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Existence and Uniqueness of a Chemotaxis System Influenced by Cancer Cells

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Abstract We present a mathematical analysis of a reaction-diffusion model in a bounded open domain $\Omega \subset R^2$, which describes vascular endothelial growth factor(VEGF), endothelial cells and oxygen. We use the parabolic theory to prove the existence of the solution in the function space $W_4^{2,1}(Q)$ under the homogeneous Neumann conditions. Then we get the existence of nonnegative solution in $C^{2+\alpha,\ 1+\alpha/2}\left(\bar{Q}\right)$ by using the global Schauder estimation.

Keywords: *existence and uniqueness, parabolic system, chemotaxis system influenced by cancer*

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1. Introduction

Angiogenesis is a physiological process, which involves the formation of new capillary network germinated from the existing vascular network, and plays an important role in embryo development, wound healing and tumor growth. For example, it has been recognized that the growth of capillaries through blood vessels leads to the vascularization of tumors, which provides the tumor with its own dedicated blood supply, thus allowing rapid growth and metastasis of tumors. In the past decade, a lot of work has been done on the mathematical model of tumor growth; for example, see [1,2,3,4,5,6,7] and the references therein. In particular, the role of angiogenesis in tumor growth has also attracted wide attention, see [8,9,10,11,12] and the cited literature.

This paper is concerned with the chemotaxis system which has been proposed in [13] as a modification of the angiogenesis model, in order to describe how cancer cells affect vascular endothelial growth factor (VEGF), endothelial cells and oxygen in angiogenesis. Let $\Omega \subset R^2$, be an open and bounded domain, and denote $Q = \Omega \times (0, T)$ and $\Gamma = \partial\Omega \times (0, T)$. In this paper, we study the following chemotaxis system

$$\begin{cases} \partial V/\partial t = \Delta V + \lambda_1 C - \mu_1 V, & \text{in } Q, \\ \partial E/\partial t = \Delta E + \lambda_2 V - \nabla \cdot (E \nabla V) - \mu_2 E, & \text{in } Q, \\ \partial W/\partial t = \Delta W + \lambda_3 E - \mu_3 W, & \text{in } Q, \\ \partial V/\partial \eta = \dfrac{\partial E}{\partial \eta} = \dfrac{\partial W}{\partial \eta} = 0, & \text{on } \Gamma, \\ V(\cdot,0) = V_0(\cdot), E(\cdot\ 0) = E_0(\cdot), W(\cdot\ 0) = W_0(\cdot), \text{ in } \Omega, & \end{cases} \quad (1.1)$$

where $\partial/\partial\eta$ is the derivative in the outward normal direction on Γ, and η is the unit outer normal vector field on Γ, C is the cancer cell density, V is VEGF density, E is the number of endothelial cells, and W is oxygen, λ_i, μ_i $(i = 1, 2, 3)$ are positive constants denoting the growth rate and the death rate, respectively.

In the mathematical modeling of self-organization of living cells, the Keller-Segel system of partial differential equations, has played an increasingly important role in the last decades. It is used to describe the overall behavior of a collection of cells under the influence of chemotaxis. Under such circumstances, the movement of each individual cell, though still not precisely predictable, follows a favorite direction, namely that towards higher concentrations of a certain chemical signal substance, see [2]. The first equation in (1.1) represents the hypothesis that the model depends on the growth of cancer cells. The second equation in (1.1) thus reflects the interplay of undirected diffusion movement on the hand and chemotactical movement driven by ∇V on the other. The third equation in (1.1) expresses the hypothesis that oxygen is produced by endothelial cells in addition to diffusion.

VEGF is an important regulatory specific factor for endothelial cell proliferation, migration, and in physiological and pathological angiogenesis. Endothelial cells are the cells that line the inner surface of blood vessels, they ensure that blood does not leak out, and if damage occurs, they respond by secreting proteins, signaling for help to other cells. VEGF, when combined with two receptors KDR and Flt-1 on endothelial cells with high affinity, can directly stimulate the proliferation of vascular endothelial cells, induce their migration and form lumen like structure, and finally promote the new blood vessels which can provide extra oxygen and other nutrients to tumor through the induction of interstitial production, see [13].

In the past two decades, a large number of mathematical models describing tumor invasion have been developed from different aspects, see [1,2]. In addition, the model is completely based on the reaction diffusion equation, and the core of these models assumes the convergence mechanism of the tactility, which means that the attractants are non-proliferation. The analysis results of this kind of approach system essentially include the evolution problems of some memory types, such as subsystems, which are still quite fragmentary up to now, mainly concentrated on these systems, see [3,4].

In this paper, we assume that C satisfies the following problem

$$\begin{cases} \dfrac{\partial C}{\partial t} = \Delta C + \lambda_c(1-\dfrac{C}{k_C}) - \mu C, & \text{in } Q, \\ \dfrac{\partial C}{\partial \eta} = 0, & \text{on } \Gamma, \\ C(\cdot,0) = C_0(\cdot), & \text{in } \Omega. \end{cases} \tag{1.2}$$

In [13], the original problem is a system of C, V, E and W. But the equation of C in (1.2) has only its own growth and death, and has no connection with any other cell. Hence, in this paper, C is a known solution obtained from the initial condition of C. Therefore, the aim of this paper is to get clear how does the known solution of C affect V, E and W.

The literature [14] shows that this chemotaxis cross diffusion may also have a strong destabilizing effect: for example, the Keller-Segel system

$$\begin{cases} u_t = \Delta u - \nabla\cdot(u\nabla z), \\ z_t = \Delta z - z + u, \end{cases} \tag{1.3}$$

is widely considered as the prototype model of chemical attraction process, and its solution is known to be global and bounded. In (1.3) substances secreted by cells immediately induce chemotaxis, while in (1.1), such chemicals only produce indirect chemotaxis by stimulating signals. Based on a good initial boundary value of C, this paper aims to clarify how C affects other vascular endothelial growth factors V, endothelial cells E and oxygen W, and to what extent this indirect chemotactic can enhance the regularity and boundedness of the solution.

Problem (1.1) will be studied in the standard functional spaces denoted by

$$W_4^{2,1}(Q) = \left\{ f \in L^q(Q) : D^\alpha f \in L^q(Q), \forall 1 \le |\alpha| \le 2, f_t \in L^q(Q) \right\}$$

and

$$W = \left\{ f \in L^\infty(Q) : f_t \in L^q(Q) \right\}.$$

For $1 \le p < \infty$, $\theta \ge 0$, $L^{p,\theta}(Q,\delta)$ is used to represent the linear space composed of all functions u in $L^p(Q)$ satisfying

$$[u]_{L^{p,\theta}(Q,\delta)} := \left\{ \sup_{X\in\Omega} |Q(X,\rho)|^{-\theta} \int_{Q(X,\rho)} |u(Y)|\, dY \right\}^{1/p} < \infty.$$

For $p \ge 1$, $\theta \ge 0$, $\ell^{p,\theta}(Q,\delta)$ is used to represent the linear space composed of all functions u in $L^p(Q)$ satisfying

$$[u]_{\ell^{p,\theta}(Q,\delta)} := \left\{ \sup_{X\in\Omega} |Q(X,\rho)|^{-\theta} \int_{Q(X,\rho)} |u(Y) - u_{X,\rho}|\, dY \right\}^{1/p} < \infty,$$

and the norm is defined as

$$\|u\|_{\ell^{p,\theta}(Q,\rho)} := \left\{ \|u\|^p_{L^p(\Omega)} + [u]^p_{\ell^{p,\theta}(Q,\delta)} \right\}^{1/p},$$

where

$$u_{X,\rho} = |Q(X,\rho)|^{-1} \int_{Q(X,\rho)} u(Y)dY,$$

$$Q(X,\rho) = Q \cap Q_r(X),$$

$$\delta(X,Y) = \max\left\{ |x-y|, |t_x - t_y|^{1/2} \right\},$$

$Q_r(X)$ is a sphere about δ with X as the center and r as the radius, δ is the parabolic distance.

Before stating our main theorem, we present some technical hypotheses that will be assumed through out this article:

(H1) $\Omega \subset \mathrm{R}^2$ is a bounded C^2 domain; $0 < T < \infty$ and $Q = \Omega \times (0,T)$;

(H2) $V_0, E_0, W_0 \in W_4^{3/2}(\Omega)$ satisfying $\dfrac{\partial V_0}{\partial \eta} = \dfrac{\partial E_0}{\partial \eta} = \dfrac{\partial W_0}{\partial \eta} = 0$ on Γ;

(H3) $C \in W_4^{2,1}(Q)$;

(H4) $C \in \ell^{p,\theta}(Q,\delta)$.

Theorem 1.1. Let λ_i, μ_i $(i = 1, 2, 3)$ be positive constants, assume that (H1)-(H3) hold, then for $(V_0, E_0, W_0) \in [W_4^{3/2}(\Omega)]^3$, there exists a unique solution $(V, E, W) \in [W_4^{2,1}(Q)]^3$ of the problem (1.1). Furthermore, the following results hold:

(1) Assume that $C \in \ell^{p,\theta}(Q,\delta)$ and (H3) is replaced by (H4), then there exists a unique classical solution $(V, E, W) \in [C^{2+\alpha,1+\alpha/2}(\bar{Q})]^3$ of the problem (1.1).

(2) If $V_0 \ge 0$, $E_0 \ge 0$, $W_0 \ge 0$, then $V \ge 0$, $E \ge 0$, $W \ge 0$.

In Theorem 1.1, for the sake of simplicity, we use $[W_4^{3/2}(\Omega)]^3$, $[W_4^{2,1}(Q)]^3$ and $[C^{2+\alpha,1+\alpha/2}(\bar{Q})]^3$ to denote the functions spaces

$$W_4^{3/2}(\Omega) \times W_4^{3/2}(\Omega) \times W_4^{3/2}(\Omega),$$

$$W_4^{2,1}(Q)\times W_4^{2,1}(Q)\times W_4^{2,1}(Q)$$

and

$$C^{2+\alpha,1+\alpha/2}(\bar{Q})\times C^{2+\alpha,1+\alpha/2}(\bar{Q})\times C^{2+\alpha,1+\alpha/2}(\bar{Q}),$$

respectively.

This paper is organized as follows. In Section 2, we show some theorems, definitions and Schauder estimate theorem, which will be used in later sections. In Section 3, we prove the existence, uniqueness and the estimates of nonnegative solutions $(V,E,W)\in[W_4^{2,1}(Q)]^3$, and use the global Schauder estimation in Theorem 2.4 to get the solution $(V,E,W)\in[C^{2+\alpha,1+\alpha/2}(\bar{Q})]^3$.

2. Preliminaries

In this section, we present some definitions, theorems and the global Schauder estimation in [15]. These definitions, estimates and theorems will be used in the next sections.

For ease of reference, we give the following embedding results for Sobolev space of type $W_p^{r,s}(Q)$. The first one is a consequence of Theorem 5.4 in [16]. The second one is a particular case of Theorem 3.3 in [17] by taking $l=1$ and $r=s=0$.

Theorem 2.1. Suppose that $\Omega\subset \mathrm{R}^n$ satisfies the cone property and $1<p<\infty$. The following continuous embeddings hold:

(1) $W_p^2(\Omega)\to W_q^{2-2/q}(\Omega)$, for all $p\le q\le 5p/3$ if $n\le 3$;

(2) If $kp<n$ then $W_p^k(\Omega)\to L^q(\Omega)$, for all $p\le q\le np/(n-kp)$;

(3) If $kp=n$ then $W_p^k(\Omega)\to L^q(\Omega)$, for all $p\le q<\infty$;

(4) If $kp>n$ then $W_p^k(\Omega)\to L^\infty(\Omega)$.

Theorem 2.2. Let Ω be a domain of R^n with boundary $\partial\Omega$ satisfying the cone property. Then the functional space $W_p^{2,1}(Q)$ is continuously embedded in $u\in L^q(Q)$ for q satisfying any one of the following conditions:

(i) $1\le q\le \dfrac{p(n+2)}{n+2-2p}$, if $p<\dfrac{n+2}{2}$;

(ii) $1\le q<\infty$, if $p=\dfrac{n+2}{2}$;

(iii) $q=\infty$, if $p>\dfrac{n+2}{2}$.

In particular, for such q and any function $u\in W_p^{2,1}(Q)$, we have that

$$\|u\|_{L^q(Q)}\le R\|u\|_{W_p^{2,1}(Q)},$$

where R is a constant depending only on Ω, T, p, q and n.

In the cases (ii), (iii) or in (i) when $1\le q\le \dfrac{p(n+2)}{n+2-2p}$, the embeddings mentioned above are compact.

Then, we consider the following general and simple parabolic initial-boundary value problem

$$\begin{cases}\dfrac{\partial u}{\partial t}-\displaystyle\sum_{i,j=1}^{n}a_{ij}(x,t)\frac{\partial u^2}{\partial x_i\partial x_j}\\ +\displaystyle\sum_{i=1}^{n}a_i(x,t)\frac{\partial u}{\partial x_i}+a(x,t)u=f, \text{ in } Q,\\ \displaystyle\sum_{i=1}^{n}b_i(x,t)\frac{\partial u}{\partial x_i}+b(x,t)u=0, \quad \text{on } \Gamma,\\ u(\cdot,0)=u_0(\cdot), \quad \text{in } \Omega.\end{cases}\tag{2.1}$$

Existence and uniqueness of solutions for problem (2.1) is a particular case of Theorem 9.1 in [17] for the case of Neumann boundary condition, (see also the remarks at the end of Section 9 in [17]). In the following, we state this particular result, stressing the dependencies on certain norms of the coefficients, which will be used in our later arguments.

Theorem 2.3. Let Ω be a bounded domain in R^n, with a C^2 boundary $\partial\Omega$, a_{ij} be bounded continuous functions in Q, and $q>1$. Assume that

(1) $a_{ij}\in C(\bar{Q}), i,j=1,\dots,n; [a_{ij}]_{n\times n}$ is a real positive matrix such that for some positive constant β we have $\displaystyle\sum_{i,j=1}^{n}a_{ij}(x,t)\xi_i\xi_j\ge\beta|\xi|^2$ for all $(x,t)\in Q$ and all $\xi\in R^n$;

(2) $f\in L^p(Q)$;

(3) $a_i\in L^r(Q)$ with either r=max(p, $n+2$) if $p\ne n+2$ or $r=n+2+\varepsilon$, for any $\varepsilon>0$, if $p=n+2$;

(4) $a\in L^s(Q)$ with either s=max(p, $n+2$) if $p\ne (n+2)/2$ or $s=(n+2)/2+\varepsilon$, for any $\varepsilon>0$, if $p=(n+2)/2$;

(5) $b_i, b\in C^2(\Gamma), i=1,\dots,n,$ and the coefficients $b_i(x,t)$ satisfy the condition $\left|\displaystyle\sum_{i=1}^{n}b_i(x,t)\eta_i(x)\right|\ge\delta>0$ for a.e. in $\partial\Omega\times(0,T)$, where $\eta_i(x)$ is the i^{th}-component of the unitary outer normal vector to $\partial\Omega$ in $x\in\partial\Omega$;

(6) $u_0\in W_p^{2-2/p}(\Omega)$ with $p\ne 3$ and satisfying the compatibility condition $\displaystyle\sum_{i=1}^{n}b_i(x,t)\frac{\partial u_0}{\partial x_i}+bu_0=0$ on $\partial\Omega$ when $p>3$.

Then, there exists a unique solution $u\in W_p^{2,1}(Q)$ of the problem (2.1). Moreover, there is a positive Constant $\tilde{R}$ such that the solution satisfies the following estimate

$$\|u\|_{W_p^{2,1}(Q)} \le \tilde{R}(\|f\|_{L^p(Q)} + \|u_0\|_{W_p^{2-2/p}(\Omega)}. \quad (2.2)$$

Such a constant $\tilde{R}$ depends only on $\Omega, T, p, r, s, \beta, \delta$ and on the norms $\|b_i\|_{C^2(\bar{\Gamma})}$, $\|b\|_{C^2(\bar{\Gamma})}$, $\|a_{ij}\|_{C(\bar{Q})}$, $\|a_i\|_{L^r(Q)}$, $\|a\|_{L^s(Q)}$. Moreover, we may assume that the dependencies of $\tilde{R}$ on stated the norms are nondecreasing.

We use the definitions and theorems in [15] to promote the solution from $W_p^{2,1}(Q)$ space to $C^{2+\alpha,\ 1+\alpha/2}(\bar{Q})$ space, which will be used in Section 3.

Definition 2.1. For $0<\alpha\le 1$, $C^{\alpha}(\bar{Q},\delta)$ is used to express the linear space composed of all functions u satisfying

$$[u]_{\alpha,Q} := \sup_{X\in Q, d\ge\rho>0} \frac{u(X)-u(Y)}{\delta(X,Y)} < \infty,$$

on which norm is given

$$|u|_{\alpha,Q} := \sup_{Q}|u| + [u]_{\alpha,Q}.$$

For positive integers k and $0<\alpha<1$, the linear space composed of functions satisfying

$$|u|_{k+\alpha,Q} := \sum_{0\le r+2t\le k}\left[D_t^s D_s^r u\right]_{0,Q} + [u]_{k+\alpha,Q} < \infty,$$

in $C(\bar{Q})$ is used as $C^{k+\alpha,(k+\alpha/2)}(\bar{Q})$ or $C^{k+\alpha}(\bar{Q},\delta)$.

Theorem 2.4. Let $u \in W_2^{2,1}(Q)$ is a solution of equation (2.1) in Q, and u=0 on $\partial_p\Omega$. Let $\partial\Omega \in C^{2,\alpha}$ and a_{ij} satisfy uniform parabolic condition and a_{ij}, b_i, $c \in C^{\alpha}(\bar{Q},\delta)$ $(0<\alpha<1)$, for $1\le\theta\le 1+\frac{2\alpha}{n+2}$, if

$$f \in \begin{cases} L^{2,1}(Q,\delta), & \text{when } \theta = 1, \\ \ell^{2,\theta}(Q,\delta), & \text{when } 1<\theta\le 1+\frac{2\alpha}{n+2}, \end{cases}$$

if $\theta>1$, $f=0$, on $\partial\Omega\times\{t=0\}$, then $D_t u, D^2 u \in \ell^{2,\theta}(Q,\delta)$, and satisfy the following estimate

$$\|u\|^2_{\ell^{2,\theta}(Q,\delta)} \le \begin{cases} R(\|u\|_{W_2^{2,1}(Q)} + \|C\|_{L^{2,1}(Q,\delta)}), & \theta=1, \\ R(\|u\|_{W_2^{2,1}(Q)} + \|C\|_{\ell^{2,\theta}(Q,\delta)}), & 1<\theta\le 1+\frac{2\alpha}{n+2}. \end{cases}$$

Especially, when $\theta = 1+\frac{2\alpha}{n+2}$, the above formula can be written as

$$|u|_{2+\alpha,1+\alpha/2,Q} \le R(\|u\|_{W_2^{2,1}(Q)} + \|c\|_{\alpha,Q}),$$

where R is depending on n, $\lambda, \Lambda, |a_{ij}|_{\alpha,Q}, |b_i|_{\alpha,Q}, |c|_{\alpha,Q}$ and $\partial\Omega$.

3. Existence and Uniqueness of *V*, *E* and *W*

In this Section, we use Theorem 2.3 to prove the existence and uniqueness of solutions for V, E and W, and then use Theorem 2.4 to improve the solutions from $W_p^{2,1}(Q)$ to $C^{2+\alpha,\ 1+\alpha/2}(\bar{Q})$. The nonnegativity of V, E and W are proved when $V_0\ge 0$, and $W_0\ge 0$ respectively. By the regularity of V, we solve the complexity of the convection term in the proof of nonnegativity of E when $E_0\ge 0$.

Theorem 3.1. Assume that (H1)-(H3) hold, $V_0 \in W_4^{3/2}(\Omega)$, then the following problem

$$\begin{cases} \dfrac{\partial V}{\partial t} = \Delta V + \lambda_1 C - \mu_1 V, & \text{in } Q, \\ \dfrac{\partial V}{\partial \eta} = 0, & \text{on } \Gamma, \\ V(\cdot,0) = V_0(\cdot), & \text{in } \Omega, \end{cases} \quad (3.1)$$

exists a unique solution $V\in W_4^{2,1}(Q)$, and if $V_0\ge 0$ almost everywhere in Ω, then $V\ge 0$ almost everywhere in Q. Moreover, if (H3) is replaced by (H4), there exists solution $V\in C^{2+\alpha,\ 1+\alpha/2}(\bar{Q})$ of problem (3.1).

Proof. Since the coefficients of (3.1) satisfy the hypotheses of Theorem 2.3, there exists a unique solution $V\in W_4^{2,1}(Q)$ of (3.1) by Theorem 2.3. Moreover, V satisfies the following estimate:

$$\begin{aligned} \|V\|_{W_4^{2,1}(Q)} &\le R_1(\lambda_1\|C\|_{L^4(Q)} + \|V_0\|_{W_4^{3/2}(\Omega)}) \\ &\le R_1(\lambda_1 R + \|V_0\|_{W_4^{3/2}(\Omega)}). \end{aligned} \quad (3.2)$$

Multiplying the first equation in (3.1) by V^- and integrating in Ω, we have

$$-\frac{1}{2}\frac{d}{dt}\int_\Omega (V^-)^2 dx = \int_\Omega \left|\nabla V^-\right|^2 dx + \lambda_1\int_\Omega CV^- dx + \mu_1\int_\Omega (V^-)^2 dx.$$

Using the fact that $C\ge 0$, we get

$$\frac{d}{dt}\int_\Omega (V^-)^2 dx \le 0.$$

We conclude that $\left\|V^-(\cdot,t)\right\|_{L^2(\Omega)} = 0$ for all $t\in(0,T)$, that is $V^-=0$ almost everywhere in Q, by using Gronwall's in-equality and the fact that $V^-\ge 0$ almost everywhere in Ω. Therefore $V\ge 0$ almost everywhere in Q.

Because $V\in W_4^{2,1}(Q)$ is a solution of problem (3.1), and $\partial\Omega\in C^2$, the right coefficients of the first equation in (3.1) are 1, $-\mu_1 \in C^{\alpha}(\bar{Q},\delta)(0<\alpha\le 1)$ respectively. It follows that $\lambda_1 C \in \ell^{2,\theta}(Q,\delta)$. When $\theta = 1+\frac{2\alpha}{n+2}$, from

Theorem 2.4, we conclude that $V \in C^{2+\alpha,\, 1+\alpha/2}\left(\bar{Q}\right)$.

Theorem 3.2. Assume that (H1)-(H3) hold, $E_0 \in W_4^{3/2}(\Omega)$, then the following problem

$$\begin{cases} \dfrac{\partial E}{\partial t} = \Delta E + \lambda_2 V - \nabla \cdot (E \nabla V) - \mu_2 E, & \text{in } Q, \\ \dfrac{\partial E}{\partial \eta} = 0, & \text{on } \Gamma, \\ E(\cdot, 0) = E_0(\cdot), & \text{in } \Omega, \end{cases} \tag{3.3}$$

exists a unique solution $E \in W_4^{2,1}(Q)$, and if $E_0 \geq 0$ almost everywhere in Ω, then $E \geq 0$ almost everywhere in Q. Moreover, if (H3) is replaced by (H4), there exists solution $E \in C^{2+\alpha,\, 1+\alpha/2}\left(\bar{Q}\right)$ of problem (3.3).

Proof. Since the coefficients of (3.3) satisfy the hypotheses of Theorem 2.3, there exists a unique solution $E \in W_4^{2,1}(Q)$ of (3.3) by Theorem 2.3. Moreover, E satisfies the following estimate:

$$\begin{aligned} \|E\|_{W_4^{2,1}(Q)} &\leq R_1(\lambda_2 \|V\|_{L^4(Q)} + \|E_0\|_{W_4^{3/2}(\Omega)}) \\ &\leq R_2(\lambda_2 R + \|V_0\|_{W_4^{3/2}(\Omega)} + \|E_0\|_{W_4^{3/2}(\Omega)}). \end{aligned} \tag{3.4}$$

Multiplying the first equation in (3.3) by E^- and integra-ting in Ω, we have

$$\begin{aligned} -\frac{1}{2}\frac{d}{dt}\int_\Omega (E^-)^2 dx &= \int_\Omega \left|\nabla E^-\right|^2 dx + \lambda_2 \int_\Omega V E^- dx \\ &\quad - \int_\Omega \nabla \cdot (E \nabla V) dx + \mu_2 \int_\Omega (E^-)^2 dx. \end{aligned}$$

Using the fact that $V \geq 0$, we get

$$\begin{aligned} \frac{d}{dt}\int_\Omega (E^-)^2 dx &\leq 2\int_\Omega \nabla \cdot (E \nabla V) E^- dx \\ &= 2\left(\int_\Omega E^- \nabla E \nabla V dx - \int_\Omega (E^-)^2 \Delta V dx\right). \end{aligned}$$

Let $M = \int_\Omega (E^-)^2 dx$, we have

$$\begin{aligned} -\int_\Omega (E^-)^2 \Delta V dx &\leq \int_\Omega (E^-)^2 \sup_\Omega |\Delta V| dx \\ &= \sup_\Omega |\Delta V| \int_\Omega (E^-)^2 dx \\ &= M \sup_\Omega |\Delta V|, \end{aligned}$$

and

$$\begin{aligned} \int_\Omega E^- \nabla E \nabla V dx &\leq \frac{1}{2}\int_\Omega (E^-)^2 dx + \frac{1}{2}\int_\Omega (\nabla E^- \nabla V)^2 dx \\ &\leq \frac{1}{2}\int_\Omega (E^-)^2 dx + \frac{1}{2}\int_\Omega \left|\nabla E^-\right|^2 |\nabla V|^2 dx \\ &\leq \frac{1}{2}\int_\Omega (E^-)^2 dx + \frac{1}{2}\sup_\Omega |\nabla V|^2 \int_\Omega \left|\nabla E^-\right|^2 dx \\ &\leq \frac{1}{2}\int_\Omega (E^-)^2 dx + \frac{1}{2} R_1 \sup_\Omega |\nabla V|^2 \int_\Omega \left|E^-\right|^2 dx \\ &\leq \frac{1}{2} M + \frac{1}{2} R_1 M \sup_\Omega |\nabla V|^2. \end{aligned}$$

From the above inequalities, we get

$$\begin{aligned} \frac{d}{dt} M &\leq 2\left(\frac{1}{2} M + \frac{1}{2} R_1 M \sup_\Omega |\nabla V|^2 + M \sup_\Omega |\Delta V|\right) \\ &= (1 + R_1 \sup_\Omega |\nabla V|^2 + \sup_\Omega |\Delta V|) M. \end{aligned}$$

Let $a(t) = 1 + R_1 \sup_\Omega |\nabla V|^2 + \sup_\Omega |\Delta V|$, we have

$$\frac{d}{dt}\int_\Omega (E^-)^2 dx \leq a(t)\int_\Omega (E^-)^2 dx.$$

Hence, by Gronwall's inequality we get

$$\int_\Omega (E^-)^2 dx \leq e^{\int_0^T a(s) ds} \int_\Omega (E_0^-)^2 dx = 0 \quad .$$

We conclude that $\left\|E^-(\cdot, t)\right\|_{L^2(\Omega)} = 0$ for all $t \in (0, T)$, that is $E^- = 0$ almost everywhere in Q. By using Gronwall's inequality and the fact that $E^- \geq 0$ almost everywhere in Ω. Therefore $E \geq 0$ almost everywhere in Q.

Because $E \in W_4^{2,1}(Q)$ is a solution of problem (3.3), and $\partial\Omega \in C^2$, the right coefficients of the first equation in (3.3) are 1, $-\nabla V$, $-\nabla V - \mu_2 \in C^\alpha(\bar{Q}, \delta)(0 < \alpha \leq 1)$, re-spectively. It follows that $\lambda_2 V \in \ell^{2,\theta}(Q, \delta)$. When $\theta = 1 + \dfrac{2\alpha}{n+2}$, from Theorem 2.4, we conclude that $E \in C^{2+\alpha,\, 1+\alpha/2}\left(\bar{Q}\right)$.

Remark 3.1. If the cancer cell density C is not smooth enough, then the regularity of C will be reduced, and the nonnegativity of E can not be proved using the argument in Theorem 3.2.

Theorem 3.3. Assume that (H1)-(H3) hold, $W_0 \in W_4^{3/2}(\Omega)$, then the following problem

$$\begin{cases} \partial W/\partial t = \Delta W + \lambda_3 E - \mu_3 W, & \text{in } Q, \\ \partial W/\partial \eta = 0, & \text{on } \Gamma, \\ W(\cdot, 0) = W_0(\cdot), & \text{in } \Omega, \end{cases} \tag{3.5}$$

exists a unique solution $W \in W_4^{2,1}(Q)$, and if $W_0 \geq 0$ almost everywhere in Ω, then $W \geq 0$ almost everywhere in Q. Moreover, if (H3) is replaced by (H4), there exists solution $W \in C^{2+\alpha,\, 1+\alpha/2}\left(\bar{Q}\right)$ of problem (3.5).

Proof. Since the coefficients of (3.5) satisfy the hypotheses of Theorem 2.3, there exists a unique solution $W \in W_4^{2,1}(Q)$ of (3.5) by Theorem 2.3. Moreover, W satisfies the following estimate:

$$\begin{aligned} \|W\|_{W_4^{2,1}(Q)} &\leq R_1(\lambda_3 \|E\|_{L^4(Q)} + \|W_0\|_{W_4^{3/2}(\Omega)}) \\ &\leq R_2(\lambda_3 R + \|V_0\|_{W_4^{3/2}(\Omega)} + \|E_0\|_{W_4^{3/2}(\Omega)} \\ &\quad + \|W_0\|_{W_4^{3/2}(\Omega)}). \end{aligned} \tag{3.6}$$

Multiplying the first equation in (3.5) by W^- and integrating in Ω, we have

$$-\frac{1}{2}\frac{d}{dt}\int_\Omega (W^-)^2 dx = \int_\Omega \left|\nabla W^-\right|^2 dx + \lambda_3 \int_\Omega EW^- dx + \mu_3 \int_\Omega (W^-)^2 dx.$$

Using the fact that $E \ge 0$, we get

$$\frac{d}{dt}\int_\Omega (W^-)^2 dx \le 0.$$

We conclude that $\left\|W^-(\cdot,t)\right\|_{L^2(\Omega)} = 0$ for all $t \in (0,T)$, that is $W^- = 0$ almost everywhere in Q, by using Gronwall's inequality and the fact that $W^- \ge 0$ almost everywhere in Ω. Therefore $W \ge 0$ almost everywhere in Q.

Because $W \in W_4^{2,1}(Q)$ is a solution of problem (3.5), and $\partial\Omega \in C^2$, the right coefficients of the first equation in (3.5) are 1, $-\mu_3 \in C^\alpha(\bar{Q},\delta)(0 < \alpha \le 1)$, respectively. It follows that $\lambda_3 E \in \ell^{2,\theta}(Q,\delta)$. When $\theta = 1 + \frac{2\alpha}{n+2}$, from Theorem 2.4, we conclude that $W \in C^{2+\alpha,\, 1+\alpha/2}\left(\bar{Q}\right)$.

We will prove the existence of problem (1.1). The uniqueness of problem (1.1) will be proved by using Young's inequality and Gronwall's inequality. Then the main result, Theorem 1.1, readily follows.

Theorem 3.4. Assume that (H1)-(H4) hold, there is a unique nonnegative solution $(V, E, W) \in [C^{2+\alpha,1+\alpha/2}(\bar{Q})]^3$ of the problem (1.1).

Proof. From Theorem 3.1, Theorem 3.2 and Theorem 3.3, we conclude that there exists $(V, E, W) \in [C^{2+\alpha,1+\alpha/2}(\bar{Q})]^3$ and V, E and W are nonnegative. Let (V_1, E_1, W_1) and (V_2, E_2, W_2) be solutions to problem (1.1). Setting $\tilde{V} = V_1 - V_2$, $\tilde{E} = E_1 - E_2$, $\tilde{W} = W_1 - W_2$, then $\tilde{V}, \tilde{E}$ and $\tilde{W}$ satisfy the following problems, respectively:

$$\begin{cases} \dfrac{\partial \tilde{V}}{\partial t} = \Delta\tilde{V} + \lambda_1 \tilde{C} - \mu_1 \tilde{V}, & \text{in } Q, \\ \dfrac{\partial \tilde{V}}{\partial \eta} = 0, & \text{on } \Gamma, \\ \tilde{V}(\cdot,0) = \tilde{V}_0(\cdot), & \text{in } \Omega, \end{cases} \tag{3.7}$$

$$\begin{cases} \dfrac{\partial \tilde{E}}{\partial t} = \Delta\tilde{E} + \lambda_2 \tilde{V} - \nabla\cdot(\tilde{E}\nabla\tilde{V}) - \mu_2 \tilde{E}, & \text{in } Q, \\ \dfrac{\partial \tilde{E}}{\partial \eta} = 0, & \text{on } \Gamma, \\ \tilde{E}(\cdot,0) = \tilde{E}_0(\cdot), & \text{in } \Omega, \end{cases} \tag{3.8}$$

and

$$\begin{cases} \dfrac{\partial \tilde{W}}{\partial t} = \Delta\tilde{W} + \lambda_3 \tilde{E} - \mu_3 \tilde{W}, & \text{in } Q, \\ \dfrac{\partial \tilde{W}}{\partial \eta} = 0, & \text{on } \Gamma, \\ \tilde{W}(\cdot,0) = \tilde{W}_0(\cdot), & \text{in } \Omega. \end{cases} \tag{3.9}$$

Multiplying the first equation in $(3.7)_1$ by $\tilde{V}$ and integrating in Ω, we have

$$\frac{1}{2}\frac{d}{dt}\int_\Omega (\tilde{V})^2 dx = -\int_\Omega \left|\nabla\tilde{V}\right|^2 dx + \lambda_1 \int_\Omega \tilde{C}\tilde{V} dx - \mu_1 \int_\Omega (\tilde{V})^2 dx \le R\int_\Omega (\tilde{V}^2 + \tilde{E}^2 + \tilde{W}^2) dx,$$

where R depends on λ_1. Multiplying the first equation in $(3.8)_1$ by $\tilde{E}$ and integrating in Ω, we have

$$\frac{1}{2}\frac{d}{dt}\int_\Omega (\tilde{E})^2 dx = -\int_\Omega \left|\nabla\tilde{E}\right|^2 dx + \lambda_2 \int_\Omega \tilde{V}\tilde{E} dx - \int_\Omega \nabla\cdot(\tilde{E}\nabla\tilde{V}) dx - \mu_2 \int_\Omega (\tilde{E})^2 dx \le R\int_\Omega (\tilde{V}^2 + \tilde{E}^2 + \tilde{W}^2) dx,$$

where R depends on λ_2. Multiplying the first equation in $(3.9)_1$ by $\tilde{E}$ and integrating in Ω, we have

$$\frac{1}{2}\frac{d}{dt}\int_\Omega (\tilde{W})^2 dx = -\int_\Omega \left|\nabla W^-\right|^2 dx + \lambda_3 \int_\Omega \tilde{E}\tilde{W} dx - \mu_3 \int_\Omega (\tilde{W})^2 dx \le R\int_\Omega (\tilde{V}^2 + \tilde{E}^2 + \tilde{W}^2) dx,$$

where R depends on λ_3. Thus, we obtain

$$\frac{d}{dt}\int_\Omega (\tilde{V}^2 + \tilde{E}^2 + \tilde{W}^2) dx \le \int_\Omega (\left|\tilde{V}\right|^2 + \left|\tilde{E}\right|^2 + \left|\tilde{W}\right|^2) dx.$$

By Gronwall's inequality, we get

$$\int_\Omega (\tilde{V}^2 + \tilde{E}^2 + \tilde{W}^2) dx \le \int_\Omega (\left|\tilde{V}_0\right|^2 + \left|\tilde{E}_0\right|^2 + \left|\tilde{W}_0\right|^2) dx,$$

namely,

$$\left\|\tilde{V}(\cdot,t)\right\|_{L^2(\Omega)}^2 + \left\|\tilde{E}(\cdot,t)\right\|_{L^2(\Omega)}^2 + \left\|\tilde{W}(\cdot,t)\right\|_{L^2(\Omega)}^2 = 0,$$

for all $t \in (0,T)$. We then have $\tilde{V} = \tilde{E} = \tilde{W} = 0$ almost everywhere in Q and hence $V_1 = V_2, E_1 = E_2, W_1 = W_2$ almost everywhere in Q. Then the uniqueness assertion is proved.

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