Communication in Mathematical Modeling and Applications

http://ntmsci.com/cmma

A mathematical analysis of a 2D model for tumor angiogenesis: An initial data perturbation approximation

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Received: 15 November 2017, Accepted: 15 January 2018
Published online: 26 January 2018.

Abstract: We present a 2D - mathematical model for tumor angiogenesis and solve it by linearizing it using an initial data perturbation approximation method. This method is a well-known and highly effective method to obtain solutions of coupled non-linear differential equations. This method shows that a few terms of the obtained approximate solution are enough to get an idea about the movement of endothelial, macrophage and pericyte cells in the extra cellular matrix, which are needed for the initiation of tumor angiogenesis. MATLAB-generated figures are provided.

Keywords: Tumor angiogenesis, linearization, perturbation, approximation.

1 Introduction

Angiogenesis is known as the process through which new blood vessels form from pre-existing vessels. It is crucial to tumor growth, but it is not unique to that process: formation of a functional vascular network occurs during embryogenesis and later in growing tissues. Tumor-induced angiogenesis provides the crucial link between the avascular phase of solid tumor growth and the more harmful vascular phase. It is also known that it occurs in three sequential steps [1]. First, the endothelial cells(EC)lining the vascular basal lamina(BL)(or basement membrane)degrade this membrane. Second, the EC migrate and proliferate (via mitosis) into the extracellular matrix (ECM). Finally, capillary loops form. One of the major components of the ECM is fibronectin, a large, highly adhesive glycoprotein particularly abundant in plasma, connective tissue matrices, and BL [2]. It is also known to enhance EC adhesion to collagen and is produced by EC [3]. As stated in [4, 5] EC are stimulated by a tumor angiogenic factor for angiogenesis to occur. Also, active enzyme stimulates the EC migration [6]. Once the EC are stimulated, the tendency of them as time evolves is towards the transition probability density function (TPDF) [7] of active enzyme and fibronectin (see [8] for mathematical proof of this). Endothelial cell migration and proliferation also occur during endothelial repair in situ; the ability to penetrate the vascular basement membrane, on the other hand, is an aspect of endothelial cell behavior uniquely expressed during angiogenesis[9]. We have also introduced pericyte cells (PC) and macrophage cells (MC) to our model to examine their role in angiogenesis. As stated in [23] PC are adjacent to capillaries. These cell types have a small, oval cell body with multiple processes extending for some distance along the vessel axis. These primary processes then give rise to orthogonal secondary branches which encircle the vascular wall and penetrate the BL to directly contact the underlying endothelium. Tumor cells are also able to attract inflammatory cells, such as MC, which contribute to the production of angiogenic factors in an environment already enriched with angiogenic stimuli [23].

There have been many mathematical models on tumor angiogenesis (see[10-13] and references therein). For example, in [11] the authors propose a review and critical analysis of the asymptotic limit methods focused on the derivation of macroscopic equations for a class of equations modeling complex multicellular systems by methods of the kinetic theory

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for active particles, and in [12] the authors deal with the derivation of macroscopic equations of biological tissues for a class of nonlinear equations, with quadratic type nonlinearity, modeling complex multicellular systems. Also, in [13] a continuous model for three early stage events in angiogenesis, initiation, sprout extension, and vessel maturation, is presented, and in [8,14], a mathematical model for capillary network formation is presented, and a mathematical analysis of it is given in one and two dimensions, respectively. On the other hand, in [15] the authors study some qualitative properties of the solutions of a nonlinear flux-limited equation arising in the transport of morphogens in biological systems, and in [16], to eliminate non biological behaviors from diffusion models the authors introduce flux-limited spreading, which implies a restricted velocity for morphogen propagation and a nonlinear mechanism of transport.

The lay out of the rest of the paper is as follows. First, we write down our two dimensional model equations [24]. In fact, the derivation of eq. (5) only may be found in [17]. The others will be similar. Also, the details of the derivation of the one dimensional version of our model can be found in [20]). Second, we linearize our model using an initial data perturbation method and solve it with some parameter values. Finally, we close the paper by presenting the conclusion and results section to emphasize the biological importance of our mathematical analysis.

2 The model

In the $x-y$ plane we envisage a capillary segment of length l_2 microns located along the y axis on the interval $[0,l_2]$ with a tumor source located somewhere along the line $x=l_1$ (Figure1)[8]. We rescale x by x/l_1 and y by y/l_2 so that this rectangle becomes a unit square. Therefore, we now have $0\leq x,y\leq 1$. Basically, the problem consists of two parts: (i) the dynamics on the y axis, namely, in the capillary (1D model);(ii)the dynamics in the unit square, namely, in the ECM (2D model). We couple those two dynamics via some boundary conditions (see [17] for details). An initial data perturbation solution of the 1D model, a model in which only endothelial cell has been considered as a tumor cell, is obtained in [22], and an initial data perturbation solution of the 2D model is the focus of this paper.

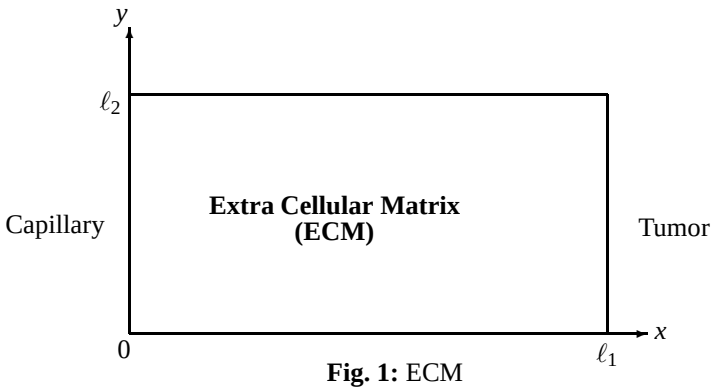

Fig. 1: ECM

The following set of differential equations model the angiogenesis mechanisms in the extra cellular matrix (ECM), where we assume there are no proliferation of cells in the ECM [24]

$$\frac{\partial U}{\partial t}=-\frac{\lambda_2 UM}{1+\nu_2 U}, \tag{1}$$

$$\frac{\partial V}{\partial t}=\frac{\lambda_2 UM}{1+\nu_2 U}-\frac{\lambda_1 VN}{1+\nu_1 V}, \tag{2}$$

$$\frac{\partial C}{\partial t} = \frac{\lambda_1 VN}{1+\nu_1 V} - \mu C, \tag{3}$$

$$\frac{\partial F}{\partial t} = \beta(1-F)FN - \frac{\lambda_4 CF}{1+\nu_4 F}, \tag{4}$$

$$\frac{\partial N}{\partial t} = D_N \nabla.\left(N\nabla\left(\ln\left(\frac{N}{T(C,F)}\right)\right)\right), \tag{5}$$

$$\frac{\partial S}{\partial t} = D_S \nabla.\left(S\nabla\left(\ln\left(\frac{S}{T_3(F)}\right)\right)\right), \tag{6}$$

$$\frac{\partial M}{\partial t} = D_M \nabla.\left(M\nabla\left(\ln\left(\frac{M}{T_4(U)}\right)\right)\right). \tag{7}$$

Here

$U =$ chemotactic agent

$V =$ angiogenic factor

$C =$ proteolytic enzyme

$F =$ fibronectin

$N =$ endothelial cell density

$S =$ pericyte cell density

$M =$ macrophage cell density.

The equations (1)-(4) are obtained by using the law of mass action whereas the cell equations (5)-(7) are obtained by using the reinforced random walk idea [18]. Our initial conditions are $U(x,y,0) = \varepsilon\theta_1(x,y), V(x,y,0) = \varepsilon\theta_2(x,y), C(x,y,0) = 0, F(x,y,0) = 1, N(x,y,0) = S(x,y,0) = M(x,y,0) = 1$, while our boundary conditions are $N_x = S_x = M_x = 0 \quad \text{at } x = 0,1 \text{ and } \quad N_y = S_y = M_y = 0 \quad \text{at } y = 0,1.$

Here ε is some small positive perturbation parameter. We choose the functions $\theta_i(x,y)(i=1,2)$ of the form

$$\theta_i(x,y) = Ax^2(1-x)y, (i=1,2)$$

where A is a constant such that

$$\int_0^1 \int_0^1 \theta_i(x,y)dxdy = 1.$$

Also, we take $T(C,F) = T_1(C)T_2(F)$, where $T_1(C) = (\frac{C+\alpha_1}{C+\alpha_2})^{\gamma_1}$, and $T_2(F) = (\frac{F+\beta_1}{F+\beta_2})^{\gamma_2}$, and $T_3(F) = (\frac{F+\alpha_3}{F+\alpha_4})^{\gamma_3}$, $T_4(U) = (\frac{U+\beta_3}{U+\beta_4})^{\gamma_4}$. Here α_i, β_i and γ_i are some positive constants such that $0 < \alpha_1 \ll 1 < \alpha_2$, $0 < \beta_2 \ll 1 < \beta_1$, $0 < \alpha_3 \ll 1 \ll \alpha_4$ and $0 < \beta_3 \ll 1 \ll \beta_4$.

3 Model analysis and solutions

To solve our model using initial data perturbation analysis we let

$$\begin{aligned} &U(x,y,t) = \varepsilon U^*(x,y,t,\varepsilon), \quad V(x,y,t) = \varepsilon V^*(x,y,t,\varepsilon), \\ &F(x,y,t) = 1-\varepsilon F^*(x,y,t,\varepsilon), \quad C(x,y,t) = \varepsilon C^*(x,y,t,\varepsilon), \\ &N(x,y,t) = 1+\varepsilon N^*(x,y,t,\varepsilon), \quad S(x,y,t) = 1+\varepsilon S^*(x,y,t,\varepsilon), \\ &M(x,y,t) = 1+\varepsilon M^*(x,y,t,\varepsilon), \end{aligned} \tag{8}$$

where ε is as above. As it is clear, equations (5)-(7) can be written as follows

$$\begin{aligned}
\tfrac{\partial N}{\partial t} &= D_N \tfrac{\partial}{\partial x}\left(N \tfrac{\partial}{\partial x} \ln\left(\tfrac{N}{T(C,F)}\right)\right) + D_N \tfrac{\partial}{\partial y}\left(N \tfrac{\partial}{\partial y} \ln\left(\tfrac{N}{T(C,F)}\right)\right) \\
\tfrac{\partial S}{\partial t} &= D_S \tfrac{\partial}{\partial x}\left(S \tfrac{\partial}{\partial x} \ln\left(\tfrac{S}{T_3(F)}\right)\right) + D_S \tfrac{\partial}{\partial y}\left(S \tfrac{\partial}{\partial y} \ln\left(\tfrac{S}{T_3(F)}\right)\right) \\
\tfrac{\partial M}{\partial t} &= D_M \tfrac{\partial}{\partial x}\left(M \tfrac{\partial}{\partial x} \ln\left(\tfrac{M}{T_4(U)}\right)\right) + D_M \tfrac{\partial}{\partial y}\left(M \tfrac{\partial}{\partial y} \ln\left(\tfrac{M}{T_4(U)}\right)\right)
\end{aligned}$$

or, equivalently

$$\frac{\partial N}{\partial t} = D_N \left[\frac{\partial}{\partial x}\left(N_x - N\frac{T_1'}{T_1}C_x - N\frac{T_2'}{T_2}F_x\right) + \frac{\partial}{\partial y}\left(N_y - N\frac{T_1'}{T_1}C_y - N\frac{T_2'}{T_2}F_y\right)\right] \tag{9}$$

$$\frac{\partial S}{\partial t} = D_S \frac{\partial}{\partial x}\left(S_x - S\frac{T_3'}{T_3}F_x\right) + D_S \frac{\partial}{\partial y}\left(S_y - S\frac{T_3'}{T_3}F_y\right) \tag{10}$$

$$\frac{\partial M}{\partial t} = D_M \frac{\partial}{\partial x}\left(M_x - M\frac{T_4'}{T_4}U_x\right) + D_M \frac{\partial}{\partial y}\left(M_y - M\frac{T_4'}{T_4}U_y\right). \tag{11}$$

Here

$$\frac{T_1'}{T_1} = \gamma_1 \frac{\alpha_2 - \alpha_1}{(\alpha_1 + C)(\alpha_2 + C)}, \quad \frac{T_2'}{T_2} = \gamma_2 \frac{\beta_2 - \beta_1}{(\beta_1 + F)(\beta_2 + F)},$$

and

$$\frac{T_3'}{T_3} = \gamma_3 \frac{\alpha_4 - \alpha_3}{(\alpha_3 + F)(\alpha_4 + F)}, \quad \frac{T_4'}{T_4} = \gamma_4 \frac{\beta_4 - \beta_3}{(\beta_3 + U)(\beta_4 + U)}.$$

If we use the variables given by eq. (8), the eqs. (1)-(4) become

$$\begin{aligned}
\varepsilon U_t^* &= -\frac{\lambda_2 \varepsilon U^*(1+\varepsilon M^*)}{1+\nu_2 \varepsilon U^*}, \\
\varepsilon V_t^* &= \frac{\lambda_2 \varepsilon U^*(1+\varepsilon M^*)}{1+\nu_2 \varepsilon U^*} - \frac{\lambda_1 \varepsilon V^*(1+\varepsilon N^*)}{1+\nu_1 \varepsilon V^*}, \\
\varepsilon C_t^* &= \frac{\lambda_1 \varepsilon V^*(1+\varepsilon N^*)}{1+\nu_1 \varepsilon V^*} - \mu \varepsilon C^*, \\
-\varepsilon F_t^* &= \beta \varepsilon F^*(1-\varepsilon F^*)(1+\varepsilon N^*) - \frac{\lambda_4 \varepsilon C^*(1-\varepsilon F^*)}{1+\nu_4(1-\varepsilon F^*)}
\end{aligned}$$

Letting $\varepsilon \to 0$ we obtain the following set of differential equations:

$$U_t^* = -\lambda_2 U^*, \tag{12}$$

$$V_t^* = \lambda_2 U^* - \lambda_1 V^*, \tag{13}$$

$$C_t^* = \lambda_1 V^* - \mu C^*, \tag{14}$$

$$F_t^* = -\beta F^* + \frac{\lambda_4}{1+\nu_4} C^*. \tag{15}$$

Solving (12) yields

$$U^*(x,y,t,\varepsilon) = \theta_1(x,y) e^{-\lambda_2 t}. \tag{16}$$

Writing this U^* in (13) to get

$$V_t^* + \lambda_1 V^* = \lambda_2 \theta_1(x,y) e^{-\lambda_2 t},$$

which is a linear equation whose solution is

$$V^*(x,y,t,\varepsilon) = \frac{\lambda_2}{\lambda_1 - \lambda_2}\theta_1(x,y)(e^{-\lambda_2 t} - e^{-\lambda_1 t}) + e^{-\lambda_1 t}\theta_2(x,y). \tag{17}$$

Writing this V^* in equation (14) and solving the resulting equations we get

$$\begin{aligned} C^*(x,y,t,\varepsilon) = &\frac{\lambda_1\lambda_2}{(\lambda_1-\lambda_2)(\mu-\lambda_2)}\theta_1(x,y)e^{-\lambda_2 t} - \frac{\lambda_1\lambda_2}{(\lambda_1-\lambda_2)(\mu-\lambda_1)}\theta_1(x,y)e^{-\lambda_1 t} \\ &+ \frac{\lambda_1}{\mu-\lambda_1}\theta_2(x,y)e^{-\lambda_1 t} + e^{-\mu t}\left(\frac{\lambda_1\lambda_2}{(\mu-\lambda_1)(\mu-\lambda_2)}\theta_1(x,y) - \frac{\lambda_1}{\mu-\lambda_1}\theta_2(x,y)\right). \end{aligned} \tag{18}$$

We now write this C^* in equation (15) and obtain the solution of the resulting equation as

$$\begin{aligned} F^*(x,y,t,\varepsilon) = &\frac{\lambda_1\lambda_2\lambda_4}{(\lambda_1-\lambda_2)(\mu-\lambda_2)(\beta-\lambda_2)(1+\nu_4)}\theta_1(x,y)e^{-\lambda_2 t} \\ &- \frac{\lambda_1\lambda_2\lambda_4}{(\lambda_1-\lambda_2)(\mu-\lambda_1)(\beta-\lambda_1)(1+\nu_4)}\theta_1(x,y)e^{-\lambda_1 t} + \frac{\lambda_1\lambda_4}{(\mu-\lambda_1)(\beta-\lambda_1)(1+\nu_4)}\theta_2(x,y)e^{-\lambda_1 t} \\ &+ \frac{e^{-\mu t}}{\beta-\mu}\left(\frac{\lambda_1\lambda_2\lambda_4}{(\mu-\lambda_1)(\mu-\lambda_2)(1+\nu_4)}\theta_1(x,y) - \frac{\lambda_1\lambda_4}{(\mu-\lambda_1)(1+\nu_4)}\theta_2(x,y)\right) \\ &+ \frac{e^{-\beta t}}{\beta-\mu}\left[\frac{\lambda_1\lambda_2\lambda_4\theta_1(x,y)}{(\lambda_1-\lambda_2)(1+\nu_4)}\left(\frac{1}{(\mu-\lambda_1)(\beta-\lambda_1)} - \frac{1}{(\mu-\lambda_2)(\beta-\lambda_2)}\right)\right. \\ &\left. - \frac{\lambda_1\lambda_2\lambda_4}{(\mu-\lambda_1)(\mu-\lambda_2)(\beta-\mu)(1+\nu_4)}\theta_1(x,y) + \frac{\lambda_1\lambda_4}{(\beta-\mu)(1+\nu_4)}\theta_2(x,y)\right]. \end{aligned}$$

Similarly, if we plug the variables in (8) in equations (9)-(11) we obtain

$$\begin{aligned} \varepsilon N_t^* &= D_N\frac{\partial}{\partial x}\left[\varepsilon N_x^* - (1+\varepsilon N^*)\gamma_1\frac{\alpha_2-\alpha_1}{(\alpha_1+\varepsilon C^*)(\alpha_2+\varepsilon C^*)}\varepsilon C_x^* - (1+\varepsilon N^*)\gamma_2\frac{\beta_2-\beta_1}{(\beta_1+1-\varepsilon F^*)(\beta_2+1-\varepsilon F^*)}(-\varepsilon F_x^*)\right] \\ &\quad + D_N\frac{\partial}{\partial y}\left[\varepsilon N_y^* - (1+\varepsilon N^*)\gamma_1\frac{\alpha_2-\alpha_1}{(\alpha_1+\varepsilon C^*)(\alpha_2+\varepsilon C^*)}\varepsilon C_y^* - (1+\varepsilon N^*)\gamma_2\frac{\beta_2-\beta_1}{(\beta_1+1-\varepsilon F^*)(\beta_2+1-\varepsilon F^*)}(-\varepsilon F_y^*)\right] \\ \varepsilon S_t^* &= D_S\frac{\partial}{\partial x}\left[\varepsilon S_x^* - (1+\varepsilon S^*)\gamma_3\frac{\alpha_4-\alpha_3}{(\alpha_3+1-\varepsilon F^*)(\alpha_4+1-\varepsilon F^*)}(-\varepsilon F_x^*)\right] \\ &\quad + D_S\frac{\partial}{\partial y}\left[\varepsilon S_y^* - (1+\varepsilon S^*)\gamma_3\frac{\alpha_4-\alpha_3}{(\alpha_3+1-\varepsilon F^*)(\alpha_4+1-\varepsilon F^*)}(-\varepsilon F_y^*)\right] \\ \varepsilon M_t^* &= D_M\frac{\partial}{\partial x}\left[\varepsilon M_x^* - (1+\varepsilon M^*)\gamma_4\frac{\beta_4-\beta_3}{(\beta_3+\varepsilon U^*)(\beta_4+\varepsilon U^*)}\varepsilon U_x^*\right] \\ &\quad + D_M\frac{\partial}{\partial y}\left[\varepsilon M_y^* - (1+\varepsilon M^*)\gamma_4\frac{\beta_4-\beta_3}{(\beta_3+\varepsilon U^*)(\beta_4+\varepsilon U^*)}\varepsilon U_y^*\right]. \end{aligned} \tag{19}$$

Letting $\varepsilon \to 0$ we obtain

$$\begin{aligned} N_t^* &= D_N\left(N_{xx}^* - \frac{\gamma_1(\alpha_2-\alpha_1)}{\alpha_1\alpha_2}C_{xx}^* + \frac{\gamma_2(\beta_2-\beta_1)}{(\beta_1+1)(\beta_2+1)}F_{xx}^*\right) \\ &\quad + D_N\left(N_{yy}^* - \frac{\gamma_1(\alpha_2-\alpha_1)}{\alpha_1\alpha_2}C_{yy}^* + \frac{\gamma_2(\beta_2-\beta_1)}{(\beta_1+1)(\beta_2+1)}F_{yy}^*\right) \\ S_t^* &= D_S\left(S_{xx}^* - \frac{\gamma_3(\alpha_4-\alpha_3)}{\alpha_3\alpha_4}F_{xx}^*\right) + D_S\left(S_{yy}^* - \frac{\gamma_3(\alpha_4-\alpha_3)}{(\alpha_3+1)(\alpha_4+1)}F_{yy}^*\right) \\ M_t^* &= D_M\left(M_{xx}^* - \frac{\gamma_4(\beta_4-\beta_3)}{\beta_3\beta_4}U_{xx}^*\right) + D_M\left(M_{yy}^* - \frac{\gamma_4(\beta_4-\beta_3)}{\beta_3\beta_4}U_{yy}^*\right). \end{aligned} \tag{20}$$

If we compute the constant A above we find $A = 24$. Therefore $\theta_{i_{xx}} = 48(1-3x)y$ and $\theta_{i_{yy}} = 0, (i = 1,2)$.

On the other hand, we find that $C^*_{yy} = F^*_{yy} = U^*_{yy} = 0$, and

$$\begin{aligned}
C^*_{xx} &= 48(1-3x)y\left[\frac{\lambda_1\lambda_2}{(\lambda_1-\lambda_2)(\mu-\lambda_2)}e^{-\lambda_2 t} - \frac{\lambda_1\lambda_2}{(\lambda_1-\lambda_2)(\mu-\lambda_1)}e^{-\lambda_1 t}\right.\\
&\quad \left. + \frac{\lambda_1}{\mu-\lambda_1}e^{-\lambda_1 t} + e^{-\mu t}\left(\frac{\lambda_1\lambda_2}{(\mu-\lambda_1)(\mu-\lambda_2)} - \frac{\lambda_1}{\mu-\lambda_1}\right)\right]\\
U^*_{xx} &= 48(1-3x)ye^{-\lambda_2 t}\\
F^*_{xx} &= 48(1-3x)y\left\{\frac{\lambda_1\lambda_2\lambda_4}{(\lambda_1-\lambda_2)(\mu-\lambda_2)(\beta-\lambda_2)(1+\nu_4)}e^{-\lambda_2 t}\right.\\
&\quad - \frac{\lambda_1\lambda_2\lambda_4}{(\lambda_1-\lambda_2)(\mu-\lambda_1)(\beta-\lambda_1)(1+\nu_4)}e^{-\lambda_1 t} + \frac{\lambda_1\lambda_4}{(\mu-\lambda_1)(\beta-\lambda_1)(1+\nu_4)}e^{-\lambda_1 t}\\
&\quad + \frac{e^{-\mu t}}{\beta-\mu}\left(\frac{\lambda_1\lambda_2\lambda_4}{(\mu-\lambda_1)(\mu-\lambda_2)(1+\nu_4)} - \frac{\lambda_1\lambda_4}{(\mu-\lambda_1)(1+\nu_4)}\right)\\
&\quad + e^{-\beta t}\left[\frac{\lambda_1\lambda_2\lambda_4}{(\lambda_1-\lambda_2)(1+\nu_4)}\left(\frac{1}{(\mu-\lambda_1)(\beta-\lambda_1)} - \frac{1}{(\mu-\lambda_2)(\beta-\lambda_2)}\right)\right.\\
&\quad \left.\left. - \frac{\lambda_1\lambda_2\lambda_4}{(\mu-\lambda_1)(\mu-\lambda_2)(\beta-\mu)(1+\nu_4)} + \frac{\lambda_1\lambda_4}{(\beta-\mu)(1+\nu_4)}\right]\right\}.
\end{aligned}$$

Therefore, eqs. (21) now have the following form

$$\begin{aligned}
N^*_t &= D_N(N^*_{xx} + N^*_{yy}) + f(x,y,t),\\
S^*_t &= D_S(S^*_{xx} + S^*_{yy}) + g(x,y,t),\\
M^*_t &= D_M(M^*_{xx} + M^*_{yy}) + h(x,y,t),
\end{aligned} \tag{21}$$

Here

$$\begin{aligned}
f(x,y,t) &= -D_N\frac{\gamma_1(\alpha_2-\alpha_1)}{\alpha_1\alpha_2}C^*_{xx} + D_N\frac{\gamma_2(\beta_2-\beta_1)}{(\beta_1+1)(\beta_2+1)}F^*_{xx},\\
g(x,y,t) &= D_S\frac{\gamma_3(\alpha_4-\alpha_3)}{\alpha_3\alpha_4}F^*_{xx},\\
h(x,y,t) &= -D_M\frac{\gamma_4(\beta_4-\beta_3)}{\beta_3\beta_4}U^*_{xx},
\end{aligned} \tag{22}$$

where C^*_{xx}, F^*_{xx} and U^*_{xx} are as above. In fact, equations (22) are all diffusion equations with forcing terms. They are to be solved with initial conditions

$$N^*(x,y,0,\varepsilon) = S^*(x,y,0,\varepsilon) = M^*(x,y,0,\varepsilon) = 0,$$

and boundary conditions

$$N^*_x = S^*_x = M^*_x = 0 \quad \text{at} \quad x = 0,1 \quad \text{and} \quad N^*_y = S^*_y = M^*_y = 0 \quad \text{at} \quad y = 0,1.$$

First we solve the homogeneous part of equations in (22) by the method of separation of variables. To do this we let $N^*(x,y,t,\varepsilon) = X(x)Y(y)T(t)$. Then, we get the following boundary value problem (BVP):

$$\begin{aligned}
&X'' + \lambda X = 0 \quad \text{with} \quad X'(0) = X'(1) = 0,\\
&Y'' + \mu Y = 0 \quad \text{with} \quad Y'(0) = Y'(1) = 0, T' + D_N(\lambda+\mu)T = 0.
\end{aligned}$$

If $\lambda = 0$ we have $X_0(x) = B_0 = \text{constant}, \quad Y_0(y) = C_0 = \text{constant}.$

If $\lambda > 0$ we have $\lambda_n = n^2\pi^2, \quad n = 1,2,\cdots \quad \text{with} \quad X_n(x) = B_n cos(n\pi x).$

If $\mu > 0$ we have $\mu_m = m^2\pi^2, \quad m = 1,2,\cdots \quad \text{with} \quad Y_m(y) = C_m cos(m\pi y).$

It is clear that the above BVP has no negative eigenvalues. Thus the above BVP has the eigenvalues $\gamma_{n,m} = \lambda_n + \mu_m = (n^2+m^2)\pi^2$ and the corresponding eigenfunctions $\varphi_{nm}(x,y) = X_n(x)Y_m(y) = cos(n\pi x)cos(m\pi y)$. We now solve the following inhomogeneous boundary value problem (IBVP):

$N^*_t = D_N(N^*_{xx} + N^*_{yy}) + f(x,y,t) = D_N\Delta N^* + f(x,y,t)$ with the initial condition $N^*(x,y,0,\varepsilon) = 0$ and the boundary conditions $N^*_x = 0 \quad \text{at} \quad x = 0,1 \quad \text{and} \quad N^*_y = 0 \quad \text{at} \quad y = 0,1$. Note that $N^*(x,y,t,\varepsilon)$ can be represented by its series expansion [21]

$$N^*(x,y,t,\varepsilon) = B + \sum_{m,n=1}^{\infty} B_{nm}(t)\varphi_{nm}(x,y). \tag{23}$$

Here $B = 4\int_0^1\int_0^1 N^*(x,y,0,\varepsilon)dxdy = 0$ and

$$B_{nm}(t) = 4\int\int_D N^*(x,y,t,\varepsilon)\varphi_{nm}(x,y)dxdy, \tag{24}$$

where $D = [0,1]\times[0,1]$. Differentiating equation (25) with respect to t and using the given partial differential equation we get

$$\frac{dB_{nm}(t)}{dt} = 4\int\int_D \frac{\partial N^*}{\partial t}\varphi_{nm}dxdy = 4\int\int_D D_N(\Delta N^*)\varphi_{nm}dxdy + 4\int\int_D f\varphi_{nm}dxdy. \tag{25}$$

The last integral on the right side is

$$f_{nm}(t) = 4\int\int_D f(x,y,t)\varphi_{nm}(x,y)dxdy,$$

which is a known function of t. The first integral on the right can be transformed by Green's formula, and because $\Delta\varphi_{nm} = -\gamma_{nm}\varphi_{nm}$ we obtain

$$4\int\int_D D_N(\Delta N^*)\varphi_{nm}dxdy = -\gamma_{nm}D_N 4\int\int_D N^*\varphi_{nm}dxdy + 4D_N\int_{\partial D}\left(\frac{\partial N^*}{\partial n}\varphi_{nm} - N^*\frac{\partial\varphi_{nm}}{\partial n}\right)dS$$

where n is the outer normal vector to the boundary of D.

Since both $\frac{\partial N^*}{\partial n}$ and $\frac{\partial\varphi_{nm}}{\partial n}$ are zero on ∂D, the second integral on the right side is zero. The first integral on the right side is equal to $-\gamma_{nm}D_N B_{nm}(t)$ and hence equation (26) becomes

$$\frac{dB_{nm}}{dt} = -\gamma_{nm}D_N B_{nm} + f_{nm}(t). \tag{26}$$

If we let $t \to 0$ in equation (26) and use the initial condition $N^*(x,y,0,\varepsilon) = 0$ we get [21]

$$B_{nm}(0) = 0. \tag{27}$$

Solving differential equation (27) with the initial condition (28) gives

$$B_{nm}(t) = \int_0^t e^{-\gamma_{nm}D_N(t-\tau)}f_{nm}(\tau)d\tau. \tag{28}$$

Thus the solution of the given IBVP is complete. We now set

$$c_1=\frac{\lambda_1\lambda_2\lambda_4}{(\lambda_1-\lambda_2)(\mu-\lambda_2)(\beta-\lambda_2)(1+\nu_4)},\quad c_2=\frac{\lambda_1\lambda_2\lambda_4}{(\lambda_1-\lambda_2)(\mu-\lambda_1)(\beta-\lambda_1)(1+\nu_4)},$$

$$c_3=\frac{\lambda_1\lambda_4}{(\mu-\lambda_1)(\beta-\lambda_1)(1+\nu_4)},$$

$$c_4=\frac{\lambda_1\lambda_2\lambda_4}{(\beta-\mu)(\mu-\lambda_1)(\mu-\lambda_2)(1+\nu_4)}-\frac{\lambda_1\lambda_4}{(\beta-\mu)(\mu-\lambda_1)(1+\nu_4)},$$

$$c_5=\frac{\lambda_1\lambda_2\lambda_4}{(\lambda_1-\lambda_2)(1+\nu_4)}\left(\frac{1}{(\mu-\lambda_1)(\beta-\lambda_1)}-\frac{1}{(\mu-\lambda_2)(\beta-\lambda_2)}\right)$$

$$-\frac{\lambda_1\lambda_2\lambda_4}{(\mu-\lambda_1)(\mu-\lambda_2)(\beta-\mu)(1+\nu_4)}+\frac{\lambda_1\lambda_4}{(\beta-\mu)(1+\nu_4)},$$

$$c_6=\frac{\lambda_1\lambda_2}{(\lambda_1-\lambda_2)(\mu-\lambda_2)},\quad c_7=\frac{\lambda_1\lambda_2}{(\lambda_1-\lambda_2)(\mu-\lambda_1)},\quad c_8=\frac{\lambda_1}{\mu-\lambda_1},$$

$$c_9=\frac{\lambda_1\lambda_2}{(\mu-\lambda_1)(\mu-\lambda_2)}.$$

Then, one has

$$F^*_{xx}=48(1-3x)y\left(c_1e^{-\lambda_2 t}+(c_3-c_2)e^{-\lambda_1 t}+c_4e^{-\mu t}+c_5e^{-\beta t}\right),$$

$$C^*_{xx}=48(1-3x)y\left(c_6e^{-\lambda_2 t}+(c_8-c_7)e^{-\lambda_1 t}+(c_9-c_8)e^{-\mu t}\right),$$

$$U^*_{xx}=48(1-3x)ye^{-\lambda_2 t}.$$

We also set,

$$c_{10}=-D_N\frac{\gamma_1(\alpha_2-\alpha_1)}{\alpha_1\alpha_2},\quad c_{11}=D_N\frac{\gamma_2(\beta_2-\beta_1)}{(\beta_1+1)(\beta_2+1)},$$

$$c_{12}=D_S\frac{\gamma_3(\alpha_4-\alpha_3)}{\alpha_3\alpha_4},\quad c_{13}=-D_M\frac{\gamma_4(\beta_3-\beta_4)}{\beta_3\beta_4}.$$

Therefore, we get

$$f(x,y,t)=c_{10}C^*_{xx}+c_{11}F^*_{xx},\quad g(x,y,t)=c_{12}F^*_{xx},\quad h(x,y,t)=c_{13}U^*_{xx},$$

so that these functions can be written as follows

$$f(x,y,t)=48(1-3x)yf_1(t),\ g(x,y,t)=48c_{12}(1-3x)yg_1(t),\ h(x,y,t)=48c_{13}(1-3x)ye^{-\lambda_2 t},$$

where

$$f_1(t)=(c_1c_{10}+c_6c_{11})e^{-\lambda_2 t}+(c_{10}(c_3-c_2)+c_{11}(c_8-c_7))e^{-\lambda_1 t}+(c_4c_{10}+c_{11}(c_9-c_8))e^{-\mu t}+c_{10}c_5e^{-\beta t}$$
$$g_1(t)=c_1e^{-\lambda_2 t}+(c_3-c_2)e^{-\lambda_1 t}+c_4e^{-\mu t}+c_5e^{-\beta t}.$$

Thus we obtain

$$f_{nm}(t) = 192 f_1(t) \int_0^1 \int_0^1 (1-3x) y \cos(n\pi x) \cos(m\pi y) dxdy = -\frac{2304}{(2n-1)^2(2m-1)^2\pi^4} f_1(t), \quad n,m = 1,2,\cdots.$$

Similarly we consider the following two IBVPs:

$$\begin{aligned} &S_t^* = D_S(S_{xx}^* + S_{yy}^*) + g(x,y,t), \\ &S^*(x,y,0,\varepsilon) = 0, \quad S_x^* = 0 \quad \text{at} \quad x = 0,1, \quad S_y^* = 0 \quad \text{at} \quad y = 0,1, \end{aligned} \tag{29}$$

and

$$\begin{aligned} &M_t^* = D_M(M_{xx}^* + M_{yy}^*) + h(x,y,t), \\ &M^*(x,y,0,\varepsilon) = 0, \quad ,M_x^* = 0 \quad \text{at} \quad x = 0,1, \quad M_y^* = 0 \quad \text{at} \quad y = 0,1. \end{aligned} \tag{30}$$

If the solutions of the equations (30) and (31) are represented by their eigenfunction expansion,

$$\begin{aligned} &S^*(x,y,t,\varepsilon) = C + \textstyle\sum_{n,m=1}^{\infty} C_{nm}(t)\varphi_{nm}(x,y), \\ &M^*(x,y,t,\varepsilon) = H + \textstyle\sum_{n,m=1}^{\infty} H_{nm}(t)\varphi_{nm}(x,y), \end{aligned} \tag{31}$$

respectively, we obtain $C = H = 0$, and

$$\begin{aligned} C_{nm}(t) &= 4 \int \int_D S^*(x,y,t,\varepsilon)\varphi_{nm}(x,y)dxdy, \\ H_{nm}(t) &= 4 \int \int_D M^*(x,y,t,\varepsilon)\varphi_{nm}(x,y)dxdy. \end{aligned}$$

If we set

$$g_{nm}(t) = 4 \int \int_D g(x,y,t)\varphi_{nm}(x,y)dxdy, \; h_{nm}(t) = 4 \int \int_D h(x,y,t)\varphi_{nm}(x,y)dxdy, \tag{32}$$

one obtains

$$C_{nm}(t) = \int_0^t e^{-\gamma_{nm}D_S(t-\tau)} g_{nm}(\tau)d\tau, \; H_{nm}(t) = \int_0^t e^{-\gamma_{nm}D_M(t-\tau)} h_{nm}(\tau)d\tau, \tag{33}$$

$$\text{where } g_{nm}(t) = \frac{-2304c_{12}}{(2n-1)^2(2m-1)^2\pi^4} g_1(t), \; h_{nm}(t) = \frac{-2304c_{13}}{(2n-1)^2(2m-1)^2\pi^4} e^{-\lambda_2 t}.$$

On the other hand, we calculate

$$\begin{aligned} B_{nm}(t) =& e^{-\gamma_{nm}D_N t} \int_0^t e^{\gamma_{nm}D_N \tau} f_{nm}(\tau)d\tau \\ =& -\frac{2304}{(2n-1)^2(2m-1)^2\pi^4} e^{-\gamma_{nm}D_N t} \int_0^t e^{\gamma_{nm}D_N \tau} f_1(\tau)d\tau \\ =& -\frac{2304}{(2n-1)^2(2m-1)^2\pi^4} e^{-\gamma_{nm}D_N t} \int_0^t e^{\gamma_{nm}D_N \tau} \Big[(c_1c_{10} + c_6c_{11}) e^{-\lambda_2 \tau} \\ &+ (c_{10}(c_3 - c_2) + c_{11}(c_8 - c_7)) e^{-\lambda_1 \tau} + (c_4c_{10} + c_{11}(c_9 - c_8)) e^{-\mu\tau} + c_{10}c_5 e^{-\beta\tau} \Big] d\tau \\ =& -\frac{2304}{(2n-1)^2(2m-1)^2\pi^4} e^{-(n^2+m^2)\pi^2 D_N t} \times \Bigg[\frac{c_1c_{10} + c_6c_{11}}{(n^2+m^2)\pi^2 D_N - \lambda_2} \left(e^{((n^2+m^2)\pi^2 D_N - \lambda_2)t} - 1 \right) \\ &+ \frac{c_{10}(c_3 - c_2) + c_{11}(c_8 - c_7)}{(n^2+m^2)\pi^2 D_N - \lambda_1} \left(e^{((n^2+m^2)\pi^2 D_N - \lambda_1)t} - 1 \right) + \frac{c_4c_{10} + c_{11}(c_9 - c_8)}{(n^2+m^2)\pi^2 D_N - \mu} \left(e^{((n^2+m^2)\pi^2 D_N - \mu)t} - 1 \right) \\ &+ \frac{c_{10}c_5}{(n^2+m^2)\pi^2 D_N - \beta} \left(e^{((n^2+m^2)\pi^2 D_N - \beta)t} - 1 \right) \Bigg] \end{aligned}$$

and

$$
\begin{aligned}
C_{nm}(t) &= e^{-\gamma_{nm}D_S t}\int_0^t e^{\gamma_{nm}D_S\tau}g_{nm}(\tau)d\tau \\
&= -\frac{2304c_{12}}{(2n-1)^2(2m-1)^2\pi^4}e^{-\gamma_{nm}D_S t}\int_0^t e^{\gamma_{nm}D_S\tau}\times\left[c_1e^{-\lambda_2\tau}+(c_3-c_2)e^{-\lambda_1\tau}+c_4e^{-\mu\tau}+c_5e^{-\beta\tau}\right]d\tau \\
&= -\frac{2304c_{12}}{(2n-1)^2(2m-1)^2\pi^4}e^{-(n^2+m^2)\pi^2D_S t}\times\left[\frac{c_1}{(n^2+m^2)\pi^2D_S-\lambda_2}\left(e^{((n^2+m^2)\pi^2D_S-\lambda_2)t}-1\right)\right. \\
&+\frac{c_3-c_2}{(n^2+m^2)\pi^2D_S-\lambda_1}\left(e^{((n^2+m^2)\pi^2D_S-\lambda_1)t}-1\right)+\frac{c_4}{(n^2+m^2)\pi^2D_S-\mu}\left(e^{((n^2+m^2)\pi^2D_S-\mu)t}-1\right) \\
&\left.+\frac{c_5}{(n^2+m^2)\pi^2D_S-\beta}\left(e^{((n^2+m^2)\pi^2D_S-\beta)t}-1\right)\right], \\
H_{nm}(t) &= e^{-\gamma_{nm}D_M t}\int_0^t e^{\gamma_{nm}D_M\tau}h_{nm}(\tau)d\tau \\
&= -\frac{2304}{(2n-1)^2(2m-1)^2\pi^4}e^{-\gamma_{nm}D_M t}\int_0^t e^{\gamma_{nm}D_M\tau}e^{-\lambda_2\tau}d\tau \\
&= -\frac{2304}{(2n-1)^2(2m-1)^2\pi^4}e^{-(n^2+m^2)\pi^2D_M t}\frac{1}{D_M(n^2+m^2)\pi^2-\lambda_2}\times\left(e^{((n^2+m^2)\pi^2D_M-\lambda_2)t}-1\right).
\end{aligned}
$$

As a result, the solutions N^*, S^* and M^* are all found now. Therefore, the desired solutions of equations (5)–(7) are $N(x,y,t)=1+\varepsilon N^*(x,y,t,\varepsilon), S(x,y,t)=1+\varepsilon S^*(x,y,t,\varepsilon), M(x,y,t)=1+\varepsilon M^*(x,y,t,\varepsilon)$.

4 Numerical example

The figures below have been generated by using MATLAB with the parameter values $\lambda_1=3.65; \lambda_2=2\lambda_1; \lambda_4=\lambda_2; \mu=0.1; \beta=0.025; \nu_4=0.014; \gamma_1=1; \alpha_1=.85; \alpha_2=1; \gamma_2=1; \beta_1=10; \beta_2=8; \gamma_3=1; \alpha_3=.85; \alpha_4=1; \gamma_4=1; \beta_3=.85; \beta_4=1; D_N=3.6\times10^{-5}; D_S=3.6\times10^{-2}; D_M=3.6\times10^{-4}; \varepsilon=0.01$. Figures 2–5 show the chemotactic agent, angiogenic factor, enzyme, and fibronectin densities, while Figures 6–8 show the endothelial, pericyte and macrophage cell densities at $t=2$, respectively. To obtain the numerical solutions of the cell equations we have used only four terms of the series given by the eqs. (24) and (32).

5 Conclusion and results

In this paper we have presented a 2D mathematical model for capillary formation in tumor angiogenesis and solved it by linearizing it using an initial data perturbation method. This method has been applied in [22] to a 1D model, a model in which only endothelial cell has been considered as a tumor cell and originally presented in [19], and it was very effective to get the numerical solution of the model. However, in [20] the one dimensional version of the model considered here has been solved numerically by a classical explicit method which takes too much time to get the solution. We believe that the initial data perturbation method applied here is much more easier, faster and effective. Even with four-term expansion of the series solutions we have obtained what we expect to see biologically for the endothelial, pericyte and macrophage cell movements in the ECM. This shows the effectiveness of this method. Of course, a more effective solution for the cell equations can be obtained by expanding more terms of the series solution.

We must also mention the importance of the choices of the functions $\theta_i(x,y)$ appearing in the initial data. They are the functions that initiate the dynamics in the model equations. If they are zero, all of the variables in the model stay dormant, and no action begins in the ECM for the initiation of angiogenesis.

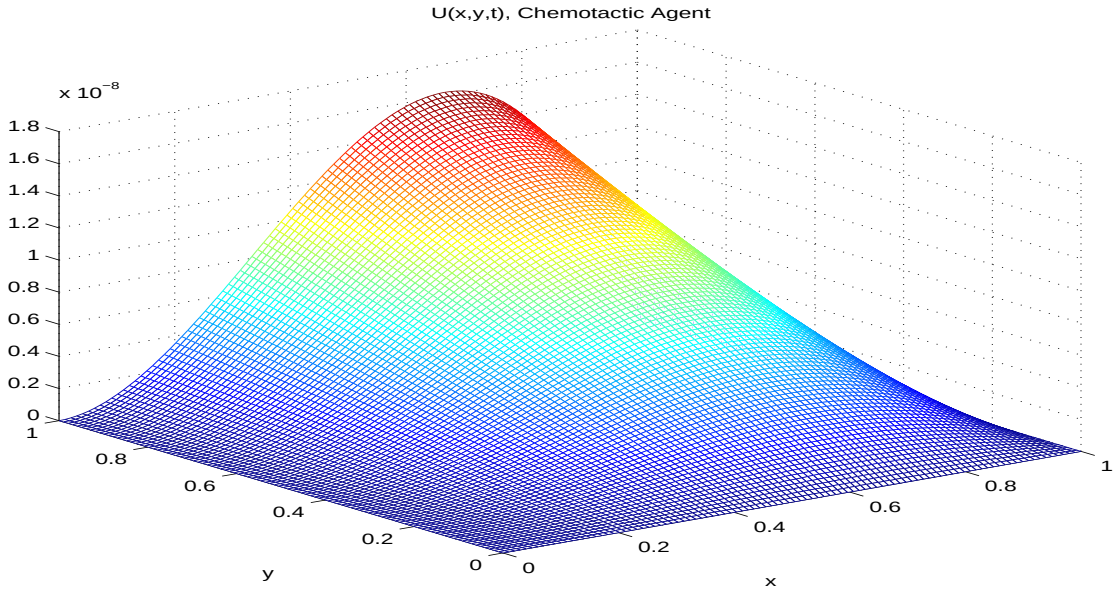

Fig. 2: Chemotactic agent at $t = 2$.

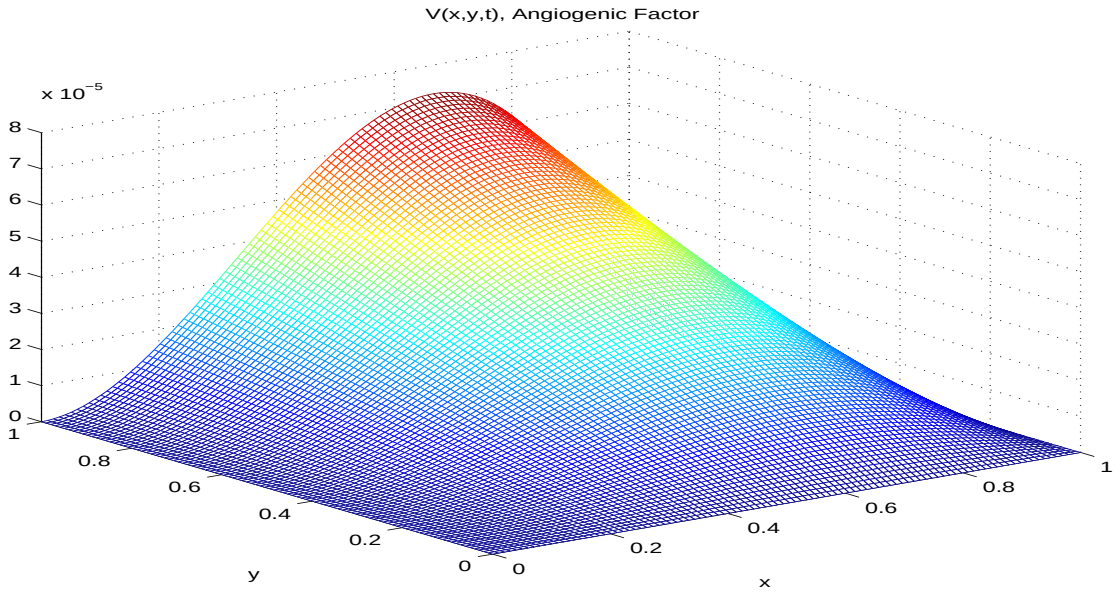

Fig. 3: Angiogenic factor at $t = 2$.

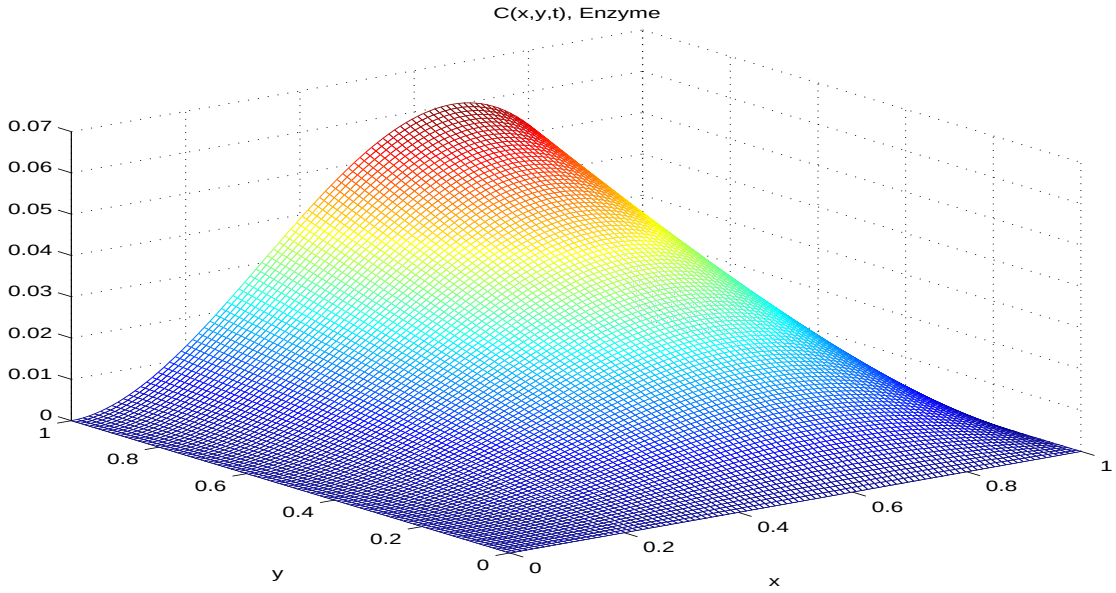

Fig. 4: Enzyme at $t = 2$.

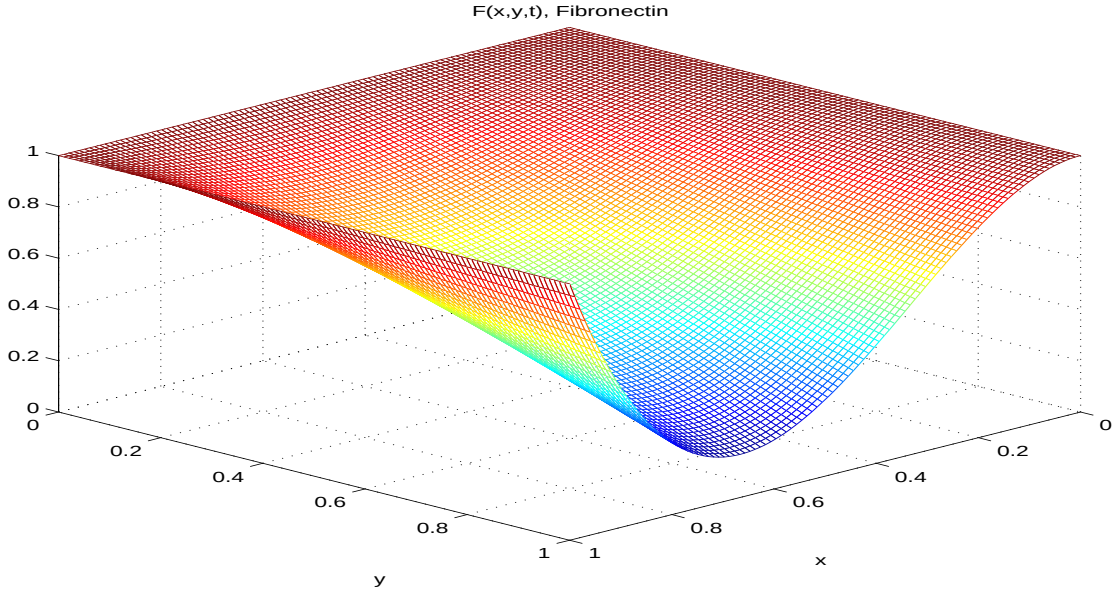

Fig. 5: Fibronectin at $t = 2$.

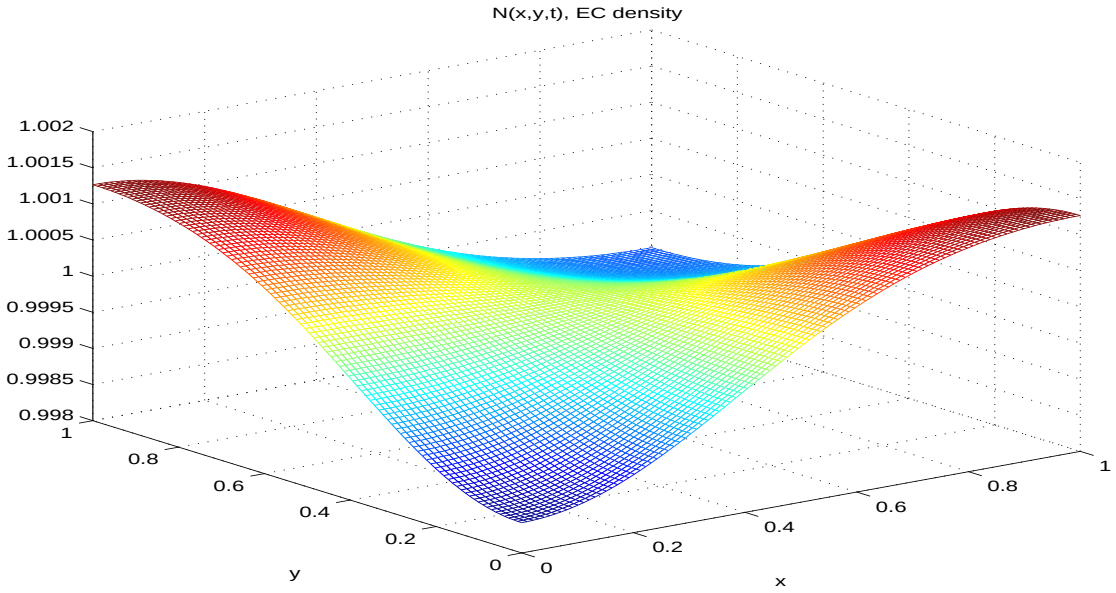

Fig. 6: Four-term series solution of Endothelial cell equation at $t = 2$.

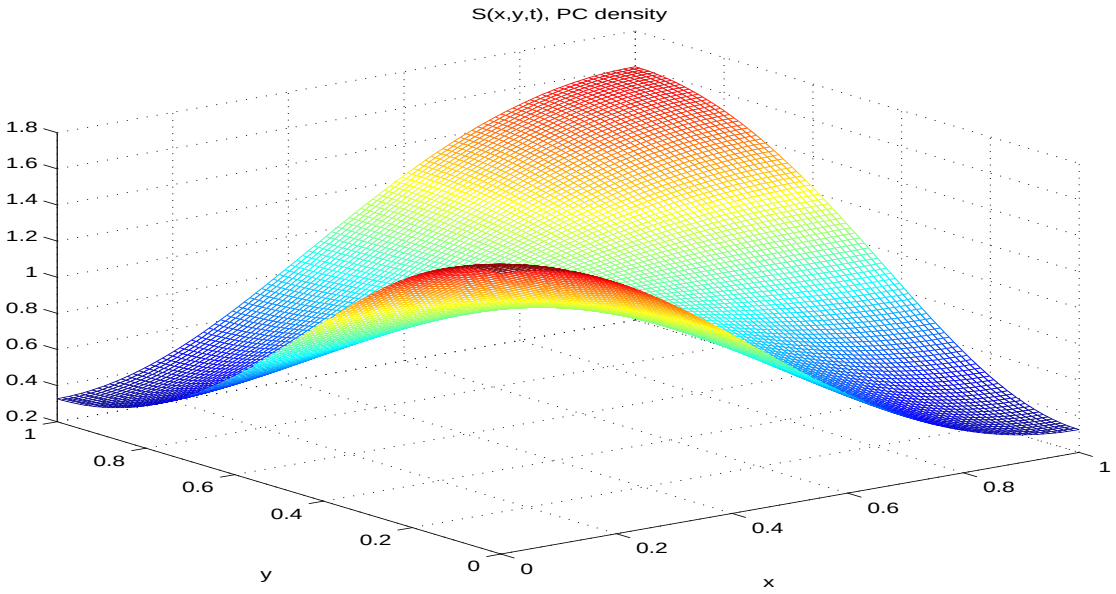

Fig. 7: Four-term series solution of Pericyte cell equation at $t = 2$.

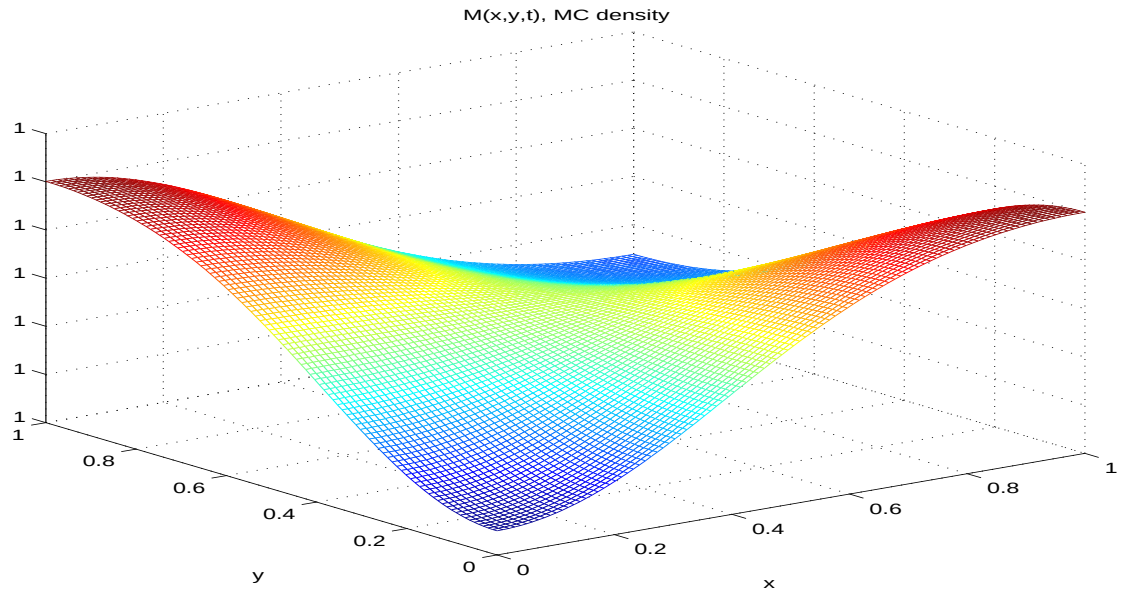

Fig. 8: Four-term series solution of Macrophage cell equation at $t = 2$.

Acknowledgement

This work has been supported by Scientific and Technological Research Council of Turkey, TUBITAK, project no: 115F538.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

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

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