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.

Keywords:
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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].

\[ \frac{\partial \eta}{\partial t} = D_\eta \frac{\partial^2 \eta}{\partial y^2} \left( \eta \frac{\partial}{\partial y} \left( \ln \left( \frac{\eta}{\tau} \right) \right) \right) \]  

(1)

with the boundary conditions \( \eta_y = 0 \) at \( y = 0, 1 \). Here \( D_\eta \) is a positive constant, the EC diffusion coefficient in the capillary, and \( \eta = \eta(y,t) \) is the EC density, and \( \tau \) 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

\[ \tau = \frac{\sigma c_4 f}{\tau} \]

(2)

where \( c_4 = c_4(y,t) \) 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 \( \tau(c_4, f) = c_4 \gamma f \) for positive constant \( \gamma(i = 1, 2) \) [2]. The biological interpretation of this choice is that endothelial cells prefer to move into regions where \( c_4 \) 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., \( c_4(y,t) = c(y,t) \).

We took the transition probability function as follows in [2,3]:

\[ \tau(c, f) = \left( \frac{a_1 c + b_1 f}{a_2 + b_2 f} \right)^\gamma \left( \frac{b_1 f}{a_2 + b_2 f} \right)^\gamma \]  

(3)

Here the \( a_i, b_i \) are positive constants such that \( 0 < a_1 << a_2 \) and \( b_2 > b_1 > b_3 > 0 \).Clearly then, \( \tau \) is not singular for small or large values of \( c, f \) and will approximate \( c^\gamma f^{1/2} \) reasonably well over a considerable
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]

\[
c(y)=Ay^n(1-y)^n, \quad f(y)=1-By^n(1-y)^n, \quad 0 \leq y \leq 1
\]

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

\[
\frac{\alpha}{\beta} y = \frac{Ay^n(1-y)^n}{1-By^n(1-y)^n} \approx Cy^n(1-y)^n
\]

for some positive constant C, since \( y^n(1-y)^n \ll 1 \). Figure 1 shows the transition probability function \( \tau \) with \( C = 140 \times 10^7 \).

![Transition Probability Function](image)

**Figure 1.** Transition probability function.

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

\[
\frac{\partial v(x, y, t)}{\partial t} = D_v \left( \frac{\partial^2 v(x, y, t)}{\partial x^2} + \frac{\partial^2 v(x, y, t)}{\partial y^2} \right)
\]

with the boundary condition

\[
\frac{\partial V(0, y, t)}{\partial x} = -\alpha V(0, y, t) = 0
\]

\[
V(0, y, t) = \phi(y, t)
\]

\[
\frac{\partial V(x, 0, t)}{\partial y} = \frac{\partial V(x, 1, t)}{\partial y} = 0
\]

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 \( \beta \) 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 \( \varepsilon \), such that when \( \varepsilon = 0 \) the problem becomes solvable [6,8]. Consider,

\[
y(x, \varepsilon) = y_0(x) + \varepsilon y_1(x) + \varepsilon^2 y_2(x) + \ldots
\]

This series is called a perturbation series. Here \( \varepsilon \) is small parameter, \( y_0 \) is the known solution to the exactly solvable initial problem and \( y_1, y_2, \ldots \) the higher order terms [6,7]. For small \( \varepsilon \) 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:

\[
\eta \varepsilon = D_v(\eta_{yy} - \Lambda \eta_y - \varepsilon A \eta)
\]

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

\[
0 = \eta_{yy} - \Lambda \eta_y - \varepsilon A \eta
\]

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

\[
\eta(y, t, \varepsilon) = \eta_0(y, t) + \varepsilon \eta_1(y, t) + \varepsilon^2 \eta_2(y, t) + \ldots
\]

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

\[
\varepsilon^0: \eta_{0yy} - \Lambda \eta_{0y} = 0, \quad \eta_{0y}(0,t) = \eta_{0y}(1,t) = 0
\]

\[
\varepsilon^1: \eta_{1yy} - \Lambda \eta_{1y} = A \eta_0, \quad \eta_{1y}(0,t) = \eta_{1y}(1,t) = 0
\]

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

\[
\eta_0 = \int_0^\tau c_1 \tau du + c_2
\]

Similarly, let's take \( v_1 = \eta_{1y} \) in Eq. (15). Thus, we obtain
\[ \eta_i = \int_x^y \left( \int_0^{\frac{A_x \eta_0}{\tau}} ds \right) du + c_i \]  

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

\[ \eta(y,t,\varepsilon) = \int c_1 \tau du + c_2 + \varepsilon \left[ \int \tau \int_0^{\frac{A_x \eta_0}{\tau}} ds \right] du + c_3 + \ldots \]  

where \( c_1, c_2, c_3 \) are arbitrary constants. Since \( \tau(y) = C y^n (1-y)^n \) for \( n \geq 16 \) the calculation is difficult. Therefore we can calculate \( \eta_0 \) and \( \eta_1 \) with Matlab program.

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

\[ V = \varepsilon D_y \left( V_{xx} + V_{yy} \right) \]  

where \( \varepsilon \) is a small positive constant. Let us assume that the solutions have expansion in the form

\[ V(x,y,\varepsilon) = V_0(x,y,t) + \varepsilon V_1(x,y,t) + \varepsilon^2 V_2(x,y,t) + \ldots \]  

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

\[ \varepsilon^0 : V_{0x} = 0 \]  

\[ \varepsilon^1 : V_{1t} = V_{0xx} + V_{0yy} \]  

and conditions

\[ V_{0x}(0,y,t) - \alpha V_0(0,y,t) = 0 \]  

\[ V_0(1,y,t) = 1 - \beta \cos(2\pi y) \]  

\[ V_{0y}(x,0,t) = V_{0y}(x,1,t) = 0 \]  

\[ V_{1x}(0,y,t) - \alpha V_1(0,y,t) = 0 \]  

\[ V_1(1,y,t) = 0 \]  

\[ V_{1y}(x,0,t) = V_{1y}(x,1,t) = 0 \]  

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:

\[ g(x,y) = \frac{1+\alpha x}{1+\alpha} \beta \cos(2\pi y) \left( \frac{\cosh(2\pi x)}{\cosh(2\pi x)^2 + \sinh(2\pi x)^2} \right) \]  

\[ h(x,y) = \left( 1 - \cos(2\pi x) \right) \left( 1 - \cos(2\pi y) \right) \]  

where \( \alpha, \beta \) are arbitrary functions. Hence, two – order perturbation solution is obtained in the form

\[ V(x,y,t,\varepsilon) = \frac{1+\alpha x}{1+\alpha} \beta \cos(2\pi y) \left( \frac{\cosh(2\pi x)}{\cosh(2\pi x)^2 + \sinh(2\pi x)^2} \right) + \varepsilon \left[ 1 - \cos(2\pi x) \right] \left( 1 - \cos(2\pi y) \right) + \ldots \]  

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 \( \eta_0 \) and \( \eta_1 \) 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 \( \tau \). When we look at Figure 1 and Figure 2 we have achieved a good approach in the interval of \( 0 < \chi < 0.5 \). If more terms could be found by perturbation method, Figure 2 would approach the figure of \( \tau \) in the interval of \( 0.5 < \chi < 1 \). 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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