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Stationary patterns and stability in a tumor-immune interaction model with immunotherapy

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ABSTRACT

This paper examines a diffusive tumor-immune system with immunotherapy under homogeneous Neumann boundary conditions. We first investigate the large-time behavior of nonnegative equilibria and then explore the persistence of solutions to the time-dependent system. In particular, we present the sufficient conditions for tumor-free states. We also determine whether nonconstant positive steady-state solutions (i.e., a stationary pattern) exist for this coupled reaction–diffusion system when the parameter of the immunotherapy effect is small. The results indicate that this stationary pattern is driven by diffusion effects. For this study, we employ the comparison principle for parabolic systems and the Leray–Schauder degree.

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1. Introduction

This paper examines a diffusive tumor-immune interaction system with immunotherapy in a spatially inhomogeneous environment *in vivo*.

Let u and v be the density of effector cells and that of tumor cells, respectively, and w be the concentration of the cytokine interleukin-2 (IL-2). Then the following mathematical model can be proposed:

$$\begin{cases} u_t - d_1\Delta u = cv - \mu_2 u + \dfrac{p_1 uw}{1+w} + s_1, \\ v_t - d_2\Delta v = v(1-bv) - \dfrac{auv}{g+v}, \\ w_t - d_3\Delta w = \dfrac{p_2 uv}{1+v} - \mu_3 w + s_2 \quad \text{in } (0,\infty)\times\Omega, \\ \dfrac{\partial u}{\partial \nu} = \dfrac{\partial v}{\partial \nu} = \dfrac{\partial w}{\partial \nu} = 0 \quad \text{on } (0,\infty)\times\partial\Omega, \\ u(0,x) = u_0(x), \qquad v(0,x) = v_0(x), \qquad w(0,x) = w_0(x) \quad \text{in } \Omega, \end{cases} \tag{1.1}$$

where Ω is the bounded domain in $\mathbb{R}^N$ with a smooth boundary $\partial\Omega$; the coefficients c, b, μ_i, p_i, a and g are all positive constants; s_i are nonnegative constants; and ν is the outward unit normal vector on $\partial\Omega$. The nonnegative initial functions u_0, v_0 and w_0 are not identically zero in Ω.

Among other things, *immunotherapy* is a cancer treatment the use of cytokines and adoptive cellular immunotherapy (ACI). Cytokines are protein hormones produced mainly by activated T cells (lymphocytes) in cell-mediated immunity.

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Interleukin-2 (IL-2), produced mainly by CD4+T cells, is the main cytokine responsible for lymphocyte activation, growth, and differentiation. ACI refers to the injection of cultured immune cells that have anti-tumor reactivity into the tumor-bearing host, which is typically achieved in conjunction with large amounts of IL-2 by using the following two methods: lymphokine-activated killer cell (LAK) therapy and tumor-infiltrating lymphocyte (TIL) therapy. LAK cells, derived from in vitro culturing using high concentrations of IL-2 from peripheral blood leukocytes removed from the patient, are injected back into the cancer site. TIL cells are derived from lymphocytes recovered from the patient's tumor. These cells, incubated with high concentrations of IL-2 in vitro and composed of activated NK cells and CTL cells, are injected back into the tumor site. In this paper, we consider immunotherapy to be ACI (LAK or TIL therapy) and/or IL-2 delivery either separately or in combination in the interaction site among effector cells, the tumor, and IL-2. Thus, the dynamics of the proposed system are examined by applying each therapy separately or by applying both therapies simultaneously. In model (1.1), s_1 indicates a treatment by an external source of effector cells (e.g., LAK or TIL cells), and s_2 is a treatment by an external input of IL-2 into the patient. For more information on immune-tumor models with immunotherapy that depend only on time, the reader is referred to [2,5,10,15] and the references therein. Adam and Bellemo [1] provided a summary of tumor-immune dynamics.

Kirschner et al. [8] considered a model describing tumor-immune dynamics together with the feature of IL-2 dynamics. They used three populations: $E(t)$, activated immune system cells (commonly referred to as effector cells) such as cytotoxic T-cells, macrophages, and natural killer cells cytotoxic to tumor cells; $T(t)$, tumor cells; and $I_L(t)$, the concentration of IL-2 in the single tumor-site compartment. They proposed a spatially homogeneous predator–prey model describing the interaction between effector cells, tumor cells, and cytokine (IL-2):

$$\begin{cases} \dfrac{dE}{d\tau} = cT - \mu_2 E + \dfrac{p_1 E I_L}{g_1 + I_L} + s_1, \\ \dfrac{dT}{d\tau} = r_2 T(1 - bT) - \dfrac{aET}{g_2 + T}, \\ \dfrac{dI_L}{d\tau} = \dfrac{p_2 ET}{g_3 + T} - \mu_3 I_L + s_2, \\ E(0) = E_0, \qquad T(0) = T_0, \qquad I_L(0) = I_{L_0}. \end{cases} \tag{PP}$$

For the non-dimensionalized system (PP), we adopt the following scaling:

$$t = \frac{r_2}{\tau}, \quad u = E, \quad v = \frac{T}{g_3}, \quad w = \frac{I_L}{g_1}, \quad \tilde{b} = bg_3, \quad \tilde{c} = \frac{cg_3}{r_2}, \quad \tilde{\mu}_2 = \frac{\mu_2}{r_2}, \quad \tilde{p}_1 = \frac{p_1}{r_2},$$
$$\tilde{s}_1 = \frac{s_1}{r_2}, \quad \tilde{s}_2 = \frac{s_2}{g_1 r_2}, \quad \tilde{\mu}_3 = \frac{\mu_3}{r_2}, \quad \tilde{a} = \frac{a}{g_3 r_2}, \quad \tilde{g} = \frac{g_2}{g_3}, \quad \tilde{p}_2 = \frac{p_2}{g_1 r_2}.$$

Then (PP) is converted into the following simple form:

$$\begin{cases} \dfrac{du}{dt} = cv - \mu_2 u + \dfrac{p_1 uw}{1 + w} + s_1, \quad u(0) > 0, \\ \dfrac{dv}{dt} = v(1 - bv) - \dfrac{auv}{g + v}, \quad v(0) > 0, \\ \dfrac{dw}{dt} = \dfrac{p_2 uv}{1 + v} - \mu_3 w + s_2, \quad w(0) > 0. \end{cases}$$

We assume that the diffusion of each population occurs for the tumor-immune interaction system, and thus, we establish a model for a diffusive tumor-immune interaction system with immunotherapy in a spatially inhomogeneous environment.

Therefore, model (1.1) is proposed to represent a tumor-immune interaction system with immunotherapy under homogeneous Neumann boundary conditions. First, we examine the large time behavior of nonnegative equilibria and the persistence of solutions to the time-dependent system (1.1). In particular, we provide the sufficient conditions for tumor-free states.

Finally, we present the conditions for the existence of nonconstant positive steady-state solutions to the following time-independent system when the parameter of the immunotherapy effect is small:

$$\begin{cases} -d_1 \Delta u = cv - \mu_2 u + \dfrac{p_1 uw}{1 + w} + s_1, \\ -d_2 \Delta v = v(1 - bv) - \dfrac{auv}{g + v}, \\ -d_3 \Delta w = \dfrac{p_2 uv}{1 + v} - \mu_3 w + s_2 \quad \text{in } \Omega, \\ \dfrac{\partial u}{\partial \nu} = \dfrac{\partial v}{\partial \nu} = \dfrac{\partial w}{\partial \nu} = 0 \quad \text{on } \partial\Omega. \end{cases} \tag{1.2}$$

We show that this stationary pattern is driven by diffusion effects.

The rest of this paper is organized as follows. Section 2 presents the conditions for the existence of all nonnegative equilibria. Section 3 discusses the large-time behavior of time-dependent solutions, which are the persistence and global attractor of solutions, and investigates the stability of nonnegative constant solutions. Section 4 examines the existence and nonexistence of nonconstant positive steady-state solutions to the time-independent system (1.1).

2. Equilibria

We investigate all nonnegative constant solutions to (1.1). In particular, to determine the sufficient conditions for the existence of a unique positive constant solution, we consider only the case of $\mu_2 \geqslant p_1$ because if $\mu_2 < p_1$, then the component u of the solution to (1.1) may increase exponentially (see Theorem 3.4).

First, note that (1.1) (and thus (1.2)) has the following nonnegative constant solutions which have at least one component zero:

(a) $(0,0,0)$, if $s_1 = 0$ and $s_2 = 0$;
(b) $(s_1/\mu_2, 0, 0)$, if $s_1 > 0$ and $s_2 = 0$;
(c) $(0, 0, s_2/\mu_3)$, if $s_1 = 0$, $s_2 > 0$ and $\frac{p_1 s_2}{\mu_3+s_2} \neq \mu_2$;
(d) $(\frac{s_1(\mu_3+s_2)}{\mu_2\mu_3+s_2(\mu_2-p_1)}, 0, \frac{s_2}{\mu_3})$ if $s_1 > 0$, $s_2 > 0$ and $\mu_2\mu_3 + s_2(\mu_2 - p_1) > 0$.

The cases (b) and (d) are realistic tumor-free states. On the other hand, (a) and (c) are not realistic because the effector (or immune) cells do not disappear, although the immune system can be weak. Thus, in the next section, to investigate the tumor-free states in (1.1), we examine the global stability at the constant steady states provided in the cases (b) and (d).

We now provide two sufficient conditions that guarantee the existence of a unique positive equilibrium point $\mathbf{e}_* := (u_*, v_*, w_*)$ of (1.1).

Lemma 2.1. *If one of the following inequalities*

$$\text{(i)} \qquad gc \geqslant (1-bg)s_1 \quad \textit{and} \quad \frac{\mu_2 - p_1}{a} g > s_1, \tag{PE1}$$

$$\text{(ii)} \qquad gc > s_1, \qquad \frac{\mu_2 g}{a} > s_1\left(\frac{s_2}{\mu_3} + 1\right) \quad \textit{and} \quad \mu_2 = p_1 \tag{PE2}$$

hold, then (1.1) *has a unique positive constant steady state* $\mathbf{e}_*$.

Proof. (i) First, assume that (PE1) holds. Note that (u_*, v_*, w_*) must satisfy the following identities

$$\begin{aligned}
u_* &= \frac{1}{a}(1 - bv_*)(g + v_*) := F(v_*),\\
w_* &= \frac{1}{\mu_3}\left(s_2 + p_2 \frac{F(v_*)v_*}{1+v_*}\right) := H(v_*),\\
w_* &= \frac{\mu_2 F(v_*) - s_1 - cv_*}{s_1 + cv_* + (p_1 - \mu_2)F(v_*)} := G(v_*).
\end{aligned}$$

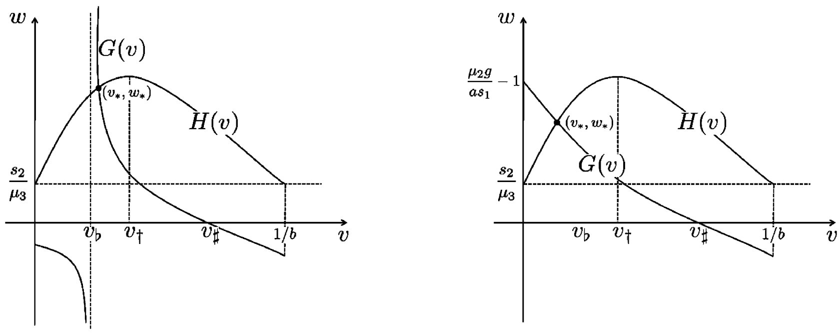
Furthermore, we have $v_* < 1/b$ from the first identities $\mu_2 F(v_*) - s_1 - cv_* > 0$ and $s_1 + cv_* + (p_1 - \mu_2)F(v_*) > 0$ in $G(v_*)$ because $w_* > 0$ and $s_1 + cv_* - \mu_2 F(v_*) < s_1 + cv_* + (p_1 - \mu_2)F(v_*)$. Denote

$$\begin{aligned}
\mu_2 F(v) - s_1 - cv &= -\frac{\mu_2}{a}bv^2 + \left(-c + \frac{\mu_2}{a}(1-bg)\right)v + \frac{\mu_2}{a}g - s_1 := A(v),\\
s_1 + cv + (p_1 - \mu_2)F(v) &= \frac{\mu_2 - p_1}{a}bv^2 + \left(c - \frac{\mu_2 - p_1}{a}(1-bg)\right)v + s_1 - \frac{\mu_2 - p_1}{a}g := B(v).
\end{aligned}$$

Clearly, the second inequality of (PE1) guarantees that $A(v) = 0$ and $B(v) = 0$ have one simple positive root in $(0, 1/b)$, say $v_\sharp$ and $v_\flat$, respectively. Moreover, $v_\flat < v_\sharp$ holds because $B(v_\sharp) = \frac{p_1}{\mu_2}(s_1 + cv_\sharp) > 0$. Note that $H(0) = H(1/b) = s_2/\mu_2$, $G(v) > 0$ only in $(v_\flat, v_\sharp)$ and that $\lim_{v \to v_\flat+} G(v) = \infty$.

By a simple calculation, we know that

$$\begin{aligned}
H_v(v) &= \frac{p_2/\mu_3}{(1+v)^2}\left\{F(v) + v(1+v)F_v(v)\right\} = \frac{p_2/\mu_3}{a(1+v)^2}\widetilde{H}(v),\\
H_{vv}(v) &= \frac{p_2/\mu_3}{(1+v)^3}\left\{2(1+v)F_v(v) + v(1+v)^2 F_{vv}(v) - 2F(v)\right\} = \frac{2p_2/\mu_3}{a(1+v)^3}\widehat{H}(v),
\end{aligned}$$



(a) When (PE1) holds (b) When (PE2) holds

Fig. 1. Graphs of $H(v)$ and $G(v)$.

$$G_v(v)=\frac{p_1}{(B(v))^2}\big\{(s_1+cv)F_v(v)-cF(v)\big\}=\frac{p_1}{a(B(v))^2}\widetilde{G}(v),$$
$$G_{vv}(v)=\frac{p_1}{(B(v))^3}\big\{(s_1+cv)F_{vv}(v)B(v)-2\big((s_1+cv)F_v(v)-cF(v)\big)B_v(v)\big\}=\frac{2p_1}{a(B(v))^3}\widehat{G}(v),$$

where

$$\widetilde{H}(v):=-2bv^3+(1-bg-3b)v^2+2(1-bg)v+g,$$
$$\widehat{H}(v):=-bv^3-3bv^2-3bv+1-bg-g,$$
$$\widetilde{G}(v):=-bcv^2-2bs_1v+(1-bg)s_1-cg,$$
$$\widehat{G}(v):=\frac{\mu_2-p_1}{a}b^2cv^3+3\frac{\mu_2-p_1}{a}b^2s_1v^2+\frac{\mu_2-p_1}{a}3b\big(cg-(1-bg)s_1\big)v-bs_1^2$$
$$-\left\{(1-bg)c-\frac{\mu_2-p_1}{a}\big(bg+(1-bg)^2\big)\right\}s_1+cg\left(c-\frac{\mu_2-p_1}{a}(1-bg)\right).$$

Then $\widetilde{H}(v)=0$ has only one simple positive root in $(0,1/b)$, say $v_\dagger$, because $g>0$, and $\widehat{H}_v(v)$ have critical points at $v=-1$ and $\frac{1-bg}{3b}$. If $1-bg-g\leqslant 0$, then $\widehat{H}(v)<0$ in $(0,1/b)$, and if $1-bg-g>0$, then $\widehat{H}(v)=0$ has only one positive root in $(0,1/b)$. Further, the root is located in $(0,v_\dagger)$ since

$$2(1+v_\dagger)F_v(v_\dagger)+v_\dagger(1+v_\dagger)^2F_{vv}(v_\dagger)-2F(v_\dagger)=\big(2F_v(v_\dagger)+v_\dagger F_{vv}(v_\dagger)\big)(1+v_\dagger)^2$$
$$=\frac{2}{a}(1-bg-3bv_\dagger)<0$$

is derived from the fact that $\frac{1-bg}{3b}<v_\dagger$ and $F(v_\dagger)=-v_\dagger(1+v_\dagger)F_v(v_\dagger)$. Thus, $H(v)$ is strictly increased in $(0,v_\dagger)$ and strictly decreased in $(v_\dagger,1/b)$. In addition, $H(v)$ is concave down in $(0,1/b)$ or has only one inflection point in $(0,v_\dagger)$.

On the other hand, because of the first inequality of (PE1), $\widetilde{G}(v)<0$ in $(0,1/b)$. When the constant term of $\widehat{G}(v)$ is nonnegative, it is clear that $\widehat{G}(v)>0$ in $(v_\flat,v_\sharp)$. Note that

$$v_\flat>v_\flat^*:=\frac{-c+\frac{\mu_2-p_1}{a}(1-bg)}{\frac{\mu_2-p_1}{a}2b}$$

since $B(v_\flat^*)<0$, and thus,

$$B_v(v_\flat)=c-(\mu_2-p_1)F_v(v_\flat)=c-\frac{\mu_2-p_1}{a}(1-bg)+\frac{\mu_2-p_1}{a}2bv_\flat>0.$$

With this result, we determine that

$$(s_1+cv_\flat)F_{vv}(v_\flat)B(v_\flat)-2\big((s_1+cv_\flat)F_v(v_\flat)-cF(v_\flat)\big)B_v(v_\flat)$$
$$=-2\big((s_1+cv_\flat)F_v(v_\flat)-cF(v_\flat)\big)B_v(v_\flat)=-2\widetilde{G}(v_\flat)B_v(v_\flat)>0$$

since $\widetilde{G}(v_\flat)<0$. Thus, even when the constant term of $\widehat{G}(v)$ is negative, $\widehat{G}(v)>0$ in $(v_\flat,v_\sharp)$ because $\widehat{G}_v(v)>0$. Therefore, $G(v)$ strictly decreases and is concave up in $(v_\flat,v_\sharp)$.

From the above, it is clear that $H(v)$ and $G(v)$ meet at only one point in $(v_\flat, v_\sharp)$, say $v = v_*$ (see Fig. 1(a)). Thus, $w_* = H(v_*) = G(v_*)$ and $u_* = F(v_*)$ can be found. Consequently, (1.1) has only one positive constant solution under (PE1).

(ii) In the case of $\mu_2 = p_1$, $B(v) = s_1 + cv > 0$ in $(0, 1/b)$. Note that the first inequality of (PE2) yields $gc > (1 - bg)s_1$ and that the second inequality of (PE2) implies $\mu_2 g/a > s_1$ and $G(0) > H(0)$. Moreover, $\widehat{G}(v)$ is independent of v and is positive under the first inequality of (PE2). Thus, as in the case above, we see that if (PE2) holds, then (1.1) has only one positive constant solution (see Fig. 1(b)). □

When $s_1 = 0$ in (PE1) and (PE2), (1.1) has a unique positive constant solution if only $\mu_2 \geqslant p_1$ is provided.

We now present simple relations among u_*, v_* and w_*, which are used in the subsequent section to determine the local stability at the positive constant steady state and the emergence of a stationary pattern.

Lemma 2.2. *Assume that* (PE1) *holds for the existence of a positive constant solution* $\mathbf{e}_*$. *Then we have the following*:

(i) $$\mu_3\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) > \frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 v_*}{1+v_*}.$$

(ii) *If either* $bg \geqslant 1$ *or*

$$c \leqslant \frac{2b}{1-bg}\left(F\left(\frac{1-bg}{2b}\right)\frac{\mu_2 + (\mu_2 - p_1)H(\frac{1-bg}{2b})}{H(\frac{1-bg}{2b})+1} - s_1\right) \quad \text{and} \quad bg < 1 \tag{2.1}$$

holds, then

$$-b + \frac{au_*}{(g+v_*)^2} \leqslant 0.$$

(iii) *If*

$$c > \frac{2b}{1-bg}\left(F\left(\frac{1-bg}{2b}\right)\frac{\mu_2 + (\mu_2 - p_1)H(\frac{1-bg}{2b})}{H(\frac{1-bg}{2b})+1} - s_1\right) \quad \text{and} \quad bg < 1, \tag{2.2}$$

then

$$-b + \frac{au_*}{(g+v_*)^2} > 0.$$

(iv) *If*

$$c \leqslant \frac{1}{v_\dagger}\left(F(v_\dagger)\frac{\mu_2 + (\mu_2 - p_1)H(v_\dagger)}{H(v_\dagger)+1} - s_1\right), \tag{2.3}$$

then $H_v(v_*) \leqslant 0$.

(v) $$\frac{acv_*}{g+v_*} + v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) > 0.$$

Proof. (i) Using $\frac{p_2 u_* v_*}{1+v_*} = \mu_3 w_* - s_2$,

$$\begin{aligned}\mu_3\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) - \frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 v_*}{1+v_*} &= \mu_3\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) - \frac{p_1}{(1+w_*)^2}(\mu_3 w_* - s_2)\\ &= \frac{1}{(1+w_*)^2}\left\{\mu_3(\mu_2 - p_1)w_*^2 + 2\mu_3(\mu_2 - p_1)w_* + \mu_2\mu_3 + p_1 s_2\right\}\\ &> 0\end{aligned}$$

is derived.

(ii) Note that

$$-b + \frac{au_*}{(g+v_*)^2} = -b + \frac{1 - bv_*}{g+v_*} = \frac{1 - bg - 2bv_*}{g+v_*}.$$

First, if $bg \geqslant 1$ is given, then the desired result follows. Next, assume that (2.1) holds. We see that $(\mu_2 - p_1)F(\frac{1-bg}{2b}) > s_1$

from the second condition in (PE1) because $bg < 1$. If

$$c \leqslant \frac{2b}{1-bg}\left((\mu_2 - p_1)F\left(\frac{1-bg}{2b}\right) - s_1\right),$$

then $B(\frac{1-bg}{2b}) \leqslant 0$, and so $v_\flat \geqslant \frac{1-bg}{2b}$. Thus $v_* \geqslant \frac{1-bg}{2b}$ follows from the fact that $v_* \geqslant v_\flat$. If

$$\frac{2b}{1-bg}\left((\mu_2 - p_1)F\left(\frac{1-bg}{2b}\right) - s_1\right) < c \leqslant \frac{2b}{1-bg}\left(F\left(\frac{1-bg}{2b}\right)\frac{\mu_2 + (\mu_2 - p_1)H(\frac{1-bg}{2b})}{H(\frac{1-bg}{2b}) + 1} - s_1\right),$$

then $B(\frac{1-bg}{2b}) > 0$ and $G(\frac{1-bg}{2b}) \geqslant H(\frac{1-bg}{2b})$. Thus $v_* \geqslant \frac{1-bg}{2b}$ is satisfied.

(iii) Since (2.2) yields $v_\flat < \frac{1-bg}{2b}$ and $G(\frac{1-bg}{2b}) < H(\frac{1-bg}{2b})$, the desired assertion follows.

(iv) It is clear that

$$(\mu_2 - p_1) < \frac{\mu_2 + (\mu_2 - p_1)H(v_\dagger)}{H(v_\dagger) + 1}.$$

Thus we consider the following two cases:

(a) $c \leqslant \frac{1}{v_\dagger}((\mu_2 - p_1)F(v_\dagger) - s_1)$,

(b) $\frac{1}{v_\dagger}((\mu_2 - p_1)F(v_\dagger) - s_1) < c \leqslant \frac{1}{v_\dagger}(F(v_\dagger)\frac{\mu_2+(\mu_2-p_1)H(v_\dagger)}{H(v_\dagger)+1} - s_1)$.

If the case (a) holds, then $B(v_\dagger) \leqslant 0$. Thus $v_\dagger \leqslant v_\flat$, which implies the desired result. Moreover, under the case (b), we can also obtain the same result since $v_\dagger > v_\flat$ and $G(v_\dagger) \geqslant H(v_\dagger)$ are satisfied.

(v) Using the fact that $\mu_2 - \frac{p_1 w_*}{1+w_*} = \frac{cv_*+s_1}{u_*}$ and $\frac{au_* v_*}{g+v_*} = v_*(1 - bv_*)$, we have

$$\begin{aligned}
\frac{acv_*}{g+v_*} + v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) &= \frac{acv_*}{g+v_*} + v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\frac{cv_* + s_1}{u_*} \\
&= \frac{v_*}{u_*}\left\{c(1-bv_*) + \left(b - \frac{1-bv_*}{g+v_*}\right)(cv_* + s_1)\right\} \\
&= \frac{v_*}{u_*(g+v_*)}\left\{bcv_*^2 + 2bs_1 v_* + gc - (1-bg)s_1\right\} \\
&> 0
\end{aligned}$$

by the first condition given in (PE1). □

When (PE2) holds, we obtain the following results, which are special cases of the above lemma.

Lemma 2.3. *Assume that* (PE2) *holds for the existence of a positive constant solution* $\mathbf{e}_*$. *Then we have the following*:

(i) $$\mu_3\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) > \frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 v_*}{1+v_*}.$$

(ii) *If either* $bg \geqslant 1$ *or*

$$c \leqslant \frac{2b}{1-bg}\left(F\left(\frac{1-bg}{2b}\right)\frac{\mu_2}{H(\frac{1-bg}{2b}) + 1} - s_1\right) \quad \text{and} \quad bg < 1 \tag{2.4}$$

holds, then

$$-b + \frac{au_*}{(g+v_*)^2} \leqslant 0.$$

(iii) *If*

$$c > \frac{2b}{1-bg}\left(F\left(\frac{1-bg}{2b}\right)\frac{\mu_2}{H(\frac{1-bg}{2b}) + 1} - s_1\right) \quad \text{and} \quad bg < 1, \tag{2.5}$$

then

$$-b + \frac{au_*}{(g+v_*)^2} > 0.$$

(iv) *If*

$$c \leqslant \frac{1}{v_\dagger}\left(F(v_\dagger)\frac{\mu_2}{H(v_\dagger)+1} - s_1\right), \tag{2.6}$$

then $H_v(v_*) \leqslant 0$.

(v) $$\frac{acv_*}{g+v_*} + v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) > 0.$$

Proof. If $\mu_2 = p_1$, then the relations (i)–(iv) come from their corresponding results in Lemma 2.2. Moreover, (v) follows from the fact that the first inequality of (PE2) yields the first one of (PE1). □

Remark 2.4. Consider the case of $1 > bg$. Note that $\frac{1-bg}{2b} < v_\dagger$, $F_v(v) \leqslant 0$ and $H_v(v) \geqslant 0$ in the interval $[\frac{1-bg}{2b}, v_\dagger]$. Thus we know that

$$\frac{d}{dv}\left(\frac{F(v)(\mu_2 + (\mu_2 - p_1)H(v))}{H(v)+1}\right) = \frac{F_v(v)(\mu_2 + (\mu_2 - p_1)H(v)) - p_1 F(v) H_v(v)}{(H(v)+1)^2} \leqslant 0$$

in $[\frac{1-bg}{2b}, v_\dagger]$. From this result and the fact that $\frac{1-bg}{2b} < v_\dagger$, we see that (2.3) implies the first inequality of (2.1). Thus if (PE1) and (2.3) hold, then the results (i), (ii), (iv) and (v) in Lemma 2.2 are obtained. Similarly, (PE2) and (2.6) imply the results (i), (ii), (iv) and (v) in Lemma 2.3.

3. The large time behavior: Stability and tumor-free states

In this section, we examine the persistence property and the global attractor for solutions to (1.1). In addition, we provide some sufficient conditions for the stability of nonnegative constant solutions to (1.1). For this, we use mainly the comparison principle, which is frequently used in examining the large-time behavior of time-dependent solutions (for example, see [21,22]).

Theorem 3.1. *Assume that* $\mu_2 > p_1$. *Then the nonnegative solution* (u, v, w) *to* (1.1) *satisfies*

$$\lim_{t\to\infty}\sup_{\overline{\Omega}} u(t,x) \leqslant \frac{c/b + s_1}{\mu_2 - p_1}, \qquad \lim_{t\to\infty}\sup_{\overline{\Omega}} v(t,x) \leqslant \frac{1}{b}, \qquad \lim_{t\to\infty}\sup_{\overline{\Omega}} w(t,x) \leqslant \frac{1}{\mu_3}\left(p_2\frac{c/b + s_1}{\mu_2 - p_1} + s_2\right). \tag{3.1}$$

Proof. The second result in (3.1) follows easily from the comparison principle for the parabolic problem [18,20] since $v(1-bv) - a\frac{uv}{g+v} \leqslant v(1-bv)$ in $[0,\infty) \times \Omega$. Thus, for any positive constant ϵ_1, there exists $t_1 \in (0,\infty)$ such that $v(t,x) \leqslant 1/b + \epsilon_1$ in $[t_1,\infty) \times \overline{\Omega}$. Using this result, $cv - \mu_2 u + p_1\frac{uw}{1+w} + s_1 \leqslant c(1/b + \epsilon_1) + s_1 - (\mu_2 - p_1)u$ can be derived in $[t_1,\infty) \times \Omega$, and thus, for arbitrary $\epsilon_2 > 0$, there exists $t_2 \in [t_1,\infty)$ such that $u(t,x) \leqslant \frac{c/b+s_1}{\mu_2 - p_1} + \epsilon_2$ in $[t_2,\infty) \times \overline{\Omega}$. In the sequel, it is easily obtained that for any constant ϵ_3, there exists $t_3 \in [t_2,\infty)$ such that $w(t,x) \leqslant \frac{1}{\mu_3}(p_2\frac{c/b+s_1}{\mu_2-p_1} + s_2) + \epsilon_3$ in $[t_2,\infty) \times \overline{\Omega}$. Therefore, by the arbitrariness of ϵ_1, ϵ_2, and ϵ_3, the desired result is obtained. □

The following result provides the sufficient conditions for the persistence property of (1.1).

Theorem 3.2. *Assume that* $(\mu_2 - p_1)g/a > c/b + s_1$. *Then the nonnegative solution* (u, v, w) *to* (1.1) *satisfies*

$$\lim_{t\to\infty}\inf_{\overline{\Omega}} u(t,x) \geqslant \frac{1}{\mu_2}\left\{\frac{c}{b}\left(1 - \frac{a}{g}\frac{c/b + s_1}{\mu_2 - p_1}\right) + s_1\right\}, \qquad \lim_{t\to\infty}\inf_{\overline{\Omega}} v(t,x) \geqslant \frac{1}{b}\left(1 - \frac{a}{g}\frac{c/b + s_1}{\mu_2 - p_1}\right),$$

$$\lim_{t\to\infty}\inf_{\overline{\Omega}} w(t,x) \geqslant \frac{1}{\mu_3}\left[\frac{p_2}{\mu_2}\left\{\frac{c}{b}\left(1 - \frac{a}{g}\frac{c/b + s_1}{\mu_2 - p_1}\right) + s_1\right\}\frac{1}{b}\left(1 - \frac{a}{g}\frac{c/b + s_1}{\mu_2 - p_1}\right) + s_2\right].$$

Proof. Using (3.1), the proof can be done by using comparison principle (for example, see [9]). □

From the above theorem, we observe that if the antigenicity of tumor (c) and immunotherapy (s_1) are low, then the tumor cannot be completely eliminated.

Remark 3.3. Based on the assumption $p_1 < \mu_2$, consider the non-treatment case $s_1 = s_2 = 0$ in (1.1). If $v(t,x) \to 0$ uniformly in $\overline{\Omega}$ as $t \to \infty$, then $u(t,x), w(t,x) \to 0$ uniformly in $\overline{\Omega}$. As mentioned earlier, although the number of effector cells in the body can be reduced biologically, they cannot be completely eliminated. In this sense, the derivation that $u(t,x) \to 0$

uniformly in $\overline{\Omega}$ is highly unrealistic. Thus, in the non-treatment case, (1.1) does not allow for the complete clearance of the tumor.

Theorem 3.4. *Assume that* $s_2 > \frac{\mu_2\mu_3}{p_1-\mu_2} > 0$ *and* $s_1 = 0$. *Then for the nonnegative solution* (u, v, w) *of* (1.1),

$$\Big(\lim_{t\to\infty} u(t,x), \lim_{t\to\infty} v(t,x), \lim_{t\to\infty} w(t,x)\Big) = (\infty, 0, s_2/\mu_3) \quad \text{on } \overline{\Omega}.$$

Proof. First, note that there exists $t_1 \in (0,\infty)$ such that for any positive constant $\epsilon < \epsilon_1 := \frac{1}{\mu_3}(s_2 - \frac{\mu_2\mu_3}{p_1-\mu_2})$,

$$w(t,x) \geqslant s_2/\mu_3 - \epsilon \quad \text{in } [t_1,\infty)\times\overline{\Omega}, \tag{3.2}$$

since $p_2\frac{uv}{1+v} - \mu_3 w + s_2 \geqslant s_2 - \mu_3 w$ in $(0,\infty)\times\Omega$. Thus, we have

$$\begin{cases} u_t - d_1\Delta u = cv - \mu_2 u - \dfrac{p_1 uw}{1+w} \geqslant \left(\dfrac{p_1 s_2/\mu_3 - \epsilon}{1 + s_2/\mu_3 - \epsilon} - \mu_2\right)u & \text{in } [t_1,\infty)\times\Omega, \\ \dfrac{\partial u}{\partial \nu} = 0 \quad \text{on } [t_1,\infty)\times\partial\Omega, \\ u(t_1,x) > 0 \quad \text{in } \Omega. \end{cases}$$

It is clear that the constant $M(\epsilon) := \frac{p_1 s_2/\mu_3-\epsilon}{1+s_2/\mu_3-\epsilon} - \mu_2$ is positive by the assumption. So the comparison argument gives that $u(t,x) \geqslant U(t)$ for $(t,x)\in[t_1,\infty)\times\overline{\Omega}$, where $U(t)$ is the solution to the following ODE:

$$\begin{cases} U_t = M(\epsilon)U, \\ U(0) = \min\limits_{\overline{\Omega}} u(t_1,x) > 0. \end{cases}$$

Thus, we obtain

$$\lim_{t\to\infty} u(t,x) = \infty \quad \text{on } \overline{\Omega}, \tag{3.3}$$

since $U(t) = \min_{\overline{\Omega}} u(t_1,x)e^{M(\epsilon)t} \to \infty$ as $t\to\infty$. In particular, for a positive constant

$$\widehat{u} > \frac{g+1/b}{a}(1 + p_1 - \mu_2), \tag{3.4}$$

there exists $t_2 \in [t_1,\infty)$ such that $u(t_2,x) \geqslant \widehat{u}$ in $[t_2,\infty)\times\overline{\Omega}$.

Now consider the parabolic problem:

$$\begin{cases} u_t - d_1\Delta u = cv - \mu_2 u - \dfrac{p_1 uw}{1+w} & \text{in } [t_2,\infty)\times\Omega, \\ \dfrac{\partial u}{\partial \nu} = 0 \quad \text{on } [t_2,\infty)\times\partial\Omega, \\ u(t_2,x) \geqslant \widehat{u} \quad \text{in } \Omega. \end{cases}$$

Then by the same argument as above, we have that $u(t,x) \geqslant \widehat{U}(t) := \widehat{u}e^{M(\epsilon)t}$ for $(t,x)\in[t_2,\infty)\times\overline{\Omega}$.

Recall from the second result in (3.1) that for any positive constant $\epsilon < \epsilon_2 := \min\{\epsilon_1, \frac{a\widehat{u}}{g+1/b}\}$, there exists $t_3 \in [t_2,\infty)$ such that $v(t,x) \leqslant 1/b + \epsilon$ on $[t_3,\infty)\times\overline{\Omega}$. Consider the problem:

$$\begin{cases} \tilde{v}_t - d_2\Delta\tilde{v} = \tilde{v}\left(1 - \dfrac{a\widehat{u}e^{M(\epsilon)t}}{g+1/b+\epsilon} - b\tilde{v}\right) & \text{in } [t_3,\infty)\times\Omega, \\ \dfrac{\partial\tilde{v}}{\partial\nu} = 0 \quad \text{on } [t_3,\infty)\times\partial\Omega, \\ \tilde{v}(t_3,x) = v(t_3,x) > 0 \quad \text{in } \Omega. \end{cases}$$

Then $V(t) := \max_{\overline{\Omega}} v(t_3,x)e^{-N(\epsilon)t}$ is an upper solution to the above problem, where $N(\epsilon) := \frac{a\widehat{u}}{g+1/b+\epsilon} - 1$. Note that $N(\epsilon) > 0$ because of the assumption and the choice of ϵ. Moreover, $v(t,x) \leqslant \tilde{v}(t,x) \leqslant V(t)$ for $(t,x)\in[t_3,\infty)\times\overline{\Omega}$ since $v(1 - bv - a\frac{u}{g+v}) \leqslant v(1 - \frac{a\widehat{u}e^{M(\epsilon)t}}{g+1/b+\epsilon} - bv)$ holds in $[t_3,\infty)\times\Omega$. Thus, since $V(t)\to 0$ as $t\to 0$, we have

$$\lim_{t\to\infty} v(t,x) = 0 \quad \text{on } \overline{\Omega}. \tag{3.5}$$

Therefore there exists $t_4 \in [t_3,\infty)$ such that $v(t,x) \leqslant \epsilon$ on $[t_4,\infty)\times\overline{\Omega}$. In particular, t_4 can be chosen such that $\max_{\overline{\Omega}} u(t_4,x) \geqslant \widehat{u}$ as a result of (3.3). Consider the following problem:

$$\begin{cases} \tilde{u}_t - d_1 \Delta \tilde{u} = c\epsilon + (p_1 - \mu_2)\tilde{u} & \text{in } [t_4, \infty) \times \Omega, \\ \dfrac{\partial \tilde{u}}{\partial \nu} = 0 & \text{on } [t_4, \infty) \times \partial\Omega, \\ \tilde{u}(t_4, x) = u(t_4, x) > 0 & \text{in } \Omega. \end{cases}$$

Then it is routine to check that $\widetilde{U}(t) := \max_{\overline{\Omega}} u(t_4, x) e^{\widetilde{M}(\epsilon)t}$ is an upper solution to the above problem, where $\widetilde{M}(\epsilon) := \epsilon c/\widehat{u} + (p_1 - \mu_2)$. Thus $u(t,x) \leqslant \tilde{u}(t,x) \leqslant \widetilde{U}(t)$ for $(t,x) \in [t_4, \infty) \times \overline{\Omega}$ since $cv - \mu_2 u - \frac{p_1 uw}{1+w} \leqslant c\epsilon + (p_1 - \mu_2)u$ holds in $[t_4, \infty) \times \Omega$.

Finally, using the above results, we obtain

$$\begin{aligned} w_t - d_3 \Delta w &\leqslant p_2 uv - \mu_3 w + s_2 \\ &\leqslant p_2 \widetilde{U}(t) V(t) + s_2 - \mu_3 w \\ &= p_2 \max_{\overline{\Omega}} u(t_4, x) \max_{\overline{\Omega}} v(t_3, x) e^{(\epsilon \frac{c}{\hat{u}} + p_1 - \mu_2 + 1 - \frac{a\hat{u}}{g+1/b+\epsilon})t} + s_2 - \mu_3 w \end{aligned}$$

in $[t_4, \infty) \times \Omega$. Note that (3.4) implies $\epsilon \frac{c}{\hat{u}} + p_1 - \mu_2 + 1 - \frac{a\widehat{u}}{g+1/b+\epsilon} < 0$ for any positive constant $\epsilon < \min\{\epsilon_2, \epsilon_3\}$, where ϵ_3 is a unique positive solution to $c\epsilon^2/\widehat{u} + (p_1 - \mu_2 + 1 + (g + 1/b)c/\widehat{u})\epsilon + (p_1 - \mu_2 + 1)(g + 1/b) - a\widehat{u} = 0$. Thus, one can choose $t_5 \in [t_4, \infty)$ such that

$$w(t,x) \leqslant \frac{s_2}{\mu_3} + \epsilon \quad \text{in } [t_5, \infty) \times \overline{\Omega}. \tag{3.6}$$

Therefore, by using the continuity as $\epsilon \to 0$, (3.2), (3.3), (3.5) and (3.6) yield the desired conclusion. □

From the results for the above theorem, we observe that the growth of effector cells can become uncontrollable by the introduction of a large constant source s_2 (administering a high concentration of IL-2), that is, the tumor can be cleared, but the growth of effector cells (the immune system) become uncontrollable as the IL-2 concentration reaches a steady-state value. Thus, the treatment with only IL-2 does not offer a satisfactory outcome.

Theorem 3.5. *Assume that $\mu_2 > p_1$ and $s_1 > (\frac{g+1/b}{a})\frac{\mu_2\mu_3 + (\mu_2 - p_1)s_2}{\mu_3 + s_2}$. Then the nonnegative solution (u, v, w) to (1.1) satisfies*

$$\Big(\lim_{t\to\infty} u(t,x), \lim_{t\to\infty} v(t,x), \lim_{t\to\infty} w(t,x)\Big) = \left(\frac{s_1(\mu_3 + s_2)}{\mu_2\mu_3 + (\mu_2 - p_1)s_2}, 0, \frac{s_2}{\mu_3}\right) \quad \text{on } \overline{\Omega}.$$

Proof. Let a positive constant $\epsilon \ll 1$ be given. In the following, the values of ϵ are not differentiated for convenience. From (3.1) and (3.2), we know that there exists $t_1 \in (0, \infty)$ such that

$$u(t,x) \leqslant \frac{c/b + s_1}{\mu_2 - p_1} + \epsilon, \qquad v(t,x) \leqslant 1/b + \epsilon \quad \text{and} \quad w(t,x) \geqslant \widehat{W} \tag{3.7}$$

for $(t,x) \in [t_1, \infty) \times \overline{\Omega}$ and

$$\widehat{W} := \begin{cases} s_2/\mu_3 - \epsilon, & \text{if } s_2 > 0, \\ 0, & \text{if } s_2 = 0. \end{cases}$$

Using this result, we have

$$\begin{cases} u_t - d_1 \Delta u = cv - \mu_2 u - \dfrac{p_1 uw}{1+w} + s_1 \geqslant s_1 - \left(\mu_2 - \dfrac{p_1 \widehat{W}}{1 + \widehat{W}}\right)u & \text{in } [t_1, \infty) \times \Omega, \\ \dfrac{\partial u}{\partial \nu} = 0 & \text{on } [t_1, \infty) \times \partial\Omega, \\ u(t_1, x) > 0 & \text{in } \Omega. \end{cases}$$

Thus, by the comparison argument, there exists $t_2 \in [t_1, \infty)$ such that

$$u(t,x) \geqslant \frac{s_1(1 + \widehat{W})}{\mu_2 + (\mu_2 - p_1)\widehat{W}} - \epsilon := M(\epsilon) \tag{3.8}$$

holds in $[t_2, \infty) \times \overline{\Omega}$. In the sequel, the following inequality

$$v\left(1 - bv - \frac{au}{g+v}\right) \leqslant v\left(1 - \frac{aM(\epsilon)}{g + 1/b + \epsilon} - bv\right) \quad \text{in } [t_2, \infty) \times \Omega$$

is obtained using the above results. Moreover, note that $1 - \frac{aM(\epsilon)}{g+1/b+\epsilon} < 0$ for sufficiently small $\epsilon > 0$ because of the assumption $s_1 > (\frac{g+1/b}{a})\frac{\mu_2\mu_3+(\mu_2-p_1)s_2}{\mu_3+s_2}$. Thus, by applying the comparison argument again, there exists $t_3 \geqslant t_2$ such that

$$v(t,x) \leqslant \epsilon \tag{3.9}$$

on $[t_3,\infty) \times \overline{\Omega}$. It is clear that (3.9) and the first inequality of (3.7) provide the following inequality:

$$\frac{p_2uv}{1+v} - \mu_3 w + s_2 \leqslant \frac{p_2\epsilon}{1+\epsilon}\left(\frac{c/b+s_1}{\mu_2-p_1}+\epsilon\right) + s_2 - \mu_3 w$$

in $[t_3,\infty) \times \Omega$. So one can choose $t_4 \in [t_3,\infty)$ such that for $(t,x) \in [t_4,\infty) \times \overline{\Omega}$,

$$w(t,x) \leqslant s_2/\mu_3 + \epsilon. \tag{3.10}$$

In turn, we have

$$cv - \mu_2 u + p_1\frac{uw}{1+w} + s_1 \leqslant c\epsilon + s_1 - \left(\mu_2 - p_1\frac{s_2/\mu_3+\epsilon}{1+s_2/\mu_3+\epsilon}\right)u$$

in $[t_4,\infty) \times \Omega$. Thus

$$u(t,x) \leqslant \frac{s_1(s_2+\mu_3)}{\mu_2\mu_3 + s_2(\mu_2-p_1)} + \epsilon \tag{3.11}$$

follows in $[t_4,\infty) \times \overline{\Omega}$. Therefore, from (3.8)–(3.11) and the third inequality of (3.7), we have the desired conclusion by using the continuity as $\epsilon \to 0$. □

From the result for the above theorem, we observe that the tumor can be cleared by boosting the immune system by injecting IL-2. Thus, the cytokine-enhanced immune function plays an important role in the treatment of cancer. This suggests that a treatment combining ACI (an injection of cultured immune cells that have anti-tumor reactivity into the tumor bearing host) with IL-2 represents the best method for clearing a tumor.

Corollary 3.6. *Assume that $\mu_2 > p_1$, $s_1 > \frac{\mu_2}{a}(g+1/b)$ and $s_2 = 0$. Then $(s_1/\mu_2, 0, 0)$ is globally asymptotically stable, that is, $(s_1/\mu_2, 0, 0)$ attracts all positive solutions to* (1.1).

We now investigate the local stability of the positive constant solution $\mathbf{e}_* = (u_*, v_*, w_*)$. Before developing our argument, we establish the following notations.

Notation 3.7.

(i) $0 = \lambda_0 < \lambda_1 < \lambda_2 < \cdots$ are the eigenvalues of the operator $-\Delta$ on Ω under the homogeneous Neumann boundary condition.
(ii) m_i is the multiplicity of λ_i for each i.

Theorem 3.8. *Assume that* (PE1) *and* (2.3) *hold. Then equilibria $\mathbf{e}_*$ of* (1.1) *is locally asymptotically stable.*

Proof. Note from Remark 2.4 that the results (i), (ii), (iv) and (v) in Lemma 2.2 are satisfied under the assumptions, that is,

$$\mu_3\left(\mu_2 - \frac{p_1w_*}{1+w_*}\right) > \frac{p_1u_*}{(1+w_*)^2}\frac{p_2v_*}{1+v_*}, \qquad -b + \frac{au_*}{(g+v_*)^2} \leqslant 0,$$
$$H_v(v_*) \leqslant 0, \qquad \frac{acv_*}{g+v_*} + v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\left(\mu_2 - \frac{p_1w_*}{1+w_*}\right) > 0.$$

Moreover, we see from Section 2 that $H_v(v_*) \leqslant 0$ yields $\widetilde{H}(v_*) = -2bv_*^3 + (1-bg-3b)v_*^2 + 2(1-bg)v_* + g \leqslant 0$. Thus,

$$v_*\left(b - \frac{au_*}{(g+v_*)^2}\right) - \frac{1}{1+v_*}\frac{au_*}{g+v_*} = v_*\left(b - \frac{1-bv_*}{g+v_*}\right) - \frac{1-bv_*}{1+v_*}$$
$$= -\frac{\widetilde{H}(v_*)}{(g+v_*)(1+v_*)} \geqslant 0.$$

The linearization of (1.1) at the constant solution $\mathbf{e}_*$ is expressed by

$$\mathbf{u}_t = \big(\mathbf{D}\Delta + \mathbf{F_u}(\mathbf{e}_*)\big)\mathbf{u},$$

where $\mathbf{u} := (u(t,x), v(t,x), w(t,x))^T$, $\mathbf{F}(\mathbf{u}) := (cv - \mu_2 u + \frac{p_1 uw}{1+w} + s_1, v(1-bv) - \frac{auv}{g+v}, \frac{p_2 uv}{1+v} - \mu_3 w + s_2)$,

$$\mathbf{D} := \begin{pmatrix} d_1 & 0 & 0 \\ 0 & d_2 & 0 \\ 0 & 0 & d_3 \end{pmatrix} \quad \text{and} \quad \mathbf{F_u}(\mathbf{e}_*) := \begin{pmatrix} -\mu_2 + \frac{p_1 w_*}{1+w_*} & c & \frac{p_1 u_*}{(1+w_*)^2} \\ -\frac{av_*}{g+v_*} & v_*(-b + \frac{au_*}{(g+v_*)^2}) & 0 \\ \frac{p_2 v_*}{1+v_*} & \frac{p_2 u_*}{(1+v_*)^2} & -\mu_3 \end{pmatrix}.$$

In the above matrix, the component $v_*(-b + \frac{au_*}{(g+v_*)^2})$ follows using the fact $1 - bv_* - \frac{au_*}{g+v_*} = 0$. It is well known that all three eigenvalues of the operator $\mathbf{D}\Delta + \mathbf{F_u}(\mathbf{e}_*)$ have negative real parts, and thus it is concluded from [7, Theorem 5.1.1] that $\mathbf{e}_*$ is locally asymptotically stable. Moreover, from local stability theory, we know that η is an eigenvalue of $\mathbf{D}\Delta + \mathbf{F_u}(\mathbf{e}_*)$ if and only if η is an eigenvalue of the matrix $-\lambda_i \mathbf{D} + \mathbf{F_u}(\mathbf{e}_*)$ for each $i \geqslant 0$. Thus, to examine the local stability at $\mathbf{e}_*$, it is necessary to investigate the characteristic polynomial (for example, see [9,17])

$$\det\big(\eta \mathbf{I} + \lambda_i \mathbf{D} - \mathbf{F_u}(\mathbf{e}_*)\big) = \eta^3 + \beta_1 \eta^2 + \beta_2 \eta + \beta_3,$$

where

$$\begin{aligned}
\beta_1 &= (d_1+d_2+d_3)\lambda_i + \left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) + v_*\left(b - \frac{au_*}{(g+v_*)^2}\right) + \mu_3 > 0, \\
\beta_2 &= (d_1d_2 + d_2d_3 + d_1d_3)\lambda_i^2 + \left[d_1\left\{\mu_3 + v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\right\} + d_2\left(\mu_3 + \mu_2 - \frac{p_1 w_*}{1+w_*}\right)\right. \\
&\quad \left. + d_3\left\{\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) + v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\right\}\right]\lambda_i + \left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right)v_*\left(b - \frac{au_*}{(g+v_*)^2}\right) \\
&\quad + \mu_3 v_*\left(b - \frac{au_*}{(g+v_*)^2}\right) + \frac{acv_*}{g+v_*} + \left\{\mu_3\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) - \frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 v_*}{1+v_*}\right\} > 0, \\
\beta_3 &= d_1d_2d_3\lambda_i^3 + \left\{d_1d_2\mu_3 + d_1d_3 v_*\left(b - \frac{au_*}{(g+v_*)^2}\right) + d_2d_3\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right)\right\}\lambda_i^2 \\
&\quad + \left[d_1\mu_3 v_*\left(b - \frac{au_*}{(g+v_*)^2}\right) + d_2\left\{\mu_3\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) - \frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 v_*}{1+v_*}\right\}\right. \\
&\quad \left. + d_3\left\{\frac{acv_*}{g+v_*} + v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right)\right\}\right]\lambda_i \\
&\quad + v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\left\{\mu_3\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) - \frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 v_*}{1+v_*}\right\} \\
&\quad + \frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 u_*}{(1+v_*)^2}\frac{av_*}{g+v_*} + \mu_3\frac{acv_*}{g+v_*} > 0.
\end{aligned}$$

A simple calculation yields $\beta_1\beta_2 - \beta_3 = \alpha_1\lambda_i^3 + \alpha_2\lambda_i^2 + \alpha_3\lambda_i + \alpha_4$, where

$$\begin{aligned}
\alpha_1 &= d_1(d_1d_2 + d_1d_3) + (d_2+d_3)(d_1d_2 + d_2d_3 + d_1d_3) > 0, \\
\alpha_2 &= (d_1 + 2d_2 + d_3)(d_1+d_3)v_*\left(b - \frac{au_*}{(g+v_*)^2}\right) + (2d_1 + d_2 + d_3)(d_2+d_3)\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) \\
&\quad + (d_1 + d_2 + 2d_3)(d_1+d_2)\mu_3 > 0, \\
\alpha_3 &= 2(d_1+d_2+d_3)v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\left\{\mu_2 - \frac{p_1 w_*}{1+w_*} + \mu_3\right\} + (d_1+d_2)\left(\frac{acv_*}{g+v_*} + \mu_3^2\right) \\
&\quad + (d_1+d_3)\left\{\mu_3\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) - \frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 v_*}{1+v_*} + v_*^2\left(b - \frac{au_*}{(g+v_*)^2}\right)^2\right\} \\
&\quad + (d_2+d_3)\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right)^2 + (d_1 + 2d_2 + d_3)\mu_3\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) > 0, \\
\alpha_4 &= \left\{\mu_2 - \frac{p_1 w_*}{1+w_*} + v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\right\} \times \left[\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right)v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\right. \\
&\quad \left. + \mu_3 v_*\left(b - \frac{au_*}{(g+v_*)^2}\right) + \left\{\mu_3\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) - \frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 v_*}{1+v_*}\right\} + \frac{acv_*}{g+v_*}\right] \\
&\quad + \frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 v_*}{1+v_*}\left\{v_*\left(b - \frac{au_*}{(g+v_*)^2}\right) - \frac{1}{1+v_*}\frac{au_*}{g+v_*}\right\} > 0.
\end{aligned}$$

Thus, $\beta_1\beta_2 - \beta_3 > 0$ for each $i \geqslant 0$, and so we conclude from the Routh–Hurwitz criterion for each $i \geqslant 0$ that the three roots of $\det(\eta\mathbf{I} + \lambda_i\mathbf{D} - \mathbf{F_u}(\mathbf{e}_*)) = 0$ have negative real parts. □

Similarly, if $\mu_2 = p_1$, then the local stability at $\mathbf{e}_*$ can be obtained, and the proof is omitted.

Theorem 3.9. *If* (PE2) *and* (2.6) *hold, then the positive constant steady state* $\mathbf{e}_*$ *of* (1.1) *is locally asymptotically stable.*

We next investigate the global stability of the positive equilibrium point $\mathbf{e}_*$ by introducing the following Lyapunov function:

$$E(t) = \int_\Omega \left\{ \frac{1}{2}(u-u_*)^2 + \left(v - v_* - v_* \ln \frac{v}{v_*}\right) + \frac{1}{2}(w-w_*)^2 \right\} dx$$

for the solution (u, v, w) to (1.1). Note that $E(t) \geqslant 0$ for all $t \geqslant 0$, and thus, if $E_t(t) \leqslant 0$ can be derived, then we obtain the desired result from the well-known Lyapunov stability.

Theorem 3.10. *Assume that* (PE1) *holds. Then the positive constant solution* $\mathbf{e}_*$ *to* (1.1) *is globally asymptotically stable if*

$$\begin{cases} \mu_2 \geqslant p_1 + \dfrac{1}{2}\left(c + \dfrac{a}{g} + p_2 + p_1 \dfrac{c/b + s_1}{\mu_2 - p_1}\right), \\ b \geqslant \dfrac{1}{g} + \dfrac{1}{2}\left(c + \dfrac{a}{g} + p_2 \dfrac{c/b + s_1}{\mu_2 - p_1}\right), \\ \mu_3 \geqslant \dfrac{1}{2}\left(p_2 + (p_1 + p_2)\dfrac{c/b + s_1}{\mu_2 - p_1}\right). \end{cases} \tag{3.12}$$

Proof. Using (1.1) and integrating by parts, we obtain

$$\begin{aligned} \frac{dE(t)}{dt} &= \int_\Omega \left[(u-u_*)u_t + \left(1 - \frac{v_*}{v}\right)v_t + (w-w_*)w_t \right] dx \\ &= -\int_\Omega \left[d_1|\nabla u|^2 + d_2 \frac{v_*|\nabla v|^2}{v^2} + d_3|\nabla w|^2 \right] dx + \widetilde{E}(t), \end{aligned}$$

where

$$\begin{aligned} \widetilde{E}(t) = \int_\Omega \bigg[& (u-u_*)\left(cv - \mu_2 u + \frac{p_1 u w}{1+w} + s_1\right) + (v-v_*)\left(1 - bv - \frac{au}{g+v}\right) \\ & + (w-w_*)\left(\frac{p_2 u v}{1+v} - \mu_3 w + s_2\right) \bigg] dx. \end{aligned}$$

From the definition of $\mathbf{e}_*$, it is easy to see that $u_* \leqslant \frac{c/b+s_1}{\mu_2-p_1}$ and $\frac{au_*}{g+v_*} < 1$. Using these inequalities, we derive

$$\begin{aligned} \widetilde{E}(t) &= \int_\Omega \bigg[(u-u_*)\left(cv - \mu_2 u + \frac{p_1 u w}{1+w} - cv_* + \mu_2 u_* - \frac{p_1 u_* w_*}{1+w_*}\right) + (v-v_*)\left(-bv - \frac{au}{g+v} + bv_* + \frac{au_*}{g+v_*}\right) \\ &\quad + (w-w_*)\left(\frac{p_2 u v}{1+v} - \mu_3 w - \frac{p_2 u_* v_*}{1+v_*} + \mu_3 w_*\right) \bigg] dx \\ &= \int_\Omega \bigg[(u-u_*)^2\left(-\mu_2 + \frac{p_1 w}{1+w}\right) + (u-u_*)(v-v_*)\left(c - \frac{a}{g+v}\right) \\ &\quad + (v-v_*)^2\left(-b + \frac{au_*}{(g+v_*)(g+v)}\right) + (v-v_*)(w-w_*)\left(\frac{p_2 u_*}{(1+v)(1+v_*)}\right) \\ &\quad + (u-u_*)(w-w_*)\left(\frac{p_1 u_*}{(1+w)(1+w_*)} + \frac{p_2 v}{1+v}\right) + (w-w_*)^2(-\mu_3) \bigg] dx \\ &\leqslant \int_\Omega \big[(u-u_*)^2(-\mu_2 + p_1) + |u-u_*||v-v_*|(c + a/g) + (v-v_*)^2(-b + 1/g) \end{aligned}$$

$$+ |u-u_*||w-w_*|(p_1u_*+p_2) + |v-v_*||w-w_*|(p_2u_*) + (w-w_*)^2(-\mu_3)\Big]\,dx$$
$$\leqslant \int_\Omega \bigg[(u-u_*)^2\bigg\{-\mu_2+p_1+\frac{c+a/g}{2}+\frac{1}{2}\bigg(p_2+p_1\frac{c/b+s_1}{\mu_2-p_1}\bigg)\bigg\}$$
$$+(v-v_*)^2\bigg(-b+\frac{1}{g}+\frac{c+a/g}{2}+\frac{p_2}{2}\frac{c/b+s_1}{\mu_2-p_1}\bigg)$$
$$+(w-w_*)^2\bigg\{-\mu_3+\frac{1}{2}\bigg(p_2+p_1\frac{c/b+s_1}{\mu_2-p_1}\bigg)+\frac{p_2}{2}\frac{c/b+s_1}{\mu_2-p_1}\bigg\}\bigg]\,dx \leqslant 0.$$

The last inequality follows from assumption (3.12). Thus $\frac{dE}{dt}(t) \leqslant 0$ implies the desired assertion. □

The conditions given in (3.12) are satisfied for large b, μ_2 and μ_3. From Theorem 3.1, we know that the densities of u, v and w can be as low as $t \to \infty$ if b, μ_2 and μ_3 are large. This means that the solution to (1.1) with large b, μ_2 and μ_3, is not dropped to the zero and that, in this case, no tumor-free states can be observed.

4. The existence and nonexistence of nonconstant positive steady states

In this section, we discuss the existence and nonexistence of nonconstant positive solutions to (1.2) by using index theory. To do this, we first obtain the *a priori* bound for positive solutions to (1.2). The following two lemmas can be found in [12,14].

Lemma 4.1 *(Maximum principle). Suppose that $g \in C(\overline{\Omega} \times \mathbf{R})$. If $\phi \in C^2(\Omega) \cap C^1(\overline{\Omega})$ satisfies*

$$\Delta\phi + g\big(x,\phi(x)\big) \geqslant 0 \quad \text{in } \Omega, \qquad \frac{\partial\phi}{\partial\nu} \leqslant 0 \quad \text{on } \partial\Omega \tag{4.1}$$

and $\phi(x_0) = \max_{\overline{\Omega}}\phi$, then $g(x_0,\phi(x_0)) \geqslant 0$. Similarly, if the two inequalities in (4.1) are reversed and $\phi(x_0) = \min_{\overline{\Omega}}\phi$, then $g(x_0,\phi(x_0)) \leqslant 0$.

Lemma 4.2 *(Harnack inequality). Let $\phi \in C^2(\Omega) \cap C^1(\overline{\Omega})$ be a positive solution to $\Delta\phi + c(x)\phi = 0$ in Ω subject to homogeneous Neumann boundary condition with $c \in C(\overline{\Omega})$. Then there exists a positive constant $C_* = C_*(\|c\|_\infty)$ such that*

$$\max_{\overline{\Omega}}\phi \leqslant C_* \min_{\overline{\Omega}}\phi.$$

We now estimate the upper bound for positive solutions to (1.2) when $\mu_2 \geqslant p_1$. For notational convenience, denote the set of constants, s_i, μ_i, p_i, c, b and a by Γ.

Theorem 4.3. *Let d be a fixed positive constant. If $\mu_2 \geqslant p_1$ holds, then there exists a positive constant $\widetilde{C}(\Gamma, d)$ such that for any d_1, d_2 and $d_3 \geqslant d$, all positive solutions (u, v, w) to (1.2) satisfy*

$$\max_{\overline{\Omega}} u, \max_{\overline{\Omega}} w \leqslant \widetilde{C} \quad \text{and} \quad \max_{\overline{\Omega}} v \leqslant \frac{1}{b} \quad \text{in } \Omega. \tag{4.2}$$

Proof. If $\mu_2 > p_1$, then by directly applying Lemma 4.1 to the equations in (1.2), we obtain

$$\max_{\overline{\Omega}} u \leqslant \frac{c/b+s_1}{\mu_2-p_1}, \qquad \max_{\overline{\Omega}} v \leqslant \frac{1}{b} \quad \text{and} \quad \max_{\overline{\Omega}} w \leqslant \frac{1}{\mu_3}\bigg(p_2\frac{c/b+s_1}{\mu_2-p_1}+s_2\bigg).$$

From this point forward, we assume that $\mu_2 = p_1$. First, we already know from the maximum principle that $\max_{\overline{\Omega}} v \leqslant 1/b$. To estimate the upper bound of u and w, we argue by contradiction. Suppose that the first two assertions in (4.2) are not true. Then there exist sequences $(d_{1,n}, d_{2,n}, d_{3,n})$ with $d_{i,n} \geqslant d$, and the corresponding positive solution (u_n, v_n, w_n) to system (1.2) such that $\max_{\overline{\Omega}} v_n \leqslant 1/b$ and

$$\max_{\overline{\Omega}} u_n \to \infty \quad \text{or} \quad \max_{\overline{\Omega}} w_n \to \infty \quad \text{as } n \to \infty. \tag{4.3}$$

Note that by applying the maximum principle to the first differential equation in (1.2) and by using the fact that $\max_{\overline{\Omega}} v_n \leqslant 1/b$, we have

$$(c/b+s_1)\Big(1+\max_{\overline{\Omega}} w_n\Big) \geqslant \mu_2 \max_{\overline{\Omega}} u_n. \tag{4.4}$$

Thus, if $\lim_{n\to\infty}\max_{\overline{\Omega}} u_n = \infty$, then $\lim_{n\to\infty}\max_{\overline{\Omega}} w_n = \infty$. Similarly, we can also obtain from the third equation in (1.2) that

$$\Bigl(p_2 \max_{\overline{\Omega}} u_n + s_2\Bigr) \geqslant \mu_3 \max_{\overline{\Omega}} w_n, \tag{4.5}$$

and thus if $\lim_{n\to\infty}\max_{\overline{\Omega}} w_n = \infty$, then $\lim_{n\to\infty}\max_{\overline{\Omega}} u_n = \infty$. As a consequence, (4.3) gives that $\lim_{n\to\infty}\max_{\overline{\Omega}} u_n = \infty$ and $\lim_{n\to\infty}\max_{\overline{\Omega}} w_n = \infty$.

Let $\tilde{u}_n = \frac{u_n}{\|u_n\|_\infty}$ and $\tilde{w}_n = \frac{w_n}{\|w_n\|_\infty}$. Then $\|\tilde{u}_n\|_\infty = 1$, $\|\tilde{w}_n\|_\infty = 1$, and $(\tilde{u}_n, v_n, \tilde{w}_n)$ solves

$$\begin{cases} -d_{1,n}\Delta\tilde{u}_n = c\dfrac{v_n}{\|u_n\|_\infty} - \dfrac{\mu_2\tilde{u}_n}{1+\|w_n\|_\infty\tilde{w}_n} + \dfrac{s_1}{\|u_n\|_\infty}, \\ -d_{2,n}\Delta v_n = v_n\Bigl(1 - bv_n - a\|u_n\|_\infty\dfrac{\tilde{u}_n}{g+v_n}\Bigr), \\ -d_{3,n}\Delta\tilde{w}_n = p_2\dfrac{\|u_n\|_\infty}{\|w_n\|_\infty}\dfrac{\tilde{u}_n v_n}{1+v_n} - \mu_3\tilde{w}_n + \dfrac{s_2}{\|w_n\|_\infty} \quad \text{in } \Omega, \\ \dfrac{\partial\tilde{u}_n}{\partial\nu} = \dfrac{\partial v_n}{\partial\nu} = \dfrac{\partial\tilde{w}_n}{\partial\nu} = 0 \quad \text{on } \partial\Omega. \end{cases} \tag{4.6}$$

From (4.4) and (4.5), it is easy to see that

$$\frac{c/b+s_1}{\mu_2}\Bigl(\frac{1}{\|w_n\|_\infty}+1\Bigr) \geqslant \frac{\|u_n\|_\infty}{\|w_n\|_\infty} \geqslant \frac{\mu_3}{p_2} - \frac{s_2}{p_2\|w_n\|_\infty},$$

and thus, by passing to a subsequence if necessary, we can assume that $\frac{\|u_n\|_\infty}{\|w_n\|_\infty} \to \beta_1$ for some positive constant β_1 since $\lim_{n\to\infty}\max_{\overline{\Omega}} w_n = \infty$. Further, since $\tilde{u}_n$, $\tilde{w}_n$, $\Delta\tilde{u}_n$, $\Delta\tilde{w}_n$ are bounded, by standard regularity results, we may also assume that $d_{i,n} \to \tilde{d}_i$, $i = 1,2,3$, and $\tilde{u}_n \to \tilde{u}$ and $\tilde{w}_n \to \tilde{w}$ weakly in $W^{2,p}$ for $p > N$, where $\tilde{d}_i \in [d,\infty]$, $\|\tilde{u}\|_\infty = 1$, $\|\tilde{w}\|_\infty = 1$. So applying Sobolev Embedding Theorems [6,20], we see that $\tilde{u}$, $\tilde{w} \in C^{1+\alpha}(\overline{\Omega})$ for some $0 < \alpha < 1$ and $\tilde{u}_n \to \tilde{u}$ and $\tilde{w}_n \to \tilde{w}$ in $C^{1+\alpha}(\overline{\Omega})$. Also since v_n is bounded and satisfies $-d_{2,n}\Delta v_n \leqslant v_n$, $v_n \to \tilde{v}$ strongly in $L^p(\Omega)$, $\tilde{v} \in [0, 1/b]$.

When $\tilde{d}_3 < \infty$, the third equation to (4.6) gives

$$-\tilde{d}_3\Delta\tilde{w} + \mu_3\tilde{w} = p_2\beta_1\frac{\tilde{u}\tilde{v}}{1+\tilde{v}} \quad \text{in } \Omega, \qquad \frac{\partial\tilde{w}}{\partial\nu} = 0 \quad \text{on } \partial\Omega.$$

Then by the strong maximum principle [6, Theorem 9.6] and the Hopf boundary lemma [4, Theorem 2.11] for the $W^{2,N}(\Omega)$ solution, $\tilde{w} > 0$ on $\overline{\Omega}$ since $\tilde{w} \not\equiv 0$. When $\tilde{d}_3 = \infty$, we have

$$-\Delta\tilde{w} = 0 \quad \text{in } \Omega, \qquad \frac{\partial\tilde{w}}{\partial\nu} = 0 \quad \text{on } \partial\Omega.$$

Thus, since $\|\tilde{w}\|_\infty = 1$, $\tilde{w} \equiv 1$ holds. As a consequence, for any $\tilde{d}_3 \geqslant d$, we can choose a positive constant β_2 such that $\tilde{w} \geqslant \beta_2$ on $\overline{\Omega}$. Hence, $\tilde{w}_n \geqslant \beta_2/2$ for any large n. Using this result for the first equation in (4.6), we know that if $\tilde{d}_1 = \infty$, $\tilde{u}$ solves

$$-\Delta\tilde{u} = 0 \quad \text{in } \Omega, \qquad \frac{\partial\tilde{u}}{\partial\nu} = 0 \quad \text{on } \partial\Omega,$$

otherwise, $\tilde{u}$ solves

$$-\tilde{d}_1\Delta\tilde{u} = 0 \quad \text{in } \Omega, \qquad \frac{\partial\tilde{u}}{\partial\nu} = 0 \quad \text{on } \partial\Omega,$$

since $\|u_n\|_\infty \to \infty$ and $\|w_n\|_\infty \to \infty$. In both cases, we have $\tilde{u} \equiv 1$ on $\overline{\Omega}$. Thus there exists a positive constant β_3 such that $\tilde{u}_n \geqslant \beta_3/2$ for any large n. Using this result and $\max_{\overline{\Omega}} v_n \leqslant 1/b$ in the integral identity obtained by integrating the second equation in (4.6) over Ω, we have

$$0 = \int_\Omega v_n\Bigl(1 - bv_n - a\|u_n\|_\infty\frac{\tilde{u}_n}{g+v_n}\Bigr)dx \leqslant \int_\Omega v_n\Bigl(1 - a\|u_n\|_\infty\frac{\beta_3/2}{g+1/b}\Bigr)dx < 0$$

for large n because $\|u_n\|_\infty \to \infty$ as $n \to \infty$, which is a contradiction. □

Note from (4.2) that when $\mu_2 \geqslant p_1$, positive solutions to (1.2) are contained in $[C^{2+\alpha}(\overline{\Omega})]^3$ by the regularity theorem for elliptic equations [6,20].

Theorem 4.4. *Let d be a fixed positive number. Assume that $\mu_2 \geqslant p_1$ and that one of the following cases holds*:

(i) $s_1 = s_2 = 0$;
(ii) $s_2 = 0$ *and* $\frac{\mu_2}{a} g > s_1 > 0$;
(iii) $s_1 = 0$ *and* $s_2 > 0$;
(iv) $s_2 > 0$ *and* $\frac{\mu_2\mu_3 + (\mu_2 - p_1)s_2}{\mu_3 + s_2} \frac{g}{a} > s_1 > 0$.

Then there exists a positive constant $\widehat{C}(\Gamma, d)$ such that, when $d_1, d_2, d_3 \geqslant d$, all positive solutions (u, v, w) to (1.2) *satisfy $u, v, w \geqslant \widehat{C}$.*

Proof. Suppose for the contradiction argument that the result is not true. Then there exists a sequence $\{(d_{1,n}, d_{2,n}, d_{3,n})\}$ such that $d_{1,n}, d_{2,n}, d_{3,n} \geqslant d$ and a corresponding positive solution (u_n, v_n, w_n) to (1.2) such that

$$\min_{\overline{\Omega}} u_n \to 0, \quad \text{or} \quad \min_{\overline{\Omega}} v_n \to 0, \quad \text{or} \quad \min_{\overline{\Omega}} w_n \to 0 \quad \text{as } n \to \infty,$$

and (u_n, v_n, w_n) satisfies

$$\begin{cases} -d_{1,n}\Delta u_n = c v_n - \mu_2 u_n + \dfrac{p_1 u_n w_n}{1 + w_n} + s_1 \quad \text{in } \Omega, & \dfrac{\partial u_n}{\partial \nu} = 0 \quad \text{on } \partial\Omega, \\ -d_{2,n}\Delta v_n = v_n\left(1 - b v_n - \dfrac{a u_n}{g + v_n}\right) \quad \text{in } \Omega, & \dfrac{\partial v_n}{\partial \nu} = 0 \quad \text{on } \partial\Omega, \\ -d_{3,n}\Delta w_n = \dfrac{p_2 u_n v_n}{1 + v_n} - \mu_3 w_n + s_2 \quad \text{in } \Omega, & \dfrac{\partial w_n}{\partial \nu} = 0 \quad \text{on } \partial\Omega. \end{cases} \tag{4.7}$$

By integrating the second equation in (4.7) over Ω by parts, we have

$$0 = \int_{\Omega} v_n\left(1 - b v_n - \frac{a u_n}{g + v_n}\right) dx. \tag{4.8}$$

Note that $\|\frac{1}{d_{2,n}}(1 - b v_n - a\frac{u_n}{g + v_n})\|_\infty < \infty$ can be derived from Theorem 4.3, and thus, by Lemma 4.2, there exists a positive constant C_* such that

$$\max_{\overline{\Omega}} v_n \leqslant C_* \min_{\overline{\Omega}} v_n. \tag{4.9}$$

Let a positive constant $\epsilon \ll 1$ be given. Although the values of ϵ used below may be different from line to line, they are not differentiated for convenience.

(i) Assume that $\min_{\overline{\Omega}} v_n \to 0$ as $n \to \infty$. Then by (4.9), $\max_{\overline{\Omega}} v_n \to 0$ as $n \to \infty$. By applying Lemma 4.1 to the third equation in (4.7), we obtain that $\max_{\overline{\Omega}} w_n \to 0$ as $n \to \infty$ since

$$\mu_3 \max_{\overline{\Omega}} w_n \leqslant p_2 \max_{\overline{\Omega}} u_n \max_{\overline{\Omega}} v_n \leqslant p_2 \widetilde{C} \max_{\overline{\Omega}} v_n \to 0 \quad \text{as } n \to \infty.$$

Similarly, it follows that $\max_{\overline{\Omega}} u_n \to 0$ as $n \to \infty$. However, because

$$1 - b v_n - \frac{a u_n}{g + v_n} \to 1 \quad \text{as } n \to \infty,$$

(4.8) does not hold.

Assume that $\min_{\overline{\Omega}} u_n \to 0$ as $n \to \infty$. Then, again by Lemma 4.1,

$$c \min_{\overline{\Omega}} v_n \leqslant \mu_2 \min_{\overline{\Omega}} u_n \to 0 \quad \text{as } n \to \infty,$$

and thus, the above argument provides a contradiction.

If $\min_{\overline{\Omega}} w_n \to 0$ as $n \to \infty$, then Lemma 4.1 yields

$$p_2 \min_{\overline{\Omega}} u_n \frac{\min_{\overline{\Omega}} v_n}{1 + \min_{\overline{\Omega}} v_n} \leqslant \mu_3 \min_{\overline{\Omega}} w_n \to 0 \quad \text{as } n \to \infty. \tag{4.10}$$

Thus, $\min_{\overline{\Omega}} u_n$ or $\min_{\overline{\Omega}} v_n \to 0$ as $n \to \infty$. In all cases, we reach a contradiction.

(ii) By applying Lemma 4.1 to the first equation in (4.7), we have $\min_{\overline{\Omega}} u_n \geqslant s_1/\mu_2$ for any n, and thus $\min_{\overline{\Omega}} u_n \nrightarrow 0$ as $n \to \infty$. Assume that $\min_{\overline{\Omega}} v_n \to 0$ as $n \to \infty$. Then $\max_{\overline{\Omega}} v_n \to 0$ as $n \to \infty$ can be derived as in the case (i). Moreover, it follows that $\max_{\overline{\Omega}} w_n \to 0$ as $n \to \infty$. Thus there exists $n_1 \in \mathbb{N}$ such that $\max_{\overline{\Omega}} v_n, \max_{\overline{\Omega}} w_n \leqslant \epsilon$ for a small positive constant ϵ and $n \geqslant n_1$. Again, by applying Lemma 4.1 to the first equation in (4.7), we derive

$$c \max_{\overline{\Omega}} v_n + s_1 - \left(\mu_2 - \frac{p_1 \max_{\overline{\Omega}} w_n}{1 + \max_{\overline{\Omega}} w_n}\right) \max_{\overline{\Omega}} u_n \geqslant 0.$$

In particular, for $n \geqslant n_1$, it follows that

$$c\epsilon + s_1 - \left(\mu_2 - \frac{p_1\epsilon}{1+\epsilon}\right) \max_{\overline{\Omega}} u_n \geqslant 0,$$

and thus,

$$\frac{c\epsilon + s_1}{\mu_2 - \frac{p_1\epsilon}{1+\epsilon}} \geqslant \max_{\overline{\Omega}} u_n \quad \text{for } n \geqslant n_1.$$

Using the above results and the assumption $\frac{\mu_2}{a} g > s_1$, we have the following

$$1 - b v_n - \frac{a u_n}{g + v_n} \geqslant 1 - b \max_{\overline{\Omega}} v_n - \frac{a}{g} \max_{\overline{\Omega}} u_n \geqslant 1 - b\epsilon - \frac{a}{g} \frac{c\epsilon + s_1}{\mu_2 - \frac{p_1\epsilon}{1+\epsilon}} > 0 \quad \text{for } n \geqslant n_1.$$

This leads to a contradiction to (4.8). Now assume that $\min_{\overline{\Omega}} w_n \to 0$ as $n \to \infty$. Then by applying Lemma 4.1 to the third differential equation in (4.7), we have (4.10). Thus, $\min_{\overline{\Omega}} v_n \to 0$ as $n \to \infty$ because $\min_{\overline{\Omega}} u_n \geqslant s_1/\mu_2$ for any n. Once again, the above argument provides an obvious contradiction.

(iii) In this case, note that $\min_{\overline{\Omega}} w_n \geqslant s_2/\mu_3$ for any $n \geqslant 1$. Its proof is very similar to that for the above cases, and thus, it is omitted.

(iv) Since $s_1 > 0$ and $s_2 > 0$, it is easy to see that $\min_{\overline{\Omega}} u_n \geqslant s_1/\mu_2$ and $\min_{\overline{\Omega}} w_n \geqslant s_2/\mu_3$ for any $n \geqslant 1$. Now assume that $\min_{\overline{\Omega}} v_n \to 0$ as $n \to \infty$. Then we know from (4.9) that $\max_{\overline{\Omega}} v_n \to 0$ as $n \to \infty$ and that there exists $n_2 \in \mathbb{N}$ such that $\max_{\overline{\Omega}} v_n \leqslant \epsilon$ for a small positive constant ϵ and $n \geqslant n_2$. Applying this result and Lemma 4.1 to the third equation in (4.7), we have that

$$\mu_3 \max_{\overline{\Omega}} w_n \leqslant p_2 \frac{\max_{\overline{\Omega}} u_n \max_{\overline{\Omega}} v_n}{1 + \max_{\overline{\Omega}} v_n} + s_2 \leqslant \epsilon + s_2$$

for $n \geqslant n_2$. Furthermore, by applying Lemma 4.1 to the first equation in (4.7) and then using the above results, we find that

$$0 \leqslant c \max_{\overline{\Omega}} v_n + s_1 - \left(\mu_2 - \frac{p_1 \max_{\overline{\Omega}} w_n}{1 + \max_{\overline{\Omega}} w_n}\right) \max_{\overline{\Omega}} u_n \leqslant c\epsilon + s_1 - \left(\mu_2 - \frac{p_1(\epsilon + s_2)}{\mu_3 + s_2 + \epsilon}\right) \max_{\overline{\Omega}} u_n$$

for $n \geqslant n_2$. Thus for large n,

$$\max_{\overline{\Omega}} u_n \leqslant \frac{s_1(\mu_3 + s_2)}{\mu_2\mu_3 + (\mu_2 - p_1)s_2} + \epsilon. \tag{4.11}$$

Similarly, we derive

$$0 \geqslant c \min_{\overline{\Omega}} v_n + s_1 - \left(\mu_2 - \frac{p_1 \min_{\overline{\Omega}} w_n}{1 + \min_{\overline{\Omega}} w_n}\right) \min_{\overline{\Omega}} u_n \geqslant s_1 - \left(\mu_2 - \frac{p_1 s_2}{\mu_3 + s_2}\right) \min_{\overline{\Omega}} u_n$$

for large n such that

$$\min_{\overline{\Omega}} u_n \geqslant \frac{s_1(\mu_3 + s_2)}{\mu_2\mu_3 + (\mu_2 - p_1)s_2}. \tag{4.12}$$

Synthetically, from (4.11) and (4.12), we have

$$u_n \to \frac{s_1(\mu_3 + s_2)}{\mu_2\mu_3 + (\mu_2 - p_1)s_2}$$

uniformly in $\overline{\Omega}$ as $n \to \infty$. Then by the assumption $\frac{\mu_2\mu_3 + (\mu_2 - p_1)s_2}{\mu_3 + s_2} \frac{g}{a} > s_1$,

$$1 - b v_n - a \frac{u_n}{g + v_n} \to 1 - \frac{a}{g} \frac{s_1(\mu_3 + s_2)}{\mu_2\mu_3 + (\mu_2 - p_1)s_2} > 0$$

as $n \to \infty$. Hence, this result implies that (4.8) does not hold for large n, which is a contradiction. □

We now present the result for the nonexistence of nonconstant positive solutions to system (1.2). In this result, the diffusion coefficients play important roles.

Theorem 4.5. *Assume that $\mu_2 \geqslant p_1$.*

(i) *There exists a positive constant $\bar{d}_1 = \bar{d}_1(\Gamma, \Omega)$ such that* (1.2) *has no positive nonconstant solution if $d_1 > \bar{d}_1$, $d_2\lambda_1 > 1 + \frac{p_2\widetilde{C}}{2}$ and $d_3\lambda_1 > -\mu_3 + \frac{p_2\widetilde{C}}{2}$.*
(ii) *There exists a positive constant $\bar{d}_2 = \bar{d}_2(\Gamma, \Omega)$ such that* (1.2) *has no positive nonconstant solution if $d_2 > \bar{d}_2$, $d_1\lambda_1 > -\mu_2 + \frac{p_1\widetilde{C}}{1+\widetilde{C}} + \frac{p_1\widetilde{C}+p_2}{2}$ and $d_3\lambda_1 > -\mu_3 + \frac{p_1\widetilde{C}+p_2}{2}$.*
(iii) *There exists a positive constant $\bar{d}_3 = \bar{d}_3(\Gamma, \Omega)$ such that* (1.2) *has no positive nonconstant solution if $d_3 > \bar{d}_3$, $d_1\lambda_1 > -\mu_2 + \frac{p_1\widetilde{C}}{1+\widetilde{C}} + \frac{c+a/g}{2}$ and $d_2\lambda_1 > 1 + \frac{c+a/g}{2}$.*

Proof. We now prove only the case (i). Let $\overline{\phi} = \frac{1}{|\Omega|}\int_\Omega \phi\,dx$ for $\phi \in L^1(\Omega)$. Multiplying $(u-\bar{u})$, $(v-\bar{v})$ and $(w-\overline{w})$ to the first, second and third equation in (1.2), respectively, and then integrating over Ω, we have

$$\begin{aligned}
&\int_\Omega d_1|\nabla u|^2 + d_2|\nabla v|^2 + d_3|\nabla w|^2\,dx \\
&\quad= \int_\Omega \biggl[(u-\bar{u})\left(cv - \mu_2 u + \frac{p_1 uw}{1+w} + s_1 - c\bar{v} + \mu_2\bar{u} - \frac{p_1\bar{u}\overline{w}}{1+\overline{w}} - s_1\right) \\
&\qquad + (v-\bar{v})\left(v(1-bv) - \frac{auv}{g+v} - \bar{v}(1-b\bar{v}) + \frac{a\bar{u}\bar{v}}{g+\bar{v}}\right) \\
&\qquad + (w-\overline{w})\left(\frac{p_2uv}{1+v} - \mu_3 w + s_2 - \frac{p_2\bar{u}\bar{v}}{1+\bar{v}} + \mu_3\overline{w} - s_2\right)\biggr]dx \\
&\quad= \int_\Omega \biggl[(u-\bar{u})^2\left(-\mu_2 + \frac{p_1 w}{1+w}\right) + (u-\bar{u})(v-\bar{v})\left(c - \frac{av}{g+v}\right) + (v-\bar{v})^2\left(1 - b(v+\bar{v}) - \frac{ag\bar{u}}{(g+v)(g+\bar{v})}\right) \\
&\qquad + (u-\bar{u})(w-\overline{w})\left(\frac{p_1\bar{u}}{(1+w)(1+\overline{w})} + \frac{p_2 v}{1+v}\right) \\
&\qquad + (v-\bar{v})(w-\overline{w})\left(\frac{p_2\bar{u}}{(1+v)(1+\bar{v})}\right) + (w-\overline{w})^2(-\mu_3)\biggr]dx. \qquad (4.13)
\end{aligned}$$

Using (4.2), the last integral in (4.13) is less than or equal to the following

$$\begin{aligned}
&\int_\Omega \biggl[(u-\bar{u})^2\left(-\mu_2 + \frac{p_1\widetilde{C}}{1+\widetilde{C}}\right) + |v-\bar{v}||u-\bar{u}|(c+a/g) + (v-\bar{v})^2 \\
&\qquad + |u-\bar{u}||w-\overline{w}|(p_1\widetilde{C}+p_2) + |v-\bar{v}||w-\overline{w}|p_2\widetilde{C} + (w-\overline{w})^2(-\mu_3)\biggr]dx \\
&\quad\leqslant \int_\Omega \biggl[(u-\bar{u})^2\left(-\mu_2 + \frac{p_1\widetilde{C}}{1+\widetilde{C}} + \frac{c+a/g}{2\epsilon} + \frac{p_1\widetilde{C}+p_2}{2\epsilon}\right) \\
&\qquad + (v-\bar{v})^2\left(1 + \frac{c+a/g}{2}\epsilon + \frac{p_2\widetilde{C}}{2}\right) + (w-\overline{w})^2\left(-\mu_3 + \frac{p_1\widetilde{C}+p_2}{2}\epsilon + \frac{p_2\widetilde{C}}{2}\right)\biggr]dx,
\end{aligned}$$

where ϵ is an arbitrary positive constant.

By the well-known Poincaré inequality, we see that

$$\int_\Omega d_1|\nabla u|^2 + d_2|\nabla v|^2 + d_3|\nabla w|^2\,dx \geqslant \int_\Omega d_1\lambda_1(u-\bar{u})^2 + d_2\lambda_1(v-\bar{v})^2 + d_3\lambda_1(w-\overline{w})^2.$$

One can choose sufficiently small ϵ_0 such that

$$\lambda_1 d_2 > 1 + \frac{c+a/g}{2}\epsilon_0 + \frac{p_2\widetilde{C}}{2}$$

and

$$\lambda_1 d_3 > -\mu_3 + \frac{p_1\widetilde{C}+p_2}{2}\epsilon_0 + \frac{p_2\widetilde{C}}{2}$$

are satisfied from the given assumptions. By taking

$$\bar{d}_1 = -\mu_2 + \frac{p_1\widetilde{C}}{1+\widetilde{C}} + \frac{c+a/g}{2\epsilon_0} + \frac{p_1\widetilde{C}+p_2}{2\epsilon_0},$$

we conclude that $u = \bar{u}$, $v = \bar{v}$ and $w = \overline{w}$, which completes the proof. □

In the next theorem, we provide the conditions for the nonexistence of nonconstant steady states, which can be occurred even when only one or two diffusion coefficients (including d_2) are large. Note that this result can be also proved by using the implicit function theorem method in [3, Theorem 4].

Theorem 4.6. *Let d be a fixed positive number. Assume that* (PE1) *or* (PE2) *holds and that the assumptions in Theorem* 4.4 *are satisfied.*

(i) *There exists* $\bar{d}_{2,3} = \bar{d}_{2,3}(d, \Gamma, \Omega)$ *such that* (1.2) *has no nonconstant positive solution if* $d_1 \geqslant d$ *and* $d_2, d_3 \geqslant \bar{d}_{2,3}$.
(ii) *There exists* $\bar{d}_{1,2} = \bar{d}_{1,2}(d, \Gamma, \Omega)$ *such that* (1.2) *has no nonconstant positive solution if* $d_3 \geqslant d$ *and* $d_1, d_2 \geqslant \bar{d}_{1,2}$.
(iii) *There exists* $\bar{d}_2 = \bar{d}_2(d, \Gamma, \Omega)$ *such that* (1.2) *has no nonconstant positive solution if* $d_1, d_3 \geqslant d$ *and* $d_2 \geqslant \bar{d}_2$.

Proof. We use a contradiction argument to obtain the desired result. Suppose that there exist a sequence $(d_{1,n}, d_{2,n}, d_{3,n})$ and a nonconstant positive solution (u_n, v_n, w_n) to (1.2), where $(d_1, d_2, d_3) = (d_{1,n}, d_{2,n}, d_{3,n})$.

(i) Due to Theorem 4.5, it suffices to assume that $(d_{1,n}, d_{2,n}, d_{3,n}) \to (\tilde{d}_1, \infty, \infty)$ for $\tilde{d}_1 \in (0,\infty)$. Further, we assume from Theorem 4.3 and Theorem 4.4 that there exists a subsequence of $\{(u_n, v_n, w_n)\}$ (still denoted by itself) such that $(u_n, v_n, w_n) \to (\tilde{u}, V, W)$ in $[C^2(\overline{\Omega})]^3$, where V, W are positive constants and $\tilde{u}$ is a positive function in $C^2(\overline{\Omega})$. Note that $(\tilde{u}, V, W)$ solves

$$\begin{cases} -\tilde{d}_1\Delta\tilde{u} = cV - \mu_2\tilde{u} + \dfrac{p_1\tilde{u}W}{1+W} + s_1 \quad \text{in } \Omega, \qquad \dfrac{\partial\tilde{u}}{\partial\nu} = 0 \quad \text{on } \partial\Omega, \\ \displaystyle\int_\Omega \left(1 - bV - \frac{a\tilde{u}}{g+V}\right) dx = 0, \\ \displaystyle\int_\Omega \left(\frac{p_2\tilde{u}V}{1+V} - \mu_3 W + s_2\right) dx = 0. \end{cases} \tag{4.14}$$

If the given assumption (PE1) (or (PE2)) holds, then it is easy to see from the first equation in (4.14) that $\tilde{u} \equiv \frac{(cV+s_1)(1+W)}{\mu_2+(\mu_2-p_1)W}$, a positive constant. Thus, (4.14) yields that $\tilde{u} = F(V)$, $W = H(V)$ and $W = G(V)$. Further, from the given assumption (PE1) (or (PE2)), we have $(\tilde{u}, V, W) = (u_*, v_*, w_*)$. Hence (u_n, v_n, w_n) converge uniformly to the positive constant steady state $\mathbf{e}_*$ by passing to a subsequence if necessary.

We now assert that $(u_n, v_n, w_n) \equiv (u_*, v_*, w_*)$ for all n to get a contradiction. Clearly, (u_n, v_n, w_n) satisfies (4.13) with $(d_1, d_2, d_3) = (d_{1,n}, d_{2,n}, d_{3,n})$. From the above arguments, we see that $-\mu_2 + \frac{p_1 w_n}{1+w_n} \to -\mu_2 + \frac{p_1 w_*}{1+w_*} < 0$ uniformly as $n \to \infty$. Here and henceforth, we denote by C various positive constants that depend only on Γ. By applying Young's inequality to (4.13), we obtain that for $0 < \epsilon \ll 1$,

$$\begin{aligned} &\int_\Omega d_{1,n}|\nabla u_n|^2 + d_{2,n}|\nabla v_n|^2 + d_{3,n}|\nabla w_n|^2\, dx \\ &\quad \leqslant \int_\Omega \left(-\mu_2 + \frac{p_1 w_*}{1+w_*} + C\epsilon\right)(u_n - \bar{u}_n)^2 + \frac{C}{\epsilon}(v_n - \bar{v}_n)^2 + \frac{C}{\epsilon}(w_n - \overline{w}_n)^2\, dx. \end{aligned} \tag{4.15}$$

Note that we can choose $\epsilon \ll (\mu_2 - \frac{p_1 w_*}{1+w_*})/C$. Thus, by letting $d_{2,n}, d_{3,n} \to \infty$ in (4.15), we see that $\nabla u_n \equiv 0$ for large n. In turn, for all large n, $\nabla v_n \equiv 0$ and $\nabla w_n \equiv 0$. Hence u_n, v_n, and w_n are all positive constants. In particular, $(u_n, v_n, w_n) \equiv \mathbf{e}_*$ for all large n.

(ii) The desired assertion can be established similarly to that in (i).

(iii) By virtue of Theorem 4.5 and the previous cases, we assume only that $(d_{1,n}, d_{2,n}, d_{3,n}) \to (\tilde{d}_1, \infty, \tilde{d}_3)$ for $\tilde{d}_1, \tilde{d}_3 \in (0,\infty)$ and that as in case (i), there exists a subsequence of $\{(u_n, v_n, w_n)\}$ such that $(u_n, v_n, w_n) \to (\tilde{u}, V, \tilde{w})$ in $[C^2(\overline{\Omega})]^3$, where V is a positive constant and $\tilde{u}$, $\tilde{w}$ are positive functions in $C^2(\overline{\Omega})$. Moreover, $(\tilde{u}, V, \tilde{w})$ solves

$$\begin{cases} -\tilde{d}_1\Delta\tilde{u} = cV - \mu_2\tilde{u} + \dfrac{p_1\tilde{u}\tilde{w}}{1+\tilde{w}} + s_1 \quad \text{in } \Omega, \qquad \dfrac{\partial\tilde{u}}{\partial\nu} = 0 \quad \text{on } \partial\Omega, \\ \displaystyle\int_\Omega \left(1 - bV - \frac{a\tilde{u}}{g+V}\right) dx = 0, \\ -\tilde{d}_3\Delta\tilde{w} = \dfrac{p_2\tilde{u}V}{1+V} - \mu_3\tilde{w} + s_2 \quad \text{in } \Omega, \qquad \dfrac{\partial\tilde{w}}{\partial\nu} = 0 \quad \text{on } \partial\Omega. \end{cases} \tag{4.16}$$

Let $\max_{\overline{\Omega}} \tilde{u}(x) = \tilde{u}(x_1)$ and $\max_{\overline{\Omega}} \tilde{w}(x) = \tilde{w}(x_2)$. Then, by applying Lemma 4.1 to the first and third equations in (4.16), we obtain

$$cV + s_1 \geqslant \left(\mu_2 - p_1\frac{\tilde{w}(x_1)}{1+\tilde{w}(x_1)}\right)\tilde{u}(x_1) \quad \text{and} \quad p_2\frac{\tilde{u}(x_2)V}{1+V} + s_2 \geqslant \mu_3\tilde{w}(x_2),$$

which respectively imply

$$cV + s_1 \geqslant \left(\mu_2 - p_1\frac{\tilde{w}(x_2)}{1+\tilde{w}(x_2)}\right)\tilde{u}(x_1) \quad \text{and} \quad p_2\frac{\tilde{u}(x_1)V}{1+V} + s_2 \geqslant \mu_3\tilde{w}(x_2).$$

As a result, $\Psi(\tilde{u}(x_1)) \geqslant 0$ can be derived, where

$$\Psi(\psi) = -\frac{(\mu_2 - p_1)p_2V}{\mu_3(1+V)}(\psi)^2 + \left\{\frac{p_2V(s_1+cV)}{\mu_3(1+V)} - \mu_2 - \frac{(\mu_2-p_1)s_2}{\mu_3}\right\}\psi + \left(\frac{s_2}{\mu_3} + 1\right)(s_1 + cV).$$

Thus, $\tilde{u}(x_1) \leqslant \psi^*$ holds, where ψ^* is the unique positive root of $\Psi(\psi) = 0$. Similarly, we have $\psi^* \leqslant \min_{\overline{\Omega}} \tilde{u}(x)$, and so $\tilde{u} \equiv \psi^*$ is a positive constant. In turn, $\tilde{w}$ also is a positive constant. Hence because of the given assumption, $(\tilde{u}, V, \tilde{w}) \equiv \mathbf{e}_*$ must be satisfied.

To finish the proof, we now show that $(u_n, v_n, w_n) \equiv (u_*, v_*, w_*)$ for all n. First, according to the above arguments,

$$-\mu_2 + \frac{p_1w_n}{1+w_n} \to -\mu_2 + \frac{p_1w_*}{1+w_*} \quad \text{and} \quad \frac{p_1\bar{u}_n}{(1+w_n)(1+\overline{w}_n)} + \frac{p_2v_n}{1+v_n} \to \frac{p_1u_*}{(1+w_*)^2} + \frac{p_2v_*}{1+v_*}$$

uniformly as $n \to \infty$. Consider the following quadratic polynomial

$$\Phi(\phi) := \left(\frac{p_1u_*}{(1+w_*)^2}\right)^2 \phi + 2\left(\frac{p_1u_*}{(1+w_*)^2}\frac{p_2v_*}{1+v_*} - 2\mu_3\left(\mu_2 - \frac{p_1w_*}{1+w_*}\right)\right)\phi + \left(\frac{p_2v_*}{1+v_*}\right)^2.$$

Under the assumption (PE1) (or (PE2)),

$$-\frac{p_1u_*}{(1+w_*)^2}\frac{p_2v_*}{1+v_*} + \mu_3\left(\mu_2 - \frac{p_1w_*}{1+w_*}\right) > 0$$

holds (see Lemmas 2.2 (i) and 2.3 (i)). Thus, $\Phi(\phi) = 0$ has two positive roots (say ϕ_1 and ϕ_2). For the constant $\phi_* \in (\phi_1, \phi_2)$ and $0 < \epsilon \ll 1$, as in case (i), we derive

$$\int_\Omega d_{1,n}\phi_*|\nabla u_n|^2 + d_{2,n}|\nabla v_n|^2 + d_{3,n}|\nabla w_n|^2\, dx \leqslant \int_\Omega \widetilde{\Phi}(\epsilon) + \frac{C}{\epsilon}(v_n - \bar{v}_n)^2\, dx, \tag{4.17}$$

where

$$\widetilde{\Phi}(\epsilon) := \left\{\phi_*\left(-\mu_2 + \frac{p_1w_*}{1+w_*}\right) + C\epsilon\right\}(u_n - \bar{u}_n)^2 + (-\mu_3 + C\epsilon)(w_n - \overline{w}_n)^2 \\ + \left(\frac{p_1\phi_*u_*}{(1+w_*)^2} + \frac{p_2v_*}{1+v_*}\right)(u_n - \bar{u}_n)(w_n - \overline{w}_n).$$

It is clear that $\widetilde{\Phi}(0) < 0$ due to the definition of ϕ_*. Thus, we can choose proper $\epsilon \ll 1$ such that $\widetilde{\Phi}(\epsilon) \leqslant 0$. Then, by letting $d_{2,n} \to \infty$ in (4.17), we obtain that $\nabla u_n \equiv \nabla v_n \equiv \nabla w_n \equiv 0$, that is, $(u_n, v_n, w_n) \equiv \mathbf{e}_*$ for all large n. □

We now investigate the existence of nonconstant positive solutions by using Leray–Schauder degree. Define a compact operator $\mathcal{A} : [C^1(\overline{\Omega})]^3 \to [C^1(\overline{\Omega})]^3$ by

$$\mathcal{A}(\mathbf{u}) := \begin{pmatrix} (I - d_1\Delta)^{-1}(cv - \mu_2u + \frac{p_1uw}{1+w} + s_1 + u) \\ (I - d_2\Delta)^{-1}(v(1-bv) - \frac{auv}{g+v} + v) \\ (I - d_3\Delta)^{-1}(\frac{p_2uv}{1+v} - \mu_3w + s_2 + w) \end{pmatrix},$$

where $\mathbf{u} := (u(x), v(x), w(x))^T$ and $(I - d_i\Delta)^{-1}$ is the inverse of the operator $I - d_i\Delta$ under homogeneous Neumann boundary conditions. Since the operator $(I - d_i\Delta)^{-1} : C^1(\overline{\Omega}) \to C^1(\overline{\Omega})$ is compact, $\mathcal{A}$ is also compact.

Note that solving system (1.2) is equivalent to finding positive solutions to the equation $(\mathbf{I} - \mathcal{A})\mathbf{u} = 0$. To apply index theory, we investigate the eigenvalue of the problem:

$$-\big(\mathbf{I} - \mathcal{A}_{\mathbf{u}}(\mathbf{e}_*)\big)\Psi = \eta\Psi, \quad \Psi \neq \mathbf{0}, \tag{4.18}$$

where $\Psi = (\psi_1, \psi_2, \psi_3)^T$ and $\mathbf{e}_* = (u_*, v_*, w_*)$ (if it exists). If $\mathbf{I} - \mathcal{A}_{\mathbf{u}}(\mathbf{e}_*)$ is nonsingular (i.e., 0 is not an eigenvalue of (4.18)), then the Leray–Schauder theorem (Theorem 2.8.1 in [16]) implies that

$$\operatorname{index}(I - \mathcal{A}, \mathbf{e}_*) = (-1)^\gamma, \quad \gamma = \sum_{\eta > 0} \rho_\eta,$$

where ρ_η is the algebraic multiplicity of all positive eigenvalues η of (4.18). After some calculations, we can rewrite (4.18) as

$$\begin{cases} -(\eta+1)d_1\Delta\psi_1 + \left(\eta + \mu_2 - \dfrac{p_1 w_*}{1+w_*}\right)\psi_1 - c\psi_2 - \dfrac{p_1 u_*}{(1+w_*)^2}\psi_3 = 0, \\ -(\eta+1)d_2\Delta\psi_2 + \dfrac{a v_*}{g+v_*}\psi_1 + \left(\eta + v_*\left(b - \dfrac{a u_*}{(g+v_*)^2}\right)\right)\psi_2 = 0, \\ -(\eta+1)d_3\Delta\psi_3 - \dfrac{p_2 v_*}{1+v_*}\psi_1 - \dfrac{p_2 u_*}{(1+v_*)^2}\psi_2 + (\eta+\mu_3)\psi_3 = 0 \quad \text{in } \Omega, \\ \dfrac{\partial\psi_1}{\partial\nu} = \dfrac{\partial\psi_2}{\partial\nu} = \dfrac{\partial\psi_3}{\partial\nu} = 0 \quad \text{on } \partial\Omega, \\ \psi_i \neq 0. \end{cases} \tag{4.19}$$

Observe that (4.19) has a non-trivial solution if and only if $P_i(\eta; d_1, d_2, d_3) = 0$ for some $\eta \geqslant 0$ and $i \geqslant 0$, where

$$P_i(\eta, d_1, d_2, d_3) := \det\begin{pmatrix} \eta + \frac{d_1\lambda_i + \mu_2 - \frac{p_1 w_*}{1+w_*}}{d_1\lambda_i + 1} & -\frac{c}{d_1\lambda_i+1} & -\frac{\frac{p_1 u_*}{(1+w_*)^2}}{d_1\lambda_i+1} \\ \frac{a v_*}{g+v_*}\frac{1}{d_2\lambda_i+1} & \eta + \frac{d_2\lambda_i + v_*(b - \frac{a u_*}{(g+v_*)^2})}{d_2\lambda_i+1} & 0 \\ -\frac{p_2 v_*}{1+v_*}\frac{1}{d_3\lambda_i+1} & -\frac{p_2 u_*}{(1+v_*)^2}\frac{1}{d_3\lambda_i+1} & \eta + \frac{d_3\lambda_i+\mu_3}{d_3\lambda_i+1} \end{pmatrix}.$$

That is, η is an eigenvalue of (4.18) (and thus (4.19)) if and only if η is a positive root of the characteristic equation $P_i(\eta, d_1, d_2, d_3) = 0$ for $i \geqslant 0$. Therefore, if $P_i(0) \neq 0$ for all $i \geqslant 0$, we can see that

$$\operatorname{index}(I - \mathcal{A}, \mathbf{e}_*) = (-1)^\gamma, \quad \gamma = \sum_{i \geqslant 0}\sum_{\eta_i > 0} l_{\eta_i} m_i$$

(for its strict proof, see [3]) where m_i has been defined in Notation 3.7, and l_{η_i} is the multiplicity of η_i as a positive root of $P_i(\eta, d_1, d_2, d_3) = 0$.

Lemma 4.7. *Assume that* (PE1) *and* (2.2) *hold.*

(i) *If $i = 0$, then $P_0(\eta, d_1, d_2, d_3) = 0$ may have no positive root, or exactly one positive root with the multiplicity two, or two positive roots with the multiplicity one.*
(ii) *For $i \geqslant 1$, there exists a positive constant $\widehat{d}_2(\Gamma, d_1, d_3)$ such that, if $d_2 \geqslant \widehat{d}_2$, then $P_i(\eta, d_1, d_2, d_3) = 0$ has no positive root.*
(iii) *The quadratic polynomial*

$$d_2 d_3\lambda^2 + \left(d_2\mu_3 + d_3 v_*\left(b - \frac{a u_*}{(g+v_*)^2}\right)\right)\lambda + \mu_3 v_*\left(b - \frac{a u_*}{(g+v_*)^2}\right) = 0$$

has only one simple positive root, say $\lambda_* \in (\lambda_{i^*}, \lambda_{i^*+1})$ for some i^*.
(iv) *Let $i^\sharp = \inf\{i\colon \frac{d_2\lambda_i + v_*(b - \frac{a u_*}{(g+v_*)^2})}{d_2\lambda_i+1} + \frac{d_3\lambda_i+\mu_3}{d_3\lambda_i+1} > 0\}$. Then there exists $\widehat{d}_1(\Gamma, d_2, d_3)$ such that, when $d_1 \geqslant \widehat{d}_1$, the characteristic polynomial $P_i(\eta, d_1, d_2, d_3) = 0$ may have only one positive simple root for $1 \leqslant i \leqslant i^*$; no positive root, exactly one positive root with multiplicity two, or two positive simple roots for $i^* + 1 \leqslant i \leqslant \max\{i^* + 1, i^\sharp\}$; or no positive root for $\max\{i^* + 1, i^\sharp\} \leqslant i$.*

Proof. Note that the results (i), (iii) and (v) in Lemma 2.2 hold under the assumptions, that is,

$$-b + \frac{a u_*}{(g+v_*)^2} > 0,$$

$$\frac{acv_*}{g+v_*} + v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) > 0,$$
$$\mu_3\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) > \frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 v_*}{1+v_*}.$$

(i) It is easy to obtain

$$P_0(\eta, d_1, d_2, d_3) = \eta^3 - \operatorname{trace}\big(\mathbf{F_u}(\mathbf{e}_*)\big)\eta^2 + \left\{\frac{acv_*}{g+v_*} + \mu_3\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right) - \frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 v_*}{1+v_*}\right.$$
$$\left. + v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\left(\mu_2 - \frac{p_1 w_*}{1+w_*} + \mu_3\right)\right\}\eta - \det\big(\mathbf{F_u}(\mathbf{e}_*)\big),$$

where

$$-\det\big(\mathbf{F_u}(\mathbf{e}_*)\big) = \mu_3\left\{\frac{acv_*}{g+v_*} + v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\left(\mu_2 - \frac{p_1 w_*}{1+w_*}\right)\right\}$$
$$+ \frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 u_*}{(1+v_*)^2}\frac{av_*}{g+v_*} - v_*\left(b - \frac{au_*}{(g+v_*)^2}\right)\frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 v_*}{1+v_*} > 0.$$

Thus the desired claim holds.

(ii) In the case of $i \geqslant 1$, we have $P_i(\eta, d_1, d_2, d_3) = (\eta+1)\widetilde{P}_i(\eta, d_1, d_3) + O(1/d_2)$, where

$$\widetilde{P}_i(\eta, d_1, d_3) = \eta^2 + \left(\frac{d_1\lambda_i + \mu_2 - \frac{p_1 w_*}{1+w_*}}{d_1\lambda_i + 1} + \frac{d_3\lambda_i + \mu_3}{d_3\lambda_i + 1}\right)\eta$$
$$+ \frac{d_1 d_3 \lambda_i^2 + (d_1\mu_3 + d_3(\mu_2 - \frac{p_1 w_*}{1+w_*}))\lambda_i + \mu_3(\mu_2 - \frac{p_1 w_*}{1+w_*}) - \frac{p_1 u_*}{(1+w_*)^2}\frac{p_2 v_*}{1+v_*}}{(d_1\lambda_i + 1)(d_3\lambda_i + 1)}.$$

Note that $\widetilde{P}_i(\eta, d_1, d_3) > 0$ for all $i \geqslant 1$ and $\eta \geqslant 0$, and thus the desired result follows by considering d_2 that is large enough.

(iii) Since $b - \frac{au_*}{(g+v_*)^2} < 0$, the assertion holds.

(iv) Note that for $i \geqslant 1$, $P_i(\eta, d_1, d_2, d_3) = (\eta+1)\widehat{P}_i(\eta, d_2, d_3) + O(1/d_1)$, where

$$\widehat{P}_i(\eta, d_2, d_3) = \eta^2 + \left(\frac{d_2\lambda_i + v_*(b - \frac{au_*}{(g+v_*)^2})}{d_2\lambda_i + 1} + \frac{d_3\lambda_i + \mu_3}{d_3\lambda_i + 1}\right)\eta$$
$$+ \frac{d_2 d_3 \lambda^2 + (d_2\mu_3 + d_3 v_*(b - \frac{au_*}{(g+v_*)^2}))\lambda + \mu_3 v_*(b - \frac{au_*}{(g+v_*)^2})}{(d_2\lambda_i + 1)(d_3\lambda_i + 1)}.$$

Here it is easy to see that $\widehat{P}_i(\eta, d_2, d_3) = 0$ may have only one positive simple root for $1 \leqslant i \leqslant i^*$; no positive root, exactly one positive root with multiplicity two, or two positive simple roots for $i^* + 1 \leqslant i \leqslant \max\{i^*+1, i^\sharp\}$; or no positive root for $\max\{i^*+1, i^\sharp\} \leqslant i$. Consequently, the desired conclusion follows. □

We next demonstrate the existence of nonconstant positive steady-state solutions (i.e., the emergence of a stationary pattern) to (1.2).

Theorem 4.8. *Assume that* (PE1), (2.2) *and one of* (i)–(iv) *in Theorem* 4.4 *hold. If* $\sum_{i=1}^{i^*} m_i$ *is odd, then there exists a positive constant* $\widehat{d}_1$ *such that, if* $d_1 \geqslant \widehat{d}_1$, (1.2) *has at least one nonconstant positive solution.*

Proof. On the contrary, suppose that our assertion does not hold for all $d_1 > \widehat{d}_1$.

For $t \in [0,1]$, define the homotopy

$$\mathcal{A}_t(\mathbf{u}) := \begin{pmatrix} (I - (d_1^* + t(d_1 - d_1^*))\Delta)^{-1}(cv - \mu_2 u + \frac{p_1 uw}{1+w} + s_1 + u) \\ (I - (d_2^* + t(d_2 - d_2^*))\Delta)^{-1}(v(1-bv) - \frac{auv}{g+v} + v) \\ (I - (d_3^* + t(d_3 - d_3^*))\Delta)^{-1}(\frac{p_2 uv}{1+v} - \mu_3 w + s_2 + w) \end{pmatrix},$$

where d_i^* $(i = 1, 2, 3)$ are positive constants to be determined later. From Theorems 4.3 and 4.4, we know that all positive solutions to the problem

$$\mathcal{A}_t(\mathbf{u}) = \mathbf{u} \quad \text{in } \Omega, \qquad \frac{\partial \mathbf{u}}{\partial \nu} = \mathbf{0} \quad \text{on } \partial\Omega \tag{4.20}$$

are contained in

$$\Lambda := \left\{\mathbf{u} \in \left[C^1(\overline{\Omega})\right]^3 \colon \widehat{C}/2 < u, v, w < 2\widetilde{C}\right\}.$$

Then it is clear that $\mathcal{A}_1 = \mathcal{A}$ and that (4.20) has a unique positive constant solution $\mathbf{e}_*$ for any $t \in [0,1]$. Moreover, $\mathcal{A}_t(\mathbf{u}) \neq \mathbf{u}$ for all $\mathbf{u} \in \partial\Lambda$ and $\mathcal{A}_t(\mathbf{u}) : \Lambda \times [0,1] \to [C^1(\overline{\Omega})]^3$ is compact, and thus, $\deg(I - \mathcal{A}_t(\mathbf{u}), \Lambda, 0)$ is well defined.

Note that by the homotopy invariance of the topological degree,

$$\deg(I - \mathcal{A}_0, \Lambda, 0) = \deg(I - \mathcal{A}_1, \Lambda, 0). \tag{4.21}$$

Since we assume that there is no nonconstant positive solution to (1.2), the equation $\mathcal{A}_1(\mathbf{u}) = \mathbf{u}$ has only a positive constant solution $\mathbf{e}_*$ in Λ. From Lemma 4.7 (i) and (iv), we obtain

$$l_{\eta_i} = \begin{cases} 0 \text{ or } 2, & \text{if } i = 0, \\ 1, & \text{if } 1 \leqslant i \leqslant i^*, \\ 0 \text{ or } 2, & \text{if } i^* + 1 \leqslant k \leqslant \max\{i^* + 1, i^\sharp\}, \\ 0, & \text{if } \max\{i^* + 1, i^\sharp\} + 1 \leqslant i. \end{cases}$$

Thus

$$\gamma = \sum_{i=0}^{i^*} m_i + \text{even (or zero)} = \text{an odd number},$$

such that

$$\deg(I - \mathcal{A}_1, \Lambda, 0) = \operatorname{index}(\mathcal{A}_1, \mathbf{e}_*) = -1. \tag{4.22}$$

Assume

$$d_1^* = \frac{1}{\lambda_1}\left(-\mu_2 + \frac{p_1\widetilde{C}}{1+\widetilde{C}} + \frac{p_1\widetilde{C} + p_2}{2}\right) + 1, \qquad d_2^* = \max\{\widehat{d}_2, \bar{d}_2\} + 1,$$
$$d_3^* = \frac{1}{\lambda_1}\left(-\mu_3 + \frac{p_1\widetilde{C} + p_2}{2}\right) + 1,$$

where $\bar{d}_2$ has been defined in Theorem 4.5 (ii). Then, in view of Theorem 4.5 (ii), the equation $\mathcal{A}_0(\mathbf{u}) = \mathbf{u}$ has only a positive constant solution $\mathbf{e}_*$. Furthermore, since Lemma 4.7 (i) and (ii) yield $\gamma = l_{\eta_0} = 0$ or 2, we have

$$\deg(I - \mathcal{A}_0, \Lambda, 0) = \operatorname{index}(\mathcal{A}_0, \mathbf{e}_*) = 1. \tag{4.23}$$

However, (4.22) and (4.23) contradict (4.21). □

In a similar manner, we can verify the existence of a nonconstant positive steady state in (1.2) when $\mu_2 = p_1$.

Theorem 4.9. *Assume that* (PE2), (2.5) *and one of* (i)–(iv) *in Theorem* 4.4 *hold. If* $\sum_{i=1}^{i^*} m_i$ *is odd, then there exists a positive constant* $\widehat{d}_1$ *such that, if* $d_1 \geqslant \widehat{d}_1$, (1.2) *has at least one nonconstant positive solution.*

5. Concluding remarks

In this paper, we examined a model with immunotherapy under a spatially inhomogeneous environment *in vivo* that describes the interaction between effector cells, tumor cells, and IL-2. Here we provide a brief biological interpretation of the results based on mathematical consequences. The results for Theorem 3.2 suggest that the weak antigenicity of tumor (c) and the small amount of immunotherapy (s_1) do not help to clear tumor cells. In addition, tumor cells cannot be completely cleared without a treatment such as LAK and/or TIL (or a treatment combining them with IL-2). This phenomenon is consistent with the results for the non-spatial case of model [8]. We also considered two types of treatments for the tumor-immune system: *adoptive cellular immunotherapy* (ACI) and the administration of the *cytokine IL*-2. The results indicate that unlike no treatment, strong ACI can lead to a tumor-free state (Corollary 3.6).

On the other hand, Theorem 3.4 indicates that the immune system cannot be controlled by the introduction of a large constant source s_2, that is, by a strong IL-2 therapy. In this case, the tumor can be cleared, but the growth of effector cells (the immune system) can become uncontrollable as the IL-2 concentration reaches a steady-state value. It is known that this situation can result in side effects such as capillary leak syndrome [11,13,19], although the tumor-free state can be observed by administering a high concentration of IL-2. This suggests that applying a strong IL-2 therapy to the tumor site may be detrimental to cancer patients undergoing immunotherapy.

The results for Theorem 3.5 suggest that the tumor can be cleared by boosting the immune system through a monotherapy (ACI) or ACI in combination with IL-2. Thus, a treatment combining ACI with IL-2 may be better for cancer patients, and a treatment combining a large amount of s_1 (strong ACI) with a certain amount of s_2 may be the best immunotherapy for cancer patients. Thus, the cytokine-enhanced immune function may have a crucial role in the treatment of cancer.

Finally, Theorems 4.8 and 4.9 show that for the sufficiently large diffusion rate (d_1) for effector cells, the tumor-immune system can show a pattern that represents a nonconstant positive solution. This suggests that a strong diffusion rate may lead to changes in the stability of positive solutions to the tumor-immune system with immunotherapy.

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