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Dynamics of tumor–CD4$^+$–cytokine–host cells interactions with treatments

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ABSTRACT

Mathematical models of interactions between tumor cells, CD4$^+$ T cells, cytokines, and host cells are proposed to investigate the role of CD4$^+$ on tumor regression. Our results suggest that host cells along with the mechanism of production of CD4$^+$ T cells play important roles in driving tumor dynamics. Cancer cells can be eradicated if the tumor has a small growth rate and is also not competitive. Treatments by either CD4$^+$, cytokines, or a combination of the two are applied to study their effectiveness. It is concluded that doses of treatments along with the tumor size are critical in determining the fate of the tumor. Tumor cells can be eliminated completely if doses of treatments by cytokine are large. The treatments are in general more effective if the tumor size is smaller. Bistability is observed in all of the models with or without the treatment strategies indicating that there is a window of opportunity for clearing off the tumor cells.

1. Introduction

Cancer is a leading cause of death worldwide. It is a broad group of diseases involved with unregulated cell growth. It is well accepted that cancer cells have defects in regulatory circuits that govern normal cell proliferation and homeostasis, and the growth signaling pathways suffer deregulation in all human tumors [34]. In cancer, cells divide and grow uncontrollably, forming malignant tumors and invading even the distant parts of the body [34]. Many tumors express antigens that can be recognized by the adaptive immune system and therefore can be used to induce an anti-tumor immune response. The Tumor Immuno-Surveillance Hypothesis formulated in 1957 indicates that the immune system is capable of inhibiting the growth of very small tumors and eliminating them before they become clinically evident [11].

Cancer immunotherapy is the use of the immune system to treat cancer. It frequently involves adopted cellular transfers of T cells and/or cytokines. Cancer immunotherapies have focused much on the antitumor activities of white blood cells, especially T cells (usually CD8$^+$ T cells), natural killer (NK) cells, and macrophages [28]. Experiments have shown that these immune cells can lyse tumor cells very effectively [30,31]. The major histocompatibility complex (MHC) is a set of cell surface molecules encoded by a large gene family in all vertebrates. It mediates interactions of immune cells with other leukocytes or body cells [34]. The MHC gene family is divided into three subgroups: classes I–III. Most cancer immunotherapies are based on the generation of cytotoxic T lymphocyte (CTL) such as CD8$^+$ T cells that recognize tumor antigens in association with MHC class I molecules on tumor cells [24].

Many tumors, however, have evolved to evade recognitions by the white blood cells [24]. For example, it is found that certain cancer cells do not express MHC class I antigens on the cell surface [24]. Traditionally, CD4$^+$ T cells have been

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assumed to have only a helper role by activating $CD8^+$ T cells to kill cancer cells. Recent experiments have shown that $CD4^+$ T cells actually play a more direct role in killing the cancer cells [24,27,36]. Indeed, these $CD4^+$ T cells appear to have an effector role through the cytokines and chemokines that they produce [24,36]. Consequently, $CD4^+$ T cells can kill cancer cells even in the absence of $CD8^+$ T cells and NK cells. In these cases, tumor eradication may be mediated by tumoricidal myeloid cells recruited into the tumors or by anti-angiogenic cytokine, such as IL-4 secreted by $CD4^+$ T cells [24,36].

The interactions between tumor cells and other components of the tumor microenvironment are very complex and continuously changing. Consequently, devising cancer immunotherapies to treat or to cure cancer has proven a very challenging task. Mathematical modeling provides a valuable tool for understanding the complicated interactions among the many components of the tumor microenvironment [7,14,20,21]. In the following, we briefly review several mathematical models of tumor–immune interactions.

The research by Kirschner and Panetta [18] can be considered as the pioneer work in this area. Their model consists of three variables, the tumor cells T, the generic effector cells E such as $CD8^+$ T cells, macrophages or NK cells, and the IL-2 cytokine denoted by I, and is described by the following system

$$\begin{cases} T' = r_2 T(1-bT) - \dfrac{aET}{g_2+T} \\ E' = cT + \dfrac{p_1 ET}{g_1+T} - \mu_2 E + s_1 \\ I' = \dfrac{p_2 ET}{g_3+T} - \mu_3 I + s_2, \end{cases} \tag{1.1}$$

where all of the parameters are positive except possibly for s_1 and s_2 which are nonnegative. Parameters s_1 and s_2 denote continuous treatments of effector cells and IL-2, respectively. In particular, the tumor grows logistically in the absence of the effector cells and the tumor killing rate by the effector cells is modeled by the Michaelis–Menten kinetics. The production of the effector cells and cytokines is also modeled by a Michaelis–Menten term. Using tumor's antigenicity c as the bifurcation parameter, Kirschner and Panetta [18] provide a one-parameter bifurcation diagram when $s_1 = s_2 = 0$ to study the effects of c on model dynamics. Treatments by the effector cells ($s_1 > 0$, $s_2 = 0$), cytokines ($s_1 = 0$, $s_2 > 0$) or both ($s_i > 0$, $i = 1, 2$) are considered. Through numerical investigations, they conclude that treatment by the effector cells can clear off the tumor if c is not too small and the treatment dose is above a critical threshold. This critical dose is determined from local stability of the boundary steady state with the absence of tumor. However, treatment by IL-2 alone does not give a satisfactory outcome. Immunotherapy of effector cells or a combination of the effector cells and IL-2 gives promise outcome for controlling the tumor.

de Vladar and González [8] investigate the following model of tumor–immune interaction with treatments

$$\begin{cases} x' = -\mu_c x \log\dfrac{x}{x_\infty} - \gamma xy \\ y' = \mu_2(x - \beta x^2)y - \delta y + k, \end{cases} \tag{1.2}$$

where x denotes tumor volume and y is the density of effector cells. The parameter x_∞ is the tumor's carrying capacity and k is the constant treatment. Notice that the tumor's growth is modeled by the Gompertzian law which implicitly assumes that the tumor tends to grow when it is near zero. The production of effector cells stimulated by the cancer is modeled by the term $x - \beta x^2 = x(1-\beta x)$ and the killing of the tumor is modeled by a simple mass action. These assumptions are different from those used by Kirschner and Panetta [18]. The system has a unique interior equilibrium and two boundary equilibria of either no tumor or no immune cells. Their model predicts that the theory on immune surveillance is plausible and the constant dose therapies are not able to induce complete remission of the tumor if the treatment is stopped due to the Gompertzian law of tumor growth.

To study the impact of anti-immune activity by tumor on the outcome of immunotherapy, Forys et al. [13] propose the following model of two-dimensional ordinary differential equations :

$$\begin{cases} X' = w - uX + aF(X,Y)X - bXY \\ Y' = rY - cXY, \end{cases} \tag{1.3}$$

where X and Y are the sizes of specific anti-tumor immunity and tumor, respectively. The tumor is assumed to grow exponentially and the killing of tumor is modeled by a simple mass action. The parameters w and u are the constant production rate and loss rate of the immune cells respectively. The stimulation of the immune cells by tumor is assumed either of the form $F(X,Y) = F_1(X,Y) = \frac{(Y/X)^\alpha}{k_1^\alpha + (Y/X)^\alpha}$ so that the stimulation depends on the amount of signal molecules per cell, or of the form $F(X,Y) = F_2(X,Y) = \frac{Y^\alpha}{k_2^\alpha + Y^\alpha}$ where the stimulation is antigen dependent only. All of the parameters are positive except $b \geq 0$. $b > 0$ denotes anti-immunity by tumor since the immune cells are lost due to interaction with the tumor. If $b = 0$, then there is no anti-immunity by tumor. The model exhibits six different types of phase portraits with no limit cycles as analyzed by Forys et al. [13] and the patterns of asymptotic behavior of the system do not depend on the type of the stimulation function F_1 or F_2. It is concluded that weak immunity results in unrestricted tumor growth and the immune system has no control over the growth of large tumor even if there is no anti-immunity by tumor.

The above models focus on the effector roles of $CD8^+$ T cells or any generic effector cells such as NK cells, etc. Since the effector roles of $CD4^+$ have only been discovered very recently, there are two mathematical models that appeared in the

literature. The first published model of $CD4^+$ is established by Eftimie et al. [10]. Their model consists of either six or seven state variables, the tumor, $CD4^+$ cells, tumor suppressing cytokines, tumor promoting cytkoines, type 1 (by Th1 cells) and type 2 (by Th2 cells) cytokines, and possibly other immune cells such as granulocytes (e.g., neutrophils and eosinophils). Since the model is complicated with six or seven equations, we do not present it here. Using numerical simulations and the data given by Mattes et al. [24], Eftimie et al. [10] conclude that the effector role of $CD4^+$ is due to the feedback between Th2 cells and eosinophils.

Motivated by the effector roles of $CD4^+$ cells and an open question raised in a review article by Eftimie et al. [11], Anderson et al. [3] investigate the following three-dimensional model

$$\begin{cases} x' = rx(1 - x/K) - \dfrac{\delta xz}{m + x} \\ y' = \dfrac{\beta xy}{k + x} - ay + I_1 \\ z' = \dfrac{\alpha xy}{b + x} - \mu z + I_2, \end{cases} \tag{1.4}$$

where x is the tumor, y the $CD4^+$ T cells, and z the cytokines produced by the $CD4^+$ T cells. All of the parameters are positive except possibly I_1 and I_2, the constant treatments of $CD4^+$ and cytokine per unit time, respectively, which may be zero. Notice that the tumor grows logistically and the tumor killing rate by cytokines is modeled using the Michaelis–Menten kinetics. Unlike the models proposed by Kirschner and Panetta [18] and by de Vladar and González [8], where the tumor is killed by the effector cells directly, the tumor's killing in this new model (1.4) is due to the cytokines. In addition, the production of $CD4^+$ T cells depends on $CD4^+$ T cells and the tumor. Therefore, it is implicitly assumed that the $CD4^+$ is autocrine. A critical dose of treatment by cytokines is derived for which the tumor can be eliminated completely if the treatment by cytkoines exceeds the critical dose. In addition, the model exhibits periodic solutions in a large parameter space via Hopf bifurcations and the remission and relapse occur frequently.

As we will see later, our proposed new model applies different biological assumptions. In particular, the effector role is $CD4^+$ not the $CD8^+$ in which $CD4^+$ cannot kill tumor cells directly. The $CD4^+$ production is modeled differently which is no longer dependent on the $CD4^+$ as in model (1.4) but on the cytokines. This modeling assumption implies that $CD4^+$ T cells are not activated by themselves but by cytokines. In addition, the host cells are incorporated into the interaction which are absent in both of the mathematical models constructed by Eftimie et al. [10] and Anderson et al. [3].

It is known that tumor cells and normal tissue cells compete for resources and space [34]. In addition, the signaling interactions between the stromal and neoplastic tissues are important in driving tumor cell proliferation [16]. In this work, we propose mathematical models of tumor cells, normal tissue cells, $CD4^+$ T cells and cytokine interactions to investigate possible effects of $CD4^+$ on tumor regression and dormancy. In particular, $CD4^+$ T cells cannot kill tumor cells directly but can secrete and use cytokines to suppress tumor growth. Therefore, the present model is different from that of Kirschner and Panetta [18] and others [8,13,22,25] in which CTLs are killing cancer cells directly. On the other hand, the proposed system is also different from that of [3,10] in that normal tissue cells are incorporated into the present study. We then apply immunotherapies to investigate their effects on tumor regression and persistence. The treatments by $CD4^+$ T cells and cytokines are assumed to be constant over time. This simple assumption is also adopted by several other researchers such as de Pillis et al. [7], Kogan et al. [19], Kirschner and Panetta [18], and more recently by de Vladar and González [8], and Anderson et al. [3] for modeling cancer treatments. Although continuous treatments of immunotherapies are not realistic, it is the first step in understanding the effects of immunotherapy on tumor evolution. In addition to the continuous treatments and motivated by the experiment carried out by Mettes et al. [24], we also discuss pulsed treatments and compare the two treatment strategies.

It has been documented that treatments by cytokine TNF (tumor necrosis factor) may cause influenza/malaria-like side effects in cancer patients [6,17]. Such a side effect is referred to as a cytokine storm [4] recently and the phenomenon has been explored extensively for infectious diseases. In this study, we do not consider the deleterious effect of cytokine treatments on host cells. This simplification is also adopted in de Pillis et al. [7]. In addition, the TNF cytokines are produced mainly by the Th1 cells and here we focus on the cytokines secreted by the Th2 cells.

In the following section, a mathematical model is presented and analysis is carried out on the model of no treatment. Section 3 analyzes the models with treatments. Specifically, treatments by $CD4^+$ T cells are considered in Sections 3.1 and 3.2 deals with the model of treatment by cytokine. A brief discussion on the combined treatments is presented in Section 3.3. Numerical simulations are performed in Section 4. Specifically, continuous and pulsed treatments are given in Sections 4.1 and 4.2, respectively, while Section 4.3 presents sensitivity analysis. The final section provides a brief summary and discussion. The proofs of our mathematical results are given in the Appendix.

2. The model and preliminary analysis

Before presenting the model, we briefly review experiments carried out that confirm the effector roles of $CD4^+$ T cells.

Researchers designing anti-tumor treatments involving transfers of activated anti-tumor cells have long focused on the methods to elicit tumor-specific CD8 CTLs [24]. Although many of the resulting treatments have indeed been able to elicit CTLs that recognize tumor cells and/or tumor antigens in vitro, complete tumor regression has been achieved only in a

minority of patients and animal models [24]. Over the last few decades, a few studies have shown that CD4 T cells can also clear tumors completely and independently of CD8, including Fernandez-Cruz et al. [12], Greenberg et al. [15], Mumberg et al. [26], Qin and Blankenstein [29], and Corthay et al. [5]. In addition to these references just mentioned, several more recent experiments reconfirm the effector roles of $CD4^+$ without $CD8^+$. In the following, we briefly discuss each of these research works.

To elucidate the direct anti-tumor activity of Th1 and Th2 cells, particularly against tumors resistant to CTL lysis, Mattes et al. [24] design experiments using highly metastatic and CTL-resistant tumor cell line, B16 mouse melanoma. Their results demonstrate that $CD4^+$ T cells can recognize a secreted tumor-specific antigen and exhibit a cytokine secretion profile characteristic of Th2 cells. The cytokines are capable of clearing established lung and visceral metastases of a CTL-resistant melanoma. This work provides the basis for a new approach to adoptive T cell immunotherapy of cancer using $CD4^+$ T cells.

In a more recent study, Perez-Diez et al. [27] perform a direct comparison between CD4 and CD8 T cells specific for the same tumor, using TCR Tg mice, containing pure populations of CD4 or CD8 T cells in order to test each type of effector role alone without the effects of potential contaminants. Their study shows that CD4 cells are actually better than CD8 cells at rejecting tumors in every case tested using six different tumors. They conclude that CD4 cells are better effector cells even when the CD4 effectors exhibited minimal in vitro or in vivo lytic activity against the tumor cells and even when the tumor expressed major histocompatibility complex (MHC) class I but not class II molecules.

Motivated by an increasing evidence indicating that $CD4^+$ T cells are able to mediate tumor destruction without direct interaction with tumor cells and that $CD4^+$ T cells may provide even greater anti-tumor effect than $CD8^+$ T cells, Zhang et al. [36] test CD8-depleted, B-cell-deficient mice for induction of the anti-tumor immunity of $CD4^+$ T cells. They further confirm the role of $CD4^+$ T cells as effectors.

We are now ready to introduce the model of tumor–immune interactions. We shall carry out the analysis on the system of no treatments in Section 2.1. Section 2.2 provides some global results on the model of no treatment and a discussion of interior steady states is given in Section 2.3.

Let $x(t)$, $y(t)$, and $w(t)$ denote respectively the numbers of tumor cells, $CD4^+$ T cells, and the normal tissue cells at time $t \geq 0$. The cytokines at time t is given by $z(t)$. These are protein hormones that mediate immunity [34]. The cytokine in this study focuses on IL-4 or more broadly any cytokine produced by the Th2 cells. The time unit is a day. It is assumed that both the tumor and the normal tissue cells grow logistically with intrinsic growth rates r_1 and r_2 and carrying capacities $1/b_1$ and $1/b_2$, respectively. In the absence of $CD4^+$ T cells and cytokines, the interaction between tumor and normal tissue cells is described by the classical Lotka–Volterra competition equation with competition coefficients δ_1 and δ_3. These two types of cells compete for space and resources for growth. The simple Lotka–Volterra interaction is also assumed in [7,23] for studying tumor and host tissue cells.

Unlike $CD8^+$ T cells, $CD4^+$ T cells cannot kill tumor cells directly but through the cytokines that they produce [11]. We use Michaelis Menten kinetics, $\frac{c_1 xz}{a_1+x}$, to model the killing of tumor cells due to cytokine, where c_1 is the maximum killing rate by cytokine and a_1 is the half saturation constant. This tumor killing rate is also used in [3,10]. The activation of $CD4^+$ T cells is through the tumor cells and cytokines and is described by the Michaelis Menten kinetics $\frac{\beta_1 xz}{\alpha_1+x}$. The parameter β_1 is the maximum $CD4^+$ production rate and α_1 is the half saturation constant. β_1 may be interpreted as the antigenicity of the tumor. The immune system produces $CD4^+$ T cells more effectively if β_1 is larger. The rate of change of $CD4^+$ T cells increases with increasing tumor cells but is also limited by the tumor cells. This modeling assumption is different from a previous study [3] where the production of $CD4^+$ is a function of the $CD4^+$ cells. The $CD4^+$ production modeled here is similar to the one used in [10] but without incorporating tumor promoting cytokines in the present study. In addition to the apoptosis, denoted by μ_1, $CD4^+$ cells are lost due to interaction with the tumor cells and this loss rate is given by δ_2. This extra loss rate is not adopted in the previous model [3] but it is included in the models proposed by Eftimie et al. [10].

The production of cytokine depends on both the tumor and the $CD4^+$ T cells, which is also assumed in [3,10]. Let β_2 denote the maximum production rate of the cytokine and α_2 be the half saturation constant. The cytokine decays naturally at a rate μ_2. These parameters are positive constants and their biological description are summarized in Table 1. The immunotherapy treatments by $CD4^+$ T cells and cytokines are denoted by I_1 and I_2 respectively, $I_i \geq 0$, $i = 1, 2$. Thus, treatments are assumed to be continuous over time, which is also adopted in the study by de Pillis et al. [7] and Kogan et al. [19].

With these biological considerations, the interaction between tumor cells, $CD4^+$ T cells, cytokine, and normal tissue cells is described by the following system of ordinary differential equations

$$\begin{cases} x' = r_1 x(1 - b_1 x) - \dfrac{c_1 xz}{a_1 + x} - \delta_1 xw \\ y' = \dfrac{\beta_1 xz}{\alpha_1 + x} - \mu_1 y - \delta_2 xy + I_1 \\ z' = \dfrac{\beta_2 xy}{\alpha_2 + x} - \mu_2 z + I_2 \\ w' = r_2 w(1 - b_2 w) - \delta_3 xw \\ x(0) > 0, y(0) \geq 0, z(0) \geq 0, w(0) > 0. \end{cases} \tag{2.1}$$

Table 1
Parameters and their biological meanings.

Parameter	Description
r_1	Intrinsic growth rate of tumor cells
b_1	Reciprocal of carrying capacity of tumor
c_1	Maximum tumor killing rate by cytokine
a_1	Half saturation constant of the tumor killing rate
δ_1	Competition coefficient of normal tissue cells on tumor cells
β_1	Maximum $CD4^+$ production rate (antigenicity of the tumor)
α_1	Half saturation constant of the $CD4^+$ production rate
μ_1	Natural death rate of $CD4^+$ cells
δ_2	Loss rate of $CD4^+$ cells due to interaction with tumor cells
β_2	Maximum production rate of cytokine
α_2	Half saturation constant of cytokine production rate
μ_2	Natural loss rate of cytokine
r_2	Intrinsic growth rate of normal tissue cells
b_2	Reciprocal of carrying capacity of normal tissue cells
δ_3	Competition coefficient of tumor cells on normal tissue cells
I_1	Treatment by $CD4^+$
I_2	Treatment by cytokine

Table 2
Existence and stability of steady states of (2.2).

Cases	Parameter regimes	Interior steady state	Stability
1	$r_2 < \delta_3/b_1$ and $r_1 > \delta_1/b_2$	None	$(1/b_1, 0)$ is gas
2	$r_2 > \delta_3/b_1$ and $r_1 < \delta_1/b_2$	None	$(0, 1/b_2)$ is gas
3	$r_2 < \delta_3/b_1$ and $r_1 < \delta_1/b_2$	$(\bar{x}, \bar{w})$ exists	Bistability
4	$r_2 > \delta_3/b_1$ and $r_1 > \delta_1/b_2$	$(\bar{x}, \bar{w})$ exists	$(\bar{x}, \bar{w})$ is gas

Let $F = (f_1, f_2, f_3, f_4) : \mathbb{R}^4_+ \to \mathbb{R}^4$ denote the right hand side of (2.1). We first verify global existence and nonnegativity of the solutions.

Proposition 2.1. *Solutions of (2.1) exist and remain nonnegative for $t > 0$.*

When the immune system is not activated, the interaction between tumor and normal tissue cells is described by the following classical Lotka–Volterra two-dimensional competition system

$$\begin{cases} x' = r_1 x(1 - b_1 x) - \delta_1 xw \\ w' = r_2 w(1 - b_2 w) - \delta_3 xw. \end{cases} \tag{2.2}$$

This assumption of simple mass actions between cancer and normal tissue cells is also adopted by de Pillis et al. [7] and more recently by Lopez et al. [23]. Dynamics of (2.2) are well known [1] and are summarized in Table 2. Let $(\bar{x}, \bar{w})$ denote the unique interior steady state of (2.2) whenever it exists, where

$$\bar{x} = \frac{r_2(\delta_1 - r_1 b_2)}{\delta_1\delta_3 - r_1 r_2 b_1 b_2} \quad \text{and} \quad \bar{w} = \frac{r_1(\delta_3 - r_2 b_1)}{\delta_1\delta_3 - r_1 r_2 b_1 b_2}. \tag{2.3}$$

Notice that $(\bar{x}, \bar{w})$ is a saddle point for case 3 in Table 2 where bistability occurs. That is, except on the set of initial conditions lying on the stable manifold of $(\bar{x}, \bar{w})$, which has Lebesgue measure zero, nonzero solutions of (2.2) converge to either $(0, 1/b_2)$ or $(1/b_1, 0)$.

2.1. The model of no treatment

In this section, we use dynamics of (2.2) to study (2.1) when there is no treatment:

$$\begin{cases} x' = r_1 x(1 - b_1 x) - \dfrac{c_1 xz}{a_1 + x} - \delta_1 xw \\ y' = \dfrac{\beta_1 xz}{\alpha_1 + x} - \mu_1 y - \delta_2 xy \\ z' = \dfrac{\beta_2 xy}{\alpha_2 + x} - \mu_2 z \\ w' = r_2 w(1 - b_2 w) - \delta_3 xw \\ x(0) > 0, y(0) \geq 0, z(0) \geq 0, w(0) > 0. \end{cases} \tag{2.4}$$

Observe that solutions of (2.4) satisfy

Table 3
Existence and stability of steady states of (2.4).

Steady state	Existence	Stability
$E_{00} = (0, 0, 0, 0)$	Always exists	Always unstable
$E_{01} = (1/b_1, 0, 0, 0)$	Always exists	$r_2 < \delta_3/b_1$ and (2.6)
$E_{02} = (0, 0, 0, 1/b_2)$	Always exists	$r_1 < \delta_1/b_2$
$\bar{E} = (\bar{x}, 0, 0, \bar{w})$	$r_2 < \frac{\delta_3}{b_1}$ and $r_1 < \frac{\delta_1}{b_2}$	Always unstable
	$r_2 > \frac{\delta_3}{b_1}$ and $r_1 > \frac{\delta_1}{b_2}$	(2.7)

$$\limsup_{t\to\infty} x(t) \le 1/b_1 \text{ and } \limsup_{t\to\infty} w(t) \le 1/b_2. \tag{2.5}$$

Further, system (2.4) has the following boundary steady states: $E_{00} = (0, 0, 0, 0)$, $E_{01} = (1/b_1, 0, 0, 0)$, $E_{02} = (0, 0, 0, 1/b_2)$, and possibly $\bar{E} = (\bar{x}, 0, 0, \bar{w})$ for cases 3 and 4. The stability of these steady states is determined by the linearize system. The derivation of the stability is given in Appendix and is summarized in Proposition 2.2 and Table 3. Specifically, E_{01} is locally asymptotically stable if $r_2 < \delta_3/b_1$ and the following inequalities hold

$$\mu_2(\mu_1 + \delta_2/b_1) > \frac{\beta_1\beta_2}{(b_1\alpha_1 + 1)(b_1\alpha_2 + 1)}, \tag{2.6}$$

and unstable if one of these two inequalities is reversed. Similarly, $\bar{E}$ is asymptotically stable if $(\bar{x}, \bar{w})$ is asymptotically stable for (2.2) and the following inequality is satisfied:

$$\mu_2(\mu_1 + \delta_2\bar{x}) > \frac{\beta_1\beta_2\bar{x}^2}{(\alpha_1 + \bar{x})(\alpha_2 + \bar{x})}. \tag{2.7}$$

Proposition 2.2. *System (2.4) has boundary steady states $E_{00} = (0, 0, 0, 0)$, $E_{01} = (1/b_1, 0, 0, 0)$, $E_{02} = (0, 0, 0, 1/b_2)$, where E_{00} is a saddle point. E_{01} is asymptotically stable if $r_2 < \delta_3/b_1$ and (2.6) holds, and unstable if one of these two inequalities is reversed. Steady state $E_{02} = (0, 0, 0, 1/b_2)$ is asymptotically stable if $r_1 < \delta_1/b_2$ and unstable if $r_1 > \delta_1/b_2$. Steady state $\bar{E} = (\bar{x}, 0, 0, \bar{w})$ exists if $r_2 < \delta_3/b_1$ and $r_1 < \delta_1/b_2$, where $\bar{E}$ is unstable, or if $r_2 > \delta_3/b_1$ and $r_1 > \delta_1/b_2$, where $\bar{E}$ is asymptotically stable if in addition (2.7) holds.*

2.2. Some global results

Suppose the vital parameters of the tumor and host cells lie in the region of case 2, i.e., $r_2 > \delta_3/b_1$ and $r_1 < \delta_1/b_2$. Then the normal tissue cells are more competitive than the tumor cells and also have a large intrinsic growth rate. In this instance, we prove that the tumor can be eliminated completely without any treatments and independent of its initial size.

Theorem 2.3. *If $r_2 > \delta_3/b_1$ and $r_1 < \delta_1/b_2$, then steady state $E_{02} = (0, 0, 0, 1/b_2)$ is globally asymptotically stable for (2.4) in int$(\mathbb{R}^4_+)$.*

We next show that if the loss rates of CD4$^+$ T cells and cytokines are large, then the immune system is not effective and whether the tumor can establish itself or not depends solely on its interaction with the host cells.

Indeed, if

$$\mu_1\mu_2 > \frac{\beta_1\beta_2}{(\alpha_1 b_1 + 1)(\alpha_2 b_1 + 1)} \tag{2.8}$$

is satisfied, we have the following results and their proofs are given in the Appendix. Notice that the left hand side of (2.8) is the product of the loss rates of CD4$^+$ and cytokines and the right hand side of (2.8) depends on the antigenicity of the tumor, production rate of cytokines, and carrying capacities of the tumor and host cells. Inequality (2.8) states that the loss rates of CD4$^+$ and/or cytokines are large while either the carrying capacity of the tumor or the tumor's antigenicity is small. Under these circumstances, either the immune system is not effective or the tumor has a large carrying capacity, and then the fate of the tumor depends on its interaction with the host cells alone as described by the following theorem.

Theorem 2.4. *Let $\mu_1\mu_2 > \frac{\beta_1\beta_2}{(b_1\alpha_1+1)(b_1\alpha_2+1)}$. The following statements hold for (2.4).*

(a) If $r_2 < \delta_3/b_1$ and $r_1 > \delta_1/b_2$, then $E_{01} = (1/b_1, 0, 0, 0)$ is globally asymptotically stable.
(b) If $r_2 < \delta_3/b_1$ and $r_1 < \delta_1/b_2$, then except on a set of Lebesgue measure zero, positive solutions of (2.4) converge to either $E_{01} = (1/b_1, 0, 0, 0)$ or $E_{02} = (0, 0, 0, 1/b_2)$.
(c) If $r_2 > \delta_3/b_1$ and $r_1 > \delta_1/b_2$, then $\bar{E} = (\bar{x}, 0, 0, \bar{w})$ is globally asymptotically stable.

Recall that the parameters μ_1 and μ_2 are the natural loss rates of CD4$^+$ and cytokine respectively. Theorem 2.4 implies that if the product of these rates are large, then the immune system is not effective and it plays no significant role in controlling the fate of the tumor. Dynamics of (2.4) are then determined by the tumor and host cells completely via competition.

Suppose now case 4 holds, i.e., $r_2 > \delta_3/b_1$ and $r_1 > \delta_1/b_2$, and, in addition, the inequality (2.8) is reversed so that the loss rate of either cytokines, $CD4^+$ or both is not too large. Then $(\bar{x}, \bar{w})$ is globally asymptotically stable for the subsystem (2.2) by Table 2. Although the loss rates of cytokines and $CD4^+$ T cells are not too large, under the condition that they are also not too small and satisfying the following inequality

$$\frac{\beta_1\beta_2}{(\alpha_1 b_1 + 1)(\alpha_2 b_1 + 1)} > \mu_1\mu_2 > \frac{\beta_1\beta_2\bar{x}^2}{(\alpha_1 + \bar{x})(\alpha_2 + \bar{x})}, \tag{2.9}$$

then we have the following results in which the tumor and host cells coexist and there are no immune cells nor cytokines.

Theorem 2.5. *Assume $r_2 > \delta_3/b_1$, $r_1 > \delta_1/b_2$ and (2.9). Then $\bar{E} = (\bar{x}, 0, 0, \bar{w})$ is globally asymptotically stable for system (2.4).*

If case 4 holds but not (2.9), then we have the following corollary from the proof of Theorem 2.5.

Corollary 2.6. *Assume $r_2 > \delta_3/b_1$ and $r_1 > \delta_1/b_2$. Then solutions of (2.1) satisfy $\limsup_{t\to\infty} x(t) \le \bar{x}$ and $\liminf_{t\to\infty} w(t) \ge \bar{w}$.*

In other words, if both the tumor and host cells are less competitive, then the tumor cannot grow to its carrying capacity.

2.3. Interior steady states

System (2.1) may have steady states of the form $(x, y, z, 0)$. However, since there are no host cells present and the patient is dead, we dismiss its discussion. We are more interested in how the patient can survive without any treatment. We now look for interior steady states. Setting $x' = 0$, $x \neq 0$, and $w' = 0$, $w \neq 0$, we obtain $z = \frac{a_1+x}{c_1}\big(r_1(1 - b_1x) - \delta_1 w\big)$ and $w = 1/b_2 - \frac{\delta_3}{r_2 b_2}x$, respectively. It follow that $z = \frac{a_1+x}{c_1}\big(r_1(1 - b_1x) - \delta_1(1/b_2 - \frac{\delta_3}{r_2 b_2}x)\big)$.

Define

$$g_1(x) = \frac{a_1 + x}{c_1}\left(r_1 - \frac{\delta_1}{b_2} + \left(\frac{\delta_1\delta_3}{r_2 b_2} - r_1 b_1\right)x\right). \tag{2.10}$$

Notice $g_1(x) = 0$ if and only if $x = \bar{x}$, where $\bar{x} > 0$ is given in (2.3) if either case 3 or case 4 in Table 2 holds. Similarly, letting $z' = 0$, $z \neq 0$, we have $y = \frac{\mu_2(\alpha_2+x)}{\beta_2 x}g_1(x)$. Letting $y' = 0$, $y \neq 0$, and substituting z by $g_1(x)$ and y by $\frac{\mu_2(\alpha_2+x)}{\beta_2 x}g_1(x)$, we obtain

$$\left(\frac{\beta_1 x}{\alpha_1 + x} - \frac{\mu_2\delta_2(\alpha_2 + x)}{\beta_2} - \frac{\mu_1\mu_2(\alpha_2 + x)}{\beta_2 x}\right)g_1(x) = 0. \tag{2.11}$$

If $x > 0$ satisfies $g_1(x) = 0$, then $z = 0 = y$ and the x solution cannot result in an interior steady state. Therefore for x to be the x component of an interior steady state one must require $g_1(x) \neq 0$. In view of (2.11), $x > 0$ must therefore solve

$$L(x) := -Ax^3 + Bx^2 - Cx - D = 0, \tag{2.12}$$

where

$$\begin{aligned} &A = \delta_2\mu_2 > 0,\ B = \beta_1\beta_2 - \delta_2\mu_2(\alpha_1 + \alpha_2) - \mu_1\mu_2, \\ &C = \alpha_1\alpha_2\mu_2\delta_2 + \mu_1\mu_2(\alpha_1 + \alpha_2) > 0,\ D = \mu_1\mu_2\alpha_1\alpha_2 > 0. \end{aligned} \tag{2.13}$$

Then any $x^* > 0$ is the x-component of an interior steady state (x^*, y^*, z^*, w^*) of (2.4) if and only if

$$L(x^*) = 0,\ g_1(x^*) > 0,\ \text{and } x^* < r_2/\delta_3, \tag{2.14}$$

where $y^* = \frac{\mu_2(\alpha_2+x^*)}{\beta_2 x^*}g_1(x^*)$, $z^* = g_1(x^*)$ and $w = 1/b_2 - \frac{\delta_3}{r_2 b_2}x^*$.

If $B \le 0$, then $L(x) < 0$ for $x \ge 0$ and (2.12) has no positive solutions. Therefore, (2.1) has no interior steady state if $B \le 0$. Let $B > 0$. Then $L(x) = 0$ has either zero or two positive solutions by the Descartes' Rule of Signs [1]. Since $L(0) = -D < 0$, $L(\infty) = -\infty$, $L(-\infty) = \infty$ and $L(-x) = Ax^3 + Bx^2 + Cx - D$, $L(x) = 0$ has exactly one negative root. In the following, we derive some sufficient condition so that $L(x) = 0$ has two positive solutions.

Notice $L'(x) = -3Ax^2 + 2Bx - C$, where $A > 0, B > 0, C > 0$, has two roots $x_{1,2} = \frac{B \mp \sqrt{B^2 - 3AC}}{3A}$. If $B^2 - 3AC \le 0$, then $L'(x) \le 0$ and $L(x) = 0$ has no positive solution. Thus (2.4) has no interior steady states. Let $B^2 - 3AC > 0$. Then $L'(x) = 0$ has two positive roots $x_{1,2}$, denoted now by

$$x_\pm = \frac{B \pm \sqrt{B^2 - 3AC}}{3A}. \tag{2.15}$$

It is straightforward to show that

$$L(x_+) = \frac{1}{27A^2}\Big(2B^3 - 9ABC + \big(2B^2 - 6AC\big)\sqrt{B^2 - 3AC} - 27A^2D\Big). \tag{2.16}$$

Notice $L(x_-) < 0$, and $L(x) = 0$ has no positive root if $L(x_+) < 0$. If $L(x_+) > 0$, then $L(x) = 0$ has two positive solutions x_i^*, $i = 1, 2$, where $x_- < x_1^* < x_+ < x_2^*$. These roots may or may not result in interior steady states.

When $L(x_+) = 0$, then $L(x) = 0$ has a unique positive solution x_+ which result in an interior steady state if $g_1(x_+) > 0$ and $x_+ < r_2/\delta_3$. From (2.16), $L(x_+) = 0$ is equivalent to

$$2B^3 - 9ABC + \left(2B^2 - 6AC\right)\sqrt{B^2 - 3AC} - 27A^2D = 0 \tag{2.17}$$

where A, B, C and D are positive. Since A, C and D do not depend on β_i and β_i represent production efficiency of the immune system for $i = 1, 2$, we can choose either β_1 or β_2 as our bifurcation parameter. Notice $\frac{\partial B}{\partial \beta_1} = \beta_2$ and $\frac{\partial B}{\partial \beta_2} = \beta_1$. Let L_+ denote the left hand side of (2.17) and $\beta_1^0 = \frac{\sqrt{3AC}+\delta_2\mu_2(\alpha_1+\alpha_2)+\mu_1\mu_2}{\beta_2}$, i.e., $B(\beta_1^0) = \sqrt{3AC}$. Then $L_+(\beta_1^0) < 0$, $L_+(\infty) = \infty$, and $\frac{\partial L_+(\beta_1)}{\partial \beta_1}$ is

$$\begin{aligned} &6B^2\frac{\partial B}{\partial \beta_1} - 9AC\frac{\partial B}{\partial \beta_1} + 4B\frac{\partial B}{\partial \beta_1}\sqrt{B^2 - 3AC} + \left(2B^2 - 6AC\right)\frac{2B\frac{\partial B}{\partial \beta_1}}{2\sqrt{B^2 - 3AC}} \\ &= 6B^2\beta_2 - 9AC\beta_2 + 4B\beta_2\sqrt{B^2 - 3AC} + B\beta_2\frac{2B^2 - 6AC}{\sqrt{B^2 - 3AC}} > 0. \end{aligned}$$

Therefore, $L_+(\beta_1) = 0$ has a unique positive solution β_1^c, where $\beta_1^c > \beta_1^0$. It follow that $L(x_+) > 0$ if and only if $\beta_1 > \beta_1^c$, and hence $L(x) = 0$ has two positive solutions x_i^*, $i = 1, 2$, if $\beta_1 > \beta_1^c$. If both x_i^*, $i = 1, 2$, satisfy (2.14) then (2.4) has two interior steady states, and (2.4) has a unique interior steady state if exactly x_1^* or x_2^* satisfies (2.14).

Proposition 2.7. *System (2.4) has no interior steady state if either $B \le 0$, $0 < B \le \sqrt{3AC}$, or $B > \sqrt{3AC}$ and $L(x_+) < 0$. Let $B > \sqrt{3AC}$ and $L(x_+) > 0$, i.e., $\beta_1 > \beta_1^c$, and let x_i^*, $i = 1, 2$, be the two positive roots of $L(x)$. Then (2.4) has two interior steady states if $g_1(x_i^*) > 0$ and $x_i^* < r_2/\delta_3$ for $i = 1, 2$.*

If the maximal production rate of the CD4$^+$ T cells or cytokine is small or if the half saturation constants of either of these rates is large, then the interaction cannot support existence of interior steady states. The same conclusion holds if the natural loss rates of these cells and cytokines are large. In order to have a coexisting steady state, it is necessary for the magnitude of the above mentioned quantities to be reversed.

3. Models with continuous treatments and analysis

In this section, we investigate models with constant treatments. Specifically, treatments by CD4$^+$ T cells are considered in Section 3.1. Section 3.2 studies immunotherapies by the cytokines and the combination of treatments is discussed in Section 3.3.

3.1. Treatments by CD4$^+$ T cells

Let I_1 denote the constant treatment of CD4$^+$ T cells per day. The model is given by

$$\begin{cases} x' = r_1x(1 - b_1x) - \dfrac{c_1xz}{a_1 + x} - \delta_1xw \\ y' = \dfrac{\beta_1xz}{\alpha_1 + x} - \mu_1y - \delta_2xy + I_1 \\ z' = \dfrac{\beta_2xy}{\alpha_2 + x} - \mu_2z \\ w' = r_2w(1 - b_2w) - \delta_3xw \\ x(0) > 0, y(0) \ge 0, z(0) \ge 0, w(0) > 0. \end{cases} \tag{3.1}$$

Observed that steady state of the form $(1/b_1, 0, 0, 0)$ does not exist for model (3.1) and it is clear that solutions of (3.1) satisfy (2.5). Moreover, since $x'|_{x\ge 1/b_1, w>0} < 0$, we have $x(t) < 1/b_1$ for all t large. Consequently, $y' \ge I_1 - \mu_1y - \frac{\delta_2}{b_1}y$ for all t large and hence

$$\liminf_{t\to\infty} y(t) \ge \frac{b_1I_1}{\mu_1b_1 + \delta_2}. \tag{3.2}$$

There always exists a positive lower bound for the immune cells due to the constant treatments.

System (3.1) has steady states of the form $E_{10} = (0, I_1/\mu_1, 0, 0)$ and $E_{12} = (0, I_1/\mu_1, 0, 1/b_2)$. At E_{10},

$$DF(E_{10}) = \begin{pmatrix} r_1 & 0 & 0 & 0 \\ * & -\mu_1 & 0 & 0 \\ * & 0 & -\mu_2 & 0 \\ 0 & 0 & 0 & r_2 \end{pmatrix},$$

where $*$s are unimportant terms. Hence ,E_{10} is always a saddle point. At E_{12},

$$DF(E_{12}) = \begin{pmatrix} r_1 - \delta_1/b_2 & 0 & 0 & 0 \\ * & -\mu_1 & 0 & 0 \\ * & 0 & -\mu_2 & 0 \\ * & 0 & 0 & -r_2 \end{pmatrix}.$$

Therefore, E_{12} is asymptotically stable if $r_1 < \delta_1/b_2$ and it is a saddle point if $r_1 > \delta_1/b_2$.

Recall if case 2 holds, then the tumor cells can be eliminated completely without any treatment as shown in Theorem 2.5. Consequently, the tumor cells can be clear off if treatments of CD^+ T cells are implemented. The proof of the following theorem is similar to the proof of Theorem 2.5 and is therefore omitted.

Theorem 3.1. *If $r_2 > \delta_3/b_1$ and $r_1 < \delta_1/b_2$, then steady state $E_{12} = (0, I_1/\mu_1, 0, 1/b_2)$ is globally asymptotically stable for (3.1) in int$(\mathbb{R}^4_+)$.*

On the other hand if case 4 holds, $r_2 > \delta_3/b_1$ and $r_1 > \delta_1/b_2$, then using the dynamics of the xw-subsystem (2.2), we obtain that $\limsup_{t\to\infty} x(t) \le \bar{x}$ and $\limsup_{t\to\infty} w(t) \ge \bar{w}$ for all solutions of (3.1). Consequently, the tumor cannot grow to its carrying capacity.

Corollary 3.2. *Assume $r_2 > \delta_3/b_1$ and $r_1 > \delta_1/b_2$. Then solutions of (3.1) satisfy $\limsup_{t\to\infty} x(t) \le \bar{x}$ and $\liminf_{t\to\infty} w(t) \ge \bar{w}$.*

We do not consider steady state of the form $(x, y, z, 0)$ since we are interested in how the treatments can sustain the patient. Let (x, y, z, w) be an interior steady state. It can be shown that the x component satisfies $H(x) = 0$, where

$$H(x) = (\beta_1\beta_2 x^2 - \mu_1\mu_2(\alpha_1 + x)(\alpha_2 + x) - \delta_2\mu_2 x(\alpha_1 + x)(\alpha_2 + x))g_1(x) + \beta_2 x(\alpha_1 + x)I_1, \tag{3.3}$$

and g_1 is defined in (2.10). Thus $H(x)$ is a polynomial of degree 5 and any positive x^* satisfying

$$H(x^*) = 0,\ g_1(x^*) > 0,\ x^* < r_2/\delta_3 \tag{3.4}$$

results in an interior steady state (x^*, y^*, z^*, w^*), where $y^* = \frac{\mu_2(\alpha_2+x^*)}{\beta_2 x^*} g_1(x^*)$, $z^* = g_1(x^*)$, and $w^* = 1/b_2 - \frac{\delta_3 x^*}{r_2 b_2}$. It is possible for system (3.1) to have three interior steady states as demonstrated numerically in Section 4.

3.2. Treatments by cytokine

Suppose now immunotherapy of cytokine is implemented. The model is given below

$$\begin{cases} x' = r_1 x(1 - b_1 x) - \dfrac{c_1 xz}{a_1 + x} - \delta_1 xw \\ y' = \dfrac{\beta_1 xz}{\alpha_1 + x} - \mu_1 y - \delta_2 xy \\ z' = \dfrac{\beta_2 xy}{\alpha_2 + x} - \mu_2 z + I_2 \\ w' = r_2 w(1 - b_2 w) - \delta_3 xw \\ x(0) > 0, y(0) \ge 0, z(0) \ge 0, w(0) > 0, \end{cases} \tag{3.5}$$

where I_2 denotes constant treatment of cytokine per day. Since cytokine can kill tumor cells directly, it is expect that the treatments will be more effective than using $CD4^+$ T cells. Observed that steady state of the form $(1/b_1, 0, 0, 0)$ does not exist for model (3.5). Moreover, $z' \ge I_2 - \mu_2 z$ for all $t > 0$, solutions of (3.5) therefore satisfy

$$\limsup_{t\to\infty} x(t) \le 1/b_1,\ \liminf_{t\to\infty} z(t) \ge I_2/\mu_2,\ \limsup_{t\to\infty} w(t) \le 1/b_2. \tag{3.6}$$

Since cytokine can kill cancer cells directly, the tumor can never grow to its carrying capacity as shown below.

Proposition 3.3. *Solutions of (3.5) satisfy $\limsup_{t\to\infty} x(t) < 1/b_1$.*

We now study boundary steady states of (3.5). Model (3.5) always has boundary steady states $E_{20} = (0, 0, I_2/\mu_2, 0)$ and $E_{22} = (0, 0, I_2/\mu_2, 1/b_2)$. At E_{20},

$$DF(E_{20}) = \begin{pmatrix} r_1 - \dfrac{c_1 I_2}{\mu_2 a_1} & 0 & 0 & 0 \\ * & -\mu_1 & 0 & 0 \\ * & 0 & -\mu_2 & 0 \\ 0 & 0 & 0 & r_2 \end{pmatrix}, \tag{3.7}$$

and E_{20} is always a saddle point. At E_{22}, we have

$$DF(E_{22}) = \begin{pmatrix} r_1 - \delta_1/b_2 - \dfrac{c_1 I_2}{\mu_2 a_1} & 0 & 0 & 0 \\ * & -\mu_1 & 0 & 0 \\ * & 0 & -\mu_2 & 0 \\ * & 0 & 0 & -r_2 \end{pmatrix}. \tag{3.8}$$

Therefore, E_{22} is asymptotically stable if $r_1 - \delta_1/b_2 - \frac{c_1 I_2}{\mu_2 a_1} < 0$ and it is a saddle point if $r_1 - \delta_1/b_2 - \frac{c_1 I_2}{\mu_2 a_1} > 0$.

Since host cells can outcompete the tumor cells and drive the tumor to extinction without any treatment as illustrated in Theorem 2.5 when the tumor has a small growth rate and is also less competitive, the tumor cells can be clear off if the treatments by cytokine is implemented. Indeed, it can be shown that E_{22} is globally asymptotically stable for (3.5) if $r_1 < \delta_1/b_2$ and $r_2 > \delta_3/b_1$. We omit the proof.

Theorem 3.4. *If $r_2 > \delta_3/b_1$ and $r_1 < \delta_1/b_2$, then steady state $E_{22} = (0, 0, I_2/\mu_2, 1/b_2)$ is globally asymptotically stable for (3.5) in int$(\mathbb{R}^4_+)$.*

Since cytokine can kill tumor cells directly and there is an immunotherapy of cytokine, we derive a minimum dose of treatment to eliminate the tumor cells completely no matter how large the tumor is. Let

$$I_2^c = \frac{\mu_2 r_1 (a_1 b_1 + 1)}{b_1 c_1}. \tag{3.9}$$

The following theorem shows that the tumor can be completely eradicated if $I_2 > I_2^c$.

Theorem 3.5. *If $I_2 > I_2^c$, then steady state $E_{22} = (0, 0, I_2/\mu_2, 1/b_2)$ is globally asymptotically stable for (3.5).*

Theorem 3.7 indicates that even if the tumor is aggressive with a large intrinsic growth rate r_1 and a large competition coefficient δ_1, the constant treatment of cytokine can eliminate the tumor cells completely if the treatment dose is larger than I_2^c. On the other hand, since I_2^c is increasing with respect to $1/b_1$, r_1 and μ_2, the minimum dose of treatment is larger if the tumor has either a larger growth rate, a larger carrying capacity, or if the natural loss rate of cytokine is larger.

Suppose the treatment by cytokine is not large. We next derive a sufficient condition for which the tumor can be eradicated completely. Let $I_2 < I_2^c$ and assume

$$1 - \frac{c_1 I_2}{r_1 \mu_2 (a_1 + 1/b_1)} < \min\left\{ \frac{b_1 r_2}{\delta_3}, \ \frac{\delta_1}{r_1 b_2} \right\}. \tag{3.10}$$

Notice the left hand side of (3.10) is positive due to $I_2 < I_2^c$. We prove that the tumor can be clear off if (3.10) holds.

Theorem 3.6. *Let $I_2 < I_2^c$ and assume (3.10). Then $E_{22} = (0, 0, I_2/\mu_2, 1/b_2)$ is globally asymptotically stable for model (3.5).*

To study the existence of interior steady states, notice that after some calculations it can be shown that the x component of an interior steady state satisfies

$$\beta_1 \beta_2 x^2 g_1(x) - (\alpha_1 + x)(\alpha_2 + x)(\mu_1 + \delta_2 x)(\mu_2 g_1(x) - I_2) = 0, \tag{3.11}$$

where $g_1(x)$ is defined in (2.10). Let $G(x)$ denote the left hand side of (3.11). Then $x^* > 0$ results in an interior steady state (x^*, y^*, z^*, w^*) if

$$G(x^*) = 0, \ g_1(x^*) > 0, \ x^* < r_2/\delta_3,$$

where $y^* = \frac{\beta_1 x^* g_1(x^*)}{(\mu_1 + \delta_2 x^*)(\alpha_1 + x^*)}$, $z^* = g_1(x^*)$, and $w^* = 1/b_2 - \frac{\delta_3 x^*}{r_2 b_2}$. Since G is a polynomial of degree 5, it is expected that system (3.5) has multiple interior steady states as illustrated in Section 4.

3.3. Combined treatments

In this section we briefly discuss combined treatments by CD4$^+$ T cells and cytokines on controlling the tumor, i.e., (2.1) is considered. The proof of each of the mathematical results is similar to the proof of an earlier result and is omitted.

It is clear that solutions of (2.1) satisfy

$$\limsup_{t\to\infty} x(t) \le 1/b_1, \ \liminf_{t\to\infty} y(t) \ge \frac{b_1 I_1}{\mu_1 b_1 + \delta_2}, \ \liminf_{t\to\infty} z(t) \ge I_2/\mu_2, \ \limsup_{t\to\infty} w(t) \le 1/b_2. \tag{3.12}$$

System (2.1) has two boundary steady states of the form $E_{30} = (0, I_1/\mu_1, I_2/\mu_2, 0)$ and $E_{32} = (0, I_1/\mu_1, I_2/\mu_2, 1/b_2)$. The Jacobian matrix evaluated at E_{30} and E_{32} are given by (3.7) and (3.8), respectively. Therefore their stability is similar to E_{20} and E_{22}. Specifically, E_{30} is always a saddle point and E_{32} is asymptotically stable if $r_1 - \delta_1/b_2 - \frac{c_1 I_2}{\mu_1 a_1} < 0$. In addition, tumor cells can be completely eradicated for any sizes if the tumor has a small growth rate and is also less competitive than the host cells.

Table 4
Parameter values and their sources.

Parameter	Value	Unit	Reference
r_1	0.514	Day^{-1}	[10]
b_1	1.02×10^{-9}	Day^{-1}	[10]
c_1	0.2	$\text{Cell(day)}^{-1} \cdot \text{(pg/ml)}^{-1}$	[10]
a_1	10^5	Cells	[18]
δ_1	1.1×10^{-10}	(Cell day)^{-1}	[23]
β_1	(0.008, 1.008)	Cell(day)^{-1}	[10]
α_1	10^3	Cells	[2]
μ_1	0.1	Day^{-1}	[3]
δ_2	10^{-7}	(Cell day)^{-1}	[10]
β_2	5.4	$\text{pg/ml} \cdot \text{(cell day)}^{-1}$	[10]
α_2	10^3	Cells	[10]
μ_2	34	Day^{-1}	[10]
r_2	0.18	Day^{-1}	[23]
b_2	10^{-9}	Day^{-1}	[23]
δ_3	4.8×10^{-10}	(Cell day)^{-1}	[23]

Theorem 3.7. *If $r_2 > \delta_3/b_1$ and $r_1 < \delta_1/b_2$, then steady state $E_{32} = (0, I_1/\mu_1, I_2/\mu_2, 1/b_2)$ is globally asymptotically stable for (2.1) in int$(\mathbb{R}^4_+)$.*

Since combined treatments also include the treatment by cytokines, the tumor cells can be completely eliminated no matter how large the tumor is if $I_2 > I_2^c$, where I_2^c is defined in (3.9).

Theorem 3.8. *If $I_2 > I_2^c$, then steady state $E_{32} = (0, I_1/\mu_1, I_2/\mu_2, 1/b_2)$ is globally asymptotically stable for (2.1).*

We also have the following results when I_2 does not exceed I_2^c but the lumped parameters satisfy (3.10).

Theorem 3.9. *Let $I_2 < I_2^c$ and assume (3.10). Then $E_{32} = (0, I_1/\mu_1, I_2/\mu_2, 1/b_2)$ is globally asymptotically stable for model (2.1).*

4. Numerical simulations

Theorems 2.5, 3.1, 3.4 and 3.7 imply that the tumor cells can be eradicated if the tumor has a small intrinsic growth rate and is also not competitive. In this instance, the host cells drive the tumor cells to extinction due to competition without the need of the immune system. In this section we investigate tumor's regression and progression in other parameter regimes. In particular, Sections 4.1 and 4.2 simulate model (2.1) with continuous and pulsed treatments, respectively, and sensitivity analysis is carried out in Section 4.3.

The default values are given in Table 4. Using these default parameter values, we have $r_1 = 0.514 > \delta_1/b_2 = 0.11$ and $r_2 = 0.18 < \delta_3/b_1 = 0.4705$. Hence case 1 holds and the tumor will grow to its carrying capacity $1/b_1 \approx 9.804 \times 10^8$ without the aid of the immune system. The β_1 value given in Table 4 has a range between 0.008 and 1.008. Recall that β_1 is the antigenicity of the tumor so that the immune system is more active if β_1 is larger. We first investigate model (2.4) with no treatments. If $\beta_1 = 0.008$, then $\mu_1\mu_2 = 3.4 > \frac{\beta_1\beta_2}{(b_1\alpha_1+1)(b_1\alpha_2+1)} = 0.0043$ and Theorem 2.4(a) applies. Therefore, the immune system is weak and the tumor is also aggressive so that the tumor will out compete the host cells and grow to its carrying capacity without any treatments.

We compute the β_1^c value satisfying (2.17) and obtain $\beta_1^c = 0.59753$, which lies in the range given in Table 4. Let $\beta_1 = 0.7$. Then $L(x) = 0$ has two positive solutions which yield two interior steady states $E_1^* = (8.65 \times 10^4, 2.399 \times 10^6, 3.767 \times 10^5, 9.998 \times 10^8)$ and $E_2^* = (2.375 \times 10^4, 1.64 \times 10^6, 2.499 \times 10^5, 9.999 \times 10^8)$, where E_1^* is stable and E_2^* is a saddle point. The tumor size in the stable steady state is larger than the one in the unstable steady state. When the stable interior steady state loses its stability at approximately $\beta_1 = 0.834$, a Hopf bifurcation occurs [35]. Therefore model (2.4) has positive periodic solutions. However, periodic solutions only exist in a very small parameter space. Using the initial condition $(9 \times 10^3, 600, 120, 5 \times 10^5)$ and $\beta_1 = 0.835$, we observe that there is a positive periodic solution in which the tumor shrinks its size as the immune system increases its ability and the tumor cells relapse as the immune system is weakened. Moreover, the period is large and therefore it is not easy to observe this periodicity clinically. This finding is different from a previous study [3] where oscillations of the models with smaller periodicities are frequently observed. In addition, system (2.4) exhibits bistability as the solution converges to $E_{01} = (1/b_1, 0, 0, 0)$ with initial condition $(9 \times 10^8, 600, 120, 5 \times 10^5)$. Due to this bistability, it is possible to control the tumor for some period of time if the tumor's antigenicity is large and the tumor size is small.

4.1. Continuous treatments

We now study different continuous treatment strategies. For the above parameter values with treatments of $CD4^+$ T cells, we do not find the existence of three interior steady states. Suppose that all of the other parameter values are the same

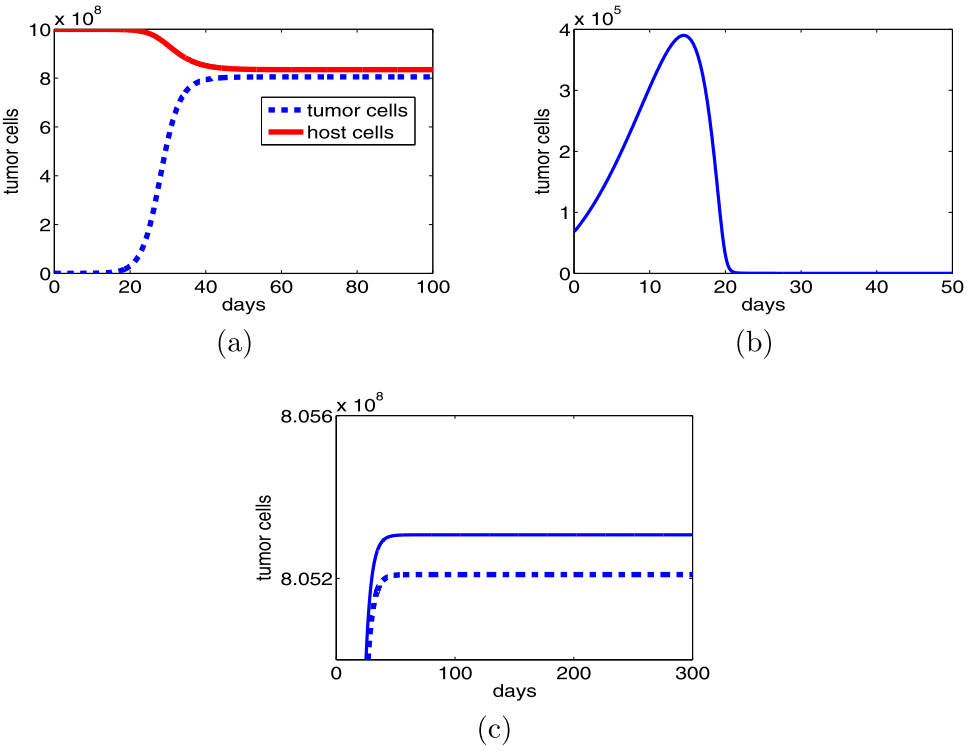

Fig. 1. The parameter values are $\beta_1 = 0.835$, $r_2 = 0.2822$ and $\delta_3 = 0.58 \times 10^{-10}$. Plots (a) and (b) use the same initial condition $X_0 = (6.77 \times 10^4, 10^6, 10^5, 10^9)$. There is no treatment in (a) and $I_1 = 7 \times 10^4$ in (b), where the tumor stabilizes at 158 in (b). The initial condition in (c) is $X_1 = (6.77 \times 10^8, 10^6, 10^5, 10^9)$ with two different doses of $CD4^+$ T cells. One solution adopts $I_1 = 7 \times 10^4$ and the other uses $I_1 = 10^8$.

with $\beta_1 = 0.835$ but vary r_2 and δ_3 to $r_2 = 0.2822$ and $\delta_3 = 0.58 \times 10^{-10}$, respectively, so that the host cells have a larger growth rate and the tumor is less competitive. Since $r_2 = 0.2822 > \delta_3/b_1 = 0.0569$, case 4 of Table 2 holds, i.e., $(\bar{x}, \bar{w}) = (8.0530 \times 10^8, 8.3449 \times 10^8)$ is globally asymptotically stable for the xw-subsystem (2.2). When $I_1 = 0$, model (3.1) has two interior steady states $E^*_{10} = (3.179 \times 10^5, 5.329 \times 10^6, 8.438 \times 10^5, 9.999 \times 10^8)$ and $E^*_{20} = (6.770 \times 10^3, 1.559 \times 10^6, 2.157 \times 10^5, 9.999 \times 10^8)$, where E^*_{10} is unstable and E^*_{20} is asymptotically stable, and the boundary steady state $\bar{E} = (\bar{x}, 0, 0, \bar{w}) = (8.0531 \times 10^8, 0, 0, 8.3449 \times 10^8)$ is also asymptotically stable since (2.7) holds. Therefore, the model exhibits bistability in the absence of any treatments. If we use initial condition $X_0 = (6.77 \times 10^4, 10^6, 10^5, 10^9)$, then the solution converges to $\bar{E} = (8.0531 \times 10^8, 0, 0, 8.3449 \times 10^8)$ when $I_1 = 0$. See Fig. 1(a). However, if $I_1 = 7 \times 10^4$ is adopted, then the tumor cells increase first but level off at 158 within 25 days as shown in Fig. 1(b). The tumor remains at the same level if we run the time longer for up to 1000 days.

Notice that in Fig. 1(a) and (b), a small initial tumor size is used. We see that the tumor grows to a huge size of 8.0531×10^8 if there is no treatment. The tumor can be easily reduced to the small size of 158 cells within the first 25 days if a small dose of 7×10^4 of $CD4^+$ T cells is implemented. On the other hand, if the initial tumor size is large, then the treatment by $CD4^+$ T cells is not effective as shown in Fig. 1(c) even with a large dose of treatment. Therefore, tumor size is a critical factor in determining treatment success. If the tumor can be detected early when it is small, then immunotherapy of $CD4^+$ cells is a good treatment option for the patient.

On the other hand, if we increase the initial tumor size to 6.77×10^8, i.e., $X_1 = (6.77 \times 10^8, 10^6, 10^5, 10^9)$ is the initial condition, then the tumor cells grow to 8.05307×10^8 under the treatment strategy of $I_1 = 7 \times 10^4$ and to 8.05209×10^8 if $I_1 = 10^8$. See Fig. 1(c). We conclude that the initial tumor size is a very important factor in determining the effects of treatments by $CD4^+$ T cells.

In [10], the treatment of Th1 or Th2 cells is 10^7 cells per day, while treatments of CTL range from 2×10^9 to 9.5×10^{10} and 2.3×10^{10} to 13.7×10^{10} number of cells per infusion in [9] and [28], respectively. Let $I_1 = 10^7$ with the above parameter values. Then (3.1) has three interior steady states $E^*_1 = (8.0529 \times 10^8, 1.242 \times 10^5, 1.973 \times 10^4, 8.3450 \times 10^8)$, $E^*_2 = (2.929 \times 10^6, 3.840 \times 10^7, 6.097 \times 10^6, 9.994 \times 10^8)$ and $E^*_3 = (12.88, 1.000 \times 10^8, 2.020 \times 10^5, 1.000 \times 10^9)$. The Jacobian matrix at E^*_i, $i = 1, 3$, has four negative real eigenvalues and thus E^*_1 and E^*_3 are asymptotically stable. The Jacobian matrix at E^*_2 has three negative real eigenvalues and one positive real eigenvalue and hence E^*_2 is a saddle point with a one-dimensional stable manifold. For the initial condition X_0, the solution converges to E^*_3 while the solution converges to E^*_1 if X_1 is the initial condition. For this initial condition X_1, the tumor will be stabilized to a large size of 6.598×10^8 even if a large dose $I_1 = 10^{11}$ is used. As a result, a careful analysis of the tumor size prior to the treatments by $CD4^+$ cells needs to be carried out.

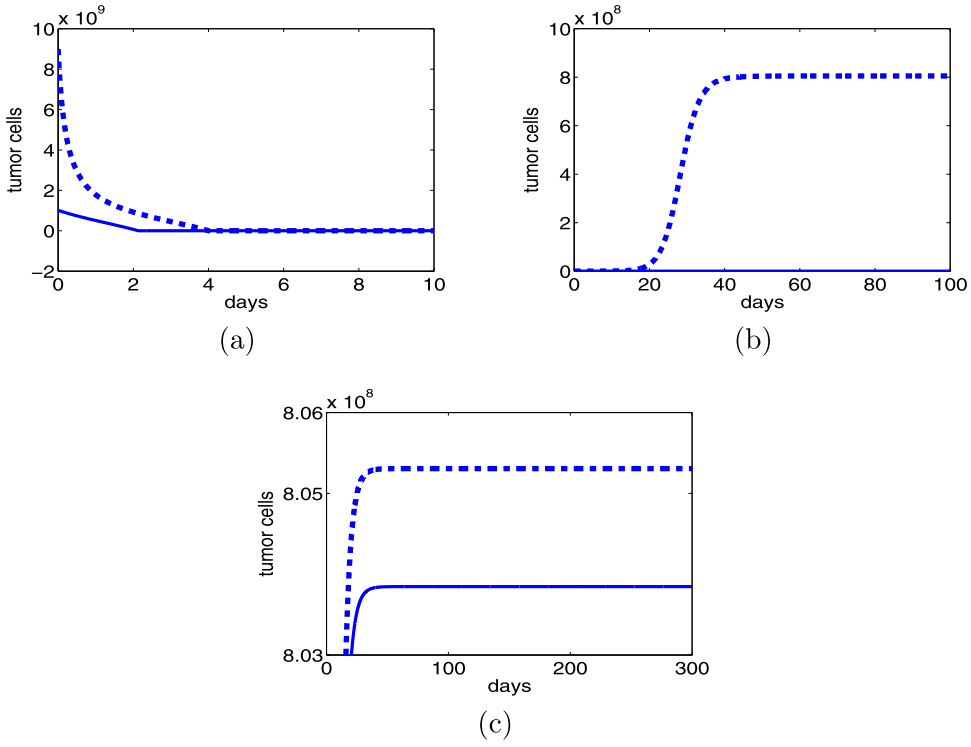

Fig. 2. The parameter values are $\beta_1 = 0.835$, $r_2 = 0.2822$ and $\delta_3 = 0.58 \times 10^{-10}$. (a) Provides time evolution of the tumor cells with two different initial conditions (10^9, 10^6, 10^5, 10^9) and (9×10^9, 10^6, 10^5, 10^9) under $I_2 = 8.6 \times 10^{10}$. The outcome of two treatment strategies on the same initial condition X_0 is given in (b), where one adopts $I_2 = 10^7$ and the other uses $I_2 = 7 \times 10^4$. The tumor can be clear off if $I_2 = 10^7$. Plot (c) uses initial condition X_1 and with two different treatments $I_2 = 7 \times 10^4$ and $I_2 = 10^8$.

If the immunotherapy by cytokine is implemented, then the minimum dose of the critical treatment I_2^c using the above parameter values is about 8.567×10^{10}, which lies in the range used by Dudley et al. [9] and Plautz et al. [28]. It is shown in Theorem 3.7 that the tumor can be eliminated completely for all sizes if the dose of treatment exceeds I_2^c. We use numerical examples to illustrate the theorem. We choose a treatment strategy $I_2 = 8.6 \times 10^{10}$ that is slightly greater than I_2^c. Then it only takes about four days to eradicate the tumor cells as shown in Fig. 2(a) where two initial conditions (9×10^9, 10^6, 10^5, 10^9) and (10^9, 10^6, 10^5, 10^9) are used. The tumor size in these two initial conditions is larger than the tumor's carrying capacity. We next examine the effects of treatments when the dose is smaller than I_2^c. For the initial condition X_0, the tumor cells disappear completely within 20 days if $I_2 = 10^7$ but the tumor grows to 8.0531×10^8 if $I_2 = 7 \times 10^4$. The inequality that determines global extinction of the tumor given in (3.10) is not satisfied for these two values of I_2. See Fig. 2(b) for the time evolution of the tumor cells. Since the cytokine can kill cancer cells directly, this is a very surprising finding as compared to the treatment of CD4$^+$ T cells discussed earlier (c.f. Fig. 1(b)), where the tumor only grows to 158 when $I_1 = 7 \times 10^4$ is used. If the initial condition X_1 is considered, then the tumor grows to 8.05306×10^8 if $I_2 = 7 \times 10^4$ and to 8.03846×10^8 if $I_2 = 10^8$ as presented in Fig. 2(c). These two final sizes of the tumor are slightly smaller than the corresponding final size of the tumor when treatments using CD4$^+$ T cells are given.

Let $I_2 = 10^7$. Then the boundary steady state $E_{22} = (0, 0, 2.941 \times 10^5, 10^9)$ is stable and (3.5) has two interior steady states $E_1^* = (8.052 \times 10^8, 3.051 \times 10^3, 2.946 \times 10^5, 8.345 \times 10^8)$ and $E_2^* = (6.440 \times 10^5, 7.616 \times 10^6, 1.502 \times 10^6, 9.999 \times 10^8)$, where E_1^* is asymptotically stable and E_2^* is unstable so that bistabilty also occurs for this treatment strategy. If we decrease the dose of treatment to 10^5, then E_{22} becomes unstable and (3.5) has three interior steady states, $E_1^* = (8.053 \times 10^8, 3.051 \times 10^1, 2.946 \times 10^3, 8.345 \times 10^8)$, $E_2^* = (3.226 \times 10^5, 5.370 \times 10^6, 8.532 \times 10^5, 9.999 \times 10^8)$ and $E_3^* = (6.416 \times 10^3, 1.543 \times 10^6, 2.150 \times 10^5, 9.999 \times 10^8)$, where E_1^* and E_3^* are asymptotically stable and E_2^* is a saddle point. Thus the model also exhibits bistability and it is expected that the basin of attraction of E_2^* provides a region of initial tumor sizes for a successful treatment by the cytokines with $I_2 = 10^5$.

We next study combination of treatments. If X_0 is used as the initial condition, then the tumor shrinks to 157 if $I_1 = 7 \times 10^4$ and $I_2 = I_1$ at the same time. This final tumor size is slightly smaller than the previous treatment of using CD4$^+$ T cells alone. The tumor shrinks further to 143 if we increase I_2 to 7×10^5. The time evolution of the tumor cells is given in Fig. 3(a). If a larger tumor size X_1 is used as an initial condition, then the tumor is stabilized at 8.0530609×10^9, 8.03747948×10^8, and 8.03846209×10^8 respectively if $I_1 = I_2 = 7 \times 10^4$, $I_1 = I_2 = 10^8$, and $I_1 = 7 \times 10^4$ and $I_2 = 10^8$. See Fig. 3(b). Since the tumor size is large under these combined treatments, we increase the dose of I_2. However, if I_2 is smaller than 10^9, we are unable to shrink the tumor significantly even if I_1 is large with $I_1 = 10^{11}$. If $I_2 = 10^9$, then we can clear off the tumor if

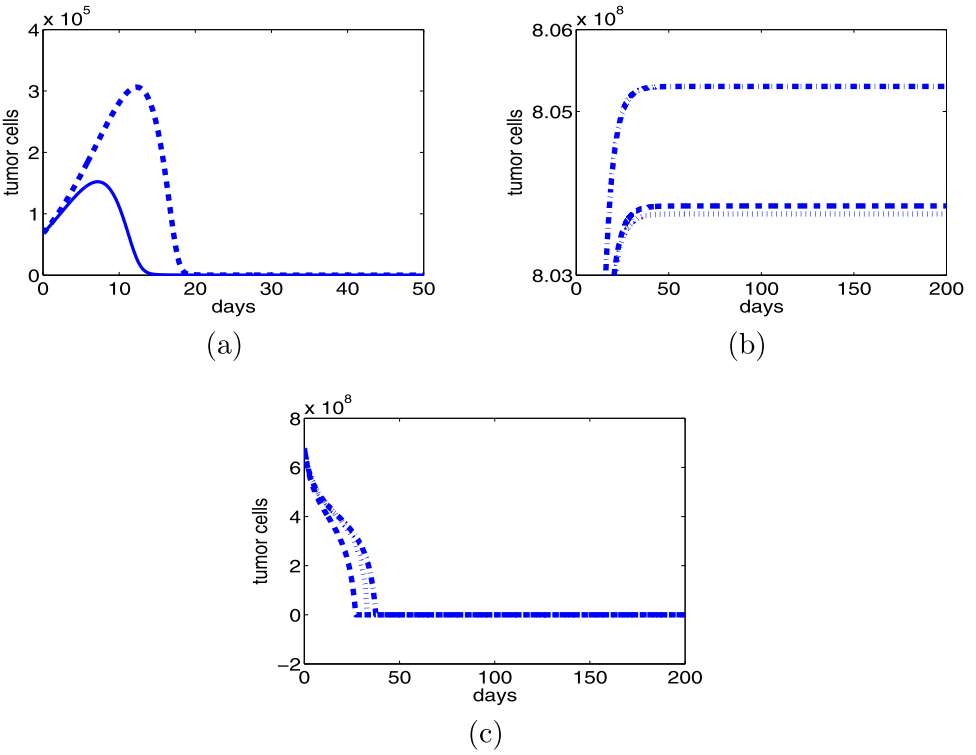

Fig. 3. The parameter values are $\beta_1 = 0.835$, $r_2 = 0.2822$ and $\delta_3 = 0.58 \times 10^{-10}$. (a) Provides time evolution of the tumor cells with initial condition X_0 and two different combined treatment strategies. Dashed line: $I_1 = I_2 = 7 \times 10^4$, solid line: $I_1 = 7 \times 10^4$ and $I_2 = 7 \times 10^5$. (b) The initial condition X_1 is used. Dash–dot line: $I_1 = I_2 = 7 \times 10^4$, dotted line: $I_1 = I_2 = 10^8$, dashed line: $I_1 = 7 \times 10^4$ and $I_2 = 10^8$. Plot (c) uses X_1 as the initial condition. Dotted line: $I_1 = 10^{10}$ and $I_2 = 1.4 \times 10^{10}$, dash–dot line: $I_1 = 10^9$ and $I_2 = 1.5 \times 10^{10}$, dashed line: $I_1 = 10^8$ and $I_2 = 1.6 \times 10^{10}$.

$I_1 \geq 5 \times 10^{11}$. If $I_2 = 10^{10}$, then the tumor can be eradicated if I_1 is larger than or equal to 5×10^{10}. Fig. 3(c) provides time evolution of the tumor cells with three combined treatments where the tumor can be eradicated within 40 days in each of the combined strategies.

If the tumor size is small, then the patient in general is healthier than the one with a large tumor load and such a patient is also more tolerant of immunotherapy. Combined treatments of $CD4^+$ and cytokines are presented in Fig. 3. In Fig. 3(a), a small tumor size is considered and such a tumor can be eradicated with a small dose of combined $CD4^+$ and cytokines. In Fig. 3(b) and (c) where tumor size is large, then a combination of small doses of $CD4^+$ and cytokines is not sufficient to control the tumor as shown in Fig. 3(b) where the tumor increases its size even though there are treatments. However, the tumor can be completely removed if the treatment doses are large as illustrated in Fig. 3(c). Although the tumor can be eliminated in both Fig. 3(a) and (c), we see that large doses of treatments are needed for the large initial tumor size. In addition, for large tumor size a longer period of treatments is required.

4.2. Pulsed treatments

The above numerical investigation focuses on the continuous treatments. In this section, we briefly discuss pulsed treatments. If $X_0 = (6.77 \times 10^4, 10^6, 10^5, 10^9)$ is used as the initial condition and a small dose s_1 of 7×10^4 $CD4^+$ T cells is injected on $t \in [7, 8] \cup [14, 15] \cup [21, 22] \cup [28, 29] \cup [35, 36]$, that is, treatments on given on day 7, 14, 21, 28 and 35, then the pulsed treatments cannot control the tumor and the tumor grows to the order of 8×10^8. Recall that continuous treatments of the same dose by $CD4^+$ T cells can control the tumor as illustrated in Fig. 1(b). However, if the dose s_1 is increased to 5×10^6 with the same treatment schedule, then the tumor can be controlled. There are about 50 cells by the end of day 50. See Fig. 4(a) where the tumor size is plotted for the first 50 days. If we run the time longer to $t = 500$, the tumor size remains very small around 100 cells at time $t = 500$ even if there is no treatment after day 35.

We next study the treatment by cytokines with the same initial condition X_0. If the dose s_2 of cytokines is $s_2 = 5 \times 10^6$ with the same treatment schedule as above, then the treatment cannot control the tumor as shown in Fig. 4(b). If we increase the treatment dose s_2 to $s_2 = 3 \times 10^7$ and $s_2 = 5 \times 10^7$, respectively, then the tumor can be controlled. See Fig. 4(c). The tumor remains small if we run the time longer to $t = 500$ with only five scheduled treatments.

If the initial condition $X_1 = (6.77 \times 10^8, 10^6, 10^5, 10^9)$ is used and the pulsed treatments by $CD4^+$ T cells are considered, then neither the dose of $s_1 = 7 \times 10^4$ nor $s_1 = 5 \times 10^6$ with the above treatment schedule is sufficient to control the tumor. The tumor grows to 8.05306×10^8 at time $t = 50$ and to 8.05307×10^8 at $t = 200$ for both doses. Even if we increase s_1 to

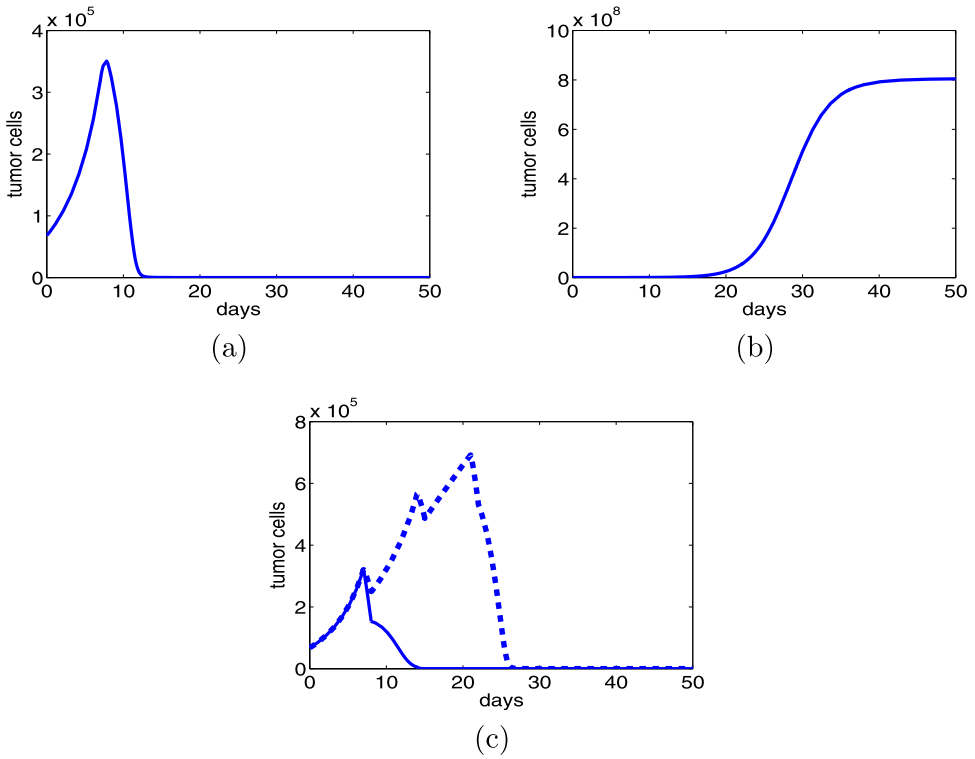

Fig. 4. The parameter values are $\beta_1 = 0.835$, $r_2 = 0.2822$ and $\delta_3 = 0.58 \times 10^{-10}$ with initial condition $X_0 = (6.77 \times 10^4, 10^6, 10^5, 10^9)$ and different pulsed treatments. In (a) $s_1 = 5 \times 10^6$, (b) $s_2 = 5 \times 10^6$, and (c) dashed line: $s_2 = 3 \times 10^7$, solid line: $s_2 = 5 \times 10^7$.

$s_1 = 5 \times 10^{10}$ with five injections as scheduled above, then the tumor grows to 8.05306×10^8 at $t = 50$. This is not too surprising since the tumor grows to a large size of order 10^8 if continuous treatments of CD4$^+$ T cells with $I_1 = 10^8$ are adopted as given in Fig. 1(c). Suppose now pulsed treatments by cytokines are administered. Then the tumor grows to 8.05306×10^8 if $s_2 = 8.6 \times 10^{10}$ with five injections as scheduled above. If combined treatments by CD4$^+$ T cells and cytokines are considered with five injections of doses $s_1 = 5 \times 10^{10}$ and $s_2 = 8.6 \times 10^{10}$, then the tumor grows to 8.06×10^8. Therefore, pulsed treatments with five injections cannot control the tumor if initial tumor size is large.

In the experiment carried out by Mattes et al. [24], 10^5 tumor cells are injected in the mouse on day zero and adopted transfer of 10^7 CD4$^+$ T cells is administered on day 7, that is, $s_1 = 10^7$ on $t \in [7, 8]$ only. See Eq. (11) of Eftimie et al. [10]. To validate our model, we use initial condition $X_2 = (10^5, 10^6, 10^5, 10^9)$, where the tumor size of 10^5 cells is the same as the experiment performed by Mattes et al. Our result is presented in Fig. 5(a) for $t = 50$ and the tumor remains very small if we run the time for up to $t = 200$. On the other hand, if initial condition $X_3 = (10^5, 10^3, 10^2, 10^9)$ is used so that the immune system is not strong, then a single dose of CD4$^+$ T cells administered on day 7 is not sufficient to control the tumor, see Fig. 5(b). Further, if a single dose of cytokines is injected at day 7 with initial condition X_2, then Fig. 5(c) shows that the treatment is not enough to control the tumor. Therefore, our model (2.1) with a single treatment of CD4$^+$ T cells on day 7 yields the experimental result of Mattes et al. [24] if the immune system of the subject is strong.

4.3. Sensitivity analysis

Since parameter values given in Table 4 may not be precise and sensitivity analysis can determine parameters which are critical to the dynamical interactions, we carry out local sensitivity analysis for model (2.1) in this section.

Using the parameter values listed in Table 4 except $\beta_1 = 0.835$, $r_2 = 0.2822$ and $\delta_3 = 0.58 \times 10^{-10}$ and the initial condition $X_0 = (6.77 \times 10^4, 10^6, 10^5, 10^9)$, we either increase or decrease each parameter value by 5% and fix all other parameters as constants. Let p and $p + \Delta p$ be the original and the resulting parameter values respectively. That is, Δp is either $0.05p$ or $-0.05p$. The tumor size at time $t = 50$ for the two corresponding parameter values are denoted by x and $x + \Delta x$, respectively. The relative changes of tumor size at time $t = 50$, $\frac{\Delta x}{x} / |\frac{\Delta p}{p}|$, are summarized in Table 5, where positive values correspond to increases in tumor size and negative values indicate reduction.

From Table 5 we see that parameters r_1, b_1, δ_1 and b_2 have the most significant impact on tumor size. Other parameters such as c_1, r_2 and β_1 are also important. We now increase the competition coefficient of host cells to $\delta_1 = 0.35 \times 10^{-9}$ with initial condition $X_3 = (10^5, 10^3, 10^2, 10^9)$ and a single treatment of CD4$^+$ T cells on day 7. Recall that the tumor grows to a huge size in the order of 8×10^8 at $t = 50$ as shown in Fig. 5(b) where $\delta_1 = 1.1 \times 10^{-10}$. The result with a larger δ_1 is given in Fig. 6(a) where the tumor is reduced to only 9 cells at $t = 50$ and is under controlled with a small size of 370 cells

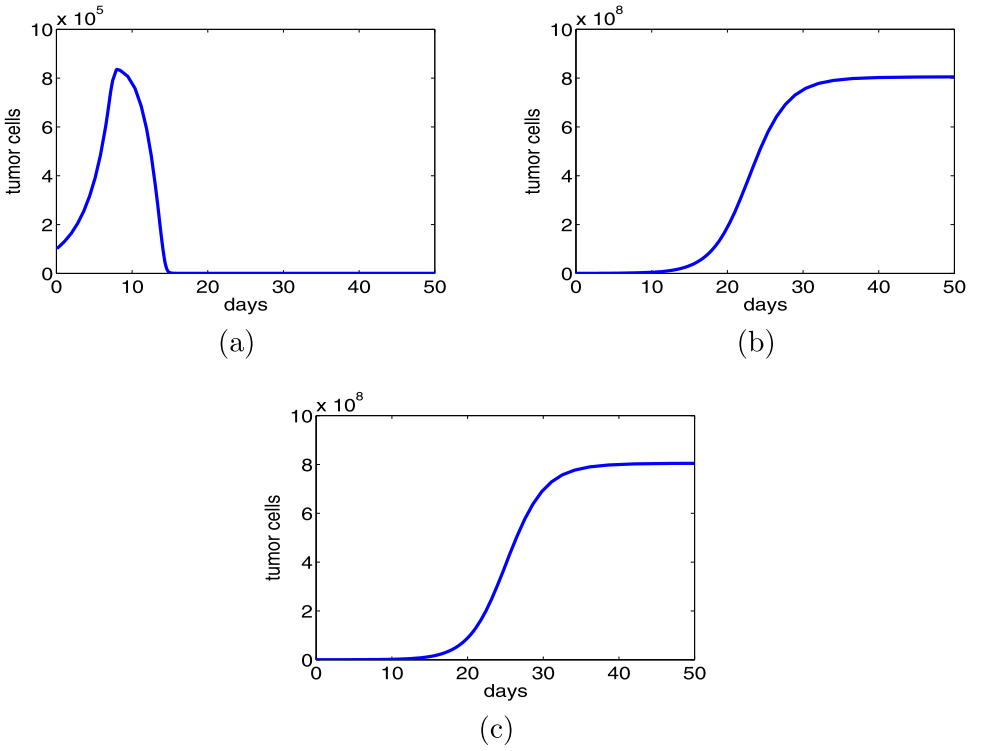

Fig. 5. The parameter values are $\beta_1 = 0.835$, $r_2 = 0.2822$ and $\delta_3 = 0.58 \times 10^{-10}$ with a single dose of treatment on day 7. Treatments by CD4$^+$ T cells are given in (a) and (b), and (c) uses cytokines. The initial conditions are: (a) $X_2 = (10^5, 10^6, 10^5, 10^9)$, (b) $X_3 = (10^5, 10^3, 10^2, 10^9)$, and (c) $X_2 = (10^5, 10^6, 10^5, 10^9)$.

Table 5
Sensitivity analysis $\frac{\Delta x}{x} / |\frac{\Delta p}{p}|$.

Parameter	Increase by 5%	Decrease by 5%
r_1	2.28321×10^{-1}	-2.84787×10^{-1}
b_1	-9.91160×10^{-1}	1.10006
c_1	-4.04650×10^{-3}	2.78653×10^{-3}
a_1	1.15069×10^{-3}	-1.40669×10^{-3}
δ_1	-2.33434×10^{-1}	2.31202×10^{-1}
β_1	-2.05652×10^{-3}	1.57777×10^{-3}
α_1	1.44765×10^{-5}	-1.45215×10^{-5}
μ_1	1.36070×10^{-4}	-1.38852×10^{-4}
δ_2	2.58629×10^{-4}	-2.71484×10^{-4}
β_2	-7.5366×10^{-3}	3.85292×10^{-3}
α_2	3.77354×10^{-5}	-3.79654×10^{-5}
μ_2	3.69854×10^{-3}	-8.08388×10^{-3}
r_2	-3.89698×10^{-2}	4.25568×10^{-2}
b_2	2.19634×10^{-1}	-2.44596×10^{-1}
δ_3	4.34876×10^{-2}	-4.33720×10^{-2}

at $t = 500$. If a single dose of cytokines is applied on day 7, then the treatment cannot control the tumor and the tumor continues to grow as given in Fig. 6(b). We now also decrease tumor's growth rate from $r_1 = 0.514$ to $r_1 = 0.4$ and apply a single dose of cytokines on day 7 in Fig. 6(c). The tumor is reduced to 109 cells on day 50 and to 378 cells on day 500 with only a single dose.

We are now ready to compare our numerical results with other studies. Since there are only two mathematical models using CD4$^+$ T cells as effectors, namely those by Eftimie et al. [10] and Anderson et al. [3], we compare our numerical results with them. Noticing first that the cell populations are in terms of number of cells in our models and in Eftimie et al. [10] while volume is the unit in Anderson et al. [3]. For the model of no treatment, there are possibly three interior steady states in [3] but only two possible interior steady states in (2.1) and in [10]. This in part is due to the different biological assumptions used. The CD4$^+$ T cell provides a positive feedback to its own production in [3] so that there is possibly one more interior steady state in [3] but not in [10] and (2.1) where production of CD4$^+$ is stimulated by the tumor and cytokines.

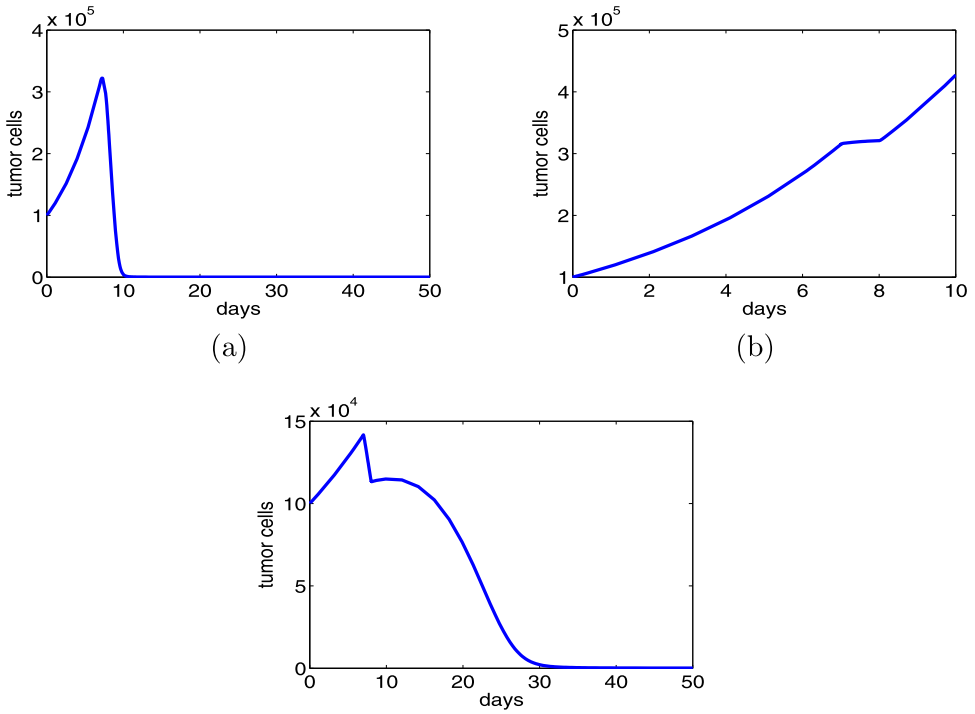

Fig. 6. The parameter values are $\beta_1 = 0.835$, $r_2 = 0.2822$ and $\delta_3 = 0.35 \times 10^{-9}$ in (a) and (b). A single dose of treatment is applied on day 7 with initial condition $X_3 = (10^5, 10^3, 10^2, 10^9)$. Treatments by CD4$^+$ T cells and cytokines are given in (a) and (b), respectively. The tumor's growth rate is reduced to $r_1 = 0.4$ in (c) with the same treatment dose of cytokines on day 7 and initial condition X_3.

Both treatment types are considered in [3] but only the treatment by CD4$^+$ T cells is numerically simulated in [10]. It is found in [3] that continuous treatments can eliminate oscillating behavior of the dynamical interactions. Since periodic solutions with small amplitudes and large periods only exist in a very small parameter space in our model, continuous treatments in our model do not yield this property. We therefore conclude that host cells along with the mechanism of CD4$^+$ production play important roles in driving tumor dynamics.

Notice that combined treatments by CD4$^+$ and cytokines are not incorporated in [3,10]. This new treatment strategy considered here shows that combined treatments allow smaller doses of CD4$^+$ and cytokines for effective therapy than when single treatment type is administered. Even though cytokines can kill tumor cells directly, our numerical results indicate that treatments by CD4$^+$ T cells may be more effective than injections of cytokines in controlling the tumor. This conclusion is also obtained in [10] by comparing two individual continuous treatments.

5. Discussion and conclusions

Cancer is a major cause of death worldwide. There are clinical methods such as surgery and/or chemo- and radiotherapies to treat the disease. Immunotherapy is the treatment of cancer by inducing, enhancing, or suppressing an immune response. It usually uses cytokines together with adoptive cellular transfer to boost the immune system. Most cancer immunotherapies have involved the generation of CD8$^+$ CTLs to kill cancer cells. As many tumors have been able to evade recognition by CTLs by losing MHC antigens, the need of other immunotherapies is urgent [24,27,36]. Recent experiments suggest that CD4$^+$ T cells can recognize tumor antigen that is CTL resistant and may be even more efficient than that of the CTLs [24,27,36].

Mathematical modeling is an important tool to study cancer–immune interactions and there are several models constructed to explore the roles of CD4$^+$ T cells on tumor rejection recently [3,10]. In this work, we extend a previous study [3] by proposing mathematical models of interactions between tumor, normal tissue cells, CD4$^+$ T cells and cytokine to explore tumor dynamics and to investigate possible mechanisms on tumor regression and dormancy. The novelty of this work is that the host cells are considered in the interaction and the production of CD4$^+$ T cells is activated through the tumor and cytokine. In [3], CD4$^+$ cells are assumed to exhibit autocrine signaling so that the production rate is proportional to the CD4$^+$ itself. This new modeling assumption of the CD4$^+$ production is motivated by the work in [10]. However, the model studied in [10] is more complicated by incorporating not only tumor suppressing cytokines but also tumor promoting cytokines.

It is proved analytically that the tumor can be clear off completely without any treatments if it has a small intrinsic growth rate and is also less competitive. See Theorem 2.5. Consequently, such a tumor will be eradicated with any treatment of cytokines, CD4$^+$ T cells, or a combination of the two (cf. Theorems 3.1, 3.3 and 3.7). In addition, if the natural loss rate

of cytokine/CD4$^+$ T cells or both is large, then the immune system is not effective in controlling the tumor. The fate of the tumor then depends on its interaction with the host cells as demonstrated in Theorem 2.4. However, the tumor cannot grow to its carrying capacity even without any treatments if the natural loss rate of either CD4$^+$ or cytokine is not too large as Theorem 2.5 implies.

If either the tumor has a large intrinsic growth rate or if it is more competitive, then bistability can occur in the tumor-immune interactions. Although oscillations are frequently observed in some previous models [3,18], where the host cells are not incorporated, oscillations are rarely present in this investigation. When oscillations do exist in the dynamic interaction, then the long periodicity is obtained and thus such an oscillatory behavior is not easily observed clinically. It is widely believed that tumor cells do not oscillate over time [10]. Therefore, our study suggests that host cells along with production of the CD4$^+$ T cells play important roles in regulating tumor dynamics.

With the constant treatment of CD4$^+$ T cells, it is certain that the tumor can never grow to its carrying capacity. The interaction may support up to three interior steady states and the model may exhibit bistability. This indicates that the long term fate of the tumor with treatments of CD4$^+$ depends on the tumor size when it is detected. Consequently, if the tumor can be detected early, then the tumor cells will be controlled with the treatment of CD4$^+$ T cells.

When the immunotherapy by cytokine is adopted, then the treatments can prevent the tumor growing to its carrying capacity. This model can also support three interior steady states. The tumor cells can be eradicated independent of the tumor size if the treatment doses are larger than a critical value given by Theorem 3.7. If the treatment dose is in the middle range, then whether the treatments are successful or not depends on tumor size. We also discuss combinations of treatments by CD4$^+$ T cells and cytokine. The effect of combined therapy is prominent if the tumor size is small. For large tumors, it is possible to clear off the tumor cells with a smaller dose of cytokine if the treatment by CD4$^+$ T cells is also adopted.

In the previous study [3] where host cells are not incorporated and the production of CD4$^+$ is also modeled differently, it is found that the model exhibits oscillations frequently in which periodicities of the oscillations depend on the tumor antigenicity. Periodic solutions on the other hand are rarely observed in the present model. A critical cytokine dose is also derived in [3], where the critical does depends on the tumor's growth rate and its carrying capacity and also on the maximal tumor killing rate along with cytokine's natural loss rate. In the present investigation, the critical cytokine dose also depends on these parameters. However, bistability does not occur in the model of no treatment in [3] while bistability is exhibited in all of the models presented here, including the model of no treatment and also the models of either treatment by CD4$^+$ T cells or the cytokines. In addition, tumor cells cannot be cleared off without any treatment in the model proposed in [3]. However, it is proved in this work that the tumor can be completely eradicated without any treatment if the tumor has a small growth rate and is also less competitive.

Similar to the results obtained in [3], this study concludes that continuous treatments by either the CD4$^+$ T cells or the cytokine is effective in controlling the tumor if the initial tumor size is small. The treatment by cytokine is in general more effective than transferring the CD4$^+$ T cells for clearing off the tumor cells since cytokines can directly kill tumor cells. However, the advantage of using cytkones over CD$^+$ T cells becomes less visible if the tumor is large. The treatment by cytokine in general is not satisfactory unless the dose is large or if the tumor is small. On the other hand, bistability exists in models of either treatment strategy. This signifies that early detection with treatment is critical in controlling the tumor. Theoretically, one can find the basin of attraction of each stable steady state for the models with and without the treatments. The dose of continuous treatment then depends on the tumor size, the method of treatment, and the expect terminal tumor size. Although a large dose of cytokine can clear off the tumor cells, its negative effects on the host cells are not considered. We plan to explore the tumor-immune interactions by incorporating a cytokine storm and also other types of immune cells into the model in the near future.

In this work and in [10], pulsed treatments are simulated using the tumor size of 10^5 cells and a single dose of 10^7 CD4$^+$ T cells administered in day 7. Whether such a pulsed treatment is successful or not depends on the feedback between CD4$^+$ T cells and eosinophils in [10], while it is found that it depends on the strength of the immune system in our model. A single dose of CD4$^+$ T cells is sufficient to reduce the tumor size significantly and prevent its further growth if the initial CD$^+$ T cells and cytokines are large.

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Appendix

Proof of Proposition 2.1. Since $F(x, y, z, w)$ is locally Lipschitz in $\mathbb{R}^4_+$, there exists a unique solution $(x(t), y(t), z(t), w(t))$ on $[0, t_0)$ for the initial value problem (2.1), where $t_0 > 0$ may depend on the initial condition. Furthermore, $x'|_{x=0} = 0$, $y'|_{y=0,x\geq 0,z\geq 0} \geq 0$, $z'|_{z=0,x\geq 0,y\geq 0} \geq 0$ and $w'|_{w=0} = 0$, solutions of (2.1) remain nonnegative on the time interval for which they are defined [33]. Let $(x(0), y(0), z(0), w(0))$ be an initial condition given arbitrarily. Let $a_0 = \max\{r_1, \beta_1, \beta_2, r_2\} > 0$ and $T = x + y + z + w$. Then $T' \leq a_0 T + I_1 + I_2$. Consider now $W' = a_0 W + I_1 + I_2$ with $W(0) = T(0)$. Since $W(t)$ is defined and bounded on any interval $[0, t_0]$, $0 < t_0 < \infty$, and $T(t) \leq W(t)$, we conclude that the solution $(x(t), y(t), z(t), w(t))$ is defined for all $t > 0$ and moreover remains nonnegative for $t > 0$. □

Proof of Proposition 2.2. At

$$E_{00} = (0,0,0,0), \quad DF(E_{00}) = \begin{pmatrix} r_1 & 0 & 0 & 0 \\ 0 & -\mu_1 & 0 & 0 \\ 0 & 0 & -\mu_2 & 0 \\ 0 & 0 & 0 & r_2 \end{pmatrix}$$

and hence E_{00} is always a saddle point. At $E_{01} = (1/b_1, 0, 0, 0)$, we have

$$DF(E_{01}) = \begin{pmatrix} -r_1 & 0 & \frac{-c_1}{b_1a_1+1} & -\delta_1/b_1 \\ 0 & -\delta_2/b_1 - \mu_1 & \frac{\beta_1}{b_1\alpha_1+1} & 0 \\ 0 & \frac{\beta_2}{b_1\alpha_2+1} & -\mu_2 & 0 \\ 0 & 0 & 0 & r_2 - \delta_3/b_1 \end{pmatrix}.$$

Therefore, E_{01} is asymptotically stable if $r_2 < \delta_3/b_1$ and (2.6) holds. It is a saddle point if one of the inequalities is reversed. Similarly, at

$$E_{02} = (0,0,0,1/b_2), \quad DF(E_{02}) = \begin{pmatrix} r_1 - \delta_1/b_2 & 0 & 0 & 0 \\ 0 & -\mu_1 & 0 & 0 \\ 0 & 0 & -\mu_2 & 0 \\ -\delta_3/b_2 & 0 & 0 & -r_2 \end{pmatrix}.$$

Hence E_{02} is locally asymptotically stable if $r_1 < \delta_1/b_2$ and it is a saddle point if $r_1 > \delta_1/b_2$.

If $\bar{E} = (\bar{x}, 0, 0, \bar{w})$ exists, then by permuting columns and rows simultaneously, $DF(\bar{E})$ is similar to

$$\begin{pmatrix} j_{11} & j_{14} & j_{13} & 0 \\ j_{41} & j_{44} & 0 & 0 \\ 0 & 0 & -\mu_2 & j_{32} \\ 0 & 0 & j_{23} & j_{22} \end{pmatrix},$$

where the upper 2×2 submatrix is the Jacobian matrix of (2.2) evaluated at $(\bar{x}, \bar{w})$, $j_{32} = \frac{\beta_2\bar{x}}{\alpha_2+\bar{x}}$, $j_{23} = \frac{\beta_1\bar{x}}{\alpha_1+\bar{x}}$ and $j_{22} = -\delta_2\bar{x} - \mu_1$. Therefore, $\bar{E}$ is locally asymptotically stable if $(\bar{x}, \bar{w})$ is locally asymptotically stable for the xw subsystem (2.2) and (2.7) holds. If either $(\bar{x}, \bar{w})$ is unstable for the subsystem (2.2) or (2.7) is reversed, then $\bar{E}$ is a saddle point. □

Proof of Theorem 2.3. By the assumption, $E_{02} = (0, 0, 0, 1/b_2)$ is asymptotically stable, $E_{01} = (1/b_1, 0, 0, 0)$ is a saddle point and $\bar{E}$ does not exist. We prove that $\lim_{t\to\infty} x(t) = 0$ and $\lim_{t\to\infty} w(t) = 1/b_2$ for any solution of (2.4). Notice $x' \le r_1x(1 - b_1x) - \delta_1xw$ and $w' \ge r_2w(1 - b_2w) - \delta_3xw$. Consider

$$\begin{aligned} T' &= r_1T(1 - b_1T) - \delta_1TS \\ S' &= r_2S(1 - b_2S) - \delta_3TS \end{aligned} \tag{A.1}$$

with $T(0) = x(0) > 0, S(0) = w(0) > 0$. Since (A.1) is a two-dimensional competitive system, solutions of (2.4) therefore satisfy $x(t) \le T(t)$ and $w(t) \ge S(t)$ for $t \ge 0$ by Smith and Waltman [32, Theorem B.1]. From the assumptions, solutions of (A.1) satisfy $\lim_{t\to\infty}(T(t), S(t)) = (0, 1/b_2)$ by Table 2. Therefore, $\limsup_{t\to\infty} x(t) \le 0$ and $\liminf_{t\to\infty} w(t) \ge 1/b_2$. Consequently, $\lim_{t\to\infty} x(t) = 0$ and $\lim_{t\to\infty} w(t) = 1/b_2$ for all solutions of (2.4) by (2.5).

Then for any $\epsilon > 0$, there exists $t_0 > 0$ such that $0 < x(t) < \epsilon$ and

$$\begin{aligned} y' &< \frac{\beta_1\epsilon z}{\alpha_1+\epsilon} - \mu_1 y \\ z' &< \frac{\beta_2\epsilon y}{\alpha_2+\epsilon} - \mu_2 z \end{aligned}$$

for all $t \ge t_0$, i.e.,

$$\begin{pmatrix} y' \\ z' \end{pmatrix} \le \begin{pmatrix} -\mu_1 & \hat{\epsilon}_1 \\ \hat{\epsilon}_2 & -\mu_2 \end{pmatrix} \begin{pmatrix} y \\ z \end{pmatrix} \text{ for } t \ge t_0, \tag{A.2}$$

where $\hat{\epsilon}_i = \frac{\beta_i\epsilon}{\alpha_i+\epsilon}$, $i = 1, 2$. Let $M = \begin{pmatrix} -\mu_1 & \hat{\epsilon}_1 \\ \hat{\epsilon}_2 & -\mu_2 \end{pmatrix}$. Then the trace of M is $tr(M) = -(\mu_1 + \mu_2) < 0$ and the determinant of M is $det(M) = \mu_1\mu_2 - \hat{\epsilon}_1\hat{\epsilon}_2$. We can choose $\epsilon > 0$ sufficiently small so that $\hat{\epsilon}_1\hat{\epsilon}_2 < \mu_1\mu_2$, i.e., $det(M) > 0$. It follow that $y(t) \to 0$ and $z(t) \to 0$ as $t \to \infty$. Therefore $(0, 0, 0, 1/b_2)$ is globally asymptotically stable. □

Proof of Theorem 2.4. Notice $x'|_{x\ge 1/b_1, w>0} < 0$ and $w'|_{w\ge 1/b_2, x>0} < 0$, solutions of (2.4) therefore satisfy $x(t) < 1/b_1$ and $w(t) < 1/b_2$ for all t large. Consequently,

$$y' \le \frac{\beta_1 z}{\alpha_1 b_1 + 1} - \mu_1 y$$
$$z' \le \frac{\beta_2 y}{\alpha_2 b_1 + 1} - \mu_2 z$$

for all t large. Consider

$$\begin{pmatrix} u' \\ v' \end{pmatrix} = \begin{pmatrix} -\mu_1 & \frac{\beta_1}{\alpha_1 b_1 + 1} \\ \frac{\beta_2}{\alpha_2 b_1 + 1} & -\mu_2 \end{pmatrix} \begin{pmatrix} u \\ v \end{pmatrix}. \tag{A.3}$$

System (A.3) is a two-dimensional cooperative system and thus $u(t) \ge y(t)$ and $v(t) \ge z(t)$ for all t large by Smith and Waltman [32]. Then (0, 0) is globally asymptotically stable for the linear system (A.3) by (2.8). It follows that $\lim_{t\to\infty} y(t) = 0 = \lim_{t\to\infty} z(t)$, and dynamics of (2.4) are asymptotically autonomous to the competitive subsystem (2.2).

By the assumption of (a), E_{01} is asymptotically stable and E_{02} is unstable. Therefore, E_{01} is globally asymptotically stable in $int(\mathbb{R}^4_+)$ since $\lim_{t\to\infty}(y(t), z(t)) = (0, 0)$. Under the assumption of (b), both E_{01} and E_{02} are locally asymptotically stable. Moreover, $\bar{E}$ exists and is a saddle point. Since solutions of (2.4) satisfy $\lim_{t\to\infty}(y(t), z(t)) = (0, 0)$, solutions with initial conditions not lying on the stable manifolds of E_{00} and $\bar{E}$ are therefore convergent to either E_{01} or E_{02}.

To prove (c), notice $\bar{x} = \frac{r_2(r_1 b_2 - \delta_1)}{r_1 r_2 b_1 b_2 - \delta_1 \delta_3} < 1/b_1$ if and only if $\delta_3 < r_2 b_1$, which holds from the assumption in (c). Hence $\bar{x} < 1/b_1$. Observe that $\frac{x^2}{(\alpha_1 + x)(\alpha_2 + x)}$ is increasing in x. Thus $\mu_1\mu_2 + \delta_2\mu_2\bar{x} - \frac{\beta_1\beta_2\bar{x}^2}{(\alpha_1+\bar{x})(\alpha_2+\bar{x})} > \mu_1\mu_2 - \frac{\beta_1\beta_2}{(b_1\alpha_1+1)(b_1\alpha_2+1)} > 0$, i.e. $\bar{E}$ is locally asymptotically stable by Proposition 2.2, and hence it is globally asymptotically stable in $\mathbb{R}^4_+$ since $\lim_{t\to\infty}(y(t), z(t)) = (0, 0)$. □

Proof of Theorem 2.5. The proof is similar to the proof of Theorem 2.5. Notice that inequality (2.9) implies (2.7) and hence $\bar{E}$ is asymptotically stable. Since $x' \le r_1 x(1 - b_1 x) - \delta_1 xw$ and $w' \ge r_2 w(1 - b_2 w) - \delta_3 xw$ for all $t \ge 0$, it follows that $\limsup_{t\to\infty} x(t) \le \bar{x}$ and $\liminf_{t\to\infty} w(t) \ge \bar{w}$ for all solutions of (2.4) by the assumptions. Therefore for any $\epsilon > 0$ there exists $t_0 > 0$ such that $x(t) < \bar{x} + \epsilon$ for all $t \ge t_0$. We can choose $\epsilon > 0$ such that $\frac{\beta_1\beta_2(\bar{x}+\epsilon)^2}{(\alpha_1+\bar{x}+\epsilon)(\alpha_2+\bar{x}+\epsilon)} < \mu_1\mu_2$. Notice for $t \ge t_0$ that

$$y' < \frac{\beta_1(\bar{x} + \epsilon)z}{\alpha_1 + \bar{x} + \epsilon} - \mu_1 y$$
$$z' < \frac{\beta_2(\bar{x} + \epsilon)y}{\alpha_2 + \bar{x} + \epsilon} - \mu_2 z.$$

Consider the following linear system

$$\begin{pmatrix} u' \\ v' \end{pmatrix} = \begin{pmatrix} -\mu_1 & \frac{\beta_1(\bar{x}+\epsilon)}{\alpha_1 + \bar{x} + \epsilon} \\ \frac{\beta_2(\bar{x}+\epsilon)}{\alpha_2 + \bar{x} + \epsilon} & -\mu_2 \end{pmatrix} \begin{pmatrix} u \\ v \end{pmatrix} \tag{A.4}$$

with $u(t_0) = y(t_0)$ and $v(t_0) = z(t_0)$. Then $y(t) \le u(t)$ and $z(t) \le v(t)$ for $t \ge 0$. By the choice of ϵ, solutions of (A.4) satisfy $\lim_{t\to\infty}(u(t), v(t)) = (0, 0)$. It follows that $\lim_{t\to\infty}(y(t), z(t)) = (0, 0)$ and hence $\bar{E}$ is globally asymptotically stable. □

Proof of Proposition 3.3. If $\limsup_{t\to\infty} x(t) = 1/b_1$, then there exists $t_n \to \infty$ such that $x(t_n) \to 1/b_1$ and $x'(t_n) \to 0$ as $n \to \infty$. From the first equation of (3.5), we then have $z(t_n) \to 0$ as $n \to \infty$, i.e., $\liminf_{t\to\infty} z(t) = 0$. We obtain a contradiction to (3.6) and the result follows. □

Proof of Theorem 3.5. As solutions of (3.5) satisfy (3.6) and $x'|_{x \ge 1/b_1, w>0} < 0$, for any $\epsilon > 0$ there exists $t_0 > 0$ such that $z(t) > I_2/\mu_2 + \epsilon$ and $x(t) < 1/b_1$ for all $t \ge t_0$. Then

$$x' < r_1 x - \frac{c_1 xz}{a_1 + x} \le x\left(r_1 - \frac{b_1 c_1 (I_2/\mu_2 + \epsilon)}{a_1 b_1 + 1}\right) \text{ for } t \ge t_0.$$

Since $I_2 > I_2^c$, we choose $\epsilon > 0$ such that $b_1 c_1 (I_2/\mu_2 + \epsilon) > r_1(a_1 b_1 + 1)$. Then $x' < \eta x$ for $t \ge t_0$ for some constant $\eta < 0$. It follows that $\lim_{t\to\infty} x(t) = 0$, and thus $\lim_{t\to\infty} y(t) = 0$, $\lim_{t\to\infty} z(t) = I_2/\mu_2$, and $\lim_{t\to\infty} w(t) = 1/b_2$. Therefore, E_{22} is globally attracting. Moreover, $I_2 > I_2^c$ implies $r_1 - \delta_1/b_2 - \frac{c_1 I_2}{\mu_2 a_1} \le r_1 - \delta_1/b_2 - \frac{r_1(a_1 b_1 + 1)}{a_1 b_1} < 0$ and E_{22} is asymptotically stable. Consequently, E_{22} is globally asymptotically stable. □

Proof of Theorem 3.6. By (3.6), for any $\epsilon > 0$ there exists $t_1 > 0$ such that $z(t) > I_2/\mu_2 - \epsilon$ and $x(t) < 1/b_1$ for $t \ge t_1$. We choose $\epsilon > 0$ such that $I_2 < I_2^c + \mu_2\epsilon$ and $1 - \frac{c_1(I_2/\mu_2 - \epsilon)}{r_1(a_1 + 1/b_1)} < \min\{\frac{b_1 r_2}{\delta_3}, \frac{\delta_1}{r_1 b_2}\}$. Then for $t \ge t_1$ there holds

$$x' \le r_1 x\left(1 - b_1 x - \frac{c_1(I_2/\mu_2 - \epsilon)}{r_1(a_1 + 1/b_1)}\right) - \delta_1 xw$$
$$w' \ge r_2 w(1 - b_2 w) - \delta_3 xw.$$

Consider the following modified Lotka–Volterra competition model

$$u' = r_1 u\left(1 - b_1 u - \frac{c_1(I_2/\mu_2 - \epsilon)}{r_1(a_1 + 1/b_1)}\right) - \delta_1 uv$$
$$v' = r_2 v(1 - b_2 v) - \delta_3 uv \tag{A.5}$$

with $u(t_1) = x(t_1)$ and $v(t_1) = w(t_1)$. A parallel analysis as in Table 2 then implies that $(0, 1/b_2)$ is globally asymptotically stable for (A.5) by the choice of ϵ and (3.10). Consequently, $\limsup_{t\to\infty} x(t) = 0$ and $\liminf_{t\to\infty} w(t) \ge 1/b_2$. Therefore, solutions of (3.5) satisfy $\lim_{t\to\infty} x(t) = 0$ and $\lim_{t\to\infty} w(t) = 1/b_2$ and hence E_{22} is globally attracting. On the other hand, (3.10) implies $r_1 < \delta_1/b_2 + \frac{c_1 I_2}{\mu_2(a_1+1/b_1)} < \delta_1/b_2 + \frac{c_1 I_2}{\mu_2 a_1}$ and thus E_{22} is locally asymptotically stable. Therefore, E_{22} is globally asymptotically stable. □

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