Asymptotic dynamics of an anti-angiogenic system in tumour growth

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ABSTRACT

This paper deals with the Neumann initial boundary problem for anti-angiogenic system in tumour growth. The known results show that the problem possesses a unique global-in-time bounded classical solution for some sufficiently smooth initial data. For the large time behaviour of the global solution, by establishing some estimates based on semigroup theory, we prove that the solution approaches to the homogeneous steady state \((\bar{n}_0, 0, 0)\) as \(t \to \infty\), where \(\bar{n}_0\) is the spatial mean of the initial data for the endothelial cell tip density.

1. Introduction

Angiogenesis is the development of new blood vessels from any nearby preexisting vasculature, and it is widely recognized to play a crucial role in cancer metastatic cascade. In the process of metastasis, the endothelial cells from the primary tumour migrate to grow giving rise to secondary tumour. Moreover, it has been observed experimentally that when the primary tumours remain, the secondary tumours cannot be discovered, whereas upon removal of the primary tumours often leads to the rapid growth of many large secondary tumours (Anderson et al., 2000; Folkman, 1995; O’Reilly et al., 1997, 1994).

In order to describe explicitly the phenomenon, Anderson et al. (2000) proposed the following partial differential equation system:

\[
\begin{align*}
\frac{\partial n}{\partial t} &= D_n \frac{\partial^2 n}{\partial x^2} - \frac{\partial}{\partial x} \left( \frac{\chi}{1 + \kappa c} \frac{\partial c}{\partial x} \right), \\
\frac{\partial c}{\partial t} &= D_c \frac{\partial^2 c}{\partial x^2} - \lambda_1 c - nc, \\
\frac{\partial a}{\partial t} &= D_a \frac{\partial^2 a}{\partial x^2} - \lambda_2 a - na,
\end{align*}
\]

where \(n(x,t), c(x,t)\) and \(a(x,t)\) are the endothelial cell tip density, the concentrations of tumour angiogenic factors and the concentrations of angiostatin in the one-dimension domain \([0,L]\), respectively. \(D_n > 0\) is the endothelial cell random motility coefficient, \(D_c > 0\) and \(D_a > 0\) respectively represent the diffusion coefficients of tumour angiogenic factors and angiostatin. The parameters \(\chi, \kappa, a_0, \lambda_1\) and \(\lambda_2\) are nonnegative constants.

It is important and interesting to qualitatively investigate the model (1). The authors in Anderson et al. (2000) studied the steady solution with the boundary condition

\[
\begin{align*}
n_x &= \frac{n}{D_n} \left( \frac{\chi}{1 + \kappa c} + a_0 a c_\infty \right), & x &= 0, L, \quad t > 0, \\
c_x(0,t) &= c_0, \quad c(L,t) = c_0, & t > 0, \\
a(0,t) &= a_0, \quad a_x(L,t) = a_0, & t > 0.
\end{align*}
\]

Moreover, under this framework, Wei and Cui (2008) proved the corresponding initial boundary value problem has a unique global classical solution. When the blood vessel is located at \(x_1\) and the secondary tumour located at \(x_2 (0 < x_1 < x_2 < L)\) and the influence of the both ends is neglected, the authors in Yang and Lu (2020) consider (1) with the special no-flux boundary conditions

\[
\begin{align*}
n_x(0,t) &= n_x(L,t) = 0, & t > 0, \\
c_x(0,t) &= c_x(L,t) = 0, & t > 0, \\
a_x(0,t) &= a_x(L,t) = 0, & t > 0.
\end{align*}
\]

and the initial conditions

\[
\begin{align*}
n(x,0) &= n_0(x), \\
c(x,0) &= c_0(x), \\
a(x,0) &= a_0(x)
\end{align*}
\]
for all $x \in (0, L)$. They obtain the boundedness of the global classical solution for system (1)–(3) with some sufficiently smooth initial data.

Compared with the global solvability results (Wei & Cui, 2008; Yang & Lu, 2020; Zhang & Tao, 2019), very few information seems to know about the qualitative asymptotic dynamics on the problem (1)–(3). In the present paper, we investigate the large time behaviour of the global solution obtained in Yang and Lu (2020) and we prove that the solution $(n, c, a)$ converges to $(\bar{n}_0, 0, 0)$ uniformly in the large time, where

$$\bar{n}_0 = \frac{1}{L} \int_0^L n_0(x) \, dx.$$ 

The rest of the paper is organized as follows. In Section 2, we derive some useful lemmas and prove the main result. In Section 3, we present a numerical example to illustrate the effectiveness of the theoretical analysis result. We then give the conclusion and discussion in Section 4. Throughout the paper, we set $\Omega = (0, L)$ and $\bar{\Omega} = [0, L]$. We denote by $C$ various positive constants which may vary from step to step. $\Gamma(\cdot)$ represents Gamma function. We define $L^p(\Omega)$ to be Lebesgue space.

2. Preliminaries and main results

As a preparation of the proof, let first give an explicit bounds for the global classical solution to the problem (1)–(3).

**Lemma 2.1:** Assume $n_0 \in C^0(\bar{\Omega})$, $c_0 \in W^{1, \infty}(\Omega)$ and $a_0 \in W^{1, \infty}(\Omega)$ are nonnegative functions. Then the problem (1)–(3) has a unique nonnegative global classical solution which is bounded in $\Omega \times (0, \infty)$. Moreover, we have

$$C(\|n_0\|_{L^1(\Omega)}) > 0 \text{ such that}$$

$$\|n(\cdot, t)\|_{L^\infty(\Omega)} \leq \left( \frac{B + \sqrt{B^2 + 4C_1}}{2} \right)^2$$  

where $B = C(\|n_0\|_{L^1(\Omega)})(1 + \Gamma(\frac{1}{4}))$, $C_1 = \|n_0\|_{L^\infty(\Omega)}$, and

$$\|c(\cdot, t)\|_{L^\infty(\Omega)} \leq \|c_0\|_{L^\infty(\Omega)}$$  

as well as

$$\|a(\cdot, t)\|_{L^\infty(\Omega)} \leq \|a_0\|_{L^\infty(\Omega)}$$

for all $t > 0$.

**Proof:** The proof of global solvability in problem (1)–(3) can be found in Yang and Lu (2020). Following the same steps as in the proof of Zhang (2016, Lemma 3.2), we get

$$\sup_{t \in (0, \infty)} \|n(\cdot, t)\|_{L^\infty(\Omega)} \leq \|n_0\|_{L^\infty(\Omega)}$$

$$+ C(\|n_0\|_{L^1(\Omega)})(1 + \Gamma(\frac{1}{4})) \sup_{t \in (0, \infty)} \|n(\cdot, t)\|_{L^\infty(\Omega)}^2$$

which yields (4) from a direct calculation. Since $n$, $c$ and $a$ are nonnegative functions, we get the differential inequalities

$$c_t - D_c c_{xx} \leq 0$$

and

$$a_t - D_a a_{xx} \leq 0$$

in $(0, L) \times (0, \infty)$. Therefore, the maximum principle gives the estimates (5) and (6).

In order to study of the large time behaviour of solutions for (1), we first establish a time-space estimate for $\frac{\partial n}{\partial x}$.

**Lemma 2.2:** Let $n_0 \in C^0(\bar{\Omega})$, $c_0 \in W^{1, \infty}(\Omega)$ and $a_0 \in W^{1, \infty}(\Omega)$, then the first component of solution satisfies

$$\int_0^\infty \int_0^L n_t^2 \, dx \, dt \leq C$$

with some $C > 0$.

**Proof:** Multiplying the second equation in (1) by $c$ and integrating over $(0, L)$, we obtain

$$\frac{1}{2} \frac{d}{dt} \int_0^L c^2 \, dx + D_c \int_0^L c_t^2 \, dx$$

$$= - \int_0^L c^2 \, dx - \int_0^L nc^2 \, dx$$

for all $t > 0$. Due to $D_c > 0$, $n \geq 0$ and $c \geq 0$, by integration over $(0, T)$, it follows that

$$\int_0^T \int_0^L c_t^2 \, dx \leq \frac{1}{2D_c} \int_0^L c_0^2 \, dx$$

for all $T > 0$. Similarly, we test the third equation in (1) by $a$ and integrating over $(0, L)$ to get

$$\int_0^T \int_0^L a_t^2 \, dx \leq \frac{1}{2D_a} \int_0^L a_0^2 \, dx$$

for all $T > 0$. Multiplying the first equation in (1) with $n$, integrating by parts and using Young’s inequality and (6),
we infer that
\[
\frac{1}{2} \frac{d}{dt} \int_0^L n^2 \, dx + D_0 \int_0^L n_x^2 \, dx = \chi \int_0^L \frac{1}{1 + k \epsilon} n n_x \, dx + a_0 \int_0^L \Delta n \, dx \\
\leq \frac{D_0}{2} \int_0^L n_x^2 \, dx + C_1 \int_0^L c_1 \, dx + C_2 \int_0^L \alpha_1^2 \, dx
\]
for all \( t > 0 \), where
\[
C_1 = \frac{\chi^2}{D_0} \|n\|_{L^\infty(\Omega)}^2
\]
and
\[
C_2 = \frac{\alpha_1^2}{D_0} \|a\|_{L^1(\Omega)} \|n\|_{L^2(\Omega)}^2.
\]
Integrating over \((0, T)\) and using (4), (6), (8) and (9), we get (7).

We now establish the \( L^p \)-estimate for \( \frac{\partial c}{\partial x} \) and \( \frac{\partial a}{\partial x} \).

**Lemma 2.3:** Suppose that \( n_0 \in C^0(\bar{\Omega}), c_0 \in W^{1, \infty}(\Omega) \) and \( a_0 \in W^{1, \infty}(\Omega) \). For all \( p > 1 \), there exists \( C > 0 \) such that
\[
\|c_x(\cdot, t)\|_{L^p(\Omega)} \leq C
\]
and
\[
\|a_x(\cdot, t)\|_{L^p(\Omega)} \leq C
\]
for all \( t \in (0, \infty) \).

**Proof:** The proof is based on semigroup arguments. Differentiating the variation-of-constants formula with respect to \( x \) shows that
\[
\left\|c_x(\cdot, t)\right\|_{L^p(\Omega)} \leq \left\|(e^{-tA_1}c_0)_x\right\|_{L^p(\Omega)} + \int_0^t \left\|e^{-(t-s)A_1}(\lambda_1 c - nc)_x\right\|_{L^p(\Omega)} \, ds,
\]
where \( A_1 \) is the realization of the operator \( -D_{x x} \) in \( L^p(\Omega) \) equipped with homogeneous Neumann boundary conditions. According to the smoothing estimates for the Neumann heat semigroup (Winkler, 2010), we can find \( C_1 > 0 \) and \( C_2 > 0 \) such that
\[
\left\|(e^{-tA_1}c_0)_x\right\|_{L^p(\Omega)} \leq C_1 e^{-\lambda t}\|\varphi\|_{L^p(\Omega)}
\]
for all \( \varphi \in W^{1, 2}(\Omega) \) and
\[
\left\|e^{-(t-s)A_1}(\lambda_1 c - nc)_x\right\|_{L^p(\Omega)} \leq C_2 \left(1 + (t - s)^{-\frac{1}{2}}\right) e^{-\lambda t}\|\varphi\|_{L^p(\Omega)}
\]
for all \( \varphi \in L^p(\Omega) \) with \( 1 \leq p \leq \infty \). Then, we can estimate
\[
\|c_x(\cdot, t)\|_{L^p(\Omega)} \leq C_1 \|c_0\|_{L^\infty(\Omega)} + C_2 \int_0^t \left(1 + (t - s)^{-\frac{1}{2}}\right) e^{-\lambda(t-s)}\|\lambda_1 c - nc\|_{L^2(\Omega)} \, ds
\]
\[
\leq C_1 \|c_0\|_{W^{1, \infty}(\Omega)} + C_2 \|\lambda_1 c - nc\|_{L^2(\Omega)}
\]
\[
\leq C_4
\]
for all \( t \in (0, \infty) \), where
\[
C_3 = C_2 \left(\frac{1}{\lambda} + \frac{1}{\sqrt{\lambda}} \Gamma\left(\frac{1}{2}\right)\right).
\]
Let \( A_2 \) be the realization of the operator \( -D_{x x} \) in \( L^p(\Omega) \) equipped with homogeneous Neumann boundary conditions. Using similar arguments to the variation-of-constants formula of the third equation
\[
a(\cdot, t) = e^{-tA_2}a_0 + \int_0^t e^{-(t-s)A_2}(\lambda_2 a - na)(\cdot, s) \, ds,
\]
we obtain the boundedness of \( \|a_x(\cdot, t)\|_{L^p(\Omega)} \) for all \( t \in (0, T_{\text{max}}) \).

In the proof of convergence for the first component of solution \( n \), we shall need the following lemma.

**Lemma 2.4:** Let \( u \in C^0(\bar{\Omega} \times [0, \infty)) \) satisfy
\[
\left\|u\right\|_{C^0([\Omega \times [t+1]- \infty)} < \infty
\]
for all \( t \geq 1 \). If there exists a positive constant \( \bar{u} \) such that
\[
\int_0^\infty \int_0^L |u(x, t) - \bar{u}|^2 \, dx \, dt < \infty,
\]
then we have
\[
u(\cdot, t) \to \bar{u} \quad \text{in} \quad C^0(\bar{\Omega})
\]
as \( t \to \infty \).

**Proof:** The proof is based on compactness arguments, see Hirata et al. (2017, Lemma 4.6) for details.
**Lemma 2.5:** Assume that the initial data $n_0 \in C^0(\bar{\Omega})$, $c_0 \in W^{1,\infty}(\Omega)$ and $a_0 \in W^{1,\infty}(\Omega)$. Then the first component of solution for the system (1)–(3) satisfies
\[
n(x, t) \to \tilde{n}_0 \quad \text{in } L^\infty(\Omega) \quad \text{as } t \to \infty,
\]
where $\tilde{n}_0 := \frac{1}{L} \int_0^L n_0 \, dx$.

**Proof:** We first prove that there exist $\theta > 0$ and $C > 0$ such that
\[
\|n\|_{C^0([0, \infty) \times [t])} \leq C
\]
for all $t \geq 1$. In fact, note that $n$ is the solution of the Neumann problem
\[
n_t - \left( D_n n_x - \frac{x}{1 + \kappa} n c_x - \alpha_0 a n a_x \right)_x = 0
\]
with $n(x, 0) = n_0(x)$. Since
\[
n_t \left( D_n n_x - \frac{x}{1 + \kappa} n c_x - \alpha_0 a n a_x \right)
\geq \frac{D_n}{2} n_x^2 - C(c_x^2 + a_x^2)
\]
by the Cauchy inequality and
\[
\left| D_n n_x - \frac{x}{1 + \kappa} n c_x - \alpha_0 a n a_x \right|
\leq \frac{D_n}{2} |n_x| + C(|c_x| + |a_x|).
\]
Therefore, by the use of (10) and (11), according to the standard parabolic regularity arguments (see Li et al., 2015, Lemma 4.3 and Porzio & Vespri, 1993, Theorem 1.3), we have (14).

Applying the Poincaré’s inequality
\[
\left\| \varphi - \frac{1}{|\Omega|} \int_\Omega \varphi \right\|_{L^2(\Omega)}^2 \leq C_p \| \nabla \varphi \|_{L^2(\Omega)}^2
\]
with $\varphi = n$ and $\Omega = (0, L)$, it follows from (7) that
\[
\int_0^\infty \int_0^L |n(x, t) - \tilde{n}_0|^2 \, dx \, dt
\leq C_p \int_0^\infty \int_0^L |n_x|^2 \, dx \, dt
\leq C_4
\]
with some $C_4 > 0$. As a direct consequence of Lemma 2.4, we have
\[
n(x, t) \to \tilde{n}_0 \quad \text{in } C^0(\bar{\Omega}) \quad \text{as } t \to \infty,
\]
which completes the proof of the lemma. \qed

With the aid of asymptotic property of $n$, we can now acquire the decay results concerning $c$ and $a$.

**Lemma 2.6:** For the initial data $n_0 \in C^0(\bar{\Omega})$, $c_0 \in W^{1,\infty}(\Omega)$ and $a_0 \in W^{1,\infty}(\Omega)$, we have the second and third components of solution for the system (1)–(3) fulfil
\[
c(x, t) \to 0 \quad \text{in } L^\infty(\Omega)
\]
and
\[
a(x, t) \to 0 \quad \text{in } L^\infty(\Omega)
\]
exponentially as $t \to \infty$.

**Proof:** From Lemma 2.5, we can find $T > 0$ such that
\[
n(x, t) \geq \tilde{n}_0 \quad \text{for all } (x, t) \in (0, L) \times [T, \infty).
\]
Since $c \geq 0$, we compute by the second equation in (1) to yield
\[
c_t = D_c c_x - \lambda_1 c - nc
\leq D_c c_x - \lambda_1 c - \tilde{n}_0 c
= D_c c_x - (\lambda_1 + \tilde{n}_0) c
\]
for all $(x, t) \in (0, L) \times [T, \infty)$. Let $y_1 \in C^1[0, \infty)$ be the solution of the initial-value problem
\[
\begin{cases}
y_1'(t) + (\lambda_1 + \tilde{n}_0) y_1(t) = 0, \\
y_1(T) = \|c(T)\|_{L^\infty(\Omega)}.
\end{cases}
\]
Then the comparison principle gives
\[
c(x, t) \leq y_1(t)
\]
for all $(x, t) \in (0, L) \times [T, \infty)$. Upon directly solving the initial value problem (15), we have
\[
y_1(t) = \|c(T)\|_{L^\infty(\Omega)} e^{-(\lambda_1 + \tilde{n}_0)(T-t)}
\]
for all $t \in [T, \infty)$. Then, according to (5), we get
\[
c(x, t) \leq \|c\|_{L^\infty(\Omega)} e^{-(\lambda_1 + \tilde{n}_0)(T-t)}
\]
for all $(x, t) \in (0, L) \times [T, \infty)$. Hence, we have
\[
\|c(, t)\|_{L^\infty(\Omega)} \to 0
\]
exponentially as $t \to \infty$. We can use a similar approach to obtain
\[
a(x, t) \leq y_2(t)
\]
for all $(x, t) \in (0, L) \times [T, \infty)$, where $y_2 \in C^1[0, \infty)$ denotes the solution of the initial value problem
\[
\begin{cases}
y_2'(t) + (\lambda_2 + \tilde{n}_0) y_2(t) = 0, \\
y_2(T) = \|a(T)\|_{L^\infty(\Omega)}.
\end{cases}
\]
Therefore,
\[ a(x, t) \leq \|a_0\|_{L^\infty(\Omega)} e^{-(\lambda_2 + \bar{n}_0)(t-T)} \]
for all \((x, t) \in (0, L) \times [T, \infty)\), which yields
\[ \|a(\cdot, t)\|_{L^\infty(\Omega)} \to 0 \]
exponentially as \(t \to \infty\). This completes the proof. ■

With the aid of the above lemmas, we can now get the main result of the present paper.

**Theorem 2.7:** Suppose that \(n_0 \in C^0([0, L]), \ c_0 \in W^{1,\infty}(0, L)\) and \(a_0 \in W^{1,\infty}(0, L)\) are nonnegative functions. Then the solution of the problem (1)–(3) satisfies
\[ (n, c, a) \to (\bar{n}_0, 0, 0) \]
as \(t \to \infty\) uniformly with respect to \(x \in (0, L)\), where
\[ \bar{n}_0 = \frac{1}{L} \int_0^L n_0(x) \, dx. \]

**Proof:** Employing Lemmas 2.5 and 2.6, we directly obtain Theorem 2.7. ■

### 3. Simulations

In order to illustrate the asymptotic result of the present paper, we present a numerical simulation with Python 3.7.4. Since the two equations in (1) governing the concentrations of tumour angiogenic factors and angiostatin are of the similar structure, we fix \(\alpha = 0\) for simplicity. Other system parameters are \(D_n = D_c = D_a = \chi = 1, \lambda_1 = \lambda_2 = \kappa = 0, \ L = 3\). We choose the initial data as
\[
\begin{align*}
n_0(x) &= \frac{4}{27} \left(9x^2 - 2x^3\right), \\
c_0(x) &= 1 + \cos \frac{\pi}{3}x, \\
a_0(x) &= 0.
\end{align*}
\]

From Figures 1(a and b) we find that the solution component \(n(x, t)\) approaches to 2 (the mean of \(n_0(x)\) on the interval \([0, L]\)) and \(c(x, t)\) converges to 0 uniformly as time \(t\) goes on, which is consistent with our analytical result in Theorem 2.7.

### 4. Conclusion

It is important and interesting to understand the system (1) from a mathematical point of view. In the present paper, we study the large time behaviour of the solution. We derive the solution stabilizes to the spatially uniform equilibrium \((\bar{n}_0, 0, 0)\) uniformly on \([0, L]\) as \(t \to \infty\). The result can provide deep insight into the process of suppression of secondary tumours by the primary tumour.

Time delay always accompanies with anti-angiogenic system in tumour growth, which may lead to oscillation and instability (Qian, Li, Chen, et al., 2020; Qian, Li, Zhao, et al., 2020; Suriyon & Piyapong, 2020). But these may require different method, it needs to be discussed in the future work.

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