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ON A MATHEMATICAL MODEL OF CANCER INVASION OF TISSUE

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ABSTRACT
PURPOSE. The purpose of the present paper is to analyze the interactions between cancer cells and the surrounding tissue. METHODS. We use the methods of mathematical modeling and computer simulations. RESULTS. The numerical results present possible outcomes of the interactions between the participating populations. The meaning of the computational results is explained from the point of view of cancer research. CONCLUSIONS. The results of the numerical analysis of the investigated mathematical model illustrate two important mechanisms of migration and invasion of cancer cells and confirm the usefulness of mathematical methods in the field of the cancer research.

Key words: computer simulations, reaction-diffusion-chemotaxis equations, extracellular matrix

INTRODUCTION

Cancer has different manifestations and morbid pictures, due to these reasons it is difficult to make general conclusions about life expectancy and the chances of cure in each specific case. Today about a hundred different types of cancer are known, some of which are strongly different in the chance of survival, treatment options and the formation of metastases. The disease is among the three most common causes leading to death in the world - the first is cardiovascular disease - heart attacks or strokes, secondly - accidents or incidents and thirdly – cancer diseases [1]. Each organ of the human body can be attacked by cancer, and there are large frequency differences by age, gender, social environment, geographic region, diet, etc. Finding cancer at an early stage is crucial for successful treatment [2], [3]. Different types of cancer, however, pass through different stages for different duration.

Tumor cells look in approximately the same way as the normal cell populations from which they have originated. In contrast, the tumor cells are arranged in an irregular manner, which does not allow the formation of tissue and organ structures.

Tumors may be classified as *benign* and *malignant* [4]. Benign tumors grow at a slower pace than their malignant counterparts. This habit is the reason for the existence of some of the other signs of benignancy of the tumor. Pressed by the growing tumor cell mass, normal cell populations undergo atrophic changes and subsequently die. Collagen fibers of the connective stroma of the body are pushed by the growing tumor mass, are being "collected" on the periphery of the tumor and form its capsule. Benign tumors do not metastasize.

The rate of growth of malignant tumors is much higher than of their benign counterparts. The invasive growth determines also some other features of malignant tumors. Normal organ structures are tightly arranged. In order to enter them, tumor cells must first destroy the surrounding normal tissues, to open some free space and only then to infiltrate the tissue. This ability is also due to the invasive growth of the cancer cells. Once a tumor becomes malignant, it has cellular atypia and invasive (destructive and infiltrative) growth. Because of this type of growth, it has no capsule, boundaries with the surrounding tissue are unclear and provides near and distant metastases. Also, malignant tumor can recur [5], [6], [7].

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MATERIALS AND METHODS

In this paper we use mathematical modeling approach in order to describe migration and invasive properties of tumors. We suppose that a solid tumor is at the avascular stage and focus on the interactions between the cancer cells and the surrounding tissues. We consider a mathematical model proposed by Chaplain et al. [8], [9] consisting of three partial differential reaction-diffusion-chemotaxis equations describing the temporary and space dynamics of the system variables.

Chemotaxis is a phenomenon in which living cells or organisms move towards the *gradient* (i.e. the highest concentration) of certain *soluble* substance (chemicals) recognizable by the cells. The attractive soluble chemicals are called *chemoattractants* [10]. The directional migration attracted by *insoluble* substances is called *haptotaxis* [11], [12]. Undirected migration of cells is called *chemokinesis*. It has random character [13].

The key physical variables of the model are supposed to be the cancer cell density (denoted by *n(x,t)*), extracellular matrix (ECM) density (denoted by *f(x,t)*) and the concentration of matrix degradative enzymes (MDE) (denoted by *m(x,t)*) [8], [9]. MDE are produced by cancer cells and participate in the local destruction of the surrounding ECM [13], [14]. The space variable *x* denotes the distance from the center of the tumor. It is assumed to belong to the one-dimensional interval [0,1]. The variable *t* denotes time. The model equations are:

$$\frac{\partial n}{\partial t} = d_n \frac{\partial^2 n}{\partial x^2} - \chi \frac{\partial}{\partial x}\left(n \frac{\partial m}{\partial x} \right), \quad (1)$$

$$\frac{\partial f}{\partial t} = -\eta m f, \quad (2)$$

$$\frac{\partial m}{\partial t} = d_m \frac{\partial^2 m}{\partial x^2} + \alpha n - \beta m, \quad (3)$$

with non-negative parameters.

The model system must be complemented by boundary and initial conditions.

Guided by *in vitro* experimental protocols in which invasion takes place within an isolated system, we suppose that there is no flux of tumor cells and of degradative enzymes across the boundary of the domain, namely *x=0* and *x=1*. These boundary conditions are represented by the following equations:

$$\frac{\partial n}{\partial x}(x,t) = \frac{\chi}{d_n} n(x,t) \frac{\partial m}{\partial x}(x,t) \text{ at } x = 0,1; \quad (4)$$

$$\frac{\partial m}{\partial x}(x,t) = 0 \text{ at } x = 0,1. \quad (5)$$

The initial distribution of the tumor cells, the ECM density and the MDE concentration at time *t=0* are prescribed by equations (6) below. We assume that initially there is a cluster of cancer cells already present and that they have penetrated a short distance into the ECM, while the remaining space is occupied by the matrix alone. For the MDE initial concentration we assume that it is proportional to the initial tumor density. Combining the above reasoning we have:

$$n(x,0) = \exp\left(\frac{-x^2}{\varepsilon}\right)$$

$$f(x,0) = 1 - \frac{1}{2}\exp\left(\frac{-x^2}{\varepsilon}\right), \quad (6)$$

$$m(x,0) = \frac{1}{2}\exp\left(\frac{-x^2}{\varepsilon}\right)$$

for $x \in [0,1]$ and $\varepsilon = 0.01$.

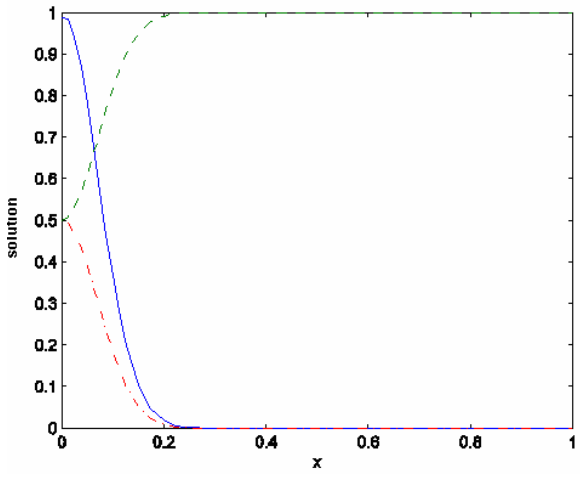

Fig. 1. The initial distribution of tumor cells (solid), ECM density (dashed) and MDE concentration (dash dot) (time *t=0*).

We solve the model system (1) – (6) by the method of finite differences.

RESULTS

Results of our numerical experiments are presented in **Figures 2-5.**

We use the parameter values:

$\alpha = 0.05, \beta = 0, \eta = 10, d_m = 0.01, N = 81,$

and various values of parameters d_n and χ specified in the captions of the figures.

First, we analyze the role of the chemotactic coefficient χ for the interactions between tumor cells and ECM. Setting

$d_n = 0.0001, \chi = 0.005,$

we obtain the following profiles presenting the system dynamics at time *t=1 (appr. 3 hours) t=10 (appr. 1 day):*

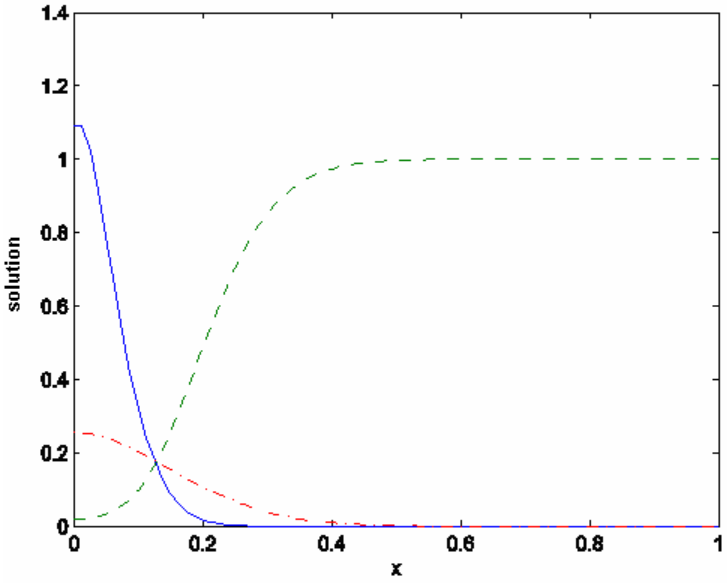

Fig. 2. The distribution of tumor cells (solid), ECM density (dashed) and MDE concentration (dash dot) at time *t=1*, $d_n = 0.0001, \chi = 0.005$.

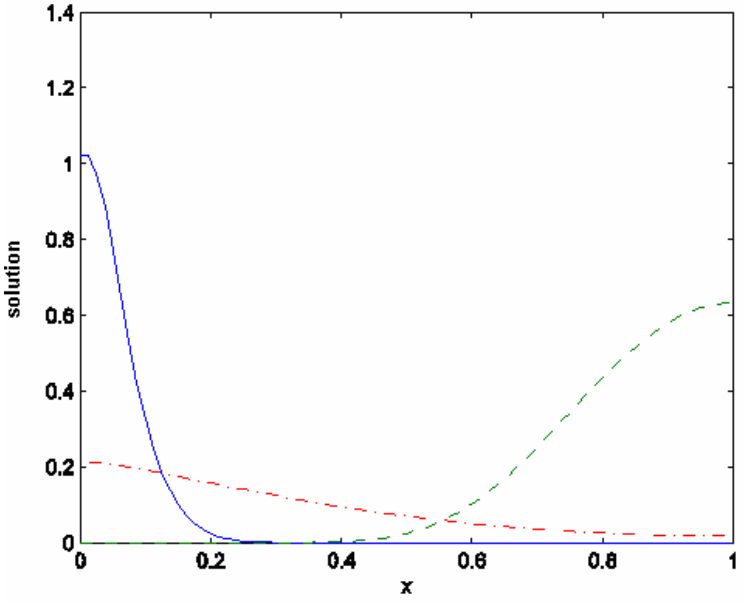

Fig. 3. The distribution of tumor cells (solid), ECM density (dashed) and MDE concentration (dash dot) at time *t=10*, $d_n = 0.0001, \chi = 0.005$.

We observe that by time *t=1* in **Fig. 2** there is a build-up of MDE at the interface between the cancer cells and the extracellular matrix. As time evolves, at time *t=10* tumor cells are still in the position that they used to occupy at time *t=1*. This is due to the fact that the leading mechanism of the cancer cell motion in this case is chemotaxis while the role of chemokinesis (random movement due to random motility) is small (due to the low value of the diffusion coefficient d_n). Therefore, the MDE-mediated gradient (directed cancer cells motion in response to high concentration of MDE) "pulls back" the tumor cells where high MDE concentrations are situated. This dynamics is even more manifested for higher values of the chemotactic coefficient, see **Fig. 4**, where $\chi = 0.05, t = 10.$

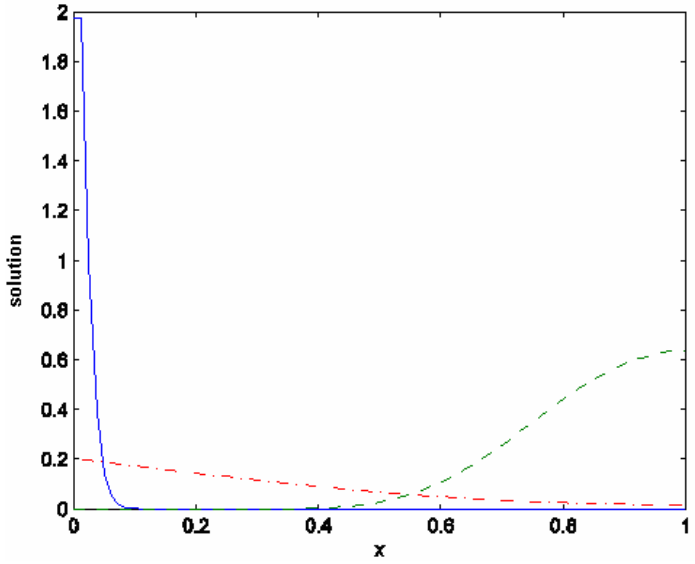

Fig. 4. The distribution of tumor cells (solid), ECM density (dashed) and MDE concentration (dash dot) at time *t=10*, $d_n = 0.0001, \chi = 0.05$.

As time evolves, almost the whole ECM has been degraded while the tumor cells have not migrated due to the presence of MDE.

In the next part of our simulations we consider the case when $\chi = 0.05$ and the coefficient of random motility (diffusion) of cancer cells is higher: $d_n = 0.01$. The results of simulations at time *t=1* and *t=5* are presented in **Figures 5 and 6.**

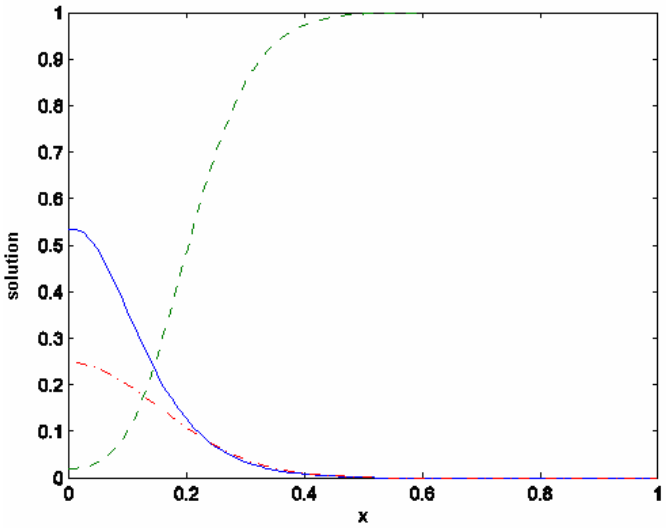

Fig. 5. The distribution of tumor cells (solid), ECM density (dashed) and MDE concentration (dash dot) at time *t=1*, $d_n = 0.01, \chi = 0.05$.

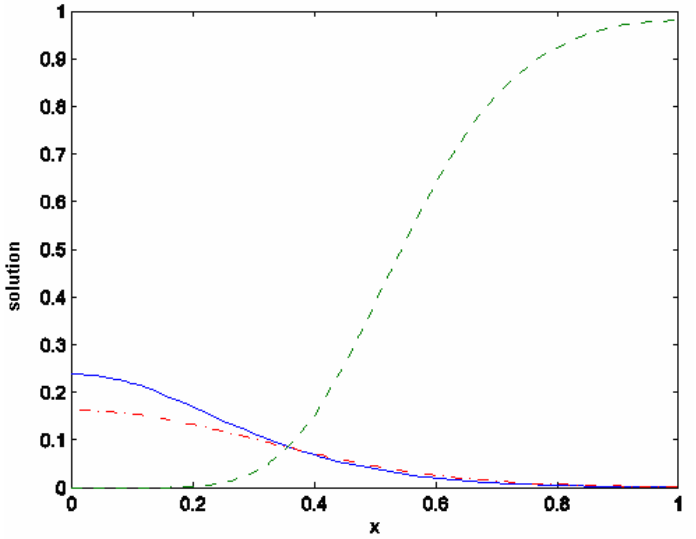

Fig. 6. The distribution of tumor cells (solid), ECM density (dashed) and MDE concentration (dash dot) at time $t=5$, $d_n = 0.01, \chi = 0.05$.

We observe that in this case the initial cluster of cancer cells spreads later through the domain due to the higher random motility.

DISCUSSION

In this paper by using a reaction-diffusion-chemotactic mathematical model we studied two possible mechanisms of cancer migration and invasion. We conclude that when more important is the role of MDE-mediated chemotactic migration of cancer cells, the tumor is not able to invade the healthy tissue. On the contrary, when more important is the role of the diffusion of cancer cells, they are able to infiltrate the surrounding tissue. This process can lead to metastasis.

The mathematical and numerical analysis of the considered two important mechanisms of cancer migration and invasion can improve their understanding.

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