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Turing Analysis of a Mathematical Model for Interaction between Tumor Cell and Its Inhibitor

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Abstract: This work has been presented at ICFAS2016, "International Congress on Fundamental and Applied Sciences, 22-26 Aug, 2016, Istanbul, Turkey". In this paper we present a 2D mathematical model which is related to the interaction between tumor cell and its inhibitor. We obtain some necessary conditions in order for Turing instability to occur. We also provide some numerical examples to verify our theoretical results.

Keywords: Turing instability; Reaction-diffusion system; Tumor cell; Inhibitor.

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. Understanding the mechanism by which various factors inhibit angiogenesis is critical to devising an effective therapeutic regimen. A tentative classification of these substances can be made on the basis of their inhibitory function, but the role of many newly-discovered inhibitors remains unknown [1].

Our whole mathematical model is studied in [2, 3]. Here we just study the submodel of our model which consists of endothelial cell (tumor cell) and angiostatin (as inhibitor) equations only.
Therefore we consider the following initial - boundary value problem:

$$\frac{\partial N}{\partial t} = D_N \nabla^2 N + Q(\kappa)\left\{ N\left[\theta(1-N) + G(C_A)\frac{\partial C_A}{\partial t}\right] H(C_A - C_{A,0}) - \mu N \right\} \quad (1.1)$$

$$\frac{\partial A}{\partial t} = D_A \nabla^2 A - \frac{\lambda A N}{1+\nu A} + a_0 H(F_{\min} - F), \quad (x, y) \in \Omega, t > 0, \quad (1.2)$$

$$\frac{\partial N}{\partial n} = \frac{\partial A}{\partial n} = 0, \quad (x, y) \in \partial\Omega \quad (1.3)$$

$$N(x, y, 0) = N_0(x, y), \qquad A(x, y, 0) = A_0(x, y), (x, y) \in \Omega. \quad (1.4)$$

where $\Omega = (0, l_1) \times (0, l_2)$, $N = N(x, y, t)$ is the endothelial cell density, $A = A(x, y, t)$ is the angiostatin density, and $C_A = C_A(x, y, t)$ is the active enzyme density, G is the growth fuction, H is the Heavyside fuction, n is the outer normal to $\partial\Omega$, D_N and D_A are diffusion coefficients of endothelial cell and angiostatin, respectively, $Q = Q(\kappa)$ is a function of the curvature κ such that $Q(0) = 0$, $Q'(x) \geq 0$. Also, $C_{A,0}$ and F_{min} are some threshold values for active enzyme, C_A, and fibronectin, F, respectively, [2, 3], θ, μ, λ, ν, and a_0 are some positive constants, l_1 and l_2 are the capillary-tumor distance and the length of the capillary, respectively, and T is some reference time for tumor progression.
If we set

$$x^* = \frac{x}{l_1}, \; y^* = \frac{y}{l_2}, \; t^* = \frac{t}{T}, \; D_N^* = \frac{D_N T}{l_1^2}, \; D_A^* = \frac{D_A T}{l_1^2}, \; N^* = \frac{N}{N_0}, \; A^* = \frac{A}{A_0}, \; \lambda^* = \lambda \mathrm{TN}_0, \; \nu^* = \nu A_0,$$

$$C_A^* = C_A / C_{A,0}, \; F^* = F/F_{\min},$$

the dimensionless system becomes, on dropping the asterisks for algebraic convenience,

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$$\frac{\partial N}{\partial t} = D_N \nabla^2 N + Q(\kappa)\left\{ N\left[\theta(1-N) + G(C_A)\frac{\partial C_A}{\partial t} \right] H(C_A - 1) - \mu N \right\} \quad (1.5)$$

$$\frac{\partial A}{\partial t} = D_A \nabla^2 A - \frac{\lambda AN}{1+\nu A} + a_0 H(1-F), \quad (x, y) \in \Omega, t > 0, \quad (1.6)$$

$$\frac{\partial N}{\partial n} = \frac{\partial A}{\partial n} = 0, \quad (x, y) \in \partial\Omega \quad (1.7)$$

$$N(x, y, 0) = N_0(x, y), \quad A(x, y, 0) = A_0(x, y), (x, y) \in \Omega. \quad (1.8)$$

In Tang and Song [4] the authors study the stability of the positive equilibrium, Turing instability, and the existence of Hopf and steady-state bifurcations for a predator-prey system with homogeneous Neumann boundary conditions. In Yang and Song [5] the Gierer-Meinhardt model without the saturating term is presented. By their linear stability analysis, the authors not only obtain the conditions ensuring the stability and Turing instability of the positive equilibrium but also get the parameter values where possible. They observe that Turing-Hopf and spatial resonance bifurcation can occur. Also, in [6, 7] the authors consider the Turing-Hopf bifurcation arising from the reaction-diffusion equations, and in [8, 9] the authors derive a necessary and sufficient condition for Turing instabilities to occur in two-component systems of reaction-diffusion equations with Neumann boundary conditions. In Pamuk and Gürbüz [10] the authors provide the stability analysis of the steady-state solution of a mathematical model in tumor angiogenesis whereas in Karaoglu and Merdan [11] Hopf bifurcation of a ratio - dependent predator-prey model involving two discrete maturation time delays is studied.

In the following section we obtain the positive equilibrium points and the Turing instability of the system (1.5)-(1.8).

2. Stability and Turing Instability

We take $Q(\kappa) \equiv 1$, $C_A > 1$, $F < 1$, $G(C_A) = \frac{N}{A}$ for biological convenience, thus the system (1.5)-(1.8) becomes as follows:

$$\frac{\partial N}{\partial t} = D_N \nabla^2 N + \frac{(1+\nu A)\mathrm{A}^2\mathrm{N}(\theta(1-N)-\mu) + \lambda AN^3 - a_0(1+\nu A)\mathrm{N}^2}{A(A-N)(1+\nu A)}, \ (x, y) \in \Omega, \ t > 0, \quad (2.1)$$

$$\frac{\partial A}{\partial t} = D_A \nabla^2 A - \frac{\lambda AN}{1+\nu A} + a_0, \ (x, y) \in \Omega, \ t > 0, \quad (2.2)$$

$$\frac{\partial N}{\partial n} = \frac{\partial A}{\partial n} = 0, \quad (x, y) \in \partial\Omega \quad (2.3)$$

$$N(x, y, 0) = N_0(x, y), \ A(x, y, 0) = A_0(x, y), \ (x, y) \in \Omega. \quad (2.4)$$

We solve the following equations to find the positive equilibrium points of system (2.1)-(2.2). We set

$$f(N, A) = \frac{(1+\nu A)\mathrm{A}^2\mathrm{N}(\theta(1-N)-\mu) + \lambda AN^3 - a_0(1+\nu A)\mathrm{N}^2}{A(A-N)(1+\nu A)} = 0,$$

$$g(N, A) = -\frac{\lambda AN}{1+\nu A} + a_0 = 0.$$

Therefore the only positive equilibrium point is

$$(N_0, A_0) = \left(\frac{\theta - \mu}{\theta}, \frac{a_0\theta}{\lambda(\theta-\mu) - a_0\nu\theta} \right), \quad (2.5)$$

where we assume $\theta - \mu > 0, \quad \lambda(\theta-\mu) - a_0\nu\theta > 0$ for biological purposes.

First, we set $D_N = D_A = 0$ and

$$w = \begin{pmatrix} N - N_0 \\ A - A_0 \end{pmatrix}, \quad (2.6)$$

Then linearizing the system (2.1)-(2.2) about the point (N_0, A_0), for $|\mathrm{w}|$ small, we obtain

$$w_t = Jw, \tag{2.7}$$

where $J = \begin{pmatrix} f_N(N_0, A_0) & f_A(N_0, A_0) \\ g_N(N_0, A_0) & g_A(N_0, A_0) \end{pmatrix}$

is the stability matrix and

$$f_N(N_0, A_0) = \frac{\partial f}{\partial N}(N_0, A_0) = \frac{(\theta-\mu)\left((\lambda(\theta-\mu)-a_0\nu\theta)^2 - a_0\theta^3\right)}{\theta(a_0\theta^2 - (\theta-\mu)(\lambda(\theta-\mu)-a_0\nu\theta))},$$

$$f_A(N_0, A_0) = \frac{\partial f}{\partial A}(N_0, A_0) = \frac{(\theta-\mu)(\lambda(\theta-\mu)-a_0\nu\theta)^4}{\lambda a_0\theta^3(a_0\theta^2 - (\theta-\mu)(\lambda(\theta-\mu)-a_0\nu\theta))},$$

$$g_N(N_0, A_0) = \frac{\partial g}{\partial N}(N_0, A_0) = -\frac{a_0\theta}{\theta-\mu},$$

$$g_A(N_0, A_0) = \frac{\partial g}{\partial A}(N_0, A_0) = -\frac{(\lambda(\theta-\mu)-a_0\nu\theta)^2}{\theta\lambda(\theta-\mu)}.$$

We now look for solution of (2.7) of the form

$$\boldsymbol{w} \propto e^{\lambda t}, \tag{2.8}$$

where λ is so-called the eigenvalue. The steady state $\boldsymbol{w} = 0$ is linearly stable if $Re\,\lambda < 0$ since the perturbation $\boldsymbol{w} \to 0$ as $t \to \infty$. The equation for the eigenvalues λ can be found from

$$|J - \lambda I| = \begin{vmatrix} f_N - \lambda & f_A \\ g_N & g_A - \lambda \end{vmatrix} = 0,$$

$$\Rightarrow \lambda^2 - (f_N + g_A)\lambda + f_N g_A - f_A g_N = 0,$$

so the eigenvalues are

$$\lambda_{1,2} = \frac{1}{2}\left((f_N + g_A) \pm ((f_N + g_A)^2 - 4(f_N g_A - f_A g_N))^{1/2}\right).$$

The case $Re\,\lambda < 0$, which is the linear stability, is guaranteed if

$$Tr\,J = f_N + g_A < 0, \quad \det J = f_N g_A - f_A g_N > 0. \tag{2.9}$$

Second, we consider the full reaction-diffusion system (2.1)-(2.2) by writing

$$\mathbf{w}_t = J\mathbf{w} + D\nabla^2\mathbf{w}, \tag{2.10}$$

where $D = \begin{pmatrix} D_N & 0 \\ 0 & D_A \end{pmatrix}$.

Let $w_k(\mathbf{r})$ be the eigenfunction corresponding to the wavenumber k. We now look for solutions $\mathbf{w}(\mathbf{r}, t)$ of (2.10) of the form

$$\mathbf{w}(\mathbf{r}, t) = \sum_k b_k e^{\lambda t} w_k(\mathbf{r}), \tag{2.11}$$

where the constants b_k are determined by Fourier expansions of the initial conditions in terms of $w_k(\mathbf{r})$. Writing (2.11) in (2.10) yields

$$\lambda w_k = J\,w_k + D\nabla^2 w_k = J\,w_k - Dk^2\,w_k. \tag{2.12}$$

We require nontrivial solutions for w_k so that λ's are determined by the roots of the characteristic polynomial

$$|J - \lambda I - Dk^2| = 0,$$

$$\text{which is, } \lambda^2 + \lambda\left(k^2(D_A + D_N) - Tr\,J\right) + h(k^2) = 0. \tag{2.13}$$

Here $h(k^2) = D_A D_N k^4 - (D_A f_N + D_N g_A)k^2 + \det J$.

For the equilibrium solution to be unstable we require $\mathrm{Re}\,\lambda(k) > 0$ for some $k \neq 0$. This can happen if either the coefficient of λ in (2.13) is negative, or if $h(k^2) < 0$ for some $k \neq 0$. Since $Tr\,J < 0$ from condition (2.9) and $k^2(D_A + D_N) > 0$ for all $k \neq 0$, we get

$k^2(D_A + D_N) - Tr\,J > 0,$ for all $k \neq 0$.

Therefore, the only way $\mathrm{Re}\,\lambda(k^2)$ can be positive is when $h(k^2) < 0$ for some k. Since we required the determinant $\det J > 0$, from (2.9) one sees that $h(k^2)$ becomes negative only if $D_A f_N + D_N g_A > 0.$ Since $f_N + g_A < 0$, (2.9) implies that

$D_A > D_N$. (2.14)

The inequality (2.14) is necessary but not sufficient for $\mathrm{Re}\,\lambda > 0$. To get $h(k^2) < 0$ for some $k \neq 0$, the minimum of $h(k^2)$, $h_{\min}$ must be negative. Elementary differentiation of $h(k^2)$ with respect to k^2 and equating to zero gives

$$k_{\mathrm{m}}^2 = \frac{D_A f_N + D_N g_A}{2D_A D_N}.$$

Therefore $h_{\min}$ becomes

$$h_{\min} = \det J - \frac{(D_A f_N + D_N g_A)^2}{4D_A D_N},$$

and the condition $h(k^2) < 0$ for some $k \neq 0$ means

$$\frac{(D_A f_N + D_N g_A)^2}{4D_A D_N} > \det J. \quad (2.15)$$

Notice that if $h_{\min} = 0$, there is a bifurcation of system (2.1)-(2.2) at its equilibrium point (N_0, A_0).

Summary: If one of the following conditions hold, then Turing instability occurs.

(i) $Tr\,J = f_N + g_A < 0, \quad \det J = f_N g_A - f_A g_N > 0,$

(ii) $D_A > D_N$,

(iii) $\dfrac{(D_A f_N + D_N g_A)^2}{4D_A D_N} > \det J.$

3. Numerical Example

We solve the system (2.1)-(2.4) numerically with the parameter values $\theta = 1,\ \mu = 0,9,\ \nu = 0,014,\ a_0 = 3,\ \lambda = 20.$ As our initial conditions we take $N_0(x, y) = (\cos \pi x \cos \pi y)^{12},\ A_0(x, y) = (3 - \cos \pi x \cos \pi y)^4.$ Figures (1)-(2) show the numerical solution of the zero diffusion case, $D_N = D_A = 0$, whereas Figures (3)-(4) show the numerical solution of the non-zero diffusion case, $D_N = 3,6 \times 10^{-5},\ D_A = 6,5 \times 10^{-3}$. Obviously, the condition (ii) above holds and therefore the system (2.1)-(2.4) is Turing unstable.

Figure-1. Graph of tumor cell $N(x,y,t)$ and inhibitor $A(x,y,t)$ with $D_N = D_A = 0$ at $t = 0,07$.

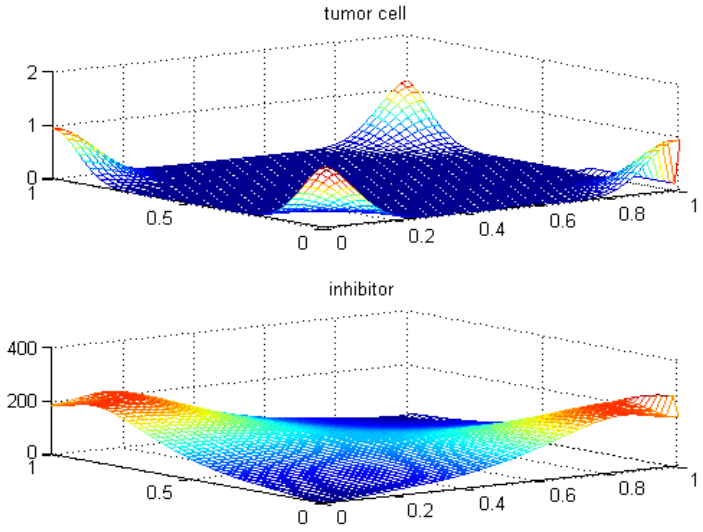


Figure-2. Graph of tumor cell $N(x,y,t)$ and inhibitor $A(x,y,t)$ with $D_N = D_A = 0$, at $t = 0,1$.

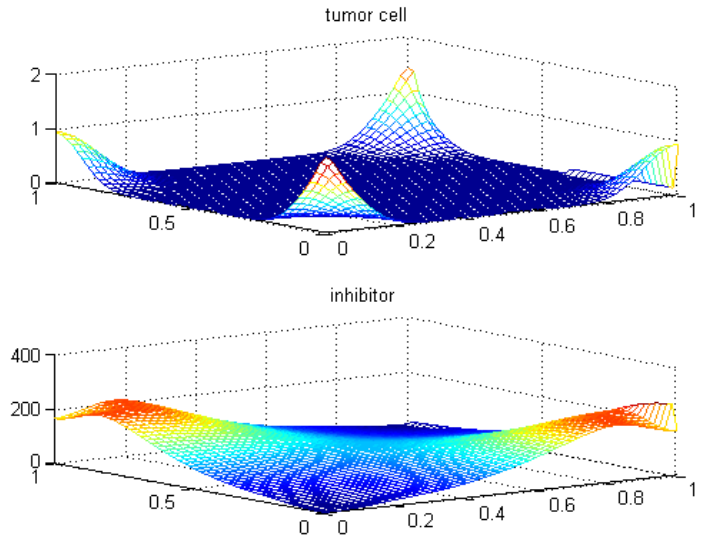


Figure-3. Graph of tumor cell $N(x,y,t)$ and inhibitor $A(x,y,t)$ with $D_N = 3,6\times10^{-5}$, $D_A = 6,5\times10^{-3}$, at $t = 0,07$.

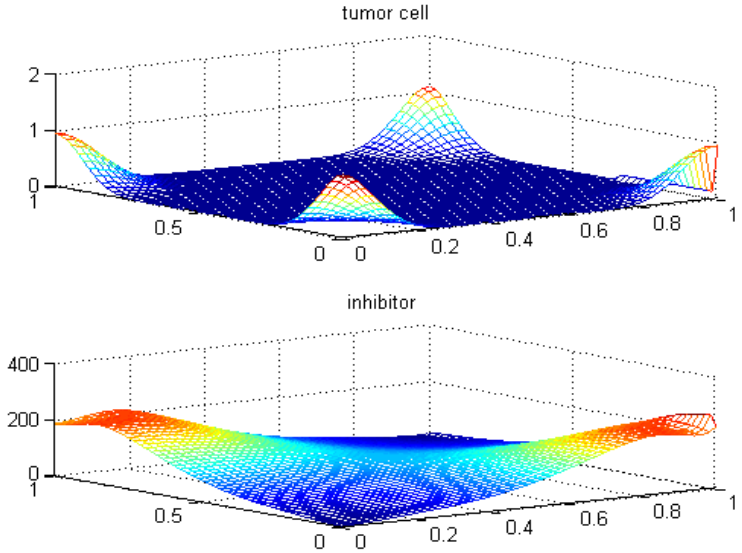
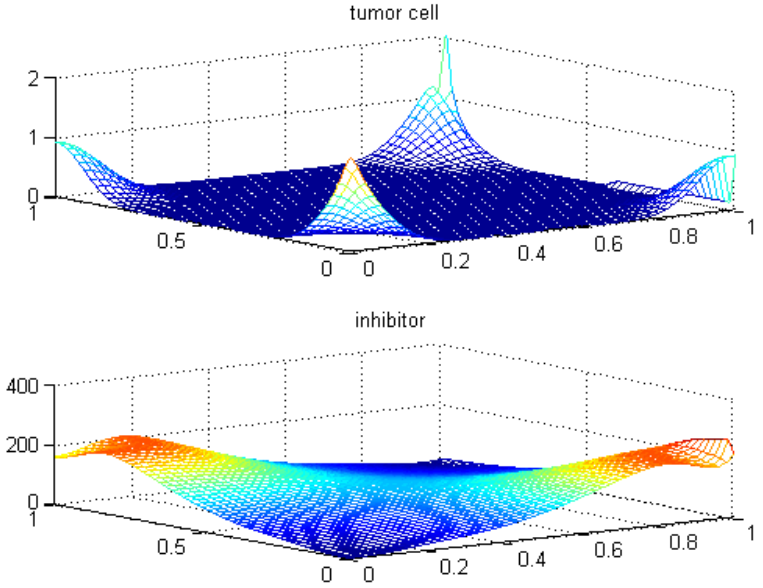


Figure-4. Graph of tumor cell $N(x,y,t)$ and inhibitor $A(x,y,t)$ with $D_N = 3,6\times10^{-5}$, $D_A = 6,5\times10^{-3}$, at $t = 0,1$.



4. Conclusion and Results

We have analyzed the Turing instability of the system (2.1)-(2.2), and determined some necessary conditions ((i)-(iii) above) for Turing instability to occur. In the above example, the zero diffusion and nonzero diffusion cases look similar until $t = 0,07$ (Fig.(1),(3)). After $t = 0,07$ we get numerical difficulty for tumor cell equation because the Laplacian $N_{xx} + N_{yy}$ starts to become large in the magnitude (Fig. (4)) near boundary, which shows that the system is Turing instable after time $t = 0,07$. Biologically this means that when the inhibitor diffuses faster than the tumor cell, our sytem becomes Turing instable after small time.

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