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Steady-State Analysis of a Two Dimensional Model for Tumor Angiogenesis in the Absence of Endothelial Cell Proliferation

Serdal Pamuk* Department of Mathematics, University of Kocaeli, Umuttepe Campus, 41800, Kocaeli – Turkey

Bushra Bajjah Department of Mathematics, University of Kocaeli, Umuttepe Campus, 41800, Kocaeli – Turkey

Abstract: This paper is an extension of the work done in [S. Pamuk, Qualitative Analysis of a Mathematical Model for Capillary Formation in Tumor Angiogenesis, Math. Models Methods Appl. Sci. 13 (1) (2003) 19-33] to a further 2D-mathematical analysis of a model for tumor angiogenesis in the absence of endothelial cell proliferation term. We actually obtain the long time dynamics of endothelial cells in the extra cellular matrix under some assumptions and using the results of a 1D-mathematical analysis. Also, the stability of the steady-state solution is studied. Some figures obtained from the numerical results are presented.

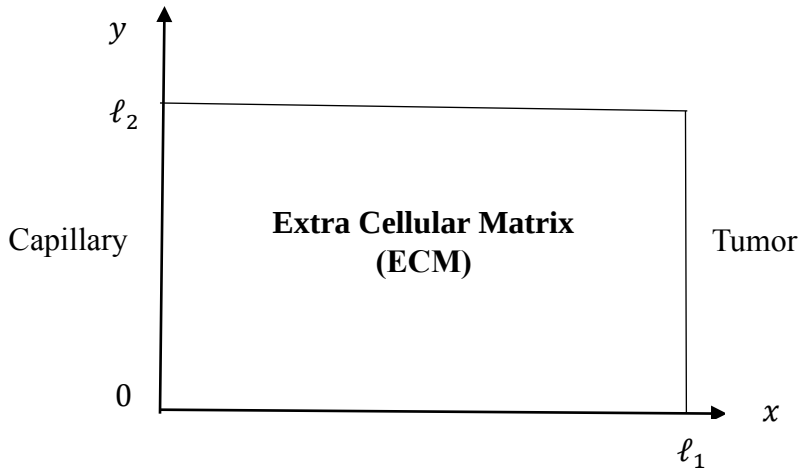
Keywords: Angiogenesis; Long-time dynamics; Steady-state solution; Mathematical analysis.

1. Introduction

Angiogenesis is a morphogenic process whereby new blood vessels are induced to grow out of a pre-existing vasculature. It is also an important feature of various pathological processes such as wound healing and cancer progression. Angiogenesis is known to occur in three sequential steps [1]. First, the endothelial cells lining the vascular basal lamina (BL) (or basement membrane) degrade this membrane. Second, the endothelial cells migrate and proliferate (via mitosis) into the ECM. Finally, capillary loops form. Studies [2-7] show that the tumor releases certain chemical known as tumor angiogenesis factor (TAF). This stimulates the endothelial cells (EC) in neighboring capillaries to migrate toward the tumor.

There have been many mathematical [8-11] describing and analyzing tumor angiogenesis mechanisms in one or more space dimensions. In our work we assume a capillary wall is located at an interval $[0, \ell_2]$ on the y axis and a TAF source is located at a subinterval of the line $x = \ell_1$. We imagine the tumor vascularization problem as shown in Figure 1. We rescale x by x/ℓ_1 and y by y/ℓ_2, so that this rectangle becomes a unit square [12-14]. Therefore we now have $0 \leq x, y \leq 1$. Basically, the problem consists of two parts; the dynamics on the y axis (1D problem over the capillary) and the dynamics in the unit square (2D problem in the ECM). We couple those two dynamics via some boundary conditions [13, 14]. In this paper we only present a mathematical analysis for EC density equation in ECM. The analysis for the first problem was done in Pamuk [12].

Figure-1. Extra cellular matrix



*Corresponding Author

In Pamuk [12] a 1D - mathematical analysis has been presented for the endothelial cell (EC) equation (over the capillary) [15-17] with no proliferation term:

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

The construction of this equation may be found in Davis [18] using the reinforced random work idea. Here D_η is the EC diffusion coefficient over the capillary, $\eta = \eta(y,t)$ is the endothelial cell density, $c = c(y,t)$ is the enzyme density, $f = f(y,t)$ is the fibronectin density, a large highly adhesive glycoprotein particularly abundant in plasma, connective tissue matrices, and basement membranes [19], and $\tau = \tau(c,f)$ is the so called transition probability function. In Pamuk [12] the authors have shown that $\lim_{t\to\infty} \eta(y,t) = \psi\tau(c,f)$ under the assumptions that enzyme and fibronectin densities are in quasi-steady state, i.e., $c = c(y,t)$ and $f = f(y,t)$ are time independent. Here ψ is a positive constant.

Biologically it means that as $t \to \infty$ endothelial cells tend to the transition probability function of enzyme and fibronectin the EC diffusion coefficient over the capillary, $\eta = \eta(y,t)$ is the EC density, $c = c(y,t)$ is the enzyme density, $f = f(y,t)$ is the fibronection density, a large highly adhesive glycoprotein particularly abundant in plasma, connective tissue matrices, and basement membranes [19], and $\tau\,(c,f)$ is the transition probability function. In Pamuk [12] the authors have shown that $\lim_{t\to\infty} \eta(y,t) = \psi\tau\,(c,f)$ where $c(y,t)$ and $f(y,t)$ are in quasi-steady state, i.e. they are time independent. Here ψ is a positive constant.

Biologically, it means that when $t \to \infty$ EC close to the transition probability function of enzyme and fibronection.

In this paper we present a 2D - mathematical analysis for the dynamics of EC equation in the extra cellular matrix (ECM). We have the following equation for EC in two dimensions

$$\frac{\partial N}{\partial t} = D_N \nabla.\left(N \nabla \ln\left(\frac{N}{\tau\,(C,F)}\right)\right) \qquad (1)$$

with the following initial and boundary conditions

$$\begin{aligned} &N = 0 \quad , \quad t = 0, \quad 0 \le x,y \le 1,\\ &N = \eta(y,t) \quad , \quad x = 0,\\ &N_x - NP = 0 \quad , \quad x = 1,\\ &N = 0 \quad , \quad y = 0,\\ &N_y - NQ = 0 \quad , \quad y = 1. \end{aligned} \qquad (2)$$

Here D_N is the EC diffusion coefficient, $N = N(x,y,t)$ is the EC density, $C = C(x,y,t)$ is the enzyme density, $F = F(x,y,t)$ is the fibronection density, $\eta(y,t)$ is the EC density over the capillary, $\tau\,(C,F)$ is the so called transition probability function, and

$$P = \frac{\partial}{\partial x} \ln \tau\,(C,F), \qquad Q = \frac{\partial}{\partial y} \ln \tau\,(C,F).$$

The second equation in eq. (2) (the boundary condition at $x = 0$) tells us that EC begin to enter into the ECM from the capillary initiating angiogenesis.

The main aim of this paper is to determine mathematically the long-time tendency of endothelial cells governed by the eq. (1), and to show that there is a close agreement between the EC steady-state solution obtained analytically and the numerically calculated steady-state.

2. Model Analysis and Solution

Eq. (1) can be written as

$$\frac{\partial N}{\partial t} = D_N\left(N_{xx} - PN_x + N_{yy} - QN_y\right). \qquad (3)$$

We take $\tau\,(C,F) = \tau\,(x,y) = e^{c_1 x + c_2 y}$ for some negative constants c_1 and c_2. Then, clearly $P = c_1$ and $Q = c_2$. Therefore, eq. (3) becomes

$$\frac{\partial N}{\partial t} = D_N\left(N_{xx} - c_1 N_x + N_{yy} - c_2 N_y\right). \qquad (4)$$

Also, since we are interested in the long time dynamics of the cells we may let $\eta(y,t) = \psi\,\tau(0,y) = \psi e^{c_2 y}$. Thus the initial and boundary conditions given in eq. (2) become

$$\begin{aligned} &N = 0 \quad \text{at} \quad t = 0\\ &N = \psi e^{c_2 y} \quad \text{at} \quad x = 0,\\ &N_x - c_1 N = 0 \quad \text{at} \quad x = 1,\\ &N = 0 \quad \text{at} \quad y = 0,\\ &N_y - c_2 N = 0 \quad \text{at} \quad y = 1. \end{aligned} \qquad (5)$$

We now define a new variable $V(x,,y,t)$ via

$$N(x,y,t) = V(x,y,t)\ \exp^{\frac{c_1}{2}x + \frac{c_2}{2}y - \frac{D_N}{4}(c_1{}^2 + c_2{}^2)t}. \qquad (6)$$

Thus we have

$$V(x,y,t) = N(x,y,t)\ \exp^{-\frac{c_1}{2}x - \frac{c_2}{2}y + \frac{D_N}{4}(c_1{}^2 + c_2{}^2)t}. \qquad (7)$$

and the initial-boundary value problem (4) - (5) become

$$V_t = D_N\left[V_{xx} + V_{yy}\right], \tag{8}$$

$$\begin{cases} V(x,y,t) = 0 & \text{at} \quad t = 0 \\ V(x,y,t) = \psi\ e^{\frac{c_2}{2}y + \frac{D_N}{4}({c_1}^2 + {c_2}^2)t} & \text{at} \quad x = 0, \\ V_x(x,y,t) - \dfrac{c_1}{2}V(x,y,t) = 0 & \text{at} \quad x = 1, \\ V(x,y,t) = 0 & \text{at} \quad y = 0, \\ V_y(x,y,t) - \dfrac{c_2}{2}V(x,y,t) = 0 & \text{at} \quad y = 1. \end{cases} \tag{9}$$

We partition the solution into a "steady-state" and a "variable" portion [20]:

$$V(x,y,t) = \underbrace{s(x,y,t)}_{\text{steady-state}} + \underbrace{u(x,y,t)}_{\text{variable}}. \tag{10}$$

If we substitute this equation into the initial-boundary value problem (8) - (9), we have

$$\begin{gathered} s_t + u_t = D_N\left[s_{xx} + u_{xx} + s_{yy} + u_{yy}\right], \\ s(x,y,0) + u(x,y,0) = 0, \\ s(0,y,t) + u(0,y,t) = \psi\ e^{\frac{c_2}{2}y + \frac{D_N}{4}({c_1}^2 + {c_2}^2)t}, \\ s_x(1,y,t) + u_x(1,y,t) - \frac{c_1}{2}\left(s(1,y,t) + u(1,y,t)\right) = 0, \\ s(x,0,t) + u(x,0,t) = 0, \\ s_y(x,1,t) + u_x(x,1,t) - \frac{c_2}{2}\left(s(x,1,t) + u(x,1,t)\right) = 0. \end{gathered} \tag{11}$$

We end up with two separate initial-boundary value problem

$$\begin{cases} s_{xx} + s_{yy} = 0, \\ s(0,y,t) = \psi\ e^{\frac{c_2}{2}y + \frac{D_N}{4}({c_1}^2 + {c_2}^2)t}, \\ s_x(1,y,t) - \dfrac{c_1}{2}\ s(1,y,t) = 0, \\ s(x,0,t) = 0, \\ s_y(x,1,t) - \dfrac{c_2}{2}\ s(x,1,t) = 0, \end{cases} \tag{12}$$

and

$$\begin{cases} u_t = D_N[u_{xx} + u_{yy}] - s_t(x,y,t), \\ u(x,y,0) = -s(x,y,0) \\ u(0,y,t) = 0, \\ u_x(1,y,t) - \dfrac{c_1}{2}\ u(1,y,t) = 0, \\ u(x,0,t) = 0, \\ u_y(x,1,t) - \dfrac{c_2}{2}\ u(x,1,t) = 0. \end{cases} \tag{13}$$

First, we solve the system (12) by separation of variables by setting $s(x,y) = X(x)Y(y)$. Then we have the following two boundary value problems

$$\begin{gathered} X''(x) - \lambda\, X(x) = 0, \\ X'(1) - \frac{c_1}{2}\ X(1) = 0, \end{gathered} \tag{14}$$

$$\begin{gathered} Y''(y) + \lambda\, Y(y) = 0, \\ Y(0) = Y'(1) - \frac{c_2}{2}\ Y(1) = 0. \end{gathered} \tag{15}$$

The solutions in the case $\lambda > 0$ are (the cases $\lambda = 0$ and $\lambda < 0$ yield contradiction if $c_2 < 0$)

$$\begin{gathered} X(x) = \mathrm{C}\cosh\left(\sqrt{\lambda}\,x\right) + \mathrm{D}\sinh\left(\sqrt{\lambda}\,x\right), \\ Y(y) = \mathrm{E}\cos\left(\sqrt{\lambda}\,y\right) + \mathrm{F}\sin\left(\sqrt{\lambda}\,y\right). \end{gathered}$$

After using the boundary conditions the eigenvalues and the corresponding eigenfunctions are as follows

$$\tan\alpha_n = \frac{2\alpha_n}{c_2}, \quad \alpha_n = \sqrt{\lambda_n}\ , n = 1,2,\ldots,$$

$$X_n(x) = \mathrm{D}\left(\frac{\alpha_n\cosh\alpha_n - \frac{c_1}{2}\sinh\alpha_n}{\frac{c_1}{2}\cosh\alpha_n - \alpha_n\sinh\alpha_n}\cosh(\alpha_n x) + \sinh(\alpha_n x)\right), \quad Y_n(y) = \mathrm{F}\sin(\alpha_n y)$$

for some constants D and F.

Therefore, we have

$$s(x,y) = \sum_{n=1}^{\infty} A_n\left(\frac{\alpha_n\cosh\alpha_n - \frac{c_1}{2}\sinh\alpha_n}{\frac{c_1}{2}\cosh\alpha_n - \alpha_n\sinh\alpha_n}\cosh(\alpha_n x) + \sinh(\alpha_n x)\right)\sin(\alpha_n y). \tag{16}$$

If we now use the boundary condition at $x = 0$ which is given in eq. (12) we obtain

$$s(x,y,t) = 2\psi \sum_{n=1}^{\infty} \frac{(B_n \cosh(\alpha_n x) + \sinh(\alpha_n x))\ \sin(\alpha_n y)}{B_n\ (\alpha_n - \sin\alpha_n \cos\alpha_n)\left(1 + \frac{{c_2}^2}{4\ {\alpha_n}^2}\right)}\ e^{\frac{D_N}{4}({c_1}^2 + {c_2}^2)t}, \tag{17}$$

$$B_n = \frac{\alpha_n \cosh\alpha_n - \frac{c_1}{2}\sinh\alpha_n}{\frac{c_1}{2}\cosh\alpha_n - \alpha_n \sinh\alpha_n}\ . \tag{18}$$

Second we solve the non-homogenous boundary value problem (13) by first considering the associated homogeneous equation:

$$u_t = D_N[u_{xx} + u_{yy}] \tag{19}$$

We solve it by separation of variables by letting $u(x,y,t) = T(t)X(x)Y(y)$. We obtain the following two boundary value problems, namely

$$X''(x) - \rho\, X(x) = 0,$$
$$X(0) = X'(1) - \frac{c_1}{2}\, X(1) = 0, \tag{20}$$
$$Y''(y) - \delta\, Y(y) = 0,$$
$$Y(0) = Y'(1) - \frac{c_2}{2}\, Y(1) = 0 \tag{21}$$

where we let $\mu = \rho + \delta$. Also, we have

$$T'(t) - \mu DT(t). \tag{22}$$

The eigenvalues and eigenfunctions in the case $\rho, \delta < 0$ are (the cases $\rho, \delta = 0$ and $\rho, \delta > 0$ yield contradiction if $c_1, c_2 < 0$)

$$\tan\sigma_n = \frac{2\sigma_n}{c_1}, \sigma_n = \sqrt{-\rho_n}\ , \tan\beta_{m=}\ \frac{2\ \beta_m}{c_2}, \beta_{m=}\sqrt{-\delta_m}\ , \qquad n, m = 1,2, \ldots,$$

$X_n(x) = \mathrm{A}_1 \sin(\sigma_n x), \quad Y_m(y) = \mathrm{A}_2 \sin(\beta_m y)$

for some constants A_1 and A_2. Then the solution $u(x,y,t)$ of the eq. (13) has the following series form

$$u(x,y,t) = \sum_{m.n=1}^{\infty} T_{mn}(t) \sin(\sigma_n x) \sin(\beta_m y). \tag{23}$$

We now solve the non-homogenous part of eq. (13) by noting that

$$-s_t(x,y,t) = -2\psi D_N({c_1}^2 + {c_2}^2) \sum_{n=1}^{\infty} \frac{(B_n \cosh(\alpha_n x) + \sinh(\alpha_n x))\ \sin(\alpha_n y)}{2B_n\ (\alpha_n - \sin\alpha_n \cos\alpha_n)\left(1 + \frac{{c_2}^2}{4\ {\alpha_n}^2}\right)}$$

$$\times\ e^{\frac{D_N}{4}({c_1}^2 + {c_2}^2)t}$$

and

$$u(x,y,0) = -s(x,y,0) = -2\psi \sum_{n=1}^{\infty} \frac{(B_n \cosh(\alpha_n x) + \sinh(\alpha_n x))\ \sin(\alpha_n y)}{2B_n\ (\alpha_n - \sin\alpha_n \cos\alpha_n)\left(1 + \frac{{c_2}^2}{4\ {\alpha_n}^2}\right)}\ . \tag{24}$$

Third we substitute eq. (23) into the partial differential equation so that we obtain

$$\sum_{m,n=1}^{\infty} (T'_{mn}(t) + D_N(\sigma_n + \beta_m)T_{mn}(t))\ \sin(\sigma_n x) \sin(\beta_m y) = -s_t(x,y,t), \tag{25}$$

where we assume the function $s_t(x,y,t)$has the following series form

$$-s_t(x,y,t) = \sum_{m,n=1}^{\infty} b_{mn}(t) \sin(\sigma_n x) \sin(\beta_m y). \tag{26}$$

Equating eqs. (25) and (26) gives the linear ordinary differential equation for the variable $T_{mn}(t)$

$$T'_{mn}(t) + D_N(\sigma_n + \beta_m)T_{mn}(t) = b_{mn}(t),$$

whose solution is

$$T_{mn}(t) = e^{-D_N(\sigma_n + \beta_m)t}\left(C_{mn} + \int_0^t b_{mn}(t')\, e^{-D_N(\sigma_n + \beta_m)t'} dt'\right), \tag{27}$$

for some arbitrary constants C_{mn}.

At $t = 0$ it follows from eqs. (23) and (27) that

$$u(x,y,0) = \sum_{m,n=1}^{\infty} C_{mn} \sin(\sigma_n x) \sin(\beta_m y), \tag{28}$$

where

$$C_{mn} = \frac{\int_0^1 \int_0^1 s(x,y,0)\sin(\sigma_n x)\sin(\beta_m y)\,dx\,dy}{\int_0^1 \sin^2(\sigma_n x)\,dx \int_0^1 \sin^2(\beta_m y)\,dy}$$
$$= \frac{-8\psi {\sigma_n}^2 \beta_m}{(\sigma_n - \sin\sigma_n\cos\sigma_n)(\beta_m - \sin\beta_m\cos\beta_m)}$$
$$\times \sum_{k=1}^{\infty} \frac{\beta_m \cos\beta_m \sin\alpha_k - \alpha_k \cos\alpha_k \sin\beta_m}{({\sigma_n}^2 - {\alpha_k}^2)({\alpha_k}^2 - {\beta_m}^2)(\alpha_k - \sin\alpha_k\cos\alpha_k)\left(1 + \frac{{c_2}^2}{4{\alpha_k}^2}\right)}.$$

Therefore one has

$$b_{mn}(t) = \frac{\int_0^1 \int_0^1 s_t(x,y,t)\sin(\sigma_n x)\sin(\beta_m y)\,dx\,dy}{\int_0^1 \sin^2(\sigma_n x)\,dx \int_0^1 \sin^2(\beta_m y)\,dy}$$
$$= \frac{D_N}{4}({c_1}^2 + {c_2}^2) C_{mn}\, e^{\frac{D_N}{4}({c_1}^2 + {c_2}^2)t},$$

and

$$T_{mn}(t) = \frac{C_{mn}}{\mu_{mn} + \frac{{c_1}^2 + {c_2}^2}{4}}\left(\mu_{mn} e^{-\mu_{mn} D_N t} + \frac{{c_1}^2 + {c_2}^2}{4}\, e^{\frac{D_N}{4}({c_1}^2 + {c_2}^2)t}\right). \quad (29)$$

Then the solution of eq. (13) becomes

$$u(x,y,t) = \sum_{m,n=1}^{\infty} \frac{C_{mn}}{\mu_{mn} + \frac{{c_1}^2 + {c_2}^2}{4}}\left(\mu_{mn} e^{-\mu_{mn} D_N t} + \frac{{c_1}^2 + {c_2}^2}{4}\, e^{\frac{D_N}{4}({c_1}^2 + {c_2}^2)t}\right)$$
$$\times \sin(\sigma_n x)\sin(\beta_m y). \quad (30)$$

Finally we have the series solution of the initial boundary value problem consisting of eqs. (4) and (5) as follows

$$N(x,y,t) = e^{\frac{1}{2}(c_1 x + c_2 y)}\left[2\psi \sum_{n=1}^{\infty} \frac{(B_n \cosh(\alpha_n x) + \sinh(\alpha_n x))\,\sin(\alpha_n y)}{B_n\,(\alpha_n - \sin\alpha_n\cos\alpha_n)\left(1 + \frac{{c_2}^2}{4\,{\alpha_n}^2}\right)}\right.$$
$$+ \sum_{m,n=1}^{\infty} \frac{C_{mn}}{\mu_{mn} + \frac{{c_1}^2 + {c_2}^2}{4}}\left(\mu_{mn} e^{-\left(\mu_{mn} + \frac{{c_1}^2 + {c_2}^2}{4}\right)D_N t}\right.$$
$$\left.\left. + \frac{{c_1}^2 + {c_2}^2}{4}\right)\sin(\sigma_n x)\sin(\beta_m y)\right] \quad (31)$$

where B_n and C_{mn} are defined as above.

3. Stability of the Steady-State Solution and Results

It is clear to see that the transition probability function $\tau(x,y) = e^{c_1 x + c_2 y}$ satisfies the eq. (4) with $\frac{\partial N}{\partial t} = 0$. Therefore it is reasonable to call it the steady-state solution of the equation. In addition, after some tedious computations we get from eq. (31) that $\lim_{t\to\infty} N(x,y,t) = \psi_1\,\tau(x,y)$ for some positive constant ψ_1, which proves that this steady-state is stable. As we have obtained in 1D case in Pamuk [12] we have shown in this paper (2D case) that as time increases endothelial cells tend to transition probability density function of enzyme and fibronectin. Fig. 2 shows the transition probability function $\tau(x,y)$ with $c_1 = -5$ and $c_2 = -5$, whereas Fig. 3.. shows the endothelial cell density obtained from the series solution eq. (31) by using only two terms. One gets much better approximation to $N(x,y,t)$ by adding new terms to the two-term expansion of the series and letting t increases.

4. Conclusions

In this paper we have provided a two - dimensional mathematical analysis of a model for tumor angiogenesis in the absence of endothelial cell proliferation term. The analysis is useful in the sense that we obtain the steady-state solution of the model by splitting the variable into steady-state and variable parts. Then we deal with an eigenvalue-eigenfunction problem for a problem with non-homogenous boundary data, and the solution follows. We have also studied the stability of this steady-state, and confirm it by presenting some pictures. We do believe that this 2D mathematical analysis will give rise to a way of solving partial differential equations with forcing term and with non-homogenous boundary data.

Biologically speaking, a mathematical analysis has shown us that as time increases endothelial cells tend to transition probability density function of enzyme and fibronectin, which is the same result as in Pamuk [12].

Figure-2. Transition Probability Function $\tau(x, y)$ with $c_1 = -5$ and $c_2 = -5$.

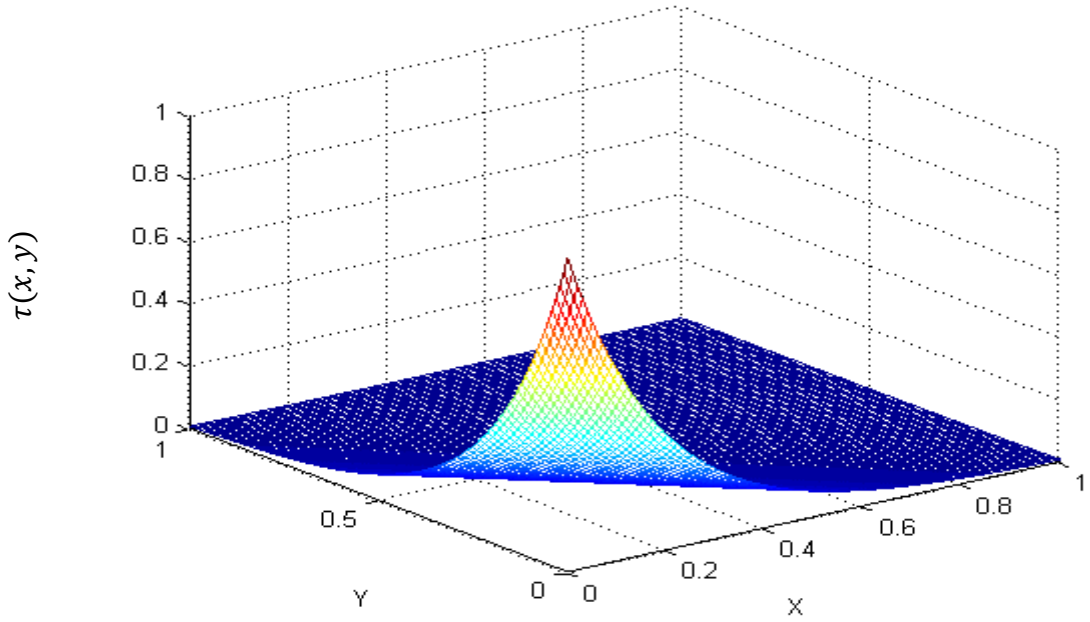
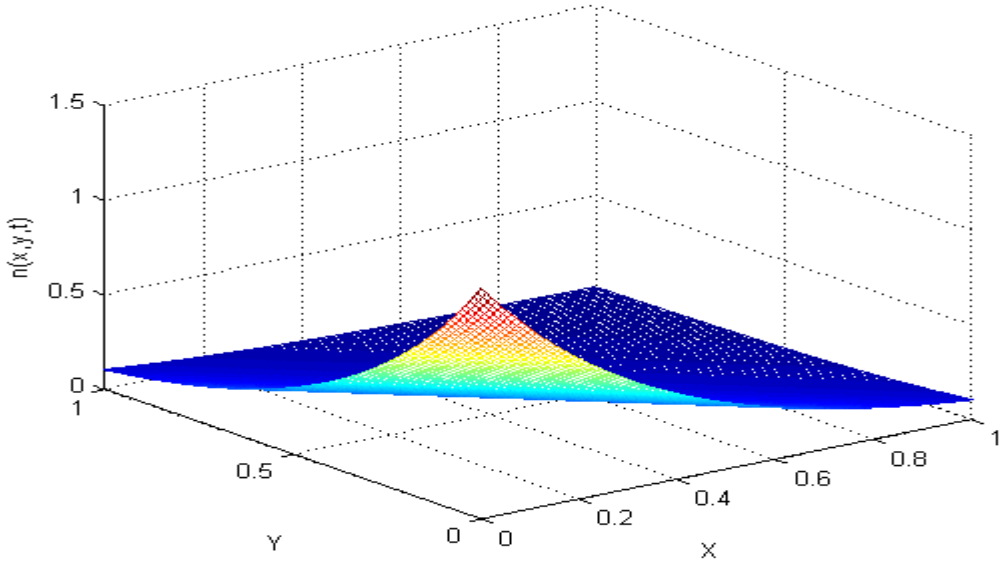


Figure-3. $N(x, y, t)$ with $c_1 = -5, c_2 = -5, \psi = 0.7 * 10^{-18}$, $B_1 = 100, B_1 = 200, \beta_1 = 30$, $\beta_2 = 50, \sigma_1 = \alpha_1 = 0.000002$, $\sigma_2 = \alpha_2 = 0.0000012$, $C_{11} = 10$, $C_{21} = 20$, $C_{12} = C_{22} = 30, \mu_{11} = \mu_{12} = \mu_{21} = \mu_{22} = 1, D_N = 3.6 * 10^{-3}$, $t = 10^5$.



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