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A Novel Mathematical Approach for Modelling of Cancer Invasion in Tissue

Mahboubeh Molavi-Arabshahi[1], Omid Nikan[1]

[1] *School of Mathematics, Iran University of Science and Technology (IUST), Narmak, Tehran, Iran*

Abstract

In this paper, we consider a relatively simple mathematical model of cancer cell invasion of tissue (extracellular matrix), which focuses on the role of a generic matrix degrading enzyme such as the urokinase-type plasminogen activator (uPA). The model consists of a system of reaction-diffusion-taxis partial differential equations describing the interactions cancer cells, the matrix degrading enzyme and the host tissue. The results of the study showed that the tumor heterogeneity can be comprehensively explained by the numerical complicated dynamics proposed in the current research. Furthermore, the performed computations of the model equations yield dynamic, heterogeneous spatio-temporal solutions, which correspondingly demonstrate the potential of such a simple model in describing and subsequent interpretation of the cancer cell progression and invasion.

Key Words: Cancer invasion of tissue, Matrix degrading enzyme, Chemotaxis, Haptotaxis, Spatio-temporal heterogeneity.

1 .Introduction

The word cancer is an “umbrella term” for approximately 200 diseases. There are two broad categories of tumors: Benign and Malignant ([1]). Benign tumors remain localized to the tissue in which they arise and although they may grow large, they will not spread to other parts of the body. Commonly, they are completely enclosed in a protective capsule of collagenous tissue and they are not typically considered fatal unlike malignant tumors. Early, if found that benign tumors can be cured either by surgical removal or in some cases by radiation therapy. Unlike benign tumors, and even though both benign and malignant tumors grow in an uncontrolled way, malignant (“cancerous”) tumors are a far more serious matter.

The most significant turning point in the disease (cancer), however, is the establishment of the metastasis. Metastasis is defined as the formation of secondary tumor foci at a site discontinuous from the primary tumor ([2], [3]). Metastasis unequivocally signifies that a tumor is malignant, and this in fact makes cancer so lethal. In principal, metastases can form the following invasion and penetration into adjacent tissues followed by dissemination of cells in the blood vascular system (hematogeneous metastasis) and lymphatic’s (lymphatic metastases) [4]. The molecular mechanisms of metastasis are poorly understood as a result of their apparent complexity. In this paper we present a mathematical model for invasion of tissue by cancerous cells, focusing on the role of matrix degrading enzymes, chemo taxis, and haptotaxis.

This initial model is a simplification of that presented in [٥] and enables one to focus on the

potential competition between chemo taxis and haptotaxis. In the development of this basic model, the inclusion of a nonlinear haptotaxis function demonstrates the ability of this simple model to produce dynamic, heterogeneous solutions.

The enzymatic system we will focus on in this paper is the urokinase plasminogen activation system (uPA system), which consists of:

uPA, the urokinase plasminogen activator,
uPAR, the urokinase plasminogen activator receptor,
Plasmin, the matrix degrading enzyme,
VN, the ECM protein vitronectin, and
PAI-1, the plasminogen activator inhibitor type-1.

A schematic diagram of the key interactions of the system is given in Fig. 1. uPA is an extracellular serine protease. Cells secrete its enzymatically inactive form pro-uPA into the extracellular space. Pro-uPA is activated by plasmin to its active form uPA [6].

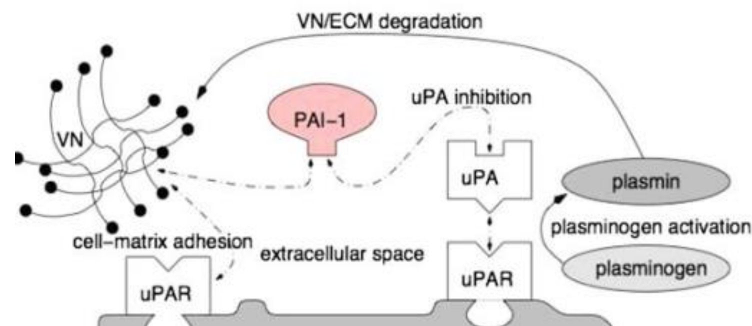

Figure 1. A schematic diagram of the uPA system showing its main components and their interactions

2. Spatio-Temporal models of the uPA system and tissue invasion

In this section, the extracellular equations (partial differential equations) describing the "kinesis", "taxis" and reactions of the urokinase plasminogen activation system (consisting of cancer cells, urokinase plasminogen activator (uPA), and extracellular matrix components i.e. vitronectin, fibronectin, laminin are derived and developed to consider several key components of the system. In this regard, the components of this section are arranged as follows.

First, we look at the previous attempts to investigate tumor invasion and metastasis using deterministic continuum models. We will then discuss the basic framework of the urokinase plasminogen activation system and the estimation of the various parameters of the model that can be obtained using experimental results whenever this is possible.

Then, we present simulation results of the model. We initially develop a mathematical model consisting of three coupled partial differential equations describing the evolution in time and space of the variables of the system. The key physical variables are assumed to be the tumor cell density (denoted by c); extracellular matrix protein density (denoted by v) and the urokinase plasminogen activator concentration (denoted by u).

In the following section, the way in which the tumor cell density $c(x,t)$, the urokinase plasminogen activator (uPA) protease concentration u(x, t) and the extracellular matrix density $v(x,t)$ are involved in the invasion and derive partial differential equations governing the evolution of each variable.

(a) Cancer cells:

We assume that there is a change in cell number density due to dispersion, arising from the random locomotion and we take D c as the cell random motility coefficient, characterizing how cells would disperse from higher to lower densities. However, in some cases we will use a physically meaningful

expression to describe their random motion other than the common linear diffusion and therefore nonlinear diffusion will be also used.

To summarize, the conservation of mass applied to the cancer cell density c leads to the following equation:

$$\frac{\partial c}{\partial t} + \nabla \cdot (J_{\text{random}} + J_{\text{chemotaxis}} + J_{\text{haptotaxis}}) = R_c$$

Here R_c is the net rate of production or loss of cells by mechanisms other than migration (e.g. proliferation or death) and hence the resulting partial differential equation for the cancer cell motion is,

$$\frac{\partial c}{\partial t} = \underbrace{\nabla \cdot (D_c \nabla c)}_{\text{dispersion}} - \underbrace{\nabla \cdot (\chi_c c \nabla \mathrm{u})}_{\text{chemotaxis}} - \underbrace{\nabla \cdot (\xi_c c \nabla v)}_{\text{haptotaxis}} + \underbrace{\mu_1 c\left(1 - \frac{c}{c_0} - \frac{v}{v_0}\right)}_{\text{proliferation}} \quad (1)$$

Where D_c is (linear or nonlinear) the random motility coefficient; χ_c and ξ_c are the chemotactic and haptotactic functions, respectively. Furthermore, μ_1 is the proliferation rate of the cells, while c_o and v_o are the maximum sustainable tumor cell and the extracellular matrix densities, respectively.

(b) Extracellular matrix

ECM is known to contain many macromolecules such as vitronectin, laminin and fibronectin, which can be degraded by several matrix degrading enzymes and especially by plasminogen activation. Since ECM is “static”, we neglect any random motion and focus solely on its degradation by the uPA protease. Using a modified logistic growth with rate constant μ2 to describe the ECM production, and taking δuv to represent the rate of degradation, we have the following equation for the extracellular matrix:

$$\frac{\partial v}{\partial t} = \underbrace{-\delta u v}_{\text{proteolysis}} + \underbrace{\mu_2 v\left(1 - \frac{c}{c_0} - \frac{v}{v_0}\right)}_{\text{re-establishment}} \quad (2)$$

[In general $\mu_1 = \mu_2$]

(c) urokinase Plasminogen Activator (uPA) protease

Factors influencing the protease concentration are assumed to be diffusion, protease production and protease decay. Specifically, uPA produced by cancer cells diffuses throughout the extracellular matrix, with constant diffusion coefficient Du, and undergoes the decay of the form β u. The equation governing the evolution of uPA concentration is therefore given by:

$$\frac{\partial u}{\partial t} = \underbrace{D_u \nabla^2 u}_{\text{dispersion}} + \underbrace{\alpha c}_{\text{production}} - \underbrace{(\beta u)}_{\text{decay}} \quad (3)$$

Hence, the complete system of the equations describing the interactions between the tumor cells, extracellular matrix and uPA is:

$$\begin{aligned} \frac{\partial c}{\partial t} &= \underbrace{\nabla \cdot (D_c \nabla c)}_{\text{dispersion}} - \underbrace{\nabla \cdot (\chi_c c \nabla \mathrm{u})}_{\text{chemotaxis}} - \underbrace{\nabla \cdot (\xi_c c \nabla v)}_{\text{haptotaxis}} + \underbrace{\mu_1 c\left(1 - \frac{c}{c_0} - \frac{v}{v_0}\right)}_{\text{proliferation}} \\ \frac{\partial v}{\partial t} &= \underbrace{-\delta u v}_{\text{proteolysis}} + \underbrace{\mu_2 v\left(1 - \frac{c}{c_0} - \frac{v}{v_0}\right)}_{\text{re-establishment}} \\ \frac{\partial u}{\partial t} &= \underbrace{D_u \nabla^2 u}_{\text{dispersion}} + \underbrace{\alpha c}_{\text{production}} - \underbrace{(\beta u)}_{\text{decay}} \end{aligned} \quad (4)$$

(d) No Dimensional

In order to solve the system numerically, we should transform equation to non-dimension. The variables and parameters in the uPA system equations and their associated boundary conditions are transformed into dimensionless quantities using the following reference variables:

1. Reference length scale, L,

e.g. The maximum invasion distance of the cancer cells at this early stage of invasion $0.1 - 1$cm

2. Reference time unit, $\tau = \frac{L}{D^2}$, where D is a reference chemical diffusion coefficient

e.g. $10^{-6} cm^2 s^{-1}$ [^]. Therefore, we deduce that τ varies between $10^4 - 10^6$sec.

3. Reference tumor cell density c_0, extracellular matrix density v_0 and reference uPA concentration u_0 where c_0, v_0 and u_0 are appropriate reference variables.

Thus, we define the non-dimensional variables:

$$\tilde{t} = \frac{t}{\tau}, \tilde{x} = \frac{x}{L}, \tilde{c} = \frac{c}{c_0}, \tilde{v} = \frac{v}{v_0}, \tilde{u} = \frac{u}{u_0}$$

and new parameters via the following scaling:

$$\widetilde{D_c} = \frac{D_c}{D}, \widetilde{D_u} = \frac{D_u}{D}, \tilde{\chi} = \chi_c \frac{u_0}{D}, \tilde{\xi} = \xi_c \frac{v_0}{D}$$

$$\widetilde{\mu_1} = \mu_1 \tau, \widetilde{\mu_2} = \mu_2 \tau, \tilde{\delta} = \delta u_0 \tau, \tilde{\alpha} = \alpha \frac{c_0}{u_0}, \tilde{\beta} = \beta \tau$$

Henceforth, with omitting the tildes for notational simplicity, the dimensionless governing equations can then be written in the following general form:

$$\frac{\partial c}{\partial t} = \underbrace{\nabla \cdot (D_c \nabla c)}_{\text{dispersion}} - \underbrace{\nabla \cdot (\chi_c c \nabla u)}_{\text{chemotaxis}} - \underbrace{\nabla \cdot (\xi_c c \nabla v)}_{\text{haptotaxis}} + \underbrace{\mu_1 c(1 - c - v)}_{\text{proliferation}}$$

$$\frac{\partial v}{\partial t} = \underbrace{-\delta u v}_{\text{proteolysis}} + \underbrace{\mu_2 v \left(1 - \frac{c}{c_0} - \frac{v}{v_0}\right)}_{\text{re-establishment}} \tag{5}$$

$$\frac{\partial u}{\partial t} = \underbrace{D_u \nabla^2 u}_{\text{dispersion}} + \underbrace{\alpha c}_{\text{production}} - \underbrace{(\beta u)}_{\text{decay}}$$

(e) Boundary and initial conditions

In order to close the system, boundary and initial conditions for c, u and v are required.

Boundary conditions: Guided by the in vitro experimental protocol in which invasion takes place within an isolated system, we assume that there is no-flux of tumor cells or protease across the boundary of the domain, namely x = 0 and x = 1, in one-space dimension. These boundary conditions are represented by the following equations,

$$\left(-D_c \frac{\partial c}{\partial x} + c\chi \frac{\partial u}{\partial x} + c\xi \frac{\partial v}{\partial x}\right) = 0, x = 0, 1 \tag{6}$$

$$\frac{\partial u}{\partial x} = 0, x = 0, 1 \tag{7}$$

Initial conditions: Finally, the initial distribution of the tumor cells, the protease concentration and the ECM density are prescribed by the system of equations (8). Initially, we assume that there is a cluster of cancer cells already present and that they have penetrated a short distance into the extracellular matrix while the remaining space is occupied by the matrix alone. Finally, for the uPA protease initial concentration we suppose that it is proportional to the initial tumor density. Combining the above we have,

$$\mathbf{c}\,(x, 0) = exp\left(\frac{-x^2}{\epsilon}\right), \in [0, 1], \epsilon > 0$$

$$v(x, 0) = 1 - \frac{1}{2} exp\left(\frac{-x^2}{\epsilon}\right), \in [0, 1], \epsilon > 0 \tag{8}$$

$$u(x,0) = 1 - \frac{1}{2} exp\left(\frac{-x^2}{\epsilon}\right), \in [0,1], \epsilon > 0$$

Where we took $\varrho = 0.01. \epsilon = 0.01$.

3. Numerical results for the PDE model.

To compute numerical solutions of our model in one space dimension we use the NAG library subroutine D03PCF. This method uses finite difference approximations to perform a spatial discretization of the model equations, thereby reducing them to a system of (time-dependent) ordinary differential equations which are readily integrated (this is the method of lines). The (stiff) ODE system is solved using a backward difference formula.

3.1. Haptotaxis-only model

In this section we will focus on the role of haptotaxis in the cancer invasion of tissue. As has already been described previously in the paper, the cancer cell membrane receptors (such as uPAR) can bind to ECM components (such as VN) and either degrade them through the activation of several proteases (such as uPA) or use them in order to move to distant sites. On the other hand, uPA production supports uPAR and VN binding. In this regard, we will try to clearly demonstrate these important interactions using as a basis the following theoretical framework, which focuses on the haptotaxis as the dominant mechanism for the movement of the cancer cells:

$$\begin{aligned}
\frac{\partial c}{\partial t} &= \underbrace{\nabla \cdot (D_c \nabla c)}_{\text{dispersion}} - \underbrace{\nabla \cdot (\chi_c c \nabla u)}_{\text{chemotaxis}} - \underbrace{\nabla \cdot (\xi_c c \nabla v)}_{\text{haptotaxis}} + \underbrace{\mu_1 c(1 - c - v)}_{\text{proliferation}} \\
\frac{\partial v}{\partial t} &= \underbrace{-\delta u v}_{\text{proteolysis}} + \underbrace{\mu_2 v\left(1 - \frac{c}{c_0} - \frac{v}{v_0}\right)}_{\text{renewal}} \qquad (9) \\
\frac{\partial u}{\partial t} &= \underbrace{D_u \nabla^2 u}_{\text{diffusion}} + \underbrace{\alpha c}_{\text{production}} - \underbrace{(\beta u)}_{\text{decay}}
\end{aligned}$$

In order to solve the system (9), we impose the boundary conditions presented by the equations (6) and (7) and we consider the initial conditions prescribed by the system (8). Additionally, to obtain the following simulations we used the following dimensionless parameter values:

$D_c = 10^{-4}, D_u = 10^{-2}, \chi_c = 0, \xi_c = 5 \times 10^{-3}, \alpha = 0.05, \beta = 0.3, \delta = 10, \mu_1 = \mu_2 = 0, L = 0.1 cm, \tau = 10^4 sec$

(Unless specified otherwise).

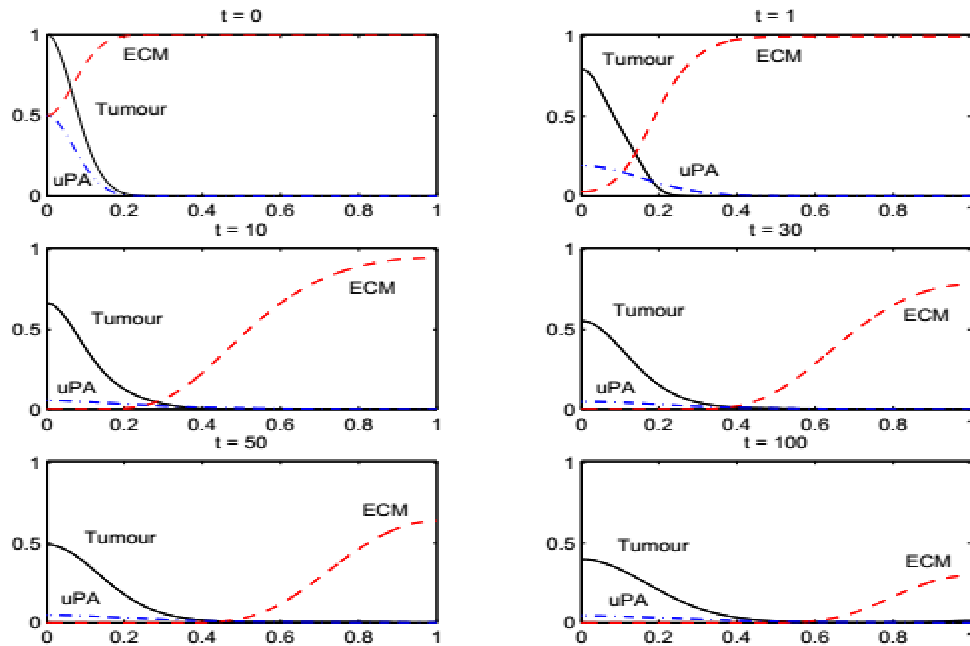

Figure 2. Sequence of profiles showing the evolution of the tumor cell density c(x, t) (solid black line), the protease concentration

u(x, t) (dot-dashed blue line) and the ECM density v(x, t) (dashed red line), in which haptotaxis dominates the cancer cells' directed movement.

Parameter values:

$$D_c = 10^{-4}, D_u = 10^{-2}, \xi_c = 0.05, \chi_c = 0, \alpha = 0.05, \beta = 0.3, \delta = 10, \mu_1 = \mu_2 = 0, L = 0.1cm, \tau = 10^4 sec.$$

In Figure 2, six snapshots in time of the tumor cell density, extracellular matrix (ECM) density and the uPA concentration are presented. Initially, by $t = 1$ ($\sim$ 3 hours) cancer cells have migrated a small distance into the domain. By $t = 30$ ($\sim$ 3.5 days), (low densities of) cancer cells have migrated almost half way through the domain due to VN-mediated migration. Therefore, as time evolves $by\ t = 100$ ($\sim$ 11 days) cancer cells continue to migrate to regions where high ECM densities are situated.

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