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Perturbation Solutions of a Mathematical Model in Tumor Angiogenesis

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Abstract

In this work, we obtain the regular perturbation solutions of a mathematical model in tumor angiogenesis in one and two space dimensions. Our results show that the solutions we have obtained are in good agreement with the solutions obtained by other methods. We also present our results in Matlab generated figures.

1. Introduction

Angiogenesis is the main feature of neovascularization, the formation of new blood vessels. It is defined as the outgrowth of new vessels from a preexisting vascular network and is fundamental to the formation of blood vessels during placental growth and wound healing, for example [1].

In this work, we study the endothelial cell (EC) equation originally presented in [2].

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

with the boundary conditions $\eta_y=0$ at y = 0,1. 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.

This model shows the stages of tumor progression. In fact, this model was solved numerically earlier [2,3]. In this study, we give perturbation solutions and compare with numerical solution. We take

$$\tau = \tau(c_a,f) \quad (2)$$

where $c_a = c_a(y,t)$ is active enzyme density and $f = f(y,t)$ is the fibronectin density ($0 < y < 1$, $t > 0$). A simple transition probability which reflects the influence of enzyme and fibronectin on the motion of endothelial cells is $\tau(c_a,f) = c_a^{\gamma_1} f^{-\gamma_2}$ for positive constant γ_i (i = 1, 2) [2]. The biological interpretation of this choice is that endothelial cells prefer to move into regions where c_a is large or where f is degraded, facts which have basis in biological experiment.

We consider that there is no angiostatin supplied to the circulatory system for simplicity as in [4]. 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 [2,3]:

$$\tau(c,f)=\left(\frac{a_1+c}{a_2+c}\right)^{\gamma_1}\left(\frac{b_1+f}{b_2+f}\right)^{\gamma_2} \quad (3)$$

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

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range of these variables [2]. This choice allows us to control the distribution of endothelial cells in the opening of the forming sprout.

We take the quasi-steady state enzyme and fibronectin concentrations to have the form [3]

$$c(y)=Ay^n(1-y)^n\ ,\quad f(y)=1-By^n(1-y)^n\ ,\quad 0\le y\le 1 \tag{4}$$

where A and B are positive constants and $n \geq 16$. We take $\gamma_1=\gamma_2=1$ in Eq. (3) for simplicity. Therefore, we have

$$\tau(y)=\frac{Ay^n(1-y)^n}{1-By^n(1-y)^n}\approx Cy^n(1-y)^n \tag{5}$$

for some positive constant C, since $y^n(1-y)^n \ll 1$. Figure 1 shows the transition probability function τ with C = 140x10^7.

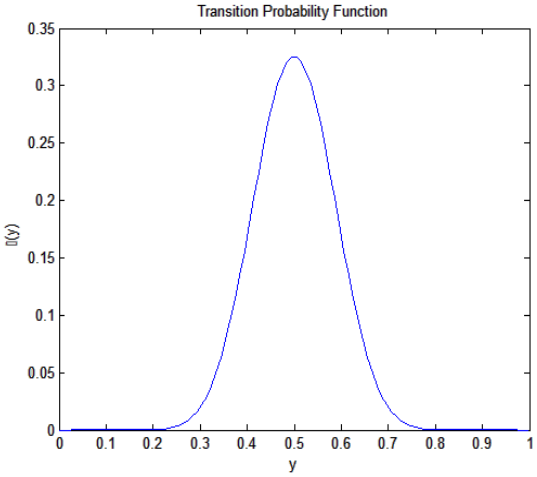

Figure 1. Transition probability function.

Secondly, we study the tumor angiogenesis factor (TAF) equation originally presented in [5]

$$\frac{\partial V(x,y,t)}{\partial t}=D_V\left(\frac{\partial^2 V(x,y,t)}{\partial x^2}+\frac{\partial^2 V(x,y,t)}{\partial y^2}\right) \tag{6}$$

with the boundary condition

$$\frac{\partial V(0,y,t)}{\partial x}-\propto V(0,y,t)=0 \tag{7}$$

$$V(0,y,t)=\phi(y,t) \tag{8}$$

$$\frac{\partial V(x,0,t)}{\partial y}=\frac{\partial V(x,1,t)}{\partial y}=0 \tag{9}$$

Here the TAF diffusion D_V is constant and V(x,y,t) is the tumor angiogenesis factor. We take $\phi(y,t)=1-\beta\cos(2\pi y)$ where β is some positive number.

2. Perturbation Solution

Perturbation theory is a collection of methods for systematic analysis of the behaviour of solutions to differential and difference equations. The general procedure of perturbation theory is to identify a small parameter, usually denoted by ε, such that when ε = 0 the problem becomes solvable [6,8]. Consider,

$$y(x,\varepsilon)=y_0(x)+\varepsilon y_1(x)+\varepsilon^2 y_2(x)+\dots \tag{10}$$

This series is called a perturbation series. Here ε is small parameter, y_0 is the known solution to the exactly solvable initial problem and $y_1, y_2, \dots$ the higher order terms [6,7]. For small ε these higher order terms are successively smaller. The perturbation solution is obtained by truncating the series, usually by keeping only the first two terms.

We can take the Eq. (1) for perturbation solution as follows:

$$\eta_t=D_\eta(\eta_{yy}-A\eta_y-\varepsilon A_y\eta) \tag{11}$$

where ε is a small positive constants and $A=\frac{\tau_y}{\tau}$. Thus, the steady-state model obtained from Eq. (11) can be written

$$0=\eta_{yy}-A\eta_y-\varepsilon A_y\eta \tag{12}$$

In determining an approximate solution is to assume the form of the expansion. Let us assume that the solutions have expansion in the form

$$\eta(y,t,\varepsilon)=\eta_1(y,t)+\varepsilon\eta_1(y,t)+\varepsilon^2\eta_2(y,t)+\dots \tag{13}$$

Substituting Eq. (13) in Eq. (12) and equating the coefficient of each power of ε to zero, we get

$$\varepsilon^0:\ \eta_{0yy}-A\eta_{0y}=0,\quad \eta_{0y}(0,t)=\eta_{0y}(1,t)=0 \tag{14}$$

$$\varepsilon^1:\ \eta_{1yy}-A\eta_{1y}=A_y\eta_0,\quad \eta_{1y}(0,t)=\eta_{1y}(1,t)=0 \tag{15}$$

Let us take $v_0=\eta_{0y}$ in Eq. (14). Then, we obtain $v_0=c_1\tau$. Therefore, the solution to the problem given by Eq. (14) becomes

$$\eta_0=\int^y c_1\tau du+c_2 \tag{16}$$

Similarly, let's take $v_1=\eta_{1y}$ in Eq. (15). Thus, we obtain

$$\eta_1 = \int^y \tau \left(\int^u \frac{A_s \eta_0}{\tau} ds \right) du + c_3 \quad (17)$$

Consequently, the perturbation solution together with initial and boundary conditions is obtained as follows:

$$\eta(y,t,\varepsilon) = \int^y c_1 \tau du + c_2 + \varepsilon \left[\int^y \tau \left(\int^u \frac{A_s \eta_0}{\tau} ds \right) du + c_3 \right] + \dots \quad (18)$$

where c_1, c_2, c_3 are arbitrary constants. Since $\tau(y) = Cy^n(1-y)^n$ for $n \geq 16$ the calculation is difficult. Therefore we can calculate η_0 and η_1 with Matlab program.

Now, we can take the Eq. (6) for perturbation solution as follows:

$$V_t = \varepsilon D_V (V_{xx} + V_{yy}) \quad (19)$$

where ε is a small positive constant. Let us assume that the solutions have expansion in the form

$$V(x,y,\varepsilon) = V_0(x,y,t) + \varepsilon V_1(x,y,t) + \varepsilon^2 V_2(x,y,t) + \dots \quad (20)$$

Substituting Eq. (20) in Eq. (19) and equating the coefficient of each power of ε to zero, we obtain

$$\varepsilon^0 : V_{0t} = 0 \quad (21)$$

$$\varepsilon^1 : V_{1t} = V_{0xx} + V_{0yy} \quad (22)$$

and conditions

$$V_{0x}(0,y,t) - \alpha V_0(0,y,t) = 0 \quad (23)$$

$$V_0(1,y,t) = 1 - \beta \cos(2\pi y) \quad (24)$$

$$V_{0y}(x,0,t) = V_{0y}(x,1,t) = 0 \quad (25)$$

$$V_{1x}(0,y,t) - \alpha V_1(0,y,t) = 0 \quad (26)$$

$$V_1(1,y,t) = 0 \quad (27)$$

$$V_{1y}(x,0,t) = V_{1y}(x,1,t) = 0 \quad (28)$$

If we solve Eq. (21), we obtain $V_0(x,y,t) = g(x,y)$ where g(x,y) is arbitrary function. Similarly, we obtain $V_1(x,y,t) = h(x,y)$ from the Eq. (22), where h(x,y) is arbitrary function. We can write these arbitrary functions with the help of Eqs. (23-25) and Eqs. (26-28) conditions as follows:

$$g(x,y) = \frac{1+\alpha x}{1+\alpha} - \beta \cos(2\pi y) \left(\frac{\cosh(2\pi x) + \frac{\alpha}{2\pi}\sinh(2\pi x)}{\cosh(2\pi) + \frac{\alpha}{2\pi}\sinh(2\pi)} \right) \quad (29)$$

$$h(x,y) = \left(1 - \cos(2\pi x)\right)\left(1 - \cos(2\pi y)\right) \quad (30)$$

where α, β are arbitrary functions. Hence, two – order perturbation solution is obtained in the form

$$V(x,y,t,\varepsilon) = \frac{1+\alpha x}{1+\alpha} - \beta \cos(2\pi y) \left(\frac{\cosh(2\pi x) + \frac{\alpha}{2\pi}\sinh(2\pi x)}{\cosh(2\pi) + \frac{\alpha}{2\pi}\sinh(2\check{g})} \right) + \varepsilon \left(1 - \cos(2\pi x)\right)\left(1 - \cos(2\pi y)\right) + \dots \quad (31)$$

3. Results and Discussion

As a result of investigations, the figures below have been created using Matlab. Figure 2 show the endothelial cell, while Figure 3 show the tumor angiogenesis factor. Figure 2 is drawn after η_0 and η_1 are calculated in Matlab for $n \geq 16$.

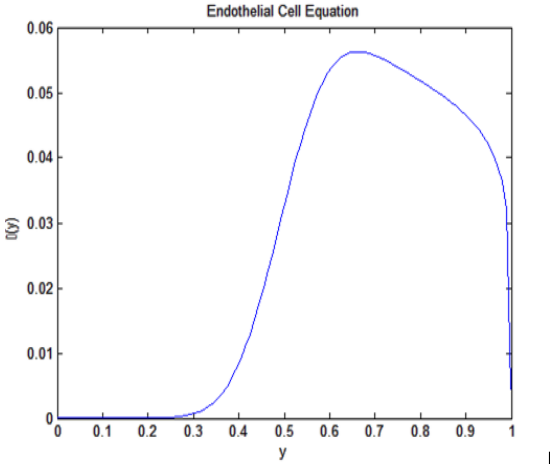

Figure 2. Endothelial cell equation.

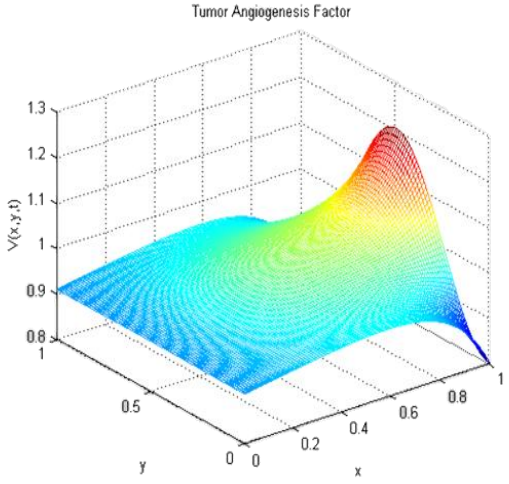

Figure 3. Tumor angiogenesis factor.

4. Conclusions

In this paper we have presented a mathematical model in tumor angiogenesis and solved it by perturbation method. The solution of the endothelial cell equation by perturbation method was expected to be a multiple of τ. When we look at Figure 1 and Figure 2 we have achieved a good approach in the interval of $0 < x < 0.5$. If more terms could be found by perturbation method, Figure 2 would approach the figure of τ in the interval of $0.5 < x < 1$. This is an indication that we are approaching the solution in [3].

The Figure 3 obtained from the solution of the TAF equation is similar to the graph in the article [3]. This shows that the two-term perturbation solution and the numerical solution are coincident.

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References

[1] Paweletz N., Knierim M., 1989. Tumor-related angiogenesis. Critical Reviews in Oncology, **9**(3), 197-242.

[2] Levine H. A., Sleeman B. D., 2000. A mathematical model for the roles of pericytes and macrophages in the initiation of angiogenesis. I. The role of protease inhibitors in preventing angiogenesis. Mathematical Biosciences, **168**, 77-115.

[3] Pamuk S., Gürbüz A., 2004. Stability analysis of the steady-state solution of a mathematical model in tumor angiogenesis. Global Analysis and Applied Mathematics, **729**, 369-373.

[4] Pamuk S., 2003. Qualitative analysis of a mathematical model for capillary formation in tumor angiogenesis. Mathematical Models and Methods in Applied Sciences, **13**(1), 19-33.

[5] Pamuk S., 2004. Steady-state analysis of a mathematical model for capillary network formation in the absence of tumor source. Mathematical Biosciences, **189**, 21-38

[6] Bender C.M., Orszag S.A., 1999. Advanced Mathematical Methods for Scientists and Engineers, Springer, New York.

[7] Hunter J.K., 2004. Asymptotic Analysis and Singular Perturbation Theory, University of California at Davis, California.

[8] Rice R. G., Do D. D., 1995. Applied Mathematics And Modeling For Chemical Engineers, John Wiley and Sons Inc., New York.