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Research Article

Global Bounded Classical Solutions for a Gradient-Driven Mathematical Model of Antiangiogenesis in Tumor Growth

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In this paper, we consider a gradient-driven mathematical model of antiangiogenesis in tumor growth. In the model, the movement of endothelial cells is governed by diffusion of themselves and chemotaxis in response to gradients of tumor angiogenic factors and angiostatin. The concentration of tumor angiogenic factors and angiostatin is assumed to diffuse and decay. The resulting system consists of three parabolic partial differential equations. In the present paper, we study the global existence and boundedness of classical solutions of the system under homogeneous Neumann boundary conditions.

1. Introduction

Angiogenesis is a crucial step in the metastatic cascade of solid tumors growth. During this process, besides tumor angiogenic factors, a primary tumor also secretes substances (angiostatin [1] and endostatin [2]) to inhibit the formation of a vasculature around the secondary tumors [1, 3]. In order to describe explicitly the effects of antiangiogenesis and explain why a primary tumor can inhibit angiogenesis in a secondary tumor, Anderson et al. [4] proposed the following system of evolution equations:

$$\begin{cases} n_t = d_1 n_{xx} - (\chi(c) n c_x)_x - (\alpha(a) n a_x)_x, \\ c_t = d_2 c_{xx} - f(c, n, x), \\ a_t = d_3 a_{xx} - g(a, n, x). \end{cases} \tag{1}$$

The relevant variables involved respectively are represented as follows:

(i) $n(x,t)$: the endothelial cell tip density in point x at time t

(ii) $c(x,t)$: the concentrations of tumor angiogenic factors in point x at time t

(iii) $a(x,t)$: the concentrations of angiostatin in point x at time t

(iv) d_i: diffusion coefficients $(i = 1, 2, 3)$

(v) $\chi(c)$: chemotactic functions of tumor angiogenic factors

(vi) $\alpha(a)$: chemotactic functions of angiostatin

(vii) $f(c, n, x)$: uptake/loss and decay function of tumor angiogenic factors

(viii) $g(a, n, x)$: uptake/loss and decay function of angiostatin

Here, $x \in (0, L)$ and $(0, L)$ is the interval in which the blood vessel and the secondary tumor are located. The endothelial cell receptors become desensitized to high concentration of tumor angiogenic factors as assumed in [4]; we therefore take the chemotactic function.

$$\chi(c) = \chi_0 \frac{k}{k + c}. \tag{2}$$

Here, the parameters $\chi_0 > 0$ and $k > 0$ denote the maximum chemotactic response and the severity of the degree of hyposensitization, respectively. To model the dose-dependent response of an endothelial cell to angiostatin, we take the angiostatin chemotactic function $\alpha(a) = \alpha_0 a$ [4], where α_0 is a real number. We shall subsequently consider the following system:

$$\begin{cases} n_t = d_1 n_{xx} - \chi_0 \left(\dfrac{k}{k+c} n c_x \right)_x - \alpha_0 (a n a_x)_x, & x \in \Omega,\ t > 0, \\ c_t = d_2 c_{xx} - f(c, n, x), & x \in \Omega,\ t > 0, \\ a_t = d_3 a_{xx} - g(a, n, x), & x \in \Omega,\ t > 0. \end{cases} \tag{3}$$

We consider the case in which the blood vessel is located at x_1 and the secondary tumor is located at x_2, where $0 < x_1 < x_2 < L$. If the interval $(0, L)$ is sufficiently long (i.e., L is large enough), we can neglect the influence of both ends. Hence, we consider (3) with the special no-flux boundary conditions:

$$n_x = c_x = a_x = 0, \quad x \in \partial\Omega,\ t > 0, \tag{4}$$

and the initial conditions

$$\begin{aligned} n(x, 0) &= n_0(x), \\ c(x, 0) &= c_0(x), \\ a(x, 0) &= v_0(x), \\ x &\in \Omega, \end{aligned} \tag{5}$$

where $\Omega := (0, L)$ and $(n_0(x), c_0(x), n_0(x)) \in (W^{1,2}(\Omega))^3$. With regard to the functions f and g throughout this paper, we shall assume that $f, g \in C^1([0, \infty) \times [0, \infty) \times \overline{\Omega})$ are nonnegative with

$$f(0, n, x) = g(0, n, x) = 0, \quad (n, x) \in ([0, \infty) \times \Omega). \tag{6}$$

Moreover, we suppose that there exist $\delta_1 > 0$ and $\delta_2 > 0$ such that

$$f(c, n, x) \le c(\delta_1 + n), \quad (c, n, x) \in ([0, \infty) \times [0, \infty) \times \overline{\Omega}), \tag{7}$$

$$g(a, n, x) \le a(\delta_2 + n), \quad (a, n, x) \in ([0, \infty) \times [0, \infty) \times \overline{\Omega}). \tag{8}$$

We note that the assumptions (6)–(8) have a definite biological meaning. For example, we can respectively take the uptake functions:

$$\begin{aligned} f(c, n, x) &= c\left(\delta + \frac{n}{1+c} \right), \\ g(a, n, x) &= \frac{an}{1+a}, \end{aligned} \tag{9}$$

as the prototypes of (6)–(8), which mean tumor angiogenic factors and angiostatin are consumed by endothelial cells according to Michaelis–Menten kinetics [5]. The steady-state solution of (3) with a no-flux boundary condition is examined by the authors in [4]. Moreover, Wei and Cui [6] prove the existence and uniqueness of global classical solution for system (3). It is interesting to investigate whether or not the tumor becomes vascularized in model (3) after a long period of time (i.e., endothelial cells at the tips of the capillaries connect with the tumor). Therefore, as a first step, we shall study the global existence and boundedness of (3)–(5) solutions for the problem (3)–(5) under the assumptions (6)–(8). Our main result reads as follows.

Theorem 1. *Let $(n_0, c_0, a_0) \in (W^{1,2}(\Omega))^3$ and let the assumptions (6)–(8) hold. Then, the problem (3)–(5) has a unique global classical solution which is bounded in $\Omega \times (0, \infty)$.*

Remark 1. Compared with the previous work of Wei and Cui [6], we further obtain the boundedness of the global classical solution.

The rest of the paper is organized as follows. In Section 2, we give the existence of local solution for system (3) and some basic properties of the solution for the problem (3)–(5). In Section 3, we study global existence and boundedness of the classical solution. Finally, we give the conclusion section.

2. Preliminaries

In this section, we provide some preliminary results which will be used in the proof of the main results. The first result concerns local existence of a classical solution to the problem (3)–(5). The idea of its proof is based on arguments in [7, 8].

Lemma 1. *Assume that the initial data are nonnegative and satisfy $(n_0, c_0, a_0) \in (W^{1,2}(\Omega))^3$. Then, the problem (3)–(5) possesses a unique local-in-time nonnegative classical solution:*

$$(n, c, a) \in \left(C\left([0, T_{\max}); W^{1,r}(\Omega) \right) \cap C^{2,1}\left(\overline{\Omega} \times (0, T_{\max}) \right) \right), \tag{10}$$

where $T_{\max}$ is the maximal existence time. Moreover, if for each $T > 0$ there exists a constant $C(T)$ such that

$$\begin{aligned} &\|(n(t), c(t), a(t))\|_{L^\infty(\Omega)} \le C(T), \quad 0 < t < \min\{T, T_{\max}\}, \\ &\text{then } T_{\max} = +\infty. \end{aligned} \tag{11}$$

Proof. Let $u := (n, c, a)^T$. Then, the system (3) can be written as

$$\begin{cases} u_t = \left(\mathscr{A}(u) u_x \right)_x + \mathscr{F}(u), & x \in \Omega,\ t > 0, \\ u_x = 0, & x \in \partial\Omega,\ t > 0, \\ u(x, 0) = \left(n_0(x), c_0(x), a_0(x) \right), & x \in \Omega, \end{cases} \tag{12}$$

where

$$\begin{aligned} \mathscr{A}(u) &= \begin{pmatrix} d_1 & -\chi(c) n & -\alpha(a) n \\ 0 & d_2 & 0 \\ 0 & 0 & d_3 \end{pmatrix}, \\ \mathscr{F}(u) &= \begin{pmatrix} 0 \\ -f(c, n, x) \\ -g(a, n, x) \end{pmatrix}. \end{aligned} \tag{13}$$

Applying Theorem 14.4, Theorem 14.6, and Theorem 15.5 of [9], we complete the proof of Lemma 1.

The following statement plays a crucial role in the proof of the main result. □

Lemma 2. *Assume that the initial data* $(n_0(x), c_0(x), n_0(x)) \in (W^{1,2}(\Omega))^3$ *are nonnegative functions. Let* f *and* g *satisfy (6)–(8). Then, the solution of the system (3) satisfies*

$$\int_\Omega n(x,t)\mathrm{d}x = \int_\Omega n_0(x)\mathrm{d}x, \text{ for all } t \in (0, T_{\max}), \tag{14}$$

$$\|c(\cdot,t)\|_{L^\infty(\Omega)} \le \|c_0\|_{L^\infty(\Omega)}, \text{ for all } t \in (0, T_{\max}), \tag{15}$$

as well as

$$\|a(\cdot,t)\|_{L^\infty(\Omega)} \le \|a_0\|_{L^\infty(\Omega)}, \text{ for all } t \in (0, T_{\max}). \tag{16}$$

Proof. By a spatial integration of the first equation in (3), we immediately obtain

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega n(x,t)dx = 0, \tag{17}$$

which implies (14). Since f and g are nonnegative functions, we get

$$\begin{aligned} c_t &\le d_2 c_{xx}, \\ a_t &\le d_2 a_{xx}. \end{aligned} \tag{18}$$

Therefore, the estimates (15) and (16) follow from an application of the comparison principle for the heat equation. □

3. Global Existence and Boundedness of Solutions

In this section, we consider the global existence and boundedness of classical solutions to the problem (3)–(5). Firstly, we have an estimate for c_x and a_x in Lebesgue space $L^2(\Omega)$.

Lemma 3. *Suppose that* $(n_0, c_0, a_0) \in (W^{1,2}(\Omega))^3$. *Then, there exists* $C > 0$ *such that*

$$\|c_x(\cdot,t)\|_{L^2(\Omega)} \le C, \tag{19}$$

$$\|a_x(\cdot,t)\|_{L^2(\Omega)} \le C, \tag{20}$$

for all $t \in (0, T_{\max})$.

Proof. An application of the variation-of-constants formula shows that

$$\begin{aligned} \|c_x(\cdot,t)\|_{L^2(\Omega)} &\le \left\|\left(e^{-tA_2}c_0\right)_x\right\|_{L^2(\Omega)} \\ &\quad + \int_0^t \left\|\left(e^{-(t-s)A_2} f(c(\cdot,s), n(\cdot,s), \cdot)\right)_x\right\|_{L^2(\Omega)} \mathrm{d}s, \end{aligned} \tag{21}$$

where A_2 is the realization of the operator $-d_2(\cdot)_{xx}$ in $L^p(\Omega)$ equipped with homogeneous Neumann boundary conditions. According to the smoothing estimates for the Neumann heat semigroup [10], we can find $C_1 > 0$ and $C_2 > 0$ such that

$$\begin{aligned} &\left\|\left(e^{-tA_2}\varphi\right)_x\right\|_{L^2(\Omega)} \le C_1 \|\varphi_x\|_{L^2(\Omega)}, \text{ for all } \varphi \in W^{1,2}(\Omega), \\ &\left\|\left(e^{-tA_2}\varphi\right)_x\right\|_{L^p(\Omega)} \le C_2\left(1 + t^{-(1/2)-(1/2)((1/q)-(1/p))}\right)\|\varphi\|_{L^q(\Omega)}, \\ &\qquad\qquad \text{for all } \varphi \in L^q(\Omega), \end{aligned} \tag{22}$$

where $1 \le q \le p \le \infty$. Then, from (7) and (14), we can estimate

$$\begin{aligned} \|c_x(\cdot,t)\|_{L^2(\Omega)} &\le C_1\|c_{0x}\|_{L^2(\Omega)} + C_2\int_0^t \left(1 + (t-s)^{-(3/4)}\right)\|f(c(\cdot,s), n(\cdot,s), \cdot)\|_{L^1(\Omega)}\mathrm{d}s \\ &\le C_1\|c_0\|_{W^{1,2}(\Omega)} + C_2\int_0^t \left(1 + (t-s)^{-(3/4)}\right)\|c(\cdot,s)(\delta_1 + n(\cdot,s))\|_{L^1(\Omega)}\mathrm{d}s \\ &\le C_1\|c_0\|_{W^{1,2}(\Omega)} + C_2\int_0^t \left(1 + (t-s)^{-(3/4)}\right)\|(\delta_1 + n(\cdot,s))\|_{L^1(\Omega)}\|c(\cdot,s)\|_{L^\infty(\Omega)}\mathrm{d}s \\ &\le C \qquad\qquad \text{for all } t \in (0, T_{\max}). \end{aligned} \tag{23}$$

Using similar arguments to the variation-of-constants formula of the third equation in (3), we obtain the boundedness of $\|a_x(\cdot,t)\|$ for all $t \in (0, T_{\max})$. □

With the above mentioned result in hand, we are in a position to establish a uniform bound on n based on the idea of the proof in [11].

Proposition 1. *Let $(n_0, c_0, a_0) \in (W^{1,2}(\Omega))^3$. Then, system (3) has a unique global classical solution that is bounded in $\Omega \times (0, \infty)$.*

Proof. Let A_1 denote the realization of the operator $-d_1(\cdot)_{xx}$ under homogeneous Neumann boundary conditions in $L^p(\Omega)$. We obtain from the variation-of-constants formula

$$n(\cdot,t) = e^{-tA_1}n_0 - \chi_0 \int_0^t e^{-(t-s)A_1}\left(\frac{k}{k+c(\cdot,s)}n(\cdot,s)c_x(\cdot,s)\right)_x \mathrm{d}s - \alpha_0 \int_0^t e^{-(t-s)A_1}\left(a(\cdot,s)n(\cdot,s)a_x(\cdot,s)\right)_x \mathrm{d}s, \tag{24}$$

together with the maximum principle and (22) that

$$\begin{aligned}
\|n(\cdot,t)\|_{L^\infty(\Omega)} &\le \left\|e^{-tA_1}n_0\right\|_{L^\infty(\Omega)} \\
&\quad + \chi_0 \int_0^t \left\|e^{-(t-s)A_1}\left(\frac{k}{k+c(\cdot,s)}n(\cdot,s)c_x(\cdot,s)\right)_x\right\|_{L^\infty(\Omega)} \mathrm{d}s \\
&\quad + \alpha_0 \int_0^t \left\|e^{-(t-s)A_1}\left(a(\cdot,s)n(\cdot,s)a_x(\cdot,s)\right)_x\right\|_{L^\infty(\Omega)} \mathrm{d}s \\
&\le \|n_0\|_{L^\infty(\Omega)} + C_2\chi_0 \int_0^t \left(1+(t-s)^{-(3/4)}\right)\left\|\left(\frac{k}{k+c(\cdot,s)}n(\cdot,s)c_x(\cdot,s)\right)\right\|_{L^2(\Omega)} \mathrm{d}s \\
&\quad + C_2\alpha_0 \int_0^t \left(1+(t-s)^{-(3/4)}\right)\left\|\left(a(\cdot,s)n(\cdot,s)a_x(\cdot,s)\right)_x\right\|_{L^2(\Omega)} \mathrm{d}s.
\end{aligned} \tag{25}$$

Here, by means of Hölder's inequality and the nonnegative of c, we can estimate both

$$\begin{aligned}
\left\|\left(\frac{k}{k+c(\cdot,s)}n(\cdot,s)c_x(\cdot,s)\right)\right\|_{L^2(\Omega)} &\le \|n(\cdot,s)\|_{L^2(\Omega)}\left\|c_x(\cdot,s)\right\|_{L^2(\Omega)} \\
&\le \|n(\cdot,s)\|_{L^\infty(\Omega)}^{(1/2)}\|n(\cdot,s)\|_{L^1(\Omega)}^{(1/2)}\left\|c_x(\cdot,s)\right\|_{L^2(\Omega)} \\
&\quad \cdot \left\|\left(a(\cdot,s)n(\cdot,s)a_x(\cdot,s)\right)_x\right\|_{L^2(\Omega)} \\
&\le \|a(\cdot,s)n(\cdot,s)\|_{L^2(\Omega)}\left\|a_x(\cdot,s)\right\|_{L^2(\Omega)} \\
&\le \|n(\cdot,s)\|_{L^\infty(\Omega)}^{(1/2)}\|n(\cdot,s)\|_{L^1(\Omega)}^{(1/2)}\|a(\cdot,s)\|_{L^\infty(\Omega)}\left\|c_x(\cdot,s)\right\|_{L^2(\Omega)}.
\end{aligned} \tag{26}$$

From (14), (16), (19), and (20), there exists $C > 0$ such that

$$\sup_{t\in(0,T)}\|n(\cdot,t)\|_{L^\infty(\Omega)} \le \|n_0\|_{L^\infty(\Omega)} + C\int_0^t \left(1+(t-s)^{-(3/4)}\right)\mathrm{d}s \sup_{t\in(0,T)}\|n(\cdot,t)\|_{L^\infty(\Omega)}^{(1/2)}, \tag{27}$$

for all $T \in (0, T_{\max})$. Thus, recalling estimates (15) and (16), the boundedness of (n, c, a) in $\Omega \times (0, \infty)$ results upon an application of Lemma 1. □

4. Conclusions

We consider a gradient-driven mathematical model of angiogenic response of endothelial cells to a secondary tumor proposed by Anderson et al. in [4]. The model consists of three semilinear parabolic PDEs and assumes that the endothelial cells respond chemotactically to two opposing chemical gradients: a gradient of tumor angiogenic factor and a gradient of angiostatin. The blood vessel is usually very long. We consider the case in which both the primary tumor and the secondary tumor are located in the middle of the blood vessel. The influence of both ends of the blood vessel is neglected. Therefore, we impose homogeneous Neumann boundary conditions on the model. We study the global existence and boundedness of classical solutions of the model. The result can be viewed as the first step to know the large time behavior for the endothelial cell density in tumor growth.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

[1] M. S. O'Reilly, L. Holmgren, Y. Shing et al., "Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a lewis lung carcinoma," *Cell*, vol. 79, no. 2, pp. 315–328, 1994.

[2] M. S. O'Reilly, T. Boehm, Y. Shing et al., "Endostatin: an endogenous inhibitor of angiogenesis and tumor growth," *Cell*, vol. 88, pp. 277–285, 1997.

[3] J. Folkman, "Angiogenesis in cancer, vascular, rheumatoid and other disease," *Nature Medicine*, vol. 1, no. 1, pp. 27–30, 1995.

[4] A. R. A. Anderson, M. A. J. Chaplain, C. García-Reimbert, and C. A. Vargas, "A gradient-driven mathematical model of antiangiogenesis," *Mathematical and Computer Modelling*, vol. 32, no. 10, pp. 1141–1152, 2000.

[5] M. A. J. Chaplain and A. M. Stuart, "A model mechanism for the chemotactic response of endothelial cells to tumour angiogenesis factor," *Mathematical Medicine and Biology*, vol. 10, no. 3, pp. 149–168, 1993.

[6] X. Wei and S. Cui, "Existence and uniqueness of global solutions for a mathematical model of antiangiogenesis in tumor growth," *Nonlinear Analysis: Real World Applications*, vol. 9, no. 5, pp. 1827–1836, 2008.

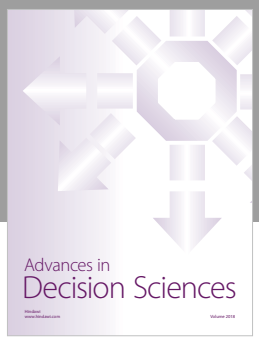
[7] M. Delgado, I. Gayte, C. Morales-Rodrigo, and A. Suárez, "An angiogenesis model with nonlinear chemotactic response and flux at the tumor boundary," *Nonlinear Analysis: Theory, Methods & Applications*, vol. 72, no. 1, pp. 330–347, 2010.

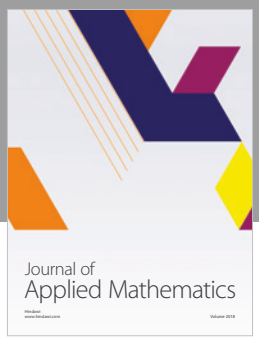
[8] Y. Tao, "Boundedness in a chemotaxis model with oxygen consumption by bacteria," *Journal of Mathematical Analysis and Applications*, vol. 381, no. 2, pp. 521–529, 2011.

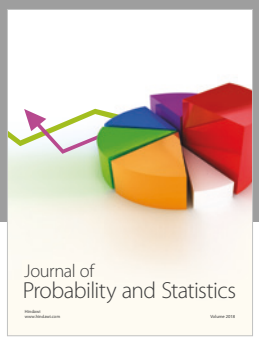
[9] H. Amann, "Nonhomogeneous linear and quasilinear elliptic and parabolic boundary value problems," in *Function Spaces, Differential Operators and Nonlinear Analysis*, pp. 9–126, Springer, Berlin, Germany, 1993.

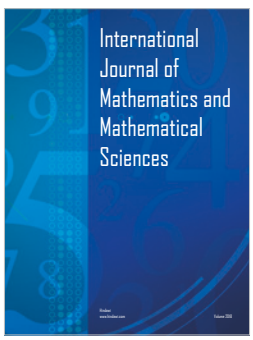
[10] M. Winkler, "Aggregation vs. global diffusive behavior in the higher-dimensional Keller-Segel model," *Journal of Differential Equations*, vol. 248, no. 12, pp. 2889–2905, 2010.

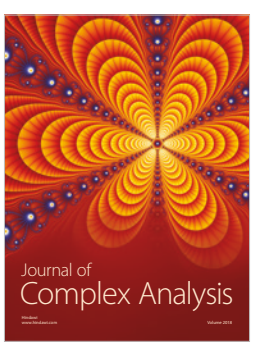
[11] Q. Zhang, "Boundedness in chemotaxis systems with rotational flux terms," *Mathematische Nachrichten*, vol. 289, no. 17-18, pp. 2323–2334, 2016.

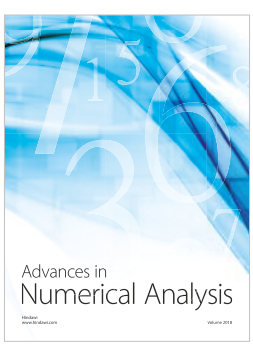


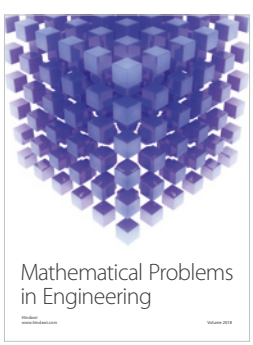


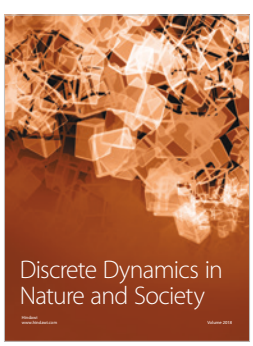


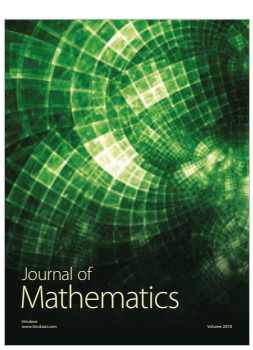


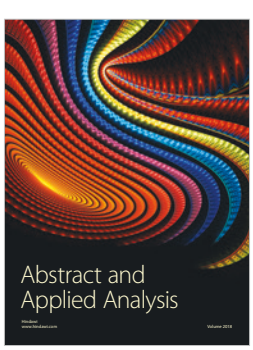


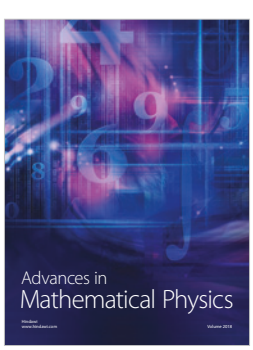












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