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On the Stability Analysis of the Steady-State Solution of a Tumor Angiogenesis Model

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Abstract: Stability analysis of the steady-state solution of endothelial cell equation in a mathematical model for tumor angiogenesis is studied. It is shown that the steady-state solution of the model is indeed the transition probability function. The biological importance of the results are expressed and some related figures are provided.

Keywords: Stability, steady-state solution, endothelial cell, tumor angiogenesis.

1 Introduction

In this paper, we study the stability of the steady-state solution of the Endothelial Cell (EC) equation originally presented in [4]

$$\frac{\partial \eta}{\partial t} = D_\eta \frac{\partial}{\partial y}\left(\eta \frac{\partial}{\partial y}\left(\ln \frac{\eta}{\tau}\right)\right), \tag{1}$$

with the zero-flux boundary conditions

$$D_\eta \eta \frac{\partial}{\partial y} \ln\left(\frac{\eta}{\tau(c_a, f)}\right) = 0 \quad (\text{at } y = 0, 1). \tag{2}$$

Here D_η is a positive constant, the EC diffusion cofficient in the capillary, and $\eta = \eta(y,t)$ is the EC density, and τ is the so called transition probability function. We take

$$\tau = \tau(c_a, f), \tag{3}$$

where $c_a = c_a(y,t)$ is the active enzyme density and $f = f(y,t)$ is the fibronectin density ($0 < y < 1$, $t > 0$). Fibronectin is a protein normally found in and around cells in various tissues in the body. A simple transition probability which reflects the influence of active enzyme and fibronectin on the motion of endothelial cells is $\tau(c_a, f) = c_a^{\gamma_1} f^{-\gamma_2}$ for positive constants γ_i $(i = 1, 2)$ [5].

The biological interpretation of this choice is that endothelial cells prefer to move into the regions where c_a is large or where f is small [7,9,10]. As in [6], we consider that there is no angiostatin supplied to the circulatory system for simplicity. Therefore, the active enzyme is the same as the total enzyme, i.e., $c_a(y,t) \equiv c(y,t)$.

We took the transition probability function as follows in [4,6]

$$\tau(c, f) = \left(\frac{a_1 + c}{a_2 + c}\right)^{\gamma_1} \left(\frac{b_1 + f}{b_2 + f}\right)^{\gamma_2}. \tag{4}$$

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Here the a_i, b_i are constants such that $0 < a_1 << 1 < a_2$ and $b_1 > 1 >> b_2 > 0$. Clearly, τ is not singular for small or large values of c, f and will approximate $c^{\gamma_1} f^{-\gamma_2}$ over a considerable range of these variables [5].

2 Approximated transition probability function

We take the quasi-steady state enzyme and fibronectin concentrations to have the form [6]

$$c(y) = Ay^n(1-y)^n, \;\; f(y) = 1 - By^n(1-y)^n, \quad 0 \le y \le 1,$$

where A and B are positive constants and $n \ge 16$. We take $\gamma_1 = \gamma_2 = 1$ in Eq.4 for simplicity. Since the function τ in Eq.4 can be approximated by a function

$$\tau(c, f) = cf^{-1},$$

(over a considerable range of the parameters) we may write

$$\tau(y) = \frac{Ay^n(1-y)^n}{1 - By^n(1-y)^n} \approx Cy^n(1-y)^n = \tau^\star(y)$$

for some constant C, since $y^n(1-y)^n \ll 1$.

Figure 1 shows the transition probability function τ. The dotted line in Fig.1 is the graph of the function given by Eq.4 with the data $a_1 = 0.0001, a_2 = 2, b_1 = 10, b_2 = 0.1, A = 28 \times 10^7, B = 0.22 \times 10^9, n = 16$, and the solid line is the graph of the function $\tau^\star$ defined above with $C = 140 \times 10^7$. 4.8in,height=3.1in Therefore, from now on, we will take $\tau^\star$ as our

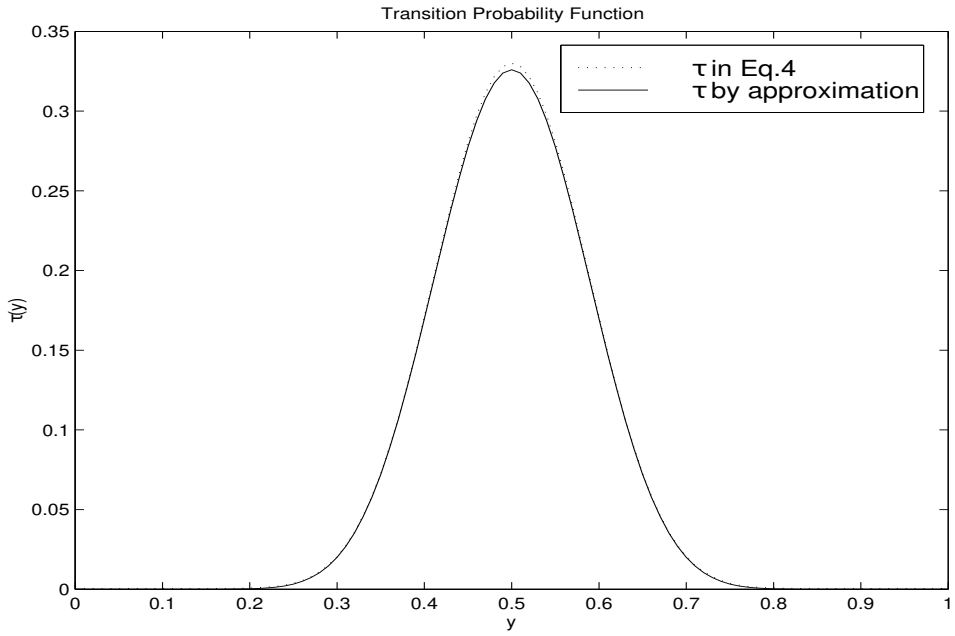

Fig. 1: Transition Probability Function

transition probability function, i.e, $\tau = \tau^\star$.

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3 Stability Analysis of the Steady-State

The steady-state model obtained from Eq.(1) can be written as follows:

$$0 = \eta_{yy} - \eta_y G - \eta G_y, \tag{5}$$

where $G = \frac{\tau_y}{\tau}$. If we let $p = \eta_y$, Eq.(5) reads

$$0 = p_y - pG - \eta G_y. \tag{6}$$

Therefore, we have the following system of ordinary differential equations:

$$\eta_y = p, \tag{7}$$
$$p_y = pG + \eta G_y. \tag{8}$$

Note that one has

$$G = n\frac{1-2y}{y-y^2}, \quad G_y = -n\frac{2y^2-2y+1}{(y-y^2)^2}, \quad 0 < y < 1. \tag{9}$$

Since $G_y < 0$ for $0 < y < 1$, (0,0) is the only equilibrium point of the system in Eqs.(7)-(8) (i.e. points satisfying $\eta_y = p_y = 0$).

The jacobien matrix $J(\eta, p)$ for the system Eqs.(7)-(8) is given by

$$J(\eta, p) = \begin{bmatrix} 0 & 1 \\ G_y & G \end{bmatrix}, \tag{10}$$

and the critical point (0,0) gives rise to the same stability matrix given above, that is $J = J(0,0) = J(\eta, p)$ since the matrix does not contain the variables η and p.

If we now let $\beta = TrJ$, $\gamma = detJ$, $\delta = \beta^2 - 4\gamma = discJ$, we have $\beta = G$, $\gamma = -G_y$, $\delta = G^2 + 4G_y$. Therefore, it follows that $\beta > 0$ for $0 < y < 1/2$, $\beta < 0$ for $1/2 < y < 1$, and $\gamma > 0$ for $0 < y < 1$, which results that the critical point (0,0) is a stable node when $1/2 < y < 1$, and is an unstable node when $0 < y < 1/2$ [1,3]. Furthermore, since

$$\delta = \frac{(4n^2-8n)y^2 - (4n^2-8n)y + n^2 - 4n}{(y-y^2)^2}, \quad 0 < y < 1,$$

we have $\delta < 0$ when

$y_1 = \frac{1}{2} - \frac{1}{2\sqrt{7}} < \frac{1}{2} - \frac{1}{\sqrt{2n-4}} < y < \frac{1}{2} + \frac{1}{\sqrt{2n-4}} < \frac{1}{2} + \frac{1}{2\sqrt{7}} = y_2, \quad n \geq 16$. But, $\beta > 0$ when $y_1 < y < 1/2$, $\beta = 0$ when $y = 1/2$, and $\beta < 0$ when $1/2 < y < y_2$. Therefore, the critical point (0,0) is unstable spiral when $y_1 < y < 1/2$, it is neutral center when $y = 1/2$, and is stable spiral when $1/2 < y < y_2$ [1,3].

Furthermore, Eq.(5) can be written as

$$\frac{\partial}{\partial y}(\eta_y - \eta G) = 0,$$

which results in

$$\eta_y - \eta G = 0,$$

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by the boundary conditions given by Eq.(2). By solving the last equation one obtains

$$\eta = \alpha\tau(c,f), \tag{11}$$

where α is a positive constant. The result we have obtained in Eq.(11) agrees with the result obtained in [6]. Therefore, we now have

$$\eta = \beta y^{16}(1-y)^{16}, \tag{12}$$

where β is a positive constant, and the system in Eq.(7)-(8) should now read

$$\eta_y = 16\beta(y-y^2)^{15}(1-2y), \tag{13}$$
$$p_y = 16\beta(y-y^2)^{14}(62y^2-62y+15). \tag{14}$$

On the other hand,

$$\eta_y = \begin{cases} > 0 \text{ when } 0 < y < 1/2, \\ < 0 \text{ when } 1/2 < y < 0, \end{cases}$$

$$p_y = \begin{cases} > 0 \text{ when } 0 < y < 0.41 \ \ or \ \ 0.58 < y < 1, \\ < 0 \text{ when } 0.41 < y < 0.58. \end{cases}$$

As it is clear from the Eq.(8) that there is a linear relation between p and η for each fixed y when we set $p_y = 0$. The equilibrium point (0,0) for the system (7)-(8) is an unstable node for $y = 0.25$, whereas it is a stable node for $y = 0.75$. We have shown that this simpler model, consisting of a single pde for the endothelial cell density, captures almost all of the features of the original model [4,6]. The analysis performed on the model has permitted us to focus upon the behaviour of the endothelial cells at the capillary. These cells effectively drive the capillary sprouts across the tissue towards the tumor. The analysis clearly indicates that the solution takes on different characteristics in two distinct regions of the domain, the point $y = 1/2$ marking the transition from one region to the next. The analysis also shows that in order for successful completion of angiogenesis to take place, both migration and proliferation are essential.

4 Long time behaviour of cells

From Eq.(4) we write $\tau(c,f) = \tau_1(c)\tau_2(f)$ where

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

so that one has

$$\frac{\partial}{\partial y}\left(\ln\frac{\eta}{\hat{\tau}}\right) = \frac{\eta_y}{\eta} - \frac{\tau_1'(c)}{\tau_1(c)}c_y - \frac{\tau_2'(f)}{\tau_2(f)}f_y. \tag{15}$$

If we set

$$\Omega(c) = \frac{\tau_1'(c)}{\tau_1(c)}, \quad \Psi(f) = \frac{\tau_2'(f)}{\tau_2(f)}, \tag{16}$$

Eqs.(1) and (2) become

$$\frac{\partial\eta}{\partial t} = D_\eta\frac{\partial}{\partial y}\Big[\eta_y - \eta S(y)\Big] \tag{17}$$

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and

$$\eta_y - \eta S(y) = 0 \quad \text{at } y = 0,1 \tag{18}$$

respectively, where

$$S(y) = \Omega(c)c_y + \Psi(f)f_y. \tag{19}$$

For simplicity we take

$$\eta(y,0) = 1, \tag{20}$$

as the initial condition.

It is clear from the strong maximum principle [11], that $\eta(y,t)$ is nonnegative for all $t \geq 0$ since $\eta(y,0)$ is nonnegative. We solve Eq.(17) using separation of variables by setting $\eta(y,t) = T(t)\Phi(y)$ to obtain

$$\frac{d}{dt}T + \lambda T = 0 \tag{21}$$

and

$$D_\eta \frac{d}{dy}\left[\frac{d}{dy}\Phi - \Phi S(y)\right] + \lambda\Phi = 0 \text{ with } \Phi_y - \Phi S(y) = 0 \quad \text{at } y = 0,1. \tag{22}$$

From Eq.(21), it is clear that $T(t)$ is of the form $\exp(-\lambda t)$. We make the substitution $\Phi = \sigma Z$, where $\sigma = \exp(\int_0^y S(\zeta)d\zeta)$ [8] to obtain the classical Sturm-Liouville problem for Z, namely

$$L[Z] = -D_\eta \frac{d}{dy}\left[\sigma\frac{dZ}{dy}\right] = \lambda\sigma Z, \;\; Z' = 0 \;\; \text{at } y = 0,1. \tag{23}$$

It is known that the eigenvalues λ_i of this problem have the following property

$$0 = \lambda_0 < \lambda_1 \leq \lambda_2 \leq \cdots.$$

The eigenfunctions for the boundary value problem in Eq.(22) are then given by $\Phi_i(y) = \sigma(y)Z_i(y)$. In particular, the eigenfunction corresponding to $\lambda = 0$ is given by

$$\Phi_0(y) = \exp\left(\int_0^y S(\zeta)d\zeta\right). \tag{24}$$

It is easy to see from Eq.(23) that

$$(Z, \frac{1}{\sigma}L[Z]) = -D_\eta \int_0^1 Z(\sigma Z')'dy = D_\eta \int_0^1 \sigma(Z')^2 dy \geq 0. \tag{25}$$

Here (.,.) is the (weighted) *Hermitian inner product* [11]. Therefore we have

$$(Z, \frac{1}{\sigma}L[Z]) = (Z, \lambda Z) = \lambda||Z||^2 \tag{26}$$

which implies that

$$\lambda_i > 0 \tag{27}$$

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for $i = 1,2,\cdots$.

It is also easy to see from Eq.(22) that

$$\int_0^1 \Phi_i(y)dy = 0 \quad (i = 1,2,...). \tag{28}$$

We can now write $\eta(y,t)$ in the following series form

$$\eta(y,t) = B_0\Phi_0(y) + \sum_{i=1}^{\infty} B_i\Phi_i(y)e^{-\lambda_i t}, \tag{29}$$

where the coefficients are determined by setting $t = 0$ and using the orthogonality properties of the eigenfunctions. From Eq.(29) we obtain

$$\eta(y,t) \to B_0\Phi_0(y) \quad \text{as } t \to \infty.$$

Notice also that

$$\int_0^y S(y)dy = \int_0^y \frac{\tau_1'(c)}{\tau_1(c)}c_y dy + \int_0^y \frac{\tau_2'(f)}{\tau_2(f)}f_y dy = \ln\left(\frac{\tau_1(c(y))}{\tau_1(c(0))}\right) + \ln\left(\frac{\tau_2(f(y))}{\tau_2(f(0))}\right) \tag{30}$$

which implies from Eq.(24) that

$$\Phi_0(y) = \frac{\tau_1(c(y))}{\tau_1(c(0))}\frac{\tau_2(f(y))}{\tau_2(f(0))} = \frac{1}{\tau_1(c(0))\tau_2(f(0))}\hat{\tau}(c(y),f(y)). \tag{31}$$

Setting $t = 0$ in Eq.(29) and using Eqs.(20) and (28) we obtain

$$B_0 = \frac{1}{\int_0^1 \Phi_0(y)dy}. \tag{32}$$

Therefore we have

$$\eta(y,t) \to \alpha\hat{\tau}(c(y),f(y)) \text{ as } t \to \infty \tag{33}$$

where

$$\alpha = \frac{B_0}{\tau_1(c(0))\tau_2(f(0))} > 0,$$

showing that in the limit the ECs follow the trail of proteolytic enzyme and fibronectin.

5 Conclusion and results

. In this paper the stability analysis of the steady-state solution of endothelial cell equation in a mathematical model for tumor angiogenesis is presented. It is proved that the steady-state solution of the model is indeed the transition probability function. we have also obtained the long time behaviour of the cells and observed that they follow the trail of proteolytic enzyme and fibronectin as stated in many biological literature.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors have contributed to all parts of the article. All authors read and approved the final manuscript.

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