = 0) cancer cells will grow exponentially. The third equation describes the removal of immune cells after killing cancer cells and the growth rate of immune cells. We will assume that the domain is cylindrically symmetric (for convenience since the system will then depend only on time and radial distance r). By considering these assumptions, the model is governed by the following system of nonlinear PDEs:

$$
\begin{aligned}
\frac{\partial \sigma}{\partial t} &= D \bigtriangledown^2 \sigma - \lambda_b \sigma \rho, \\
\frac{\partial \rho}{\partial t} &= -\lambda_d \psi \rho \int_0^t \lambda_b \sigma \rho \, d\tau + \alpha_1 \rho, \\
\frac{\partial \psi}{\partial t} &= \lambda_r A + \alpha_2 \psi,
\end{aligned} \tag{1}
$$

where D is the antibodies diffusivity, λ_b is the binding rate of antibodies to cancer cells λ_d is the death rate of cancer cells, α_1 is the growth rate of cancer cells, α_2 is the growth rate of immune cells, λ_r is the number of immune cells that are removed after killing a cancer cell, and $A = -\lambda_d \psi \rho \int_0^t \lambda_b \sigma \rho d\tau$. In the first equation we will replace the partial derivative by zero because the diffusion of antibodies is faster than the cell cycle (it does not depend on time). Thus, we need two boundary conditions for the first equation and two initial conditions for the second and third equations as follows:

$$
\begin{aligned}
\rho(r,0) &= \rho_0, \\
\psi(r,0) &= \psi_0, \\
\sigma(r_b,t) &= \sigma_0(t), \\
\frac{d\sigma}{dr}\Big|_{r=\frac{r_b}{\sqrt{BVF}}} &= 0,
\end{aligned}
\tag{2}
$$

where r_b is the raduis of the blood vessel and BVF is the blood volume fraction [15]. A large value of BVF represents a tumor with high vascularization; hence enabling more treatment to reach the tumor cell. Note that the density of cancer and immune cells is initially homogeneous and there is no flux of antibodies at the right boundary.

The PDEs model in (1) is an extension to the models represented by [15, 16] for chemotherapy, and we used similar assumptions. Indeed, if the density of immune cells is constant everywhere (they do not kill cancer and are not removed), then we get the chemotherapy case presented by [15, 16]. In that case the antibodies would have the same role as chemotherapy that is killing cancer. Therefore the three equations (1) would be reduced to two. For details about the assumptions (in particular, the integral in the second equation and replacing the partial derivative in the first equation by zero) and the choice of initial and boundary conditions, refer to [15, 16].

Nondimensionalizing

We nondimensionalize the previous system before solving it numerically to reduce the unknown

parameters for simplicity with the following scaling:

$$r^{'} = \frac{r}{L},\ t^{'} = \frac{t}{T},\ \rho^{'} = \frac{\rho}{\rho_0},\ \psi' = \frac{\psi}{\psi_0},\ \sigma^{'} = \frac{\sigma}{\overline{\sigma}_0},$$

where $L = \sqrt{\dfrac{D}{\lambda_b \rho_0}}$ is the diffusion length of antibodies, $T = (\lambda_d \lambda_b \overline{\sigma}_0 \psi_0 \rho_0)^{-\frac{1}{2}}$ is the time of the apoptotic cycles caused by immune cells after the uptake of antibodies, and $\overline{\sigma}_0 = \max_{t>0} \sigma_0(t)$. Thus, the system becomes

$$\begin{aligned} 0 &= \bigtriangledown^{'2}\sigma^{'} - \sigma^{'}\rho^{'}, \\ \frac{\partial \rho^{'}}{\partial t^{'}} &= -\psi^{'}\rho^{'}\int_0^{t^{'}} \sigma^{'}\rho^{'} d\tau + \overline{\alpha}_1 \rho^{'}, \\ \frac{\partial \psi^{'}}{\partial t^{'}} &= \overline{\lambda}_r A^{'} + \overline{\alpha}_2 \psi^{'}, \end{aligned} \tag{3}$$

with the following boundary and initial conditions

$$\begin{aligned} \rho^{'}(r^{'},0) &= 1, \\ \psi^{'}(r^{'},0) &= 1, \\ \sigma^{'}(\frac{r_b}{L},t^{'}) &\leq 1, \\ \frac{d\sigma^{'}}{dr^{'}}\,|_{r^{'}=\frac{r_b}{L\sqrt{BVF}}} &= 0, \end{aligned} \tag{4}$$

where the relative growth rates are $\overline{\alpha}_1 = \alpha_1 T$ and $\overline{\alpha}_2 = \alpha_2 T$. Also $A^{'} = -\psi^{'}\rho^{'}\int_0^{t^{'}} \sigma^{'}\rho^{'} d\tau$ and $\overline{\lambda}_r = \dfrac{\lambda_r \rho_0}{\psi_0}$. We will drop the dash for convenience. Hereafter, we will assume that $\rho_0 = \psi_0$ (thus $\overline{\lambda}_r$ is the number of immune cells that are removed after killing a cancer cell) and the growth rate of immune cells is zero ($\overline{\alpha}_2 = 0$).

3. RESULTS

3.1. long-term response. To analyze the long-term response, we suppose that the growth rate of cancer is zero ($\overline{\alpha}_1 = 0$). After a long period of time, the cancer cells will be saturated with antibodies and thus the integration in (3) becomes a constant: $\int_0^t \sigma\rho d\tau = \beta$. Thus, from the third equation we get $\psi = 1 + \overline{\lambda}_r(\rho - 1)$. Therefore,

$$\frac{\partial \rho}{\partial t} = -\rho[1 + \overline{\lambda}_r(\rho - 1)]\beta. \tag{5}$$

Here we consider four significant cases for $\overline{\lambda}_r$. First, if $\overline{\lambda}_r = 0$ we get an ideal case (unrealistic) in which the immune cells keep killing cancer cells without dying. Therefore, the density of immune cells is constant and thus from (5) cancer cells will decay exponentially ($\rho = e^{-\beta t}$). Second, if $0 < \overline{\lambda}_r < 1$, this means that every immune cell kills more than one cancer cell. For example, when $\overline{\lambda}_r = 0.5$, this represents the case where one immune cell kills two cancer cells. We will study this case numerically in section 3.3. Third, if the immune cells are removed at the same rate as cancer cells, then $\overline{\lambda}_r = 1$. Therefore, from (5) we have $\rho = 1/(1+\beta t)$. This will make the death rate less than the first case. Finally, if every cancer cell needs more than one immune cell to kill it, this gives $\overline{\lambda}_r > 1$. From (5), cancer cells will die if $-\rho[1+\overline{\lambda}_r(\rho-1)] \leq 0$. Thus, $1-\rho \leq (\overline{\lambda}_r)^{-1} < 1$. So for this case the density of cancer cells will decay to reach the value of $(\overline{\lambda}_r)^{-1}$ and they will not die completely. In addition, the death rate becomes less as the value of $\overline{\lambda}_r$ is increased since $\rho \to 1$ as $\overline{\lambda}_r \to \infty$. In the next sections, we will solve the model numerically and compare the result with this analysis.

3.2. Numerical solution. We study the nondimentionalized model (3), (4) numerically for different values of the parameters. The parameters are reduced to $\overline{\alpha}_1$, $\overline{\alpha}_2$, $\overline{\lambda}_r$, $\frac{r_b}{L}$ and BVF. We will fix the values of $\frac{r_b}{L}$ and BVF such that $\frac{r_b}{L} = 0.5$ and BVF=0.05 [15, 16]. Regarding the antibodies, they can be given periodically in cycles [17] or continuously over a certain period of time. The latter can be done using nanotechnology [18]. We will consider continuous infusion of the drug in our numerical simulations; and thus $\sigma(r_b/L,t) = 1$.

To solve the system (3), (4), we first spatially discretize the initial values of ρ and ψ. Then, at each time step, we find the value of σ in the first equation by using the finite difference method [19], where ρ is given from the previous time step. Moreover, we calculate the values of ρ and ψ in the second and third equations by using the fourth order Runge-Kutta method [20].

In each time step, we calculate the ratio of the viable cancer mass M to its mass M_0 over the cylindrically symmetric domain

$$f(t) = \frac{M}{M_0} = \frac{2\pi}{V} \int_{\frac{r_b}{L}}^{\frac{r_b}{L\sqrt{BVF}}} \rho r dr, \tag{6}$$

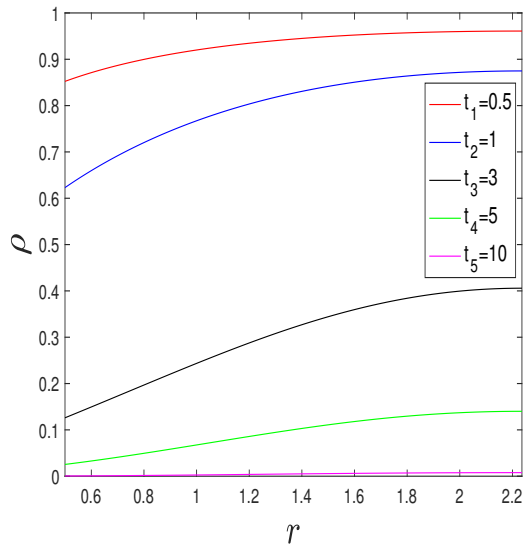
where $V = \pi \left[\left(\frac{r_b}{L\sqrt{BVF}} \right)^2 - \left(\frac{r_b}{L} \right)^2 \right]$. Note that $M_0 = V$ since $\rho(r,0) = 1$. This ratio is calculated to investigate whether the cancer will grow or decay over a period of time after giving the antibodies.

Figure 1 represents a numerical simulation of (3), (4) for BVF= 0.05, $r_b/L = 0.5$, $\overline{\lambda}_r = 0.5$, $\overline{\alpha}_1 = 3.2991 \times 10^{-6}$, and $\overline{\alpha}_2 = 0$ for 20 apoptotic cycles (caused by the antibodies). The solution in Figure 1(a) shows that the normalized density of cancer cells becomes close to zero in about 10 cycles. In Figure 1(b) the normalized density of immune cells will decay due to the killing of cancer, then becomes constant afterwards. Figure 1(c) shows that the antibodies decrease when they diffuse into cancer cells (since cancer cells uptake them). Then, after 10 cycles they begin to reach a constant value since the immune cells have almost killed the cancer cells and there is small uptake of antibodies. In Figure 1(d) the ratio of the viable cancer mass to its initial mass shows that after approximately 12 cycles the cancer cells die.

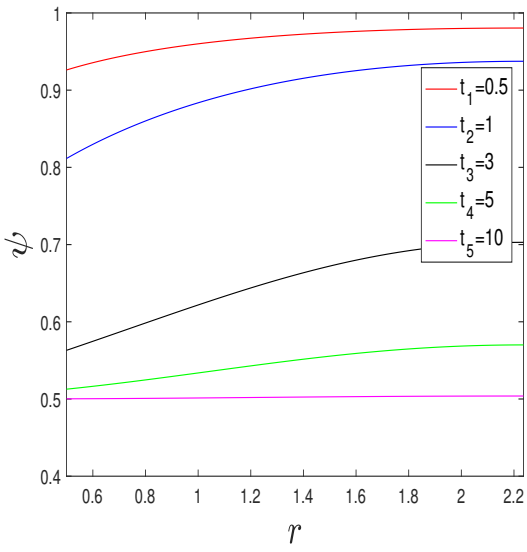
3.3. Parameter analysis. Figure 2 shows that, for the number of immune cells that are removed after killing a cancer cell ($\overline{\lambda}_r$), if $0 \leq \overline{\lambda}_r < 1$, after a short period of time all cancer cells will die (for four different values of $\overline{\alpha}_1$). This shows that, even if we increase the relative growth rate of cancer cells, the immune cells can eradicate the cancer. While, if $\overline{\lambda}_r > 1$, the cancer cells will decrease at the beginning of the treatment. Then afterwards, they will either grow continuously (for larger values of $\overline{\alpha}_1$) or will reach a steady state. When $\overline{\lambda}_r = 1$, and $\overline{\alpha}_1$ is increasing, the cancer almost reaches a steady state. In Figure 2, as the relative growth rate of cancer cells ($\overline{\alpha}_1$) increases (compare the figures clockwise for a fixed value of $\overline{\lambda}_r > 1$) we find that after the beginning of the simulation cancer cells will not have a steady state and instead, they will increase.

These simulations show that, if the number of immune cells that are removed after killing cancer cells is between zero and one or is equal to zero, we get the best result. Otherwise for $\overline{\lambda}_r > 1$, the relative growth rate of cancer cells must be very small to reduce the cancer and reach a steady state.

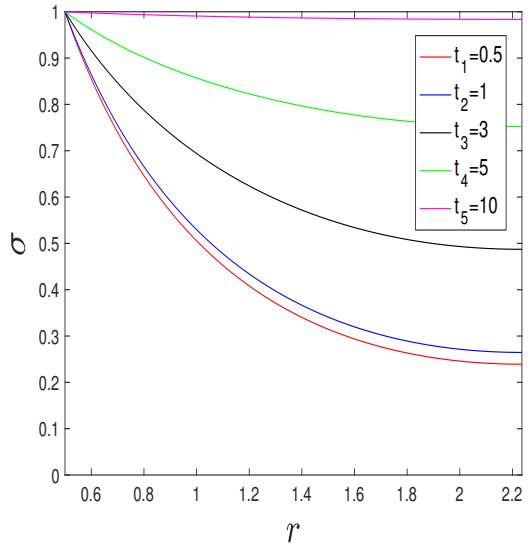
For the case where $\overline{\alpha}_1 = 0$, the simulations in Figure 2(a) show that after a long time period cancer cells decay exponentially if $\overline{\lambda}_r = 0$. The death rate becomes less when $\overline{\lambda}_r = 1$. Finally,



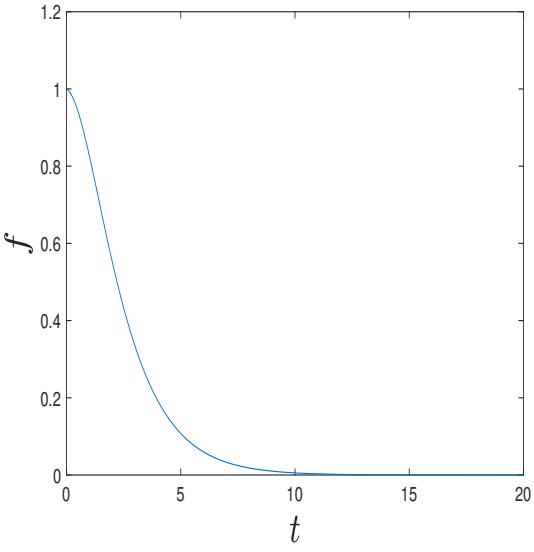
(a) Normalized cancer density



(b) Normalized immune density



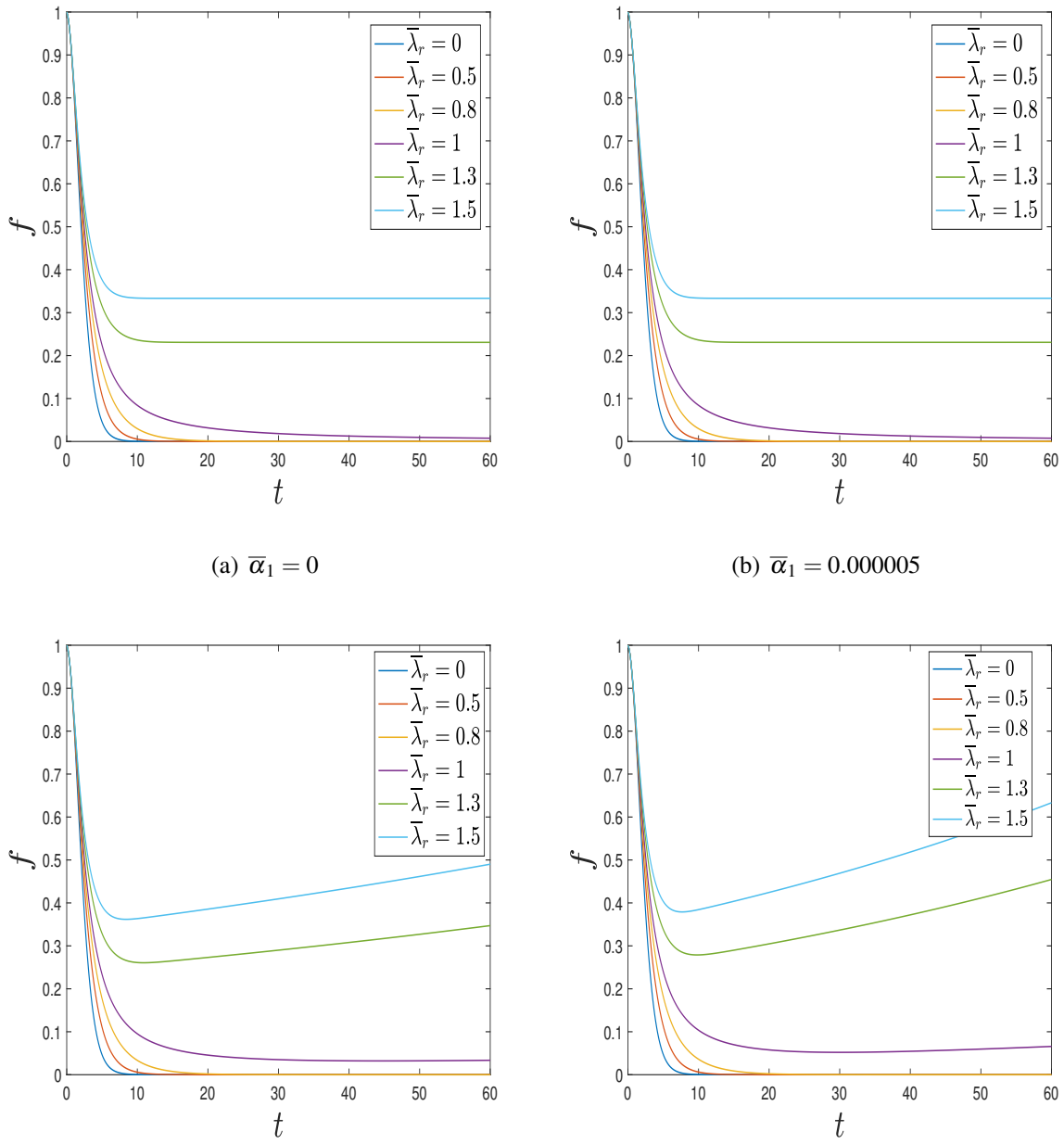
(c) Normalized antibody density



(d) Normalized cancer mass

FIGURE 1. Numerical solution of (3), (4), where BVF$=0.05$, $r_b/L=0.5$, $\overline{\alpha}_1 = 3.2991\times10^{-6}$, $\overline{\alpha}_2=0$, and $\overline{\lambda}_r=0.5$ for 20 cycles. The plot of f in (d) shows that cancer cells die after approximately 12 apoptotic cycles.

cancer cells reach a steady state such that $1-\rho=(\overline{\lambda}_r)^{-1}$ for $\overline{\lambda}_r>1$. All of these results are consistent with the long-term response analysis given in section 3.1.



(a) $\overline{\alpha}_1 = 0$

(b) $\overline{\alpha}_1 = 0.000005$

(c) $\overline{\alpha}_1 = 0.006$

(d) $\overline{\alpha}_1 = 0.01$

FIGURE 2. The curves of the normalized cancer mass plotted against t and calculated numerically from (6) with different values of $\overline{\lambda}_r$ as given in the legend in each graph. In addition, the value of $\overline{\alpha}_1$ is given under each figure. Here BVF$= 0.05$, $r_b/L = 0.5$, and $\overline{\alpha}_2 = 0$.

4. DISCUSSION AND CONCLUSION

In this paper, we formulated a mathematical model of PDEs to study the effect of immunotherapy, supported by antibodies, on cancer and to investigate the long-term response.

This model is an extension of the chemotherapy model presented by [15]. In their model, chemotherapy is given to the patient continuously over a period of time and the PDEs represent the diffusion of this drug and the cancer cell death. Later [16] studied the same model after adding a term representing the growth of cancer cells. In our model we assume that antibodies are given to the patient in the same manner as was chemotherapy given in the former models. However, after antibodies diffuse into cancer, unlike chemotherapy, they do not kill cancer cells but only attach to them. This mechanism makes the immune cells recognize and kill cancer cells. Our model simplifies the complex interaction between antibodies, cancer, and immune cells. It may help in understanding how the immune system fights cancer with the help of antibodies. We assumed that all immune cells are of one kind; therefore, in future studies different kinds of immune cells may be considered as in [21].

After introducing our model, we nondimensionalized it for simplifications; and thus the parameters are reduced to the relative growth rate of cancer and immune cells and the number of immune cells that are removed after killing a cancer cell. We also have other parameters which are BVF and r_b/L which we fixed. Afterwards we analyzed the nondimensionalized model in terms of the long-term response we found that if the growth rate of cancer cells is zero, then the result depends on the number of immune cells that are removed after killing a cancer cell. If immune cells keep killing cancer cells, then cancer will decay exponentially. On the other hand, if each immune cell kills one cancer cell then we get a death rate of cancer, which is less than the previous case. Finally, if each cancer cell needs more than one immune cell to kill it, then cancer will not die completely and it will reach a steady state. These results are consistent with the numerical simulations for the case where the growth rate of cancer cells is zero.

After considering the long-term response, we solved the system numerically with different values of the parameters. In particular, we considered the relative growth rate of cancer cells $\overline{\alpha}_1$ and the number of immune cells that are removed after killing a cancer cell $\overline{\lambda}_r$. Moreover, we assumed that the antibodies were given continuously for specific apoptotic cycles and we neglected the effect of $\overline{\alpha}_2$ (the relative growth rate of immune cells). The numerical simulation showed that if $0 \leq \overline{\lambda}_r < 1$, even if we increase the relative growth rate of cancer cells, the immune cells can still eradicate the cancer. Whereas, if $\overline{\lambda}_r > 1$, the cancer cells will have two

cases; either they grow continuously or they reach a steady state depending on the value of $\overline{\alpha}_1$. Finally, if we increase $\overline{\alpha}_1$ and if $\overline{\lambda}_r = 1$, then the cancer growth almost reaches a steady state.

We conclude that the immune cells will eradicate cancer after a few apoptotic cycles if $\overline{\lambda}_r$ is equal to zero or between zero and one. Otherwise, the cancer will be reduced to reach a steady state if $\overline{\lambda}_r$ is greater than one and the relative growth rate of cancer cells is very small.

For future research, the model can be developed more by adding variables and considering new clinical treatments. In this paper, we have taken $\overline{\alpha}_2 = 0$. In future work, $\overline{\alpha}_2$ can be varied to study the effect of changing this value on the result of the model. Also in this paper, we assumed that the drug was given continuously over a certain period of time; in future studies, the case where the drug is given in a periodic manner (convectional treatment) may be considered to improve our understanding of the effect of different delivery techniques for cancer treatment. This may help oncologists choose the optimal strategy for treatment by raising their awareness of the possible outcomes.

CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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