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On the qualitative analysis of the uniqueness of the movement of endothelial cells

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Abstract

This paper extends the work of Pamuk (2003) by showing mathematically that the movement of endothelial cells, to the regions where active enzyme is large or where fibronectin is small, is unique. To do this, we obtain the existence and uniqueness of the steady-state solution of an initial-boundary value problem which mathematically models endothelial cell movement in tumor angiogenesis. A specific example showing the instability of this steady-state solution is provided.

Key Words: Existence; uniqueness; tumor angiogenesis; steady-state solution; transition probability density function.

1. Introduction

Angiogenesis is a morphogenic process whereby new blood vessels are induced to grow out of a pre-existing vasculature. It is essential for tumor progression and is critical for the growth of primary cancer. It is well known that it occurs in three sequential steps [13]. First, the endothelial cell (EC) lining the vascular basal lamina (BL) (or basement membrane) degrade this membrane. Second, the EC migrate and proliferate (via mitosis) into the extra cellular matrix (ECM). Finally, capillary loops form. In recent years, progress has been made to understand this phenomenon at the molecular level. This includes the identification of potent angiogenic factors, the discovery of the role of proteases, the importance of the ECM, and the emerging characterization of signal transduction pathways in EC.

One of the major components of the ECM is fibronectin, a large, highly adhesive glycoprotein particularly abundant in plasma, connective tissue matrices, and BL [8]. It is also known to enhance EC adhesion to collagen and is produced by EC. The simplest unifying interpretation of these findings is that it functions as adhesive proteins that bind cells to other cells or to a substrate. Fibronectin-treated cells also migrate more rapidly, both as single cells or as masses of cells migrating out from cell aggregates [14].

As stated in [4] and [5] EC are to be stimulated by a tumor angiogenic factor for angiogenesis to occur. After the EC are stimulated they will follow the trail of transition probability density function of active enzyme and fibronectin (TPDF) (see also [11]).

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There have been many mathematical models describing tumor angiogenesis such as the models in Refs. [1], [7], [10]–[12]. Also, mathematical analyses on the foundations of cancer modeling have been presented in some of these studies. For example, in [11] the Author proves mathematically that the long-time tendency of EC governed by the model equation originally developed in [7] is toward TPDF, and shows that the steady-state solution of the equation is, in fact, stable. Similarly, a steady-state analysis of the two dimensional version of the same model in the absence of tumor source is given in [12].

The main aim of this paper is to extend the work done in [11] by showing mathematically that the tendency of EC to the TPDF is unique; i.e., we want to show that the movement of EC, into the regions where active enzyme is large or where fibronectin is small, is unique. To do this, the existence and uniqueness of the steady-state solution of an initial-boundary value problem which mathematically models EC movement in tumor angiogenesis are obtained using the Lax-Milgram Theorem.

The layout of the remainder of this paper is as follows: in Section 2 we describe our modeling assumptions, and write down our one dimensional model equations originally presented in [7]. In Section 3, we provide a mathematical analysis to obtain the existence and uniqueness of the steady-state solution of the model. In section 4, we introduce a specific example for our model by choosing TPDF that has a non-unimodal distribution form, and observe that the steady-state solution of the model is, in fact, instable. Finally, we close the paper by presenting the conclusions and the discussions on the biological importance of our results.

2. Modeling assumptions

We envisage a capillary segment of length l microns located along the x axis, and rescale x by x/l so that we have $0 \leq x \leq 1$. Also, we make the following assumptions on the biochemistry of angiogenesis and its inhibition [11].

V denotes a molecule of angiogenic factor (substrate) and R_{E} denotes a receptor on the EC wall; they combine to produce an intermediate complex, $R_{\mathrm{E}}V$ which is an activated state of the receptor that results in the production and secretion of proteolytic enzyme, C and a modified intermediate receptor R'_{E}. The receptor R'_{E} is subsequently removed from the surface by a mechanism that is presumed to be very fast in the time scale of the production of protease C. The receptor R'_{E} is then either recycled back to the cell surface to again become R_{E} or it is degraded and new R_{E} is synthesized, which then moves to the cell surface to replace the R_{E} that had been removed.

The point of view is that the receptors at the surface of the cell function in the same way as an enzyme functions in classical enzymatic catalysis. In symbols:

$$V + R_{\mathrm{E}} \rightleftharpoons \Big[R_{\mathrm{E}}V\Big] \rightarrow C + R_{\mathrm{E}}. \tag{2.1}$$

Here we consider angiostatin stimulates EC to produce an inhibitor I according to the mechanism

$$\begin{aligned} A + R_{\mathrm{EA}} &\rightleftharpoons \Big[AR_{\mathrm{EA}}\Big] \rightarrow I + R_{\mathrm{EA}}, \\ C_{\mathrm{A}} + I &\rightleftharpoons C_{\mathrm{I}}, \end{aligned} \tag{2.2}$$

where R_{EA} is a receptor protein on the endothelial cell wall and $[AR_{\mathrm{EA}}]$ is the intermediate complex. Moreover, A is angiostatin and I is a protease inhibitor produced by the endothelial cells in response to the angiostatic agent by an overall mechanism which we will assume to be of Michaelis-Menten type. Here C_{I} denotes the proteolytic enzyme molecules that are inhibited by the inhibitor I from functioning as a catalyst for fibronectin degradation while C_{A} denotes those molecules, which degrade fibronectin. In terms of concentrations, $[C] = [C_{\mathrm{A}}] + [C_{\mathrm{I}}]$. Assuming that the reaction in the second equation of (2.2) is in equilibrium, we have that $[C_{\mathrm{I}}] = \nu_e[I][C_{\mathrm{A}}]$, where ν_e is the equilibrium constant for this step. In general, the larger ν_e is, the more efficacious the angiostatin will be in the inhibition of angiogenesis.

The decay of fibronectin F via protease is assumed to satisfy a reaction mechanism of the form

$$C_{\mathrm{A}} + F \rightleftharpoons \Big[C_{\mathrm{A}}F\Big] \rightarrow \quad C_{\mathrm{A}} + F', \tag{2.3}$$

which shows that C_{A} acts as a catalyst to convert the fibronectin into products F'.

We use the following notation for the concentrations of the various chemical species along the capillary wall in units of μM (micro moles per cubic liter):

$$\begin{aligned}
v(x,t) &= \text{angiogenic factor},\\
c(x,t) &= \text{proteolytic enzyme},\\
c_{\mathrm{a}}(x,t) &= \text{active proteolytic enzyme},\\
c_{\mathrm{i}}(x,t) &= \text{inhibited proteolytic enzyme},\\
i_{\mathrm{a}}(y,t) &= \text{protease inhibitor},\\
f(x,t) &= \text{fibronectin},\\
a(x,t) &= \text{angiostatin},\\
u(x,t) &= \text{endothelial cell density},
\end{aligned}$$

where t indicates the time variable. If we now apply the law of mass action to the equations (2.1)–(2.3) (see [7] for details), which asserts that the rate of reaction is proportional to the product of the concentrations of the reactants, we obtain the following system of equations:

$$\begin{aligned}
\frac{\partial v}{\partial t} &= -\frac{\lambda_1 v}{1+\nu_1 v}\frac{u}{u_0} + v_r(x,t),\\
\frac{\partial c}{\partial t} &= \frac{\lambda_1 v}{1+\nu_1 v}\frac{u}{u_0} - \mu c,\\
\frac{\partial f}{\partial t} &= \frac{4}{T_{\mathrm{f}}} f\left(1-\frac{f}{f_0}\right)\frac{u}{u_0} - \frac{\lambda_3 c_{\mathrm{a}} f}{1+\nu_3 f},\\
\frac{\partial a}{\partial t} &= -\frac{\lambda_2 a}{1+\nu_2 a}\frac{u}{u_0} + a_r(x,t),
\end{aligned}$$

$$\begin{aligned} \frac{\partial \iota_{\mathrm{a}}}{\partial t} &= \frac{\lambda_2 a u}{1+\nu_2 a} - \frac{\iota_{\mathrm{a}}(x,t)}{T_{rel}}, \\ c &= c_{\mathrm{i}} + c_{\mathrm{a}}, \\ c_{\mathrm{i}} &= \nu_e \iota_{\mathrm{a}} c_{\mathrm{a}}, \end{aligned} \tag{2.4}$$

where $\lambda_i, \nu_i (i = 1, 2, 3)$ are kinetic parameters, u_0, f_0 are some reference numbers for EC and fibronectin, respectively, T_{f} is fibronectin generation time, T_{rel} is angiostatin relaxation time, v_r is the rate at which growth factor is being supplied to the capillary from the tumor and a_r, the source term for angiostatin, will be taken to be constant in the therapeutic case.

Furthermore, if we use the theory of reinforced random walk [2], we obtain the EC movement equation (see [7] for the derivation of the following equation) as follows

$$\frac{\partial u}{\partial t} = D \frac{\partial}{\partial x}\left(u \frac{\partial}{\partial x}\left(\ln \frac{u}{\hat{\tau}} \right) \right). \tag{2.5}$$

Here, $u = u(x,t)$ is the concentration of EC in the capillary wall. D is the EC diffusion coefficient, which we think it is probably a safe assumption to take as a positive constant in the vessel wall. However, in the ECM itself, it is probably anything but constant. Also, $\hat{\tau}$ is the so called TPDF [9]. This function has the effect of biasing the random walk of EC. In this case, we know that the walk is influenced by the active proteolytic enzyme it produces in response to the angiogenic factor that has made its way to the cell receptors, and by the fibronectin in the BL, thus, we write

$$\hat{\tau} = \hat{\tau}(c_{\mathrm{a}}, f).$$

A simple transition probability which reflects the influence of active enzyme and fibronectin on the motion of EC is $\hat{\tau}(c_{\mathrm{a}}, f) = c_{\mathrm{a}}^{\gamma_1} f^{-\gamma_2}$ for positive constants γ_i $(i = 1, 2)$ [7].
The biological interpretation of this choice is that EC prefer to move into the regions where c_{a} is large or where f is small.
In order to avoid singularities in $\ln \hat{\tau}$ and its derivatives in (2.5), it is useful to take $\hat{\tau}(c_{\mathrm{a}}, f) = \tau_1(c_{\mathrm{a}})\tau_2(f)$ where

$$\tau_1(c_{\mathrm{a}}) = \left(\frac{a_1 + c_{\mathrm{a}}}{a_2 + c_{\mathrm{a}}} \right)^{\gamma_1}, \quad \tau_2(f) = \left(\frac{b_1 + f}{b_2 + f} \right)^{\gamma_2}.$$

Here the a_i, b_i are constants such that $0 < a_1 << 1 < a_2$ and $b_1 > 1 >> b_2 > 0$. Clearly, $\hat{\tau}$ is not singular for small or large values of c_{a}, f and will approximate $c_{\mathrm{a}}^{\gamma_1} f^{-\gamma_2}$ over a considerable range of these variables [7]. We impose zero flux boundary conditions for the cells in the capillary

$$Du \frac{\partial}{\partial x} \ln\left(\frac{u}{\hat{\tau}(c_{\mathrm{a}}, f)} \right) = 0, \quad (\text{at } x = 0, 1), \tag{2.6}$$

and take $u(x, 0) = u_0 > 0$, since we assume that the capillary is initially in a rest state. As made in [11], we also assume here that the active enzyme c_{a} and fibronectin f are time-independent. Therefore, we let

$\hat{\tau}(c_{\rm a}(x), f(x)) := \kappa(x)$, and $u_0 = 1$ for simplicity, and consider the initial-boundary value problem

$$\begin{aligned} \frac{\partial u}{\partial t} = D\frac{\partial}{\partial x}\left(u\frac{\partial}{\partial x}\left(\ln\frac{u}{\kappa\,(x)}\right)\right) \quad &, \quad (x,t) \in \Omega_T := (0,1)\times(0,T], \\ u(x,0) = 1 \quad &, \quad x \in (0,1), \\ Du\frac{\partial}{\partial x}\left(\ln\frac{u}{\kappa\,(x)}\right) = 0 \quad &, \quad (\text{at } \ x = 0,1), \ \ t \in (0,T], \end{aligned} \tag{2.7}$$

which has been studied numerically in [10]. Here, T is a positive real number.

The right hand side of the first equation of (2.7) can be written

$$D\frac{\partial}{\partial x}\left(u\left(\frac{\partial}{\partial x}\left(\ln\frac{u}{\kappa(x)}\right)\right)\right) = D\left(u_{xx} - (uF(x))_x\right),$$

where $F(x) := \dfrac{\kappa'(x)}{\kappa(x)}$. Therefore, our original problem becomes

$$\begin{aligned} u_t = D(u_{xx} - (uF(x))_x) \quad &, \quad (x,t) \in \Omega_T, \\ u(x,0) = 1 \quad &, \quad x \in (0,1), \\ u_x(x,t) = uF(x) \quad &, \quad (\text{at } \ x = 0,1), \ \ t \in (0,T]. \end{aligned} \tag{2.8}$$

Throughout the paper we assume functions $c_{\rm a}(x)$ and $f(x)$ have unimodal distribution forms (as made in [7] and [11]) with the conditions $c_{\rm a}'(0) = c_{\rm a}'(1) = 0$ and $f'(0) = f'(1) = 0$. This implies that we actually assume $\kappa'(0) = \kappa'(1) = 0$. Therefore, one obtains $F(0) = F(1) = 0$, so that the boundary conditions given by the last equation of (2.8) become $u_x(x,t) = 0$ at $x = 0, 1$.

3. Existence and uniqueness of the steady-state solution

Since our aim is to investigate the existence and uniqueness of the steady-state solution of (2.8), we consider the following two-point boundary value problem (time- independent problem) with homogeneous Neumann boundary data

$$\begin{aligned} -\frac{d^2u}{dx^2} + \frac{d}{dx}(uF(x)) = 0 \quad &, \quad x \in (0,1), \\ u'(0) = u'(1) = 0. \end{aligned} \tag{3.1}$$

It is well-known that whenever $F(x) \in C^1[0,1]$ boundary value problem (3.1) possesses a unique *classical solution,* $u(x) \in C^2(0,1)$, which satisfies (3.1) for every $x \in [0,1]$. We are interested in a *generalized solution* of (3.1); i.e., a function $u(x)$ that satisfies (3.1) in some sense when $F(x)$ is not continuous; if $F(x)$ is sufficiently smooth then we want the generalized solution to coincide with the classical solution. In the sequel, we shall assume that $F'(x)$ is measurable, bounded function on [0,1] satisfying $0 < K_1 \le F'(x) \le K_2$ for all $x \in [0,1]$, where K_1 and K_2 are constants.

We will now construct a framework to pose certain weak formulations, and then state the Lax-Milgram theorem which will guarantee the existence and uniqueness of the solution of our weak formulation of the problem (3.1). To this end, we seek $u \in \mathbf{H}$ satisfying $a(u,v) = g(v)$ for all $v \in \mathbf{H}$, where $\mathbf{H}$ is a Hilbert space, $a(.,.)$ is a bilinear form on $\mathbf{H}$, and g is a bounded linear functional on $\mathbf{H}$. The following theorem presents conditions which guarantee the existence and uniqueness of its solution. The result requires that the bilinear form be bounded on the space $\mathbf{H}$; in addition, it requires that the bilinear form have the property, which is referred to as *coercivity* given in (3.3) below.

Theorem 3.1 (Lax-Milgram Theorem) Let $\mathbf{H}$ be a Hilbert space and let $a(.,.) : \mathbf{H} \times \mathbf{H} \to \mathbf{R^1}$ be a bilinear form on $\mathbf{H}$ which satisfies

$$|a(u,v)| \leq C||u||||v|| \quad \text{for all} \quad u, v \in \mathbf{H} \tag{3.2}$$

and

$$a(u,v) \geq N||u||^2 \quad \text{for all} \quad u \in \mathbf{H}, \tag{3.3}$$

where C and N are positive constants independent of $u, v \in \mathbf{H}$. Let $g : \mathbf{H} \to \mathbf{R^1}$ be a bounded linear functional on $\mathbf{H}$. Then there exists a unique $u \in \mathbf{H}$ satisfying $a(u,v) = g(v)$ for all $v \in \mathbf{H}$ [6].

Definition 3.1 (Sobolev Spaces) The *Sobolev space* $H^m(\Omega)$ is the set of functions $u \in L^2(\Omega)$ which possess generalized (weak) L^2-derivatives $D^\alpha u$ which are also in $L^2(\Omega)$ for $0 \leq |\alpha| \leq m$ [6]; i.e.,

$$H^m(\Omega) = \{u \in L^2(\Omega) : D^\alpha u \in L^2(\Omega) \text{ for } 0 \leq |\alpha| \leq m\}. \tag{3.4}$$

Clearly, $H^m(\Omega)$ is a subspace of functions $L^2(\Omega)$ and $H^0(\Omega) = L^2(\Omega)$. On $H^m(\Omega)$ we define the inner product

$$(u,v)_m = \sum_{|\alpha| \leq m} \int_\Omega D^\alpha u D^\alpha v dx = \sum_{|\alpha| \leq m} (D^\alpha u, D^\alpha v) \quad \text{for all} \quad u, v \in H^m(\Omega), \tag{3.5}$$

where $(.,.)$ denotes the standard inner product on $L^2(\Omega)$. Using this definition of inner product, we define the norm on $H^m(\Omega)$ [6] as

$$||u||_m = (u,u)_m^{1/2} = \left(\sum_{|\alpha| \leq m} ||D^\alpha u||^2 \right)^{1/2} \quad \text{for all} \quad u \in H^m(\Omega), \tag{3.6}$$

where $||.||$ denotes the standard norm on $L^2(\Omega)$. Clearly, $||.||_0 = ||.||$.

We have $\Omega = (0,1) \subset \mathbf{R^1}$ for our problem (3.1), so that D^α denotes the ordinary differential operator. Also, our underlying finite element space is $H^1(0,1)$, and the bounded linear functional g is the zero functional. The weak formulation is therefore to find $u \in H^1(0,1)$ which satisfies

$$a(u,v) = 0 \quad \text{for all} \quad v \in H^1(0,1), \tag{3.7}$$

where

$$a(u,v) = \int_0^1 (2u'v' + F'(x)uv)dx \quad \text{for all} \quad u, v \in H^1(0,1). \tag{3.8}$$

Using the definition of $a(u,v)$ and the Cauchy-Schwartz inequality, we have for $u,v \in H^1(0,1)$

$$|a(u,v)| \leq 2\int_0^1 |u'||v'|dx + K_2\int_0^1 |u||v|dx \leq 2||u'||||v'|| + K_2||u||||v||.$$

We now use the definition of the L^2- and H^1- norms, and have that

$$|a(u,v)| \leq 2||u||_1||v||_1 + K_2||u||_1||v||_1 \leq C||u||_1||v||_1,$$

where $C = 2\max(2,K_2)$. Therefore, condition (3.2) of the Lax-Milgram theorem is satisfied. Now, for $u \in H^1(0,1)$,

$$a(u,u) = 2\int_0^1 (u')^2dx + \int_0^1 F'(x)u^2dx \geq 2||u'||^2 + K_1||u||^2.$$

Again, from the definition of the L^2- and H^1- norms one has

$$a(u,u) \geq N||u||_1^2,$$

where $N = \min(2,K_1)$. This shows the condition (3.3) of the Lax-Milgram theorem is met. Thus we are guaranteed the existence and uniqueness of a solution to (3.7).

On the other hand, it is easy to see that if we integrate the ordinary differential equation given in (3.1) with respect to x, we obtain

$$\frac{du}{dx} - uF(x) = C,$$

where C is a constant. Applying the boundary conditions given in (3.1) gives $C = 0$, and hence,

$$\frac{du}{dx} = uF(x) = u\frac{\kappa'(x)}{\kappa(x)}. \tag{3.9}$$

Solving this simple differential equation gives

$$u = u(x) = A\kappa(x), \tag{3.10}$$

where A is a positive constant of integration chosen to ensure conservation of EC. In fact, if we recall the definition of $\kappa(x)$, we have

$$u(x) = A\left(\frac{a_1 + c_{\mathrm{a}}(x)}{a_2 + c_{\mathrm{a}}(x)}\right)^{\gamma_1}\left(\frac{b_1 + f(x)}{b_2 + f(x)}\right)^{\gamma_2}, \tag{3.11}$$

where $c_{\mathrm{a}}(x), f(x), a_1, a_2, \gamma_1, b_1, b_2, \gamma_2$ are the same as in Section 2. Also, in [11] the Author has shown mathematically that $u(x,t) \to A\kappa(x)$ as $t \to \infty$, where $u(x,t)$ is the solution of (2.8). This, in fact, shows that the steady-state solution obtained in (3.10) is stable.

4. A specific example

In the last part of Section 2 we emphasized that we must have $\kappa'(0) = \kappa'(1) = 0$ for our TPDF, $\kappa(x)$. As a counter example, we choose $\kappa(x) = Ce^x$, which clearly does not have these properties. Here C is a positive constant. In this case, the initial-boundary value problem (2.8) becomes

$$\begin{aligned} u_t = Du_{xx} - au_x \quad &, \quad (x,t) \in \Omega_T, \\ u(x,0) = 1 \quad &, \quad x \in (0,1), \\ u_x(x,t) = 0 \quad &, \quad (\text{at } x = 0,1),\ t \in (0,T], \end{aligned} \tag{4.1}$$

where $a = CD$. After a somewhat tedious computations [3], one obtains that $u(x,t) \equiv 1$ is the unique solution of the problem (4.1). Therefore, as $t \to \infty$, we have

$$u(x,t) \to 1 \neq Ce^x = \kappa(x), \tag{4.2}$$

which shows that the solution is instable.

5. Conclusions and discussion

In this paper we have presented a qualitative analysis on the uniqueness of the movement of EC in tumor angiogenesis. To do this, we have obtained the existence and uniqueness of the steady-state solution of an initial-boundary value problem which models EC movement. The analysis is based on the assumption that active enzyme $c_a(x,t)$, and fibronectin $f(x,t)$ are time-independent, i.e., they are in quasi-steady state.

The steady-state solution obtained in (3.11) is dependent on the magnitude of sensitivity parameters $a_i, b_i, \gamma_i, (i = 1,2)$. In [7], the influence of these sensitivity parameters on fibronectin channel opening is discussed, and shown that the larger the transition probability sensitivity factors (i.e, the more sensitive EC movement is to gradients in protease and in fibronectin), the more quickly they gather in the opening of the lumen which is created by the protease.

Since the endothelial cell equation we have here is derived as the continuous limit of a reinforced random walk [9], the transition probability function, $\kappa(x)$ provides the link between microscopic and macroscopic events. Our choice for it, therefore, reflects the known facts that EC movement depends not only upon protease and fibronectin gradients but also upon their concentrations.

On the other hand, in [11] the Author has shown mathematically that the long-time tendency of EC is toward the TPDF, $\kappa(x)$, i.e., he has proved that $u(x,t) \to B\kappa(x)$ as $t \to \infty$, where B is a positive constant. Biologically, this can be interpreted as follows. When EC equation is thought of as a diffusion process for a reinforced random walk, the long time tendency for such a process will be to drive u in such a way as to bring the ratio u/κ to unity. In other words, the "walker density equation" asserts that the walker will move in such a way as to have a large probability density where the transition probability rate is large, and a small probability density where it is small. Recalling our choice for κ, it means that EC move into the regions where active enzyme is large or where fibronectin is small. According to our results in Section 3, the steady-state

solution given in (3.10)–(3.11) is the unique solution of the boundary value problem (3.1), which shows that this movement of EC into such regions is, in fact, unique.

Also, combining the result obtained in [11] with the result we have obtained in (3.10), one can conclude that the steady-state solution $u(x)$ of the problem (2.8) is stable with $\kappa(x)$ has the form defined in Section 2 (i.e, $\kappa(x)$ has unimodal distribution form). In Section 4, we have provided a specific example by choosing $\kappa(x)$ that has a non-unimodal distribution form. In this case, the result obtained in (4.2) indicates that the steady-state solution is, in fact, instable. As a result, one has to have a unimodal distribution form of TPDF in order to have a stable movement of EC.

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