DIFFUSION MODELING OF TUMOR-CD4$^+$-CYTOKINE INTERACTIONS WITH TREATMENTS: ASYMPTOTIC BEHAVIOR AND STATIONARY PATTERNS

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Abstract. In this work, we consider a diffusive tumor-CD4$^+$-cytokine interactions model with immunotherapy under homogeneous Neumann boundary conditions. We first investigate the large-time behavior of nonnegative equilibria, including the system persistence and the stability conditions. We also give the existence of nonconstant positive steady states (i.e., a stationary pattern), which indicate that this stationary pattern is driven by diffusion effects. For this study, we employ the comparison principle for parabolic systems, linearization method, the method of energy integral and the Leray-Schauder degree.

1. Introduction. Cancer is a complex group of diseases with many possible causes. Cells divide and grow uncontrollably, forming malignant tumors and invading even distant parts of the body [16]. Immunotherapies are important methods for controlling and curing malignant tumors [15]. Tumor immunotherapy is a fast growing field of experimental and clinical studies aimed on stimulation of the immune system for destroying tumor cells and delaying tumor growth [15, 6, 7].

Cytokines are protein hormones that mediate both natural and specific immunity. They are produced mainly by activated T cells (lymphocytes) during cellular-mediated immunity. Until recently, CD4$^+$ lymphocytes were thought to contain two distinct lineages of effector cells, the Th1 and Th2 subsets that are defined by secretion of either interferon (IFN)−γ or Interleukin-4 (IL-4) [10]. IL-4 is a prototypic immunoregulatory cytokine that is secreted by activated T lymphocytes, basophils, and mast cells [4].

Based on recent observations that many tumors have been immuno-selected to evade recognition by the traditional cytotoxic T lymphocytes, Anderson, Jang and Yu [2] proposed mathematical models of tumor-CD4$^+$-cytokine interactions to investigate the role of CD4$^+$ on tumor regression. Treatments of either CD4$^+$ or

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cytokine are applied to study their effectiveness. It is found that doses of treatments are critical in determining the fate of the tumor, and tumor cells can be eliminated completely if doses of cytokine are large. Let $x$, $y$ and $z$ denote the tumor cells, CD4$^+$ T cells, and the cytokine (IL-4 or more broadly any cytokine produced by Th2), respectively. The proposed model is given by

$$
\begin{align*}
  x' &= x f(x) - d(x, z), \\
  y' &= g_y(x, y) - a_y(y) + I_1(t), \\
  z' &= g_z(x, y, z) - a_z(z) + I_2(t),
\end{align*}
$$

where $f(x)$ is the per capita growth rate of the tumor cells, $d(x, z)$ denotes the loss of tumor cells caused by cytokine, $g_y(x, y)$ is the proliferation of the CD4$^+$ T cells through interactions with the tumor cells, and $g_z(x, y)$ denotes productions of cytokine secreted by CD4$^+$ T cells. Expression $a_y(y)$ is the apoptosis (natural death) of the T cells, $a_z(z)$ denotes the loss of cytokine, and $I_1(t)$ and $I_2(t)$ are the immunotherapy treatments, which may be time-dependent.

Anderson, Jang and Yu [2] use a logistic growth equation for the tumor cells and Michaelis-Menten kinetics for all the functional forms with different half saturation constants. Consequently, it is assumed that the tumor’s growth is limited and the productions of CD4$^+$ and cytokine due to the tumor cells are also limited. With this consideration, the model is given by

$$
\begin{align*}
  x' &= r x (1 - x/K) - \frac{d x z}{m + x}, \\
  y' &= \beta x y - a y + I_1, \\
  z' &= \alpha x y - \mu z + I_2,
\end{align*}
$$

where all the parameters $r, K, m, \delta, \beta, k, a, \alpha, b,$ and $\mu$ are positive constants and $I_1 \geq 0$ and $I_2 \geq 0$ denote constant treatments of CD4$^+$ and cytokine per unit time, respectively. The parameters and their biological interpretations are summarized as follows:

- $r$: Intrinsic growth rate of the tumor;
- $K$: Carrying capacity of the tumor;
- $\delta$: Maximum tumor killing rate by cytokine;
- $m$: Half saturation constant of the tumor killing rate;
- $\beta$: Maximum CD4$^+$ production rate (antigenicity of the tumor);
- $k$: Half saturation constant of the CD4$^+$ production rate;
- $a$: Death rate of the CD4$^+$ cells;
- $\alpha$: Maximum production rate of cytokine;
- $b$: Half saturation constant of the cytokine production rate;
- $\mu$: Cytokine loss rate;
- $I_1$: Treatment by CD4$^+$;
- $I_2$: Treatment by cytokine.

By the linearized theory, comparison theorem of ordinary differential equations and some numerical simulations, they [2] use simple mathematical models of tumor, CD4$^+$, and cytokine to explore effectiveness of immunotherapies, and conclude that doses of treatments are critical in determining the fate of the tumor, and tumor cells can be eliminated completely if doses of cytokine are large. Bistability is observed in models with either of the treatment strategies, which signifies that a careful planning of the treatment strategy is necessary for achieving a satisfactory outcome. For the sake of simplicity, set $r = 1$ and let $u = x, v = y$ and $w = z$. Then
model (2) is converted into the following form

\begin{align*}
\frac{\partial u}{\partial t} - d_1 \Delta u &= u(1 - u/K) - \frac{\delta uw}{m+u}, & x \in \Omega, t > 0, \\
\frac{\partial v}{\partial t} - d_2 \Delta v &= \frac{\rho v}{\kappa + v} - av + I_1, & x \in \Omega, t > 0, \\
\frac{\partial w}{\partial t} - d_3 \Delta w &= \frac{\alpha vw}{b+u} - \mu w + I_2, & x \in \Omega, t > 0, \\
\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = \frac{\partial w}{\partial \nu} &= 0, & x \in \partial \Omega, t > 0, \\
\end{align*}

(4)

where \( \Omega \) is a bounded domain in \( \mathbb{R}^N \) with a smooth boundary \( \partial \Omega \); \( \Delta = \sum_{i=1}^{N} \frac{\partial^2}{\partial x_i^2} \) is the Laplace operator in \( \mathbb{R}^N \) and \( \nu \) is the unit outer normal vector on \( \partial \Omega \); \( u(x,t), v(x,t) \) and \( w(x,t) \) stand for the densities of the tumor cells, CD4\(^+\) T cells, and the cytokine, respectively, at time \( t \) and location \( x \); the diffusion coefficients \( d_i \) are positive constants, and the nonnegative initial functions \( u_0(x), v_0(x) \) and \( w_0(x) \) are not identically zero in \( \Omega \). Hereinafter, we assume that “\( I_1 > 0, I_2 \geq 0 \)” are constants, and all the other parameters are the same as those in (2). The steady-state system corresponding to (4) is given by

\begin{align*}
-d_1 \Delta u &= u(1 - u/K) - \frac{\delta uw}{m+u}, & x \in \Omega, \\
-d_2 \Delta v &= \frac{\rho v}{\kappa + v} - av + I_1, & x \in \Omega, \\
-d_3 \Delta w &= \frac{\alpha vw}{b+u} - \mu w + I_2, & x \in \Omega, \\
\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = \frac{\partial w}{\partial \nu} &= 0, & x \in \partial \Omega.
\end{align*}

(5)

Model (4) provides a much simplified description of the mentioned biological phenomena. Its theoretical investigation shows which treatment strategy is, in that setting, more effective for controlling the tumor (CD4\(^+\) T cells or cytokine) in terms of a diffusion. 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 system (4), 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 steady-state system (5).
2. Equilibria analysis and the large time behavior. We investigate all nonnegative constant solutions to (4). First, note that (4) (and thus (5)) has the following nonnegative constant solutions, which have at least one component zero:

1) \( E_1 = (0, I_1/a, 0) \), if \( I_1 > 0 \) and \( I_2 = 0 \);
2) \( E_2 = (0, I_1/a, I_2/\mu) \), if \( I_1 > 0 \) and \( I_2 > 0 \).

Moreover, given the complexity of the calculations and conditional statements, we only provide the sufficient conditions that guarantee the existence of a unique positive equilibrium point of (4) with \( I_2 = 0 \), and one can refer to [2] for the details. By Proposition 3.1 in [2], it follows that if \( I_1 > 0 \), \( I_2 = 0 \) and \( b + m \geq k \), then (4) (and thus (5)) has a unique positive constant solution \( E_\ast = (u_\ast, v_\ast, w_\ast) \) with \( u_\ast \leq K \).

Next, we examine the persistence property and the global attractor for solutions to (4). 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 [19, 8, 18]).

**Theorem 2.1.** Denote \( a_c = \frac{\beta K}{k + K} \). Assume that \( a > a_c \). Then the nonnegative solution \((u, v, w)\) of (4) satisfies

\[
\lim_{t \to \infty} \sup_{\Omega} u \leq K, \quad \lim_{t \to \infty} \sup_{\Omega} v \leq \frac{I_1}{a - \frac{\beta K}{k + K}}, \quad \lim_{t \to \infty} \sup_{\Omega} w \leq \frac{1}{\mu} \left( \frac{\alpha I_1}{a - \frac{\beta K}{k + K}} + I_2 \right).
\]  

**Proof.** Assume that \((u, v, w)\) is a nonnegative solution of (4). It follows from the first equation of (4) that \( u(1 - u/K) - \frac{b}{m+u} - u(1 - u/K) \). By the comparison principle for the parabolic problem [17, 14], we obtain that \( \lim_{t \to \infty} \sup_{\Omega} u \leq K \).

Thus, for any positive constant \( \epsilon_1 \), there exists \( t_1 \in (0, \infty) \) such that \( u(x,t) \leq K + \epsilon_1 \) in \([t_1, \infty) \times \Omega\). By this result and the second equation of (4),

\[
\frac{\beta uv}{k + u} - av + I_1 \leq \frac{\beta(K + \epsilon_1)v}{k + (K + \epsilon_1)} - av + I_1 = I_1 - \left[ a - \frac{\beta(K + \epsilon_1)}{k + (K + \epsilon_1)} \right] v
\]

in \([t_1, \infty) \times \Omega\). Since \( a > \frac{\beta K}{k + K} \), for some small \( \epsilon_1 \) above and any positive constant \( \epsilon_2 \), there exists \( t_2 \in (0, \infty) \) such that \( v(x,t) \leq \frac{I_1}{a - \frac{\beta K}{k + K}} + \epsilon_2 \) in \([t_2, \infty) \times \Omega\). Similarly, it is easily obtained that for any constant \( \epsilon_3 \), there exists \( t_3 \in (0, \infty) \) such that

\[
\frac{1}{\mu} \left( \frac{\alpha I_1}{a - \frac{\beta K}{k + K}} + I_2 \right) + \epsilon_3.
\]

Therefore, by the arbitrariness of \( \epsilon_1, \epsilon_2, \) and \( \epsilon_3 \), the desired result is obtained.

**Theorem 2.2.** Assume that \( a > a_c = \frac{\beta K}{k + K} \) and \((\mu m/\delta - I_2)(a - a_c) > \alpha I_1\). Then the nonnegative solution \((u, v, w)\) to (4) satisfies

\[
\lim_{t \to \infty} \inf_{\Omega} u \geq K \left[ 1 - \frac{\delta}{\mu m} \left( \frac{\alpha I_1}{a - \frac{\beta K}{k + K}} + I_2 \right) \right], \quad \lim_{t \to \infty} \inf_{\Omega} v \geq \frac{I_1}{a},
\]

\[
\lim_{t \to \infty} \inf_{\Omega} w \geq \frac{1}{a^2} \left\{ \frac{\alpha I_1}{a - \frac{\beta K}{k + K}} \left[ 1 - \frac{\delta}{\mu m} \left( \frac{\alpha I_1}{a - \frac{\beta K}{k + K}} + I_2 \right) \right] + a I_2 \right\},
\]  

\[
\lim_{t \to \infty} \inf_{\Omega} w \geq \left\{ \frac{\alpha I_1}{a - \frac{\beta K}{k + K}} \left[ 1 - \frac{\delta}{\mu m} \left( \frac{\alpha I_1}{a - \frac{\beta K}{k + K}} + I_2 \right) \right] + a I_2 \right\}.  
\]
Theorem 2.3. Assume that $a > a_c = \frac{\beta K}{k+K}$ and $\delta I_2 > \mu (m + K)$. Then the nonnegative solution $(u, v, w)$ to (4) satisfies

$$\lim_{t \to \infty} u(x, t), \lim_{t \to \infty} v(x, t), \lim_{t \to \infty} w(x, t) = (0, I_1/a, I_2/\mu) \text{ on } \overline{\Omega}. \tag{9}$$

Proof. By Theorem 2.1, for any positive constant $\epsilon_2$, there exists $t_2 \in (0, \infty)$ such that $u(x, t) \geq K \left[ 1 - \frac{\delta \mu}{\alpha} \left( \frac{\alpha I_1}{a - \frac{\beta K}{k+K}} + I_2 \right) \right] - \epsilon_2$. Similarly, there exists $t_3 \in (0, \infty)$ such that $v(x, t) \geq I_1/a - \epsilon_2$ since $\delta u_{K+a} - av + I_1 \geq I_1 - av$. By those results, we have

$$w(x, t) \geq \frac{\alpha w}{b + u} - \mu w + I_2 \geq \frac{\alpha w}{b + K} \left[ 1 - \delta \frac{\mu}{\alpha} \left( \frac{\alpha I_1}{a - \frac{\beta K}{k+K}} + I_2 \right) - \epsilon_1 \right] \cdot \left( I_1/a - \epsilon_1 \right) + I_2 - \mu w.$$

in $[\max \{t_1, t_2\}, \infty) \times \Omega$. Therefore, by the arbitrariness of $\epsilon_1$ and $\epsilon_2$, the desired result is obtained. \hfill \square
with \( a > \frac{\beta \mu}{k + u} \), we have
\[
\frac{\beta u v}{k + u} - av + I_1 \leq \frac{\beta\alpha v}{k + u} - av + I_1 = \left[ a - \frac{\beta\alpha}{k + u} \right] v \quad \text{and}
\]
\[
\frac{\alpha u w}{b + u} - \mu w + I_2 \leq I_2 + \frac{\alpha \eta}{a - \frac{\beta\alpha}{k + u} + e} - \mu w
\]
in \([\max\{t_1, t_3\}, \infty) \times \Omega\), which yield that
\[
\lim_{t \to \infty} \sup_{\Omega} v \leq I_1/a \quad \text{and} \quad \lim_{t \to \infty} \sup_{\Omega} w \leq I_2/\mu.
\]
As stated previously, the desired result is obtained. \( \square \)

**Notation.**
1) \( 0 = \lambda_0 < \lambda_1 < \lambda_2 < \cdots \) are the eigenvalues of the operator \(-\Delta\) in \(\Omega\) under the homogeneous Neumann boundary condition, \(m_i\) is the multiplicity of \(\lambda_i\) for each \(i\);
2) \( S(\lambda_i) \) is the space of eigenfunctions corresponding to \(\lambda_i\) for \(i = 0, 1, 2, \cdots\);
3) \(X_{i,j} := \{ c \cdot \phi_{i,j} : c \in \mathbb{R}^2 \}\), where \(\{\phi_{i,j}\}\) are orthonormal basis of \(S(\lambda_i)\) for \(j = 0, 1, 2, \cdots, m_i\).

We now investigate the local stability of the positive constant solution \(E_*\). From Section 2, it follows that if \( I_1 > 0, I_2 = 0 \) and \( b + m \geq k \), then (4) (and thus (5)) has a unique positive constant solutions \(E^* = (u^*, v^*, w^*)\) with \(u^* \leq K\).

Let \(U = (u, v, w)^T\), \(D = \text{diag}(d_1, d_2)\) and
\[
F(U) = \begin{pmatrix}
    u(1 - u/K) - \frac{\delta uv}{m + u} \\
    \frac{\beta \alpha uv}{k + u} - av + I_1 \\
    \frac{\alpha u w}{b + u} - \mu w
\end{pmatrix}
\]

Note
\[
F_U(E_*) = \begin{pmatrix}
    1 - 2u_* - \frac{\delta m u_*}{(m + u_*)^2} & 0 & -\frac{\delta u_*}{m + u_*} \\
    \frac{\beta \alpha u_*}{k + u_*} & \frac{\beta \alpha u_*}{k + u_*} - a & 0 \\
    \frac{\alpha u_*}{b + u_*} & \frac{\alpha u_*}{b + u_*} - \mu & -\mu
\end{pmatrix}
\]

and set
\[
\begin{cases}
    j_{11} = 1 - 2u_* - \frac{\delta m u_*}{(m + u_*)^2}, & j_{13} = -\frac{\delta u_*}{m + u_*} < 0, \\
    j_{21} = \frac{\beta \alpha u_*}{k + u_*} > 0, & j_{22} = \frac{\beta \alpha u_*}{k + u_*} - a < 0, \\
    j_{31} = \frac{\alpha u_*}{b + u_*} > 0, & j_{32} = \frac{\alpha u_*}{b + u_*} > 0, & j_{33} = -\mu < 0.
\end{cases}
\]

In the fact, by the definition of \(E_*\), we have \((\frac{\beta u_*}{k + u_*} - a)v_* + I_1 = 0\), which yields that \(j_{22} = \frac{\beta u_*}{k + u_*} - a < 0\).

**Theorem 2.4.** Assume that \( I_1 > 0, I_2 = 0 \) and \( b + m \geq k \). If \( j_{11} := 1 - 2u_* - \frac{\delta m u_*}{(m + u_*)^2} < 0 \), then the equilibrium \(E_*\) of (4) is locally asymptotically stable, for the sufficiently large \(d_3\) and \(\mu\).

**Proof.** The linearization of (4) at the constant solution \(E_*\) is expressed by \(D\Delta + F_U(U_*)\). Moreover, from local stability theory, we know that \(\eta\) is an eigenvalue of \(D\Delta + F_U(E_*)\) if and only if \(\eta\) is an eigenvalue of the matrix
\[
L_i = -\lambda_i D + F_U(E_*) = \begin{pmatrix}
    -d_1 \lambda_i + j_{11} & 0 & 0 \\
    j_{21} & -d_2 \lambda_i + j_{22} & j_{13} \\
    j_{31} & j_{32} & -d_3 \lambda_i + j_{33}
\end{pmatrix}
\]
for each $i \geq 0$. Thus, to examine the local stability at $E_*$, it is necessary to investigate the characteristic polynomial

$$
det(\eta I - L_i) = \eta^3 + a_1 \eta^2 + a_2 \eta + a_3,
$$

where

$$
a_1 = (d_1 + d_2 + d_3) \lambda_i - (j_{11} + j_{22} + j_{33}) > 0, \\
a_2 = -[j_{13}j_{31} - (d_2 \lambda_i + j_{22}) - (d_3 \lambda_i + j_{33}) - (d_1 \lambda_i + j_{11}) \\
- (d_1 \lambda_i + j_{11}) - (d_2 \lambda_i + j_{22})] \\
= (d_1 d_2 + d_1 d_3 + d_2 d_3) \lambda_i^2 - [(j_{22} + j_{33}) d_1 - (j_{11} + j_{33}) d_2 + (j_{11} + j_{22}) d_3] \lambda_i \\
+ j_{11} j_{22} + j_{11} j_{33} + j_{22} j_{33} - j_{13} j_{31} > 0, \\
a_3 = -j_{32} j_{21} j_{13} + j_{31} (d_1 \lambda_i + j_{11}) (d_2 \lambda_i + j_{22}) \\
- (d_3 \lambda_i + j_{33}) (d_1 \lambda_i + j_{11}) (d_2 \lambda_i + j_{22}) \\
= d_1 d_3 d_2 \lambda_i^3 - (d_1 d_3 j_{22} + d_2 d_3 j_{11} + d_1 d_2 j_{33}) \lambda_i^2 \\
+ (d_1 j_{12} j_{21} + d_1 j_{13} j_{31} + d_2 j_{21} j_{31} - d_3 j_{21} j_{31} - d_2 j_{11} j_{31}) \lambda_i \\
+j_{11} j_{22} j_{31} - j_{11} j_{22} j_{33} - j_{32} j_{21} j_{13} > 0.
$$

A simple calculation yields $a_1 a_2 - a_3 = b_0 \lambda_i^3 + b_1 \lambda_i^2 + b_2 \lambda_i + b_3$, where

$$
b_0 = (d_2 + d_3)(d_1^2 + d_1 d_2 + d_2 d_3) > 0, \\
b_1 = -(d_1 + d_2 + d_3)(j_{22} + j_{33}) d_1 + (j_{11} + j_{33}) d_2 + (j_{11} + j_{22}) d_3 \\
- (j_{11} + j_{22}) d_1 d_2 - (j_{11} + j_{33}) d_1 d_3 - (j_{22} + j_{33}) d_2 d_3 > 0, \\
b_2 = (j_{11} + j_{22})(j_{11} + j_{33}) d_1 + (j_{11} + j_{33}) d_2 + (j_{11} + j_{22}) d_3 \\
+(d_1 + d_2) j_{11} j_{22} + (d_1 + d_3) j_{11} j_{33} + (d_2 + d_3) j_{22} j_{33} \\
+(d_1 j_{12} j_{21} - d_1 d_2 + d_2 d_3) j_{31}, \\
b_3 = -(j_{22} + j_{33}) j_{11} j_{22} + (j_{11} + j_{33}) j_{22} j_{33} + (j_{11} + j_{22}) j_{33} \\
+ (j_{11} + j_{22} + j_{33}) j_{11} j_{31} - j_{11} j_{22} j_{31} + j_{32} j_{21} j_{13}.
$$

For the sufficiently large $d_3$ and $\mu$, $(d_1 j_{22} + d_2 j_{11}) - (d_1 + d_2 + d_3) j_{13} > 0$ and $(j_{11} + j_{22} + j_{33}) j_{13} - j_{11} j_{22} > 0$. This yields that $b_2 > 0$ and $b_3 > 0$. Thus, $a_1 a_2 - a_3 > 0$ for each $i \geq 0$, and so we conclude from the Routh-Hurwitz criterion for each $i \geq 0$ that the three roots of $det(\eta I + \lambda_i D - F_i(E_*)) = 0$ have negative real parts.

Next we investigate the global stability of the positive equilibrium point $E_*$ by introducing the following Lyapunov function:

$$
E(t) = \int_\Omega \left( (u - u_* - u_0 \ln \frac{u}{u_*} ) + \frac{1}{2} (v - v_*)^2 + \frac{1}{2} (w - w_*)^2 \right) dx
$$

for the solution $(u, v, w)$ to (4). Note that $E(t) \geq 0$ for all $t \geq 0$, and thus, if $E_i(t) \leq 0$ can be derived, then we obtain the desired result from the well-known Lyapunov stability.

**Theorem 2.5.** Assume that $a > a_0 = \frac{\beta K}{\pi + \beta}$. Then the positive constant solution $E_*$ to (4) is globally asymptotically stable if

$$
\frac{1}{\mu} \geq \frac{\beta}{\pi + \beta} - \frac{\delta}{2\pi} + \left( \frac{\beta}{\pi + \beta} + \frac{\alpha}{2} \right) \frac{L_1}{\pi + \beta}, \\
a \geq \beta + \frac{\delta}{\alpha - \frac{\beta}{\pi + \beta}} + \alpha/2, \\
\mu \geq \frac{\delta}{2\pi} + \frac{\alpha/2 + \frac{L_1}{\pi + \beta}}{\alpha - \frac{\beta}{\pi + \beta}}.
$$
Proof. Using (4) and integrating by parts, we obtain
\[
\frac{dE(t)}{dt} = \int_\Omega \left[ (1 - \frac{u_*}{u}) u + (v - v_*) v + (w - w_*) w \right] dx
\]
\[
= - \int_\Omega \left[ d_1 \frac{u_* |\nabla u|^2}{u^2} + d_2 |\nabla v|^2 + d_3 |\nabla w|^2 \right] dx + \tilde{E}(t),
\]
where
\[
\tilde{E}(t) = \int_\Omega \left[ (u - u_*) \left( 1 - \frac{u}{K} - \frac{\delta w}{m + u} \right) + (v - v_*) \left( \frac{\beta uv}{k + u} - av + I_1 \right) + (w - w_*) \left( \frac{\alpha w}{b + u} - \mu w \right) \right] dx.
\]
From the definition of \( E_* \), it is easy to see that \( v_* \leq \frac{I_1}{\alpha - \frac{\beta K}{k+K}} \) and \( \frac{\delta w_*}{m + u_*} < 1 \). Using these inequalities, we derive
\[
\tilde{E}(t) \leq \int_\Omega \left[ (u - u_*)^2 \left( - \frac{1}{K} + \frac{\delta w_*}{m + u_*/(m + u_*)} \right) - (u - u_*)(w - w_*) \frac{\delta}{m + u}
\]
\[
+ (v - v_*)^2 (\beta - a) + (v - v_*)(u - u_*) \frac{k\beta v_*}{(k + u_*)(k + u)}
\]
\[
- \mu(w - w_*)^2 + (w - w_*)(v - v_*) \frac{\alpha u}{b + u}
\]
\[
+ (w - w_*)(u - u_*) \frac{\alpha b v_*}{(b + u)(b + u_*)} \right] dx.
\]
It follows from assumption (11) that \( \tilde{E}(t) \leq 0 \). Thus \( \frac{dE(t)}{dt} \leq 0 \) implies the desired assertion. \( \square \)
3. Existence and nonexistence of nonconstant positive steady states. In this section, we will present the conditions for the existence and nonexistence of nonconstant positive steady-state solutions to the time-independent system (5) (for example, see [20, 21]). To do this, we first obtain the a priori bound for positive solutions to (5). The following two lemmas can be found in [11, 12].

**Lemma 3.1.** (Maximum principle) Suppose that $g(x, \varphi) \in C(\Omega \times R)$. If $\varphi \in C^2(\Omega) \times C^1(\Omega)$ satisfies
\[
\Delta \varphi(x) + g(x, \varphi(x)) \geq 0 \text{ in } \Omega, \quad \frac{\partial \varphi}{\partial n} \leq 0 \text{ on } \partial \Omega
\]  
and $\varphi(x_0) = \max_{\Omega} \varphi$, then $g(x_0, \varphi(x_0)) \geq 0$. Similarly, if the two inequalities in (12) are reversed and $\varphi(y_0) = \min_{\Omega} \varphi$, then $g(y_0, \varphi(y_0)) \leq 0$.

**Lemma 3.2.** (Harnack inequality) Let $\varphi \in C^2(\Omega) \times C^1(\Omega)$ be a positive solution to $\Delta \varphi + c(x) \varphi = 0$ in $\Omega$ subject to homogeneous Neumann boundary condition with $c(x) \in C(\Omega)$. Then there exists a positive constant $\bar{C} = \bar{C}(||c||_{\infty})$ such that
\[
\max_{\Omega} \varphi \leq \bar{C} \min_{\Omega} \varphi.
\]

**Theorem 3.3.** Assume that $a > a_c = \frac{\beta K}{k+K}$. Then all positive solutions $(u, v, w)$ to (5) satisfy
\[
\max_{\Omega} u \leq K, \quad \max_{\Omega} v \leq \frac{I_1}{a - \frac{\beta K}{k+K}}, \quad \max_{\Omega} w \leq \frac{1}{\mu} \left( \frac{\alpha I_1}{a - \frac{\beta K}{k+K}} + I_2 \right).
\]  

Proof. Let $x_0, y_0, z_0 \in \Omega$ and $u(x_0) = \max_{\Omega} u, v(y_0) = \max_{\Omega} v, w(z_0) = \max_{\Omega} w$. Then we have
\[
\frac{u(x_0) (1 - u(x_0)/K)}{m + u(x_0)} \geq 0 \Rightarrow 1 - u(x_0)/K \geq 0,
\]
\[
\frac{2u(y_0) - \alpha v(y_0) + I_1}{K + u(y_0)} \geq 0 \Rightarrow \frac{2u(y_0) - \alpha v(y_0) + I_1}{K + u(y_0)} \geq 0,
\]
\[
\frac{\beta u(z_0) - \mu w(z_0) + I_2}{K + u(z_0)} \geq 0 \Rightarrow \frac{\beta u(z_0) - \mu w(z_0) + I_2}{K + u(z_0)} \geq 0.
\]
By Lemma 3.1 and the above three inequalities, the desired result is obtained. 

**Remark 1.** Let $C^* = C^*(\Lambda) = \max \left\{ K, \frac{J_1}{a - \frac{\beta K}{k+K}}, \frac{1}{\mu} \left( \frac{\alpha I_1}{a - \frac{\beta K}{k+K}} + I_2 \right) \right\}$, where $\Lambda$ is the set of constants, $K, \beta, k, \alpha, I_1, \alpha$ and $\mu$. If $a > a_c = \frac{\beta K}{k+K}$, then all positive solutions $(u, v, w)$ to (5) satisfy $u, v, w \leq C^*$ by Theorem 3.3.

**Theorem 3.4.** Let $D$ be a fixed positive number. Assume that $a > a_c = \frac{\beta K}{k+K}$ and that one of the following cases holds:
1. $I_2 = 0$;
2. $m\mu/\delta > I_2 > 0$.

Then there exists a positive constant $C_*$ such that, when $d_1, d_2, d_3 > D$, all positive solutions $(u, v, w)$ to (5) satisfy $u, v, w \geq C_*$.

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 $d_{1,n}, d_{2,n}, d_{3,n} \geq d_1$ and a corresponding positive solution $(u_n, v_n, w_n)$ to (5) such that
\[
\min_{\Omega} u_n \rightarrow 0, \quad \text{or} \quad \min_{\Omega} v_n \rightarrow 0, \quad \text{or} \quad \min_{\Omega} w_n \rightarrow 0,
\]
and \((u_n, v_n, w_n)\) satisfy

\[
\begin{aligned}
-d_{1,n} \Delta u_n &= u_n (1 - u_n/K) - \frac{\delta u_n w_n}{m + u_n}, & x \in \Omega, \\
-d_{2,n} \Delta v_n &= \frac{\delta u_n v_n}{k + u_n} - av_n + I_1, & x \in \Omega, \\
-d_{3,n} \Delta v_n &= \frac{\alpha u_n w_n}{b + u_n} - \mu v_n + I_2, & x \in \Omega,
\end{aligned}
\]  

(14)

By integrating the first equation in (14) over \(\Omega\) by parts, we have

\[
\int_{\Omega} u_n \left( 1 - u_n/K - \frac{\delta w_n}{m + u_n} \right) \, dx = 0.
\]  

(15)

Note that \(\| \frac{1}{d_{1,n}} (1 - u_n/K - \frac{\delta w_n}{m + u_n}) \|_{\infty} < \infty\) can be derived from Theorem 3.3, and thus, by Lemma 3.2, there exists a positive constant \(C_*\) such that

\[
\max_{\overline{\Omega}} u_n \leq C_* \min_{\overline{\Omega}} u_n.
\]  

(16)

1) Note that \(I_1 > 0\). By applying Lemma 3.1 to the second equation in (14), we have \(\min_{\overline{\Omega}} v_n \geq I_1/a\) for any \(n\), and thus \(\min_{\overline{\Omega}} v_n \neq 0\) as \(n \to \infty\).

Assume that \(\min_{\overline{\Omega}} u_n \to 0\) as \(n \to \infty\). Then \(\max_{\overline{\Omega}} u_n \to 0\) as \(n \to \infty\) by (16).

By applying Lemma 3.1 to the third equation in (14), we obtain that \(\min_{\overline{\Omega}} w_n \to 0\) since

\[
\mu \max_{\overline{\Omega}} w_n \leq \frac{\alpha \max_{\overline{\Omega}} u_n}{b + \max_{\overline{\Omega}} u_n} \cdot v_n \leq \frac{\alpha \max_{\overline{\Omega}} u_n}{b + \max_{\overline{\Omega}} u_n} \cdot \frac{I_1}{a - \frac{\delta m}{\mu}} \to 0 \text{ as } n \to \infty.
\]

However, because

\[
1 - u_n/K - \frac{\delta w_n}{m + u_n} \to 1 \text{ as } n \to \infty,
\]

(15) does not hold.

Assume that \(\min_{\overline{\Omega}} w_n \to 0\) as \(n \to \infty\). Lemma 3.1 yields

\[
\frac{\alpha \min_{\overline{\Omega}} u_n \cdot \min_{\overline{\Omega}} v_n}{b + \min_{\overline{\Omega}} u_n} \leq \mu \min_{\overline{\Omega}} w_n \to 0 \text{ as } n \to \infty,
\]

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

2) Since \(I_1 > 0\) and \(I_2 > 0\), it is easy to see that \(\min_{\overline{\Omega}} v_n \geq I_1/a\) and

\[
\min_{\overline{\Omega}} w_n \geq I_2/\mu
\]  

(17)

for any \(n\). Now we assume that \(\min_{\overline{\Omega}} u_n \to 0\) as \(n \to \infty\). Then \(\max_{\overline{\Omega}} u_n \to 0\) as \(n \to \infty\) by (16) and that there exists \(n_1\) such that \(\max_{\overline{\Omega}} u_n \leq \epsilon\) for any positive constant \(\epsilon\) and \(n > n_1\). Applying this result and Lemma 3.1 to the third equation in (14), we have that

\[
\mu \max_{\overline{\Omega}} w_n \leq \frac{\alpha \max_{\overline{\Omega}} u_n}{b + \max_{\overline{\Omega}} u_n} \cdot \max_{\overline{\Omega}} v_n + I_2 \leq I_2 + \epsilon_1
\]  

(18)

for a small positive constant \(\epsilon_1 > 0\). Synthetically, from (17) and (18), we have

\[
w_n \to I_2/\mu.\]

Then by the assumption \(m\mu/\delta > I_2\),

\[
1 - u_n/K - \frac{\delta w_n}{m + u_n} \to 1 - \frac{\delta I_2}{m\mu} > 0 \text{ as } n \to \infty,
\]

Hence, this result implies that (15) does not hold for large \(n\), which is a contradiction. \(\square\)
3.1. Nonexistence of nonconstant positive steady states. Now we show the nonexistence of nonconstant positive solutions of (5) by the effect of large diffusivity.

**Theorem 3.5.** Assume that \( a > a_c = \frac{\beta K}{K + K} \).

1) There exists a positive constant \( \tilde{d}_1 = \tilde{d}_1(\Lambda, \Omega) \) such that (5) has no positive nonconstant solution if \( d_2 \lambda_1 > \alpha/2 + \beta, \) \( d_3 \lambda_1 > \alpha/2 - \mu \) and \( d_1 > \tilde{d}_1 \);

2) There exists a positive constant \( \tilde{d}_2 = \tilde{d}_2(\Lambda, \Omega) \) such that (5) has no positive nonconstant solution if \( d_1 \lambda_1 > 1 + \delta C^*/m + \frac{\delta}{2} + \frac{\alpha C^*}{2b} \), \( d_3 \lambda_1 > \frac{\delta}{2} - \mu + \frac{\alpha C^*}{2b} \) and \( d_2 > \tilde{d}_2 \);

3) There exists a positive constant \( \tilde{d}_3 = \tilde{d}_3(\Lambda, \Omega) \) such that (5) has no positive nonconstant solution if \( d_1 \lambda_1 > 1 + \delta C^*/m + \frac{\beta C^*}{2k} \), \( d_2 \lambda_1 > \beta + \frac{\alpha C^*}{2b} \) and \( d_3 > \tilde{d}_3 \).

**Proof.** We now prove only the case 1). Let \( \varphi = \frac{1}{\| \varphi \|} \int_\Omega \varphi(x) dx \) for \( \varphi \in L^1(\Omega) \). Multiplying \((u - \overline{u}), (v - \overline{v})\) and \((w - \overline{w})\) to the first, second and third equation in (5), respectively, and then integrating over \( \Omega \), we have

\[
\int_\Omega (d_1 |\nabla u|^2 + d_2 |\nabla v|^2 + d_3 |\nabla w|^2) dx
= \int_\Omega \{ (u - \overline{u})^2 \left[ 1 - (u - u/K) - \frac{\delta w}{m+u} - \overline{w}(1 - \overline{u}/K) + \frac{\delta \overline{w}}{m+\overline{u}} \right] + (v - \overline{v}) (v - \overline{v}) \beta - (w - \overline{w})(w - \overline{w}) \mu \} dx,
\]

By Remark 1 and (19), we have that

\[
\int_\Omega (d_1 |\nabla u|^2 + d_2 |\nabla v|^2 + d_3 |\nabla w|^2) dx
\leq \int_\Omega (u - \overline{u})^2 \left( 1 + \delta C^*/m + \frac{\delta w}{m+u} - \overline{w} \right) dx
+ \beta (v - \overline{v})^2 + (w - \overline{w})^2 \mu
+ \alpha |w - \overline{w}| |v - \overline{v}| + \alpha |w - \overline{w}| |u - \overline{u}| \frac{\alpha C^*}{b} dx,
\]

where \( \epsilon \) is an arbitrary positive constant.

By the well-known Poincaré inequality, we see that

\[
\int_\Omega (d_1 |\nabla u|^2 + d_2 |\nabla v|^2 + d_3 |\nabla w|^2) dx
\geq \int_\Omega d_1 \lambda_1 (u - \overline{u})^2 + d_2 \lambda_2 (v - \overline{v})^2 + d_3 \lambda_3 (w - \overline{w})^2 dx.
\]

One can choose sufficiently small \( \epsilon_0 \) such that

\[
d_2 \lambda_1 > \beta + \frac{\alpha C^*}{2k} + \frac{\alpha}{2} \quad \text{and} \quad d_3 \lambda_1 > \frac{\delta}{2} - \mu + \frac{\alpha C^*}{2b} \epsilon_0
\]

are satisfied from the given assumptions. By taking

\[
\tilde{d}_1 = \frac{1}{\lambda_1} \left( 1 + \delta C^*/m + \frac{\delta}{2\epsilon_0} + \frac{\beta C^*}{2k \epsilon_0} + \frac{\alpha C^*}{2b \epsilon_0} \right),
\]

\[
\tilde{d}_2 = \frac{1}{\lambda_2} \left( 1 + \delta C^*/m + \frac{\delta}{2\epsilon_0} + \frac{\beta C^*}{2k \epsilon_0} + \frac{\alpha C^*}{2b \epsilon_0} \right),
\]

\[
\tilde{d}_3 = \frac{1}{\lambda_3} \left( 1 + \delta C^*/m + \frac{\delta}{2\epsilon_0} + \frac{\beta C^*}{2k \epsilon_0} + \frac{\alpha C^*}{2b \epsilon_0} \right),
\]

we get the desired results.
we conclude that \( u = \overline{u}, v = \overline{v} \) and \( w = \overline{w} \), which completes the proof. \( \square \)

3.2. Existence of nonconstant positive steady states. In this subsection, we always require that \( I_1 > 0, I_2 = 0 \) and \( b + m \geq k \) in (5), and consider the existence of nonconstant positive solution of system (5) by the Leray-Schauder degree theory [1, 22], i.e.,

\[
\begin{align*}
- \frac{d_1\Delta u}{\kappa + u} &= u(1 - u/K) - \frac{\delta_{uw}w}{m + u}, \quad x \in \Omega, \\
- \frac{d_2\Delta v}{b + v} &= \frac{\beta_{uv}}{\kappa + v} - av + I_1, \quad x \in \Omega, \\
- \frac{d_3\Delta v}{b + v} &= \mu w, \quad x \in \Omega, \\
\partial_u = \frac{\partial v}{\partial v} = \frac{\partial w}{\partial v} &= 0, \quad x \in \partial \Omega.
\end{align*}
\]

(21)

Denote

\[
X := \{ U = (u, v, w) \in [C^2(\Omega)]^3 : \frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = \frac{\partial w}{\partial \nu} = 0, x \in \partial \Omega \},
\]

\[
X^+ := \{ U = (u, v, w) \in X : C_* / 2 < U < 2C^* \},
\]

where \( \beta_0 \) and \( C_* \) are defined respectively in Remark 1 and Theorem 3.4. Let \( U = (u, v, w) \in X^+ \) and

\[
G(U) = \begin{pmatrix}
(I - d_1\Delta)^{-1}[u(1 - u/K) - \frac{\delta_{uw}w}{m + u}]
\end{pmatrix}.
\]

(22)

where \( (I - d_1\Delta)^{-1} \) is the inverse of \( I - d_1\Delta \) with the homogeneous Neumann boundary conditions. Then (21) can be written as

\[
\begin{align*}
(I - G)U &= 0, \quad x \in \Omega, \\
\frac{\partial u}{\partial \nu} &= 0, \quad x \in \partial \Omega.
\end{align*}
\]

Then \( U \) solves (21) if and only if it satisfies (22).

Now we state some results about Leray-Schauder degree, which appeared in [1]. Note that \( I - G \) is a compact perturbation of the identity operator, the Leray-Schauder degree \( \deg(I - G, X^+, 0) \) is well defined. We know that the index of \( I - G \) at \( E_0 \) can be deduced by computing the multiplicity of all negative eigenvalues of its differential operator \( I - G_{U}(E_\beta) \). To apply index theory, we investigate the eigenvalue of the problem:

\[
- (I - G_{U}(E_\beta))U = \mu U, \quad U \neq 0.
\]

(23)

That is, if \( I - G_{U}(E_\beta) \) is invertible, then

\[
\text{index}(I - G, E_\beta) = (-1)^{\beta},
\]

where \( \beta = \sum m(\eta) \), and \( m(\eta) \) is the multiplicity of any positive eigenvalue \( \eta \) of (23).

After some calculations, we can rewrite (23) as

\[
\begin{align*}
- (1 + \eta)d_1\Delta u + (1 + \eta - j_{11})u - j_{13}w &= 0, \quad x \in \Omega, \\
- (1 + \eta)d_2\Delta v - j_{21}u + (1 + \eta - j_{22})v &= 0, \quad x \in \Omega, \\
- (1 + \eta)d_3\Delta w - j_{31}u - j_{32}v + (1 + \eta - j_{33})w &= 0, \quad x \in \Omega, \\
\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = \frac{\partial w}{\partial \nu} &= 0, \quad x \in \partial \Omega,
\end{align*}
\]

(24)

where \( j_{ik} \) are defined in (10). Observe that (24) has a non-trivial solution if and only if \( Q_i \) for some \( \eta \geq 0 \) and \( i \geq 0 \), where

\[
Q_i(\eta, d_1, d_2, d_3) :=
\]

\[
det\begin{pmatrix}
(1 + \eta)(d_1\lambda_1 + 1) - j_{11} & 0 & -j_{13} \\
-j_{21} & (1 + \eta)(d_2\lambda_1 + 1) - j_{22} & 0 \\
-j_{31} & -j_{32} & (1 + \eta)(d_3\lambda_1 + 1) - j_{33}
\end{pmatrix}.
\]
That is, $\eta$ is an eigenvalue of (23) (and thus (24)) if and only if $\eta$ is a positive root of the characteristic equation $Q_i$ for $i \geq 0$. Therefore, if $Q_i(\eta, d_1, d_2, d_3) = 0$ for all $i \geq 0$, we can see that $\text{index}(I - G, E_*) = (-1)^i$, $\gamma = \sum_{i = 0}^{\infty} \Omega_{i+1} > 0\eta_m i_m$ where $m_i$ has been defined in Notation 2, and $\eta_m$ is the multiplicity of as a positive root of $Q_i := Q_i(\eta, d_1, d_2, d_3) = 0$, where

$$Q_i = [(1 + \eta) - \frac{j_{11}}{d_1\lambda_i + 1}] \times [(1 + \eta) - \frac{j_{22}}{d_2\lambda_i + 1}] \times [(1 + \eta) - \frac{j_{33}}{d_3\lambda_i + 1}] - \frac{j_{13}}{d_1\lambda_i + 1} \frac{j_{23}}{d_2\lambda_i + 1} \frac{j_{33}}{d_3\lambda_i + 1} [(1 + \eta) - \frac{j_{22}}{d_2\lambda_i + 1}]$$

Assume that

$$1 + d_1 \lambda_i < j_{11} < \min\{3, 1 - j_{22}, \frac{j_{13} j_{31}}{j_{33} - 1}\}.$$

(25)

**Theorem 3.6.** Assume that $I_1 > 0$, $I_2 = 0$, $b + m \geq k$, and (25) holds. If $\sum_{i=1}^{n} m_i$ is odd, then there exists a positive constant $\tilde{d}_3$ such that, if $d_3 > \tilde{d}_3$, (5) has at least one nonconstant positive solution.

**Proof.** First, we give some basic facts about the existence of positive root to $Q_i$ as follows.

**Case 1.** When $i = 0$, by (25) and some simple calculations,

$$Q_0 = [\eta + 1 - j_{11}] \times [\eta + 1 - j_{22}] \times [\eta + 1 - j_{33}] - j_{13} j_{23} j_{33} \eta + j_{11} j_{22} + j_{11} j_{33} + j_{22} j_{33} - j_{11} j_{22} j_{33} > 0$$

for any $\eta \geq 0$.

**Case 2.** When $i \geq 1$ and $d_1 \to \infty$, we have

$$Q_i = (1 + \eta) [(1 + \eta) - \frac{j_{22}}{d_2\lambda_i + 1}] \times [(1 + \eta) - \frac{j_{33}}{d_3\lambda_i + 1}] + O(1/d_1).$$

Thus, it is easy to see that $Q_i = 0$ has no positive root for $i \geq 1$, since $j_{22}, j_{33} < 0$.

**Case 3.** When $i \geq 1$ and $d_3 \to \infty$, we have

$$Q_i = (1 + \eta) [(1 + \eta) - \frac{j_{11}}{d_1\lambda_i + 1}] \times [(1 + \eta) - \frac{j_{22}}{d_2\lambda_i + 1}] + O(1/d_3).$$

By (25), there exists $i_*$ such that $j_{11} > 1 + d_1 \lambda_i$ for $1 \leq i \leq i_*$ and $j_{11} < 1 + d_1 \lambda_i$ for $i > i_*$. Here it is easy to see that $Q_i = 0$ may have only one positive simple root for $1 \leq i \leq i_*$ or no positive root for $i > i_*$.

Now, we prove the existence of nonconstant positive solution to (21). On the contrary, suppose that our assertion does not hold for all $d_3 > \tilde{d}_3$. For $t \in [0,1]$, define the homotopy

$$G_t(U) = \begin{cases} (I - [D + t(d_1 - D)]^\Delta)^{-1}[u(1 - u/K) - \frac{\delta u w}{\delta u + w} + u] \\ (I - d_2\Delta)^{-1}[\frac{\beta u v}{\beta u + v} - av + I_1 + v] \\ (I - [D + t(d_1 - D)]^\Delta)^{-1}[\frac{\gamma u v}{\gamma u + w} - \mu w + w] \end{cases}.$$

for sufficiently large $D$. We know that all positive solutions to the problem

$$\begin{cases} (I - G_t)U = 0, & x \in \Omega \\ \frac{\partial U}{\partial v} = 0, & x \in \partial \Omega \end{cases}$$

are contained in $X^+$. Then it is clear that $G_1 = G$ and that (26) has a unique positive constant solution $E_*$ for any $t \in [0,1]$. Moreover, $(I - G_t)U \neq 0$ for all $U \in \partial X^+$ and $(I - G_t)U : X^+ \times [0,1] \to [C^1(\Omega)]^5$ is compact, and thus,
$\text{deg}(I - G_t, X^+, 0)$ is well defined. Note that by the homotopy invariance of the topological degree,

$$\text{deg}(I - G_0, X^+, 0) = \text{deg}(I - G_1, X^+, 0).$$

(27)

Since we assume that there is no nonconstant positive solution to (5), the equation $(I - G_1)U = 0$ has only a positive constant solution $E_*$ in $X^+$.

By the discussion of Case 1 and 3, we obtain

$$l_{in} = \begin{cases} 
0, & \text{if } i = 0, \\
1, & \text{if } 1 \leq i \leq i^*, \\
0, & \text{if } i > i^*.
\end{cases}$$

Thus

$$\gamma = 0 + \sum_{i=1}^{i^*} m_i + 0 = \text{an odd number},$$

such that

$$\text{deg}(I - G_1, X^+, 0) = \text{index}(G_1, E_*) = -1.$$  

(28)

By the discussion of Case 1 and 2, similarly we have $\gamma = 0$, such that

$$\text{deg}(I - G_0, X^+, 0) = \text{index}(G_0, E_*) = 1.$$  

(29)

However, (28) contradict (29). This yields the proof.

4. **Concluding remarks.** First, we summarize the results. We investigate a diffusive tumor-CD4$^+$-cytokine interactions model with immunotherapy under the homogeneous Neumann boundary condition. For the time-dependent system (4): conditions are given for the persistence of the system by the comparison principle for the parabolic problem; the local and global asymptotic stability of the tumor-free state and unique positive equilibrium are discussed by the linearization method and Lyapunov theory. For the steady-state system (5): respectively by the method of energy integral and the Leray-Schauder degree, the nonexistence and existence of the nonconstant positive solutions investigated in great detail.

Biologically, by controlling the deposition rate in PDE system (4), the treatment strategy (which is better or effective in controlling the tumor? CD4$^+$ T cells or cytokine?) is somewhat different with ODE system (2), which are as follows:

1. Theorem 2.1 gives the boundedness of system (4), which yields that the tumor cells cannot grow without limit.
2. Theorem 2.2 gives the persistence of system (4), which yields that the tumor cells cannot be eliminated completely if doses of CD4$^+$ T cells or cytokine are small.
3. Theorem 2.3 implies that the tumor cells can be eliminated completely if doses of cytokine are large.
4. Theorem 2.4 and 2.5 gives the local and global asymptotic stability of $E_*$, the unique positive constant solution to system (4) only by the treatments of CD4$^+$ T cells. This implies that the tumor cells out only cannot be eliminated completely, but also goes to an equilibrium state, if doses of CD4$^+$ T cells are small.
5. Theorem 3.5 and 3.6 give the non-existence and existence of non-constant positive solution to system (5), only by the treatments of CD4$^+$ T cells, which signifies that a careful planning of the treatment strategy is necessary for achieving a satisfactory outcome.
Note that for the existence of positive equilibrium point of (3) (and then (4) and (5)), we only need to solve the following equations
\[
\begin{align*}
\frac{\partial u}{\partial t} - u(1 - \frac{u}{K}) - \frac{\delta uw}{m+u} &= 0, \\
\frac{\partial v}{\partial t} - av + I_1 &= 0, \\
\frac{\partial w}{\partial t} - \mu w + I_2 &= 0.
\end{align*}
\]
(30)
If \( I_1 > 0 \) and \( I_2 > 0 \), then we can not give the concrete parameter conditional expressions to guarantee the existence of positive root of (30), in virtue of the complexity of the calculations. So, we assume \( I_2 = 0 \), i.e., to kill the tumor cells, we only choose the treatment by cytokines, which could suppress tumor growth.

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REFERENCES

[1] H. Amann, Fixed point equations and nonlinear eigenvalue problems in ordered banach spaces, SIAM Rev., 18 (1976), 620–709.

[2] L. Anderson, S. Jang and J. L. Yu, Qualitative behavior of systems of tumor-CD4+-cytokine interactions with treatments, Math. Methods Appl. Sci., 38 (2015), 4330–4344.

[3] F. Ansarizadeh, M. Singh and D. Richards, Modelling of tumor cells regression in response to chemotherapeutic treatment, Appl. Math. Modelling, 48 (2017), 96–112.

[4] M. A. Brown and J. Hural, Functions of IL-4 and control of its expression, Critical Reviews in Immunology, 17 (1997), 1–32.

[5] F. Dai and B. Liu, Optimal control problem for a general reaction-diffusion tumor-immune system with chemotherapy, J. Franklin Inst., 358 (2021), 448–473.

[6] A. D’Onofrio, Metamodelling tumor-immune system interaction, tumor evasion and immunotherapy, Math. Comput. Modelling, 47 (2008), 614–637.

[7] A. D’Onofrio, A general framework for modeling tumor-immune system competition and immunotherapy: Mathematical analysis and biomedical inferences, Physica D: Nonlinear Phenomena, 208 (2005), 220–235.

[8] A. Ducrot and J. Guo, Asymptotic behavior of solutions to a class of diffusive predator-prey systems, J. Evol. Equ., 18 (2018), 755–775.

[9] S. Habib, M. P. Carmen and S. D. Thomas, Complex dynamics of tumors: Modeling an emerging brain tumor system with coupled reaction-diffusion equations, Physica A: Statistical Mechanics and its Applications, 327 (2003), 501–524.

[10] L. E. Harrington, R. D. Hatton, P. R. Mangan, H. Turner, T. L. Murphy, K. M. Murphy and C. T. Weaver, Interleukin 17-producing cd4+ effector t cells develop via a lineage distinct from the t helper type 1 and 2 lineages, Nature Immunology, 6 (2005), 1123–1132.

[11] C. Lin, W. Ni and I. Takagi, Large amplitude stationary solutions to a chemotaxis system, J. Differ. Equations, 72 (1988), 1–27.

[12] Y. Lou and W.-M. Ni, Diffusion, self-diffusion and cross-diffusion, J. Differ. Equations, 131 (1996), 79–131.

[13] J. Manimaran and L. Shangerganesh, Solvability and numerical simulations for tumor invasion model with nonlinear diffusion, Computational and Mathematical Methods, 2 (2020), e1068, 20pp.

[14] C.-V. Pao, Nonlinear Parabolic and Elliptic Equations, Plenum Press, New York, 1992.

[15] W.-E. Paul, Fundamental Immunology, 6nd edition, Lippincott Williams & Wilkins, Philadelphia, 2008.

[16] W. Raymond and M.-D. Ruddon, Cancer Biology, 4nd edition, Oxford University Press, Oxford, 2007.

[17] J. Smoller, Shock Waves and Reaction-Diffusion Equations, 2nd edition, Springer-Verlag, New York, 1994.

[18] J. P. Tripathi, S. Abbas and M. Thakur, Dynamical analysis of a prey-predator model with Beddington-Deangelis type function response incorporating a prey refuge, Nonlinear Dyn., 80 (2015), 177–196.
[19] W. Yang, Existence and asymptotic behavior of solutions for a mathematical ecology model with herd behavior, *Math. Methods Appl. Sci.*, **43** (2020), 5629–5644.

[20] L. Yang and S. Zhong, Dynamics of a diffusive predator-prey model with modified Leslie-Gower schemes and additive allee effect, *Comput. Appl. Math.*, **34** (2015), 671–690.

[21] R. Zeng, Qualitative analysis of a strongly coupled predator-prey system with modified Holling-Tanner functional response, *Bound. Value Probl.*, **2018** (2018), Paper No. 98, 21 pp.

[22] E. Zeidler, *Nonlinear Functional Analysis and Its Applications I: Fixed-Point Theorems*, Springer-Verlag, New York, 1986.

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