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On the existence and uniqueness of the steady-state solution in a tumor angiogenesis model

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Abstract: We prove the existence and uniqueness of the steady-state solution of a nonlinear parabolic equation modeling the capillary formation in tumor angiogenesis. The analysis is based on the Lax-Milgram Theorem in variational calculus. Proving the existence and uniqueness of this steady-state shows that there is only one way for endothelial cells to follow the trail of transition probability density function.

Keywords: Existence; uniqueness; capillary formation; tumor angiogenesis; steady-state solution.

1 Introduction

Let us consider the following initial boundary-value problem:

$$\frac{\partial u}{\partial t} = D\frac{\partial}{\partial x}\left(u\frac{\partial}{\partial x}\left(\ln\frac{u}{f(x)}\right)\right), \ (x,t) \in \Omega_T := (0,1)\times(0,T], \tag{1}$$

$$u(x,0) = 1 \ , \ x \in (0,1), \tag{2}$$

$$Du\frac{\partial}{\partial x}\left(\ln\frac{u}{f(x)}\right)\Big|_{x=0,1} = 0 \ , \ t \in (0,T]. \tag{3}$$

Here

$$f(x) = \left(\frac{a+Ax^n(1-x)^n}{b+Ax^n(1-x)^n}\right)^{\alpha_1}\left(\frac{c+1-Bx^n(1-x)^n}{d+1-Bx^n(1-x)^n}\right)^{\alpha_2}, n > 10 \tag{4}$$

is the so called transition probability density function (TPDF) [1]. Also, $u(x,t)$ is the concentration of Endothelial Cells (EC), D is the cell diffusion constant and $a,b,c,d,A,B,n,\alpha_1,\alpha_2$ are some positive arbitrary constants. As stated in [4,5] ECs are to be stimulated by a tumor angiogenic factor for angiogenesis to occur. After the ECs are stimulated they will follow the trail of TPDF (see also [8]).

This model has originally been presented in [6], and has been studied numerically and qualitatively in [7,8], respectively. Also, a two dimensional steady-state analysis of a mathematical model for capillary network formation in the absence of tumor source is given in [9]. Some interesting mathematical analysis of a mathematical model of tumor dynamics in competition with the immune system is given in [1].

Eq.(1) can be written

$$\frac{\partial}{\partial x}\left(u\left(\frac{\partial}{\partial x}\left(\ln\frac{u}{f(x)}\right)\right)\right) = u_{xx} - \left(u\frac{f'(x)}{f(x)}\right)_x.$$

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Therefore, by setting $F(x) = \dfrac{f'(x)}{f(x)}$ Eq.(1) reads as follows:

$$u_t = D\left(u_{xx} - (uF)_x\right). \tag{5}$$

Therefore, our original problem becomes:

$$u_t = D(u_{xx} - (uF)_x)\ ,\ \forall (x,t) \in \Omega_T := (0,1)\times(0,T] \tag{6}$$
$$u(x,0) = 1\ ,\ \forall x \in \Omega_T \tag{7}$$
$$u_x(x,t)|_{x=0,1} = uF\ ,\ \forall t \in (0,T]. \tag{8}$$

Since $F(x) = 0$ at $x = 0,1$, the boundary conditions in Eq.(8) become:

$$u_x(x,t)|_{x=0,1} = 0.$$

2 Constructing the bilinear form

Let us consider the following operator:

$Lu := -u_{xx} + (uF)_x.$

Since we are interested in the existence and uniqueness of the steady-state solution, we consider the following initial-boundary problem:

$$-u_{xx} + (uF)_x = 0\ ,\ (x,t) \in \Omega_T \tag{9}$$
$$u(x,0) = 1\ ,\ x \in (0,1) \tag{10}$$
$$u_x(x,t)|_{x=0,1} = 0\ ,\ \forall t \in (0,T]. \tag{11}$$

One can easily see from Eq.(6) that $u(x,t) \in C^2([0,1]) \times C^1([0,T])$, $F(x) \in C^1([0,1])$. We now multiply the Eq.(9) by a function $v(x,t)$ that has the same properties as $u(x,t)$, and integrate it over Ω_T. Therefore, we have

$$\int_0^T \int_0^1 (-u_{xx}v + (uF)_x v)dxdt = \int_0^T \int_0^1 (u_x v_x - Fuv_x)dxdt. \tag{12}$$

Since the function $v(x,t)$ has the same properties as $u(x,t)$ the following equality holds for $v(x,t)$, as well. Therefore, from Eq.(9) we obtain

$$-v_{xx} + vF'(x) = -v_x F(x) \text{ on } \Omega_T. \tag{13}$$

By the aid of Eq.(13), the right hand side of the Eq.(12) becomes:

$$\int_0^T \int_0^1 (u_x v_x - u v_{xx} + u v F'(x)) dxdt = \int_0^T \int_0^1 (2u_x v_x + F'(x) uv) dxdt. \tag{14}$$

By the maximum principle, it is clear from Eq.(10) that $u(x,t) > 0$, for all $(x,t) \in \Omega_T$. On the other hand, by the first mean value theorem for integration there exists $\lambda \in [0,1]$ such that

$$\int_0^T \int_0^1 F'(x) uv dxdt = F'(\lambda) \int_0^T \int_0^1 uv dxdt. \tag{15}$$

Hence, if we plug Eq.(15) in Eq.(14) the bilinear form can be chosen as follows

$$a(u,v) = 2\int_0^T \int_0^1 u_x v_x dxdt + F'(\lambda) \int_0^T \int_0^1 uv dxdt. \tag{16}$$

In fact, by the construction of Eq.(16), we can say that the weak solution of the problem given by Eqs.(9)-(11) belongs to the class

$$W_2^1(\Omega_T) := \left\{ u \in \Omega_T | \int_{\Omega_T} [(u)^2 + (u_x)^2] d\Omega_T < \infty, \;\; u_x(x,t)|_{x=0,1} = 0 \right\}.$$

This is a first order Sobolev space endowed with a norm (for details of Sobolev Spaces see also [2])

$$\|u\|_{1,2} = \left(\int_G [(u)^2 + (u_x)^2] dG \right)^{1/2}.$$

One can easily see from the last equality that

$$\|u\|_2^2 + \|u_x\|_2^2 = \|u\|_{1,2}^2. \tag{17}$$

Here, $\|.\|_2$ indicates the L_2 norm in this space. From Eq.(17) we can see that following two inequalities hold:

$$\|u\|_2 \leq \|u\|_{1,2} \;\; \|u_x\|_2 \leq \|u\|_{1,2}. \tag{18}$$

Moreover, in the following section, we prove that the norms $\|u_x\|_2$ and $\|u\|_{1,2}$, and $\|u\|_2$ and $\|u\|_{1,2}$ are equivalent.

3 Equivalency of norms

Lemma 3.1: We consider the problem given by Eqs.(9)-(11). Then, the following inequality holds

$$\|u_x\|_2 \leq K\|u\|_2, \tag{19}$$

where $K := \max_{x\in[0,1]} |F(x)|$.

Proof: Since $F(x) \in C^1([0,1])$ it has a maximum over $[0,1]$. Let us multiply both sides of Eq.(9) by $u(x,t)$, and then integrate over Ω_T:

$$0 = \int_0^T \int_0^1 (u_x)^2 dxdt - \int_0^T \int_0^1 F u u_x dxdt. \tag{20}$$

Therefore,

$$\int_0^T \int_0^1 (u_x)^2 dxdt = \int_0^T \int_0^1 F u u_x dxdt \tag{21}$$

$$\leq K \int_0^T \int_0^1 u u_x dxdt. \tag{22}$$

Using Holder inequality for the inequality obtained in Eq.(22) we obtain

$$\|u_x\|_2^2 \leq K\|u\|_2\|u_x\|_2, \tag{23}$$

which follows that

$$\|u_x\|_2 \leq K\|u\|_2. \tag{24}$$

Lemma 3.2: *(i)* The norms $\|u\|_{1,2}$ and $\|u\|_2$ are equivalent.

(ii) The norms $\|u\|_{1,2}$ and $\|u_x\|_2$ are equivalent.

Proof: *(i)* We must show that there exist $\alpha, \beta > 0$ such that $\beta\|u\|_2 \leq \|u\|_{1,2} \leq \alpha\|u\|_2$. By Eq.(18) β must be equal to 1. On the other hand, it is easy to see from Eq.(17) and Eq.(24) that α must be equal to $\sqrt{(K^2+1)}$. This implies the following inequalities:

$$\|u\|_2 \leq \|u\|_{1,2} \leq \sqrt{(K^2+1)}\|u\|_2. \tag{25}$$

(ii) As in the previous proof, we must show that there exist $\alpha, \beta > 0$ such that $\beta\|u_x\|_2 \leq \|u\|_{1,2} \leq \alpha\|u_x\|_2$. Again β must be equal to 1. Now we must find the number α. We know from the definitions of norms $\|u\|_{1,2} < \infty$ and $\|u_x\|_2 < \infty$. Therefore, it is true that there exist $M_1, M_2 > 0$ such that $\|u\|_{1,2} = M_1$, $\|u_x\|_2 = M_2$. By the inequality in Eq.(18) we have $M_2 \leq M_1$. Finally, by the Archimedean property there exists $\alpha \in N$ such that $M_1 \leq \alpha M_2$. Then, the following holds as well:

$$\|u_x\|_2 \leq \|u\|_{1,2} \leq \alpha\|u_x\|_2. \tag{26}$$

A different proof of this Lemma is given in [11].

4 Boundedness of the bilinear form a(u,v)

Theorem 4.1: The bilinear form $a(u,v) = 2\int_0^T\int_0^1 u_x v_x dxdt + F'(\lambda)\int_0^T\int_0^1 uvdxdt$ is bounded.

Proof:

$$
\begin{aligned}
|a(u,v)| &= \left|2\int_0^T\int_0^1 u_x v_x dxdt + F'(\lambda)\int_0^T\int_0^1 uvdxdt\right| && (27)\\
&\leq 2\int_0^T\int_0^1 |u_x v_x| dxdt + |F'(\lambda)|\int_0^T\int_0^1 |uv| dxdt && (28)\\
&\leq C\left\{\int_0^T\int_0^1 |u_x v_x| dxdt + \int_0^T\int_0^1 |uv| dxdt\right\} && (29)\\
&\leq C\left\{\|u_x\|\|v_x\| + \|u\|\|v\|\right\}, && (30)
\end{aligned}
$$

by the aid of Holder inequality, where $C := max\{2, |F'(\lambda)|\}$. We now use the inequality in Eq.(24), and obtain

$$|a(u,v)| \leq M\|u\|_{1,2}\|v\|_{1,2}, \tag{31}$$

where $M := C(1+K^2)$. This shows that the bilinear form a(u,v) is bounded.

5 Coercivity of the Bilinear Form a(u,u)

Theorem 5.1: If $F'(\lambda) > -2K^2$ then the bilinear form $a(u,u) = 2\int_0^T\int_0^1 u_x^2 dxdt + F'(\lambda)\int_0^T\int_0^1 u^2 dxdt$ is coercive.

Proof: We must show that there exist a $B > 0$ such that $a(u,u) \geq B\|u\|_{1,2}^2$. Now, if we use the Lemma 3.1 and Eq.(26) we obtain

$$
\begin{aligned}
a(u,u) &= 2\int_0^T\int_0^1 u_x^2 dxdt + F'(\lambda)\int_0^T\int_0^1 u^2 dxdt && (32)\\
&\geq (2+K^{-2}F'(\lambda))\int_0^T\int_0^1 u_x^2 dxdt && (33)\\
&\geq \alpha^{-2}(2+K^{-2}F'(\lambda))\|u\|_{1,2}^2. && (34)
\end{aligned}
$$

Let $B = \alpha^{-2}(2+K^{-2}F'(\lambda)) > 0$. Hence, this implies that

$$a(u,u) \geq B\|u\|_{1,2}^2, \tag{35}$$

which shows the coercivity of the bilinear form a(u,u).

In conclusion we have proved that the steady-state solution of the problem defined by Eqs.(1)-(3) is unique according to the Lax-Milgram Theorem (For details of coercivity of a bilinear form see also [10]).

6 What if f(x) is not a transition probability density function?

The stability of the steady-state solution of the problem given in Eqs.(1)-(3) with $f(x)$ is given by Eq.(4) is studied in [8]. Suppose we now take $f(x) = Ce^x$ in Eq.(1) where C is a nonzero constant. Since this function is not of the form of Eq.(4), it is not a TPDF. In this case, the problem given in Eqs.(6)-(8) becomes:

$$u_t = Du_{xx} - au_x \ , \ \forall(x,t) \in \Omega_T \tag{36}$$

$$u(x,0) = 1 \ , \ \forall x \in (0,1) \tag{37}$$

$$u_x(x,t)|_{x=0,1} = 0 \ , \ \forall t \in (0,T] \tag{38}$$

where $a = CD$. Now, let us consider the transformation [3]

$$u(x,t) = \exp(\frac{ax}{2D} - \frac{a^2t}{4D})w(x,t), \tag{39}$$

so that the problem obtained in Eqs.(36)-(38) becomes:

$$w_t = Dw_{xx} \ , \ \forall(x,t) \in \Omega_T \tag{40}$$

$$w(x,0) = e^{-ax/2D} \ , \ \forall x \in (0,1) \tag{41}$$

$$\frac{a}{2D}w(x,t) + w_x(x,t)|_{x=0,1} = 0 \ , \ \forall t \in (0,T] \tag{42}$$

This is an initial-boundary value problem for a heat equation. We solve Eqs.(40)-(42) using separation of variables by setting $w(x,t) = \Phi(x)\Psi(t)$ to obtain

$$\frac{\Psi'(t)}{D\Psi(t)} = \frac{\Phi''(x)}{\Phi(x)} = -\lambda^2, \tag{43}$$

where λ is a constant. From Eq.(43) we obtain

$$\Psi'(t) + \lambda^2 D\Psi(t) = 0 \tag{44}$$

$$\Phi''(x) + \lambda^2\Phi(x) = 0. \tag{45}$$

In the case $\lambda = 0$ we have $\Psi(t) = \alpha$ and $\Phi(x) = c_1x + c_2$, where α, c_1 and c_2 are arbitrary constants. From the boundary conditions in Eq.(42) we obtain $c_1 = 0$. Therefore, one gets $w_0(x,t) = \kappa$, where κ is constant. Since we know from the eigenvalue property of Sturm-Liouville problem λ can not be negative. We now suppose $\lambda > 0$. In this case it is clear from Eq.(44) that $\Psi(t)$ is of the form $Me^{-\lambda^2 Dt}$, where M is a positive constant and D is the cell diffusion constant. Also, $\Phi(x)$ has the form $\Phi(x) = A\cos\lambda x + B\sin\lambda x$. From the boundary conditions in Eq.(42), we get the eigenvalues $\lambda_n = n\pi$, where $n = 1,2,3\ldots$, and the eigenfunctions corresponding to these eigenvalues $\Phi_n(x) = A\cos n\pi x + B\sin n\pi x$, and $\Psi_n(t) = Me^{-n^2\pi^2 Dt}$. Therefore, one gets the series form of the solution

$$w(x,t) = w_0(x,t) + \sum_{n=1}^{\infty} w_n(x,t) \tag{46}$$

$$= \kappa + M \sum_{n=1}^{\infty} e^{-n^2\pi^2 Dt}(A\cos n\pi x + B\cos n\pi x), \tag{47}$$

which follows that

$$u(x,t) = \exp(\frac{ax}{2D} - \frac{a^2 t}{4D})(\kappa + M \sum_{n=1}^{\infty} e^{-n^2\pi^2 Dt}(A\cos n\pi x + B\cos n\pi x)). \tag{48}$$

As it is clear from the last equality, one obtains

$$u(x,t) \to 0 \text{ as } t \to \infty. \tag{49}$$

On the other hand, since we are looking for the steady-state solution of the problem in Eqs.(36)-(38) we have to solve the following boundary value problem:

$$Du''(x) - au'(x) = 0 \ , \ \forall x \in (0,1) \tag{50}$$

$$u'(0) = u'(1) = 0. \tag{51}$$

It is clear that any nonzero constant satisfies the problem in Eqs.(50)-(51), which contradicts with the result in Eq.(49). In conclusion, the steady-state solution is unstable with this choice of $f(x)$.

7 Conclusions and Biological Discussions

In this paper we first proved the existence and uniqueness of the steady state solution of the problem in Eqs.(1)-(3). The inequalities in Eq.(31) and Eq.(35) satisfy the conditions of the Lax-Milgram Theorem. Therefore, we can say that there exists one and only one solution of the problem in Eqs.(9)-(11). This implies that the steady-state solution of the problem in Eqs.(1)-(3) is unique, which means that there is only one way for ECs to follow the trail of TPDF.

In [8] the authors took the TPDF as

$$f(x) = \left(\frac{a_1 + c_a(x)}{a_2 + c_a(x)}\right)^{\gamma_1} \left(\frac{b_1 + \tilde{f}(x)}{b_2 + \tilde{f}(x)}\right)^{\gamma_2},$$

where $c_a(x) = Ax^n(1-x)^n$ and $\tilde{f}(x) = 1 - Bx^n(1-x)^n$ are the active enzyme and fibronectin concentrations, respectively. Here a_i, b_i $(i = 1,2)$ are the constants such that $0 < a_1 \ll 1 < a_2$ and $b_1 > 1 \gg b_2 > 0$. Also, A and B are the same as in Eq.(4), and γ_1, γ_2, n are some positive constants. From the above choice of $f(x)$, they also observed that endothelial cells prefer to move into the region where c_a is large or where $\tilde{f}$ is small. By proving the uniqueness of the steady-state solution of our model equation, one observes that the preference of the ECs is unique.

We lastly showed that the steady-state solution of our model equation is unstable in the case where $f(x)$ is not a TPDF. This fact is not a surprise to us, since in [8] the authors showed that the long-time tendency of ECs are towards the TPDF.

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