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Conservative Finite Difference Schemes to a Nonlinear Parabolic System of Cancer Invasion

Mikhail K. Kolev* and Lubin G. Vulkov†

*University of Warmia and Mazury, Żolnierska 14, Olsztyn, 10-561, Poland
kolev@matman.uwm.edu.pl
†University of Rousse, Studentska 8 str., 7017 Rousse, Bulgaria
lvalkov@uni-ruse.bg

Abstract. We consider a nonlinear parabolic system of equations that describes interactions between tumor cells and microenvironmental factors such as extracellular matrix and matrix degradative enzymes.

Given the application, conservation of nonnegativity and conservation or evolution laws of total cell density, concentration of total MDEs and ECM densities are of paramount importance.

We propose finite difference approximations that maintains these properties of the continuous solution. Numerical experiments are provided to demonstrate the behaviour of the model and to illustrate some important invasive mechanisms of cancer cells.

Keywords: Cancer invasion, nonlinear parabolic problems, nonnegativity, finite difference scheme, conservation and evolution laws, convergence
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INTRODUCTION

Tumor growth is a highly complex process. This includes the initial avascular phase of growth, angiogenesis - the formulation of new blood vessels, and vascular phase of growth. Within the last three decades a number of mathematical models for tumor growth have been developed. We refer the interested reader to [2, 5] for a relatively comprehensive review of cancer modelling. The qualitative analysis of cancer models is also very interesting and some mathematical challenges have been recently reviewed [8, 9].

In contrast, tumor invasion is a relatively new area for mathematical modeling. Recently, there has been increasing biological and mathematical interest in tumor invasion and corresponding mathematical models have started to appear in the research literature [2, 3, 4].

This paper is devoted to numerical analysis of the cell-matrix interactions and cell migration model described in [1, 2]. More in detail, it serves two purposes. On one hand, we construct difference schemes that preserve the basic properties of the differential system solutions. On the other hand, we discuss effective numerical algorithms for solution of the nonlinear systems of difference equations.

The remainder of the paper is organized as follows. In Section 2 the parabolic system studied herein is briefly described. In Section 3, we present our difference schemes and in Section 4 numerical experiments are discussed. Finally in Section 5 we give some conclusions.

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THE MATHEMATICAL MODEL

The present paper is devoted to mathematical and numerical analysis of the following model of cancer invasion:

$$\begin{aligned} \frac{\partial n}{\partial t} &= d_n \frac{\partial^2 n}{\partial x^2} - \gamma \frac{\partial}{\partial x}\left(n \frac{\partial f}{\partial x} \right), \\ \frac{\partial f}{\partial t} &= -\eta m f, \\ \frac{\partial m}{\partial t} &= d_m \frac{\partial^2 m}{\partial x^2} + \alpha n - \beta m. \end{aligned} \tag{1}$$

The unknown functions $n(x,t)$, $f = f(x,t)$ $m = m(x,t)$ depend on the space variable x belonging to the scaled domain $\overline{\Omega} = [0,1]$ of tissue, and time t. The system (1) describes interactions between cancer cells (their density is denoted by the function n), extracellular matrix (ECM) (its density is denoted by the function f), and matrix degradative enzymes (MDEs) (their concentration is denoted by the function m).

This system is a part of a more general model of cancer invasion proposed by Anderson *et al.*[1] and developed later in a series of papers (see for example [2, 3, 4]). Various modifications of the model have been numerically investigated in [6] and applied to experimental data for prostate cancer growth in [7].

The system (1) will be solved numerically at the boundary conditions

$$\frac{\partial n}{\partial x}(0,t) = \frac{\gamma}{d_n} n(0,t) \frac{\partial f}{\partial x}(0,t), \;\; \frac{\partial m}{\partial x}(0,t) = 0, \tag{2}$$

$$n(1,t) = 0, \;\; m(1,t) = 0, \tag{3}$$

or the zero-flux boundary condition

$$\frac{\partial n}{\partial x}(1,t) = \frac{\gamma}{d_n} n(1,t) \frac{\partial f}{\partial x}(1,t), \;\; \frac{\partial m}{\partial x}(1,t) = 0; \tag{4}$$

and initial conditions

$$n(x,0) = n_0(x), \;\; f(x,0) = f_0(x), \;\; m(x,0) = m_0(x). \tag{5}$$

We assume that $n_0(x), f_0(x), m_0(x) \geq 0, \;\; \not\equiv 0$.

It is known (cf: [8,9]) that the problems (1), (2), (4), (5) and (1), (3), (4), (5) at sufficient smoothness of the input data admit a unique classical solution (n, f, m) globally in time. On the other hand, by using the maximum principle [8, 9], one obtains

$$n(x,t), \; f(x,t), \; m(x,t) \geq 0, \;\; \not\equiv 0 \; (x,t) \in \overline{Q}_T \equiv [0,1] \times [0,T)$$

(conservation of non-negativity)

Also, for problem (1), (2), (4), (5) after integration of the equation for $n(x,t)$ from system (1) from 0 to 1 with respect to variable x and taking into account the boundary conditions we obtain:

$$\int_0^1 n(x,t)dx = \int_0^1 n_0(x)dx \equiv n_0,\ \ t \in [0,\infty), \tag{6}$$

(conservation of total cancer cell density);

after integration of the equation for $m(x,t)$ from system (1) from 0 to 1 with respect to variable x and taking into account the boundary conditions we obtain:

$$\int_0^1 m(x,t)dx = \left(m_0 - \frac{\alpha n_0}{\beta}\right)e^{-\beta t} + \frac{\alpha n_0}{\beta},\ \ m_0 = \int_0^1 m_0(x)dx, \tag{7}$$

(evolution of total MDEs concentration);

and after division both sides with $f(x,t)$ and integration of the equation for $f(x,t)$ from system (1) from 0 to 1 with respect to variable x we obtain:

$$\int_0^1 \ln f(x,t)dx = -\frac{\eta}{\beta}\left[\alpha n_0 t + \left(m_0 - \frac{\alpha n_0}{\beta}\right)\left(1 - e^{-\beta t}\right)\right] \tag{8}$$

(evolution the logaritmic total ECM density).

In order to construct conservative finite difference scheme that preserves the discrete analogues of (6), (7) and (8) we rewrite the differential system (1) as follows:

$$\frac{\partial n}{\partial t} = \frac{\partial}{\partial x}W(x,t),\ \ W(x,t) \equiv d_n\frac{\partial n}{\partial x} - \gamma n\frac{\partial}{\partial x}F(m),$$

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

where

$$F(m) = f(x,t) = f_0(x)\exp(-\eta\int_0^t m(x,\tau)d\tau).$$

FINITE-DIFFERENCE SCHEMES

Take a positive integer I put $h = 1/(I)$. We introduce two kinds of grid points over $[0,1]$ as :

$$x_i = (i-0.5)h,\ \ \widehat{x}_i = (i-1)h,\ \ i = 1,\ldots,I+1,\ \ Ih = 1.$$

Grid points over $[0,T]$ are defined by

$$t_{j+1} = t_j + \tau_j,\ \ j = 1,\ldots,J,\ \ t_1 = 0,\ \ t_{J+1} = T,$$

where the time increment $\tau_j > 0$ will be determined later. We consider approximation of $n(x,t)$ and $m(x,t)$ on (x_i,t_i) and $(\widehat{x}_i,\widehat{t}_j)$, respectively. Thus, we would like to find $n^j \approx n(x_i,t_j)$ and $m_i^j \approx m(\widehat{x}_i,\widehat{x}_j)$. Let introduce the vectors

$$\mathbf{m^j} = (m_1^j,\ldots,m_I^j)^T \quad \text{and} \quad \mathbf{n^j} = (n_1^j,\ldots,n_{I+1}^j)^T.$$

For the time being, we suppose that $\mathbf{m^{j-1}}$ and $\mathbf{n^{j-1}}$ have been obtained and describe schemes for solving $\mathbf{m^j}$ and $\mathbf{n^j}$ separately.

Scheme for solving $\mathbf{m^j}$

We introduce

$$\widehat{n}_i^j = \begin{cases} n_1^j & ,i=1 \\ \frac{1}{2}(n_{i+1}^j + n_i^j) & ,i=1,\ldots,I, \\ n_{I+1}^j & ,i=I+1 \end{cases} \quad \widehat{\mathbf{n}}^{\mathbf{j}} = (\widehat{n}_1^j,\ldots,\widehat{n}_{I+1}^j)^T.$$

Then $\mathbf{m^j}$ is computed by the $\sigma \in [0,1]$ - weight scheme

$$\frac{m_i^{j+1}-m_i^j}{\tau_j} = \sigma d_m \frac{m_{i-1}^{j+1}-2m_i^{j+1}+m_{i+1}^{j+1}}{h^2} \tag{9}$$

$$+(1-\sigma)d_m\frac{m_{i+1}^j-2m_i^j+m_{i-1}^j}{h^2}+\alpha\widehat{n}_i^j-\beta m_i^j,$$

where m_0^j and m_{N+2}^j are eliminated by the boundary conditions

$$m_0^j = m_2^j, \;\; m_{N+2}^j = m_N^j, \;\; j=1,\ldots,J+1. \tag{10}$$

The scheme (9) with (10) is equivalently written as:

$$(\mathbf{I}+\sigma\lambda_j d_m\mathbf{A})\mathbf{m^{j+1}} = [\mathbf{I}-(1-\sigma)\lambda_j d_m\mathbf{A}]\mathbf{m^j}+\tau_j\mathbf{g^j}, \tag{11}$$

where $\lambda_j = \frac{\tau_j}{h^2}$, I is the identity matrix, and

$$\mathbf{A} = \begin{bmatrix} 2 & -2 & 0 & \ldots & \ldots & 0 \\ -1 & 2 & -1 & & & \\ & & \ldots & \ldots & & \\ & -1 & 2 & -1 & & \\ & & & & \ldots & \ldots \\ & & & & -2 & 2 \end{bmatrix}, \quad \mathbf{g^j} = \alpha\widehat{\mathbf{m}}^{\mathbf{j}} - \beta\mathbf{n^j}.$$

Scheme for solving $\mathbf{n^j}$

The key point is to introduce a *reasonable* approximation of the flux W by applying upwind technique. We set

$$\widetilde{F}(m_i^j) = f_0(x_i)\exp\left(-\eta\sum_{l=1}^{j}\tau_l m_i^l\right)$$

$$b_i^j = \frac{\widetilde{F}(m_i^j)-\widetilde{F}(m_{i-1}^j)}{h}, \;\; (2\le i\le I+1), \;\; \mathbf{b^j} = (b_1^j,\ldots,b_{I+1}^j)^T. \tag{12}$$

Further, we set

$$b_i^{j,+} = \max\{0,b_i^j\} \;\text{ and }\; b_i^{j,-} = \max\{0,-b_i^j\}.$$

Obviously, b_i^j is an approximation of $\frac{\partial}{\partial x}F(m)$ at $x = x_i$.
We note that

$$W = -d_n n_x + [b]_+ n - [b]_- n,$$

where $b = (F(m))_x$ and $[b]_\pm = \max\{0, \pm b\}$. Hence, following a technique of upwind approximation, we may suppose that n_i^j and n_{i+1}^{j+1} are carried into a a point $\widehat{x}_i$ of flows and $-b_{i+1}^{j-1,-}$, respectively.

That is, a discrete flux W_i^{j+1} of $\mathbf{n^{j+1}}$ at $x = \widehat{x}_i$ is given by

$$W_i^{j+1} = -d_n \frac{n_{i+1}^{j+1} - n_i^{j+1}}{h} + b_{i,+}^j n_i^{j+1} - b_{i+1}^{j,-} n_{i+1}^{j+1}, \ i = 2, \ldots, I.$$

Similarly, an discrete flux $\widetilde{W}_i^j$ of $\mathbf{n^j}$ at $x = \widehat{x}_i$ is given by

$$\widetilde{W}_i^j = -d_n \frac{n_{i+1}^j - n_i^j}{h} + b_i^{j-1,+} n_i^j - b_{i+1}^{j,-} n_{i+1}^j, \ i = 2, \ldots, I$$

By the boundary conditions (2), (4), we set

$$W_1^j = 0, \ W_{I+1}^j = 0, \ \widetilde{W}_1^j = 0, \ \widetilde{W}_{I+1}^j = 0. \tag{13}$$

Then our proposed scheme is as follows:

$$\frac{n_i^{j+1} - n_i^j}{\tau_j} = -\sigma \frac{W_i^{j+1} - W_{i-1}^{j+1}}{h} - (1-\sigma) \frac{\widetilde{W}_i^j - \widetilde{W}_{i-1}^j}{h}, \ i = 2, \ldots, I+1 \tag{14}$$

with boundary condition (13).
The scheme (14) with (13) is equivalently written as:

$$[\mathbf{I} + \sigma\lambda_j (d_n \mathbf{H} + \gamma h \mathbf{B^j})]\mathbf{n^{j+1}} = [\mathbf{I} - (1-\sigma)\lambda_j (d_n \mathbf{H} + \gamma h \mathbf{B^{j-1}})]\mathbf{n^j}, \tag{15}$$

where

$$\mathbf{H} = \begin{bmatrix} 1 & -1 & 0 & \ldots & \ldots & 0 \\ -1 & 2 & -1 & & & \\ & & \ldots & \ldots & & \\ & -1 & 2 & -1 & & \\ & & & & \ldots & \ldots \\ & & & & -1 & 1 \end{bmatrix},$$

$$\mathbf{B^j} = \begin{bmatrix} b_{1,+}^j & -b_{2,-}^j & 0 & \ldots & \ldots & 0 \\ -b_{1,+}^j & b_{2,+}^j + b_{2,-}^j & -b_{3,+}^j & & & \\ & & \ldots & \ldots & & \\ & -b_{i-1,+}^j & b_{i,+}^j + b_{i,-}^j & -b_{i+1,+}^j & & \\ & & & & \ldots & \ldots \\ & & & & -b_{I,+}^j & b_{I+1,-}^j \end{bmatrix}.$$

NUMERICAL SIMULATIONS

The considered model has to be closed by appropriate initial conditions (5). Following [2], we assume that the initial tumor is centered at $x = 0$, the initial MDE concentration is proportional to the initial tumor cell density with $1/2$ as the constant of the proportionality, and the MDE has already degraded the ECM, thus we consider the same initial conditions as in [2], which are presented in Fig. 1 and are defined as follows:

$$n(x,0) = \exp\left(\frac{-x^2}{\varepsilon}\right),\ f(x,0) = 1 - 0.5n(x,0),\ m(x,0) = 0.5n(x,0),\ \ \forall x \in [0,1].$$

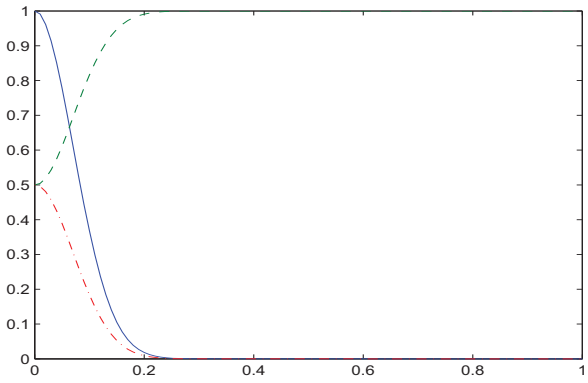

FIGURE 1. The initial distribution of cancer cell density (solid), ECM density (dashed), and MDE concentration (dashdot).

The resulting initial value problem has been solved by using the schemes described in the previous Section Thus we obtain the approximate solutions to the model (1) for tumor cells, ECM, and MDE. Results of our numerical experiments are presented in Figures 2-5.

We use the parameter values $\alpha = 0.1$, $\beta = 0.5$, $\eta = 10$ $\varepsilon = 0.01$, $d_m = 0.001$, $\gamma = 0.03$, $N = 40$ and different values of d_n specified in the captions of the figures.

The different values of d_n allow us to compare two possible mechanisms of cancer migration and invasion, namely the diffusion (random motility) described by the term $d_n\Delta^2 n$ and the haptotaxis described by $-\gamma\Delta\cdot\left(n\Delta f\right)$ of the model (1). For low values of parameter d_n more important is the haptotactic migration of tumor cells. Such situation is presented in Figs. 2-3, where d_n was set to 0.001.

For higher values of parameter d_n more important is the random motility of tumor cells. Such situation is presented in Figs. 4-5, where d_n was set to 0.01.

The numerical results show that in the case with lower diffusion coefficient d_n (presented in Figures 2 and 3) clusters of cancer cells are created at the leading edge of the tumor as a result of the haptotactic migration. As time increases, the tumor invade deeply into the tissue. In the case of higher diffusion coefficient d_n (presented in Figures 4 and

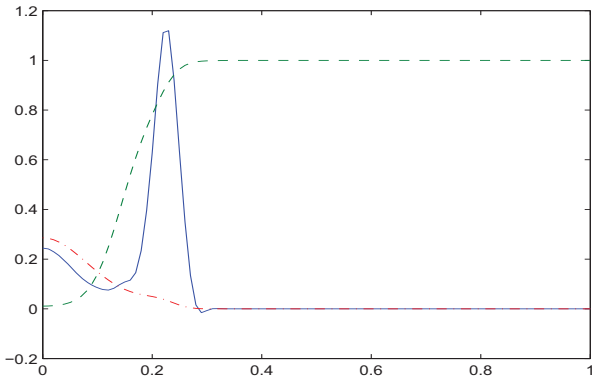

FIGURE 2. Cancer cell migration and interactions between the cancer and the surrounding tissue: cancer cell density (solid), ECM density (dashed), and MDE concentration (dashdot). Solutions to (1), (2), (4), (5) with the parameter value $d_n = 0.001$ at time $t = 1$.

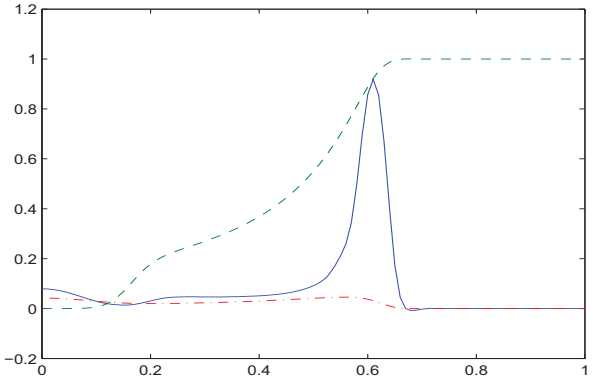

FIGURE 3. Solutions to (1), (2), (4), (5) with the parameter value $d_n = 0.001$ at time $t = 5$.

5) the moving cluster is not so high and is not able to invade very deep into the tissue during the time interval.

These two cases illustrate the possible diffusive and haptotactic mechanisms of cancer invasion through tissue. Their knowledge can be useful for choice of treatment in the respective real situations.

The proposed numerical algorithm is very efficient, it uses small amount of grid points. It maintains the nonnegativity of the solutions. In order to check its accuracy, we have calculated the differences between the left-hand and right-hand sides for the conservation and evolution properties given in Eqs. 6 - 8. For Eqs. 6 and 7 it is of the order $10^{-4} - 10^{-8}$ and for the property given in Eq. 8 is of the order 10^{-2}. The respective errors are presented it Table 1.

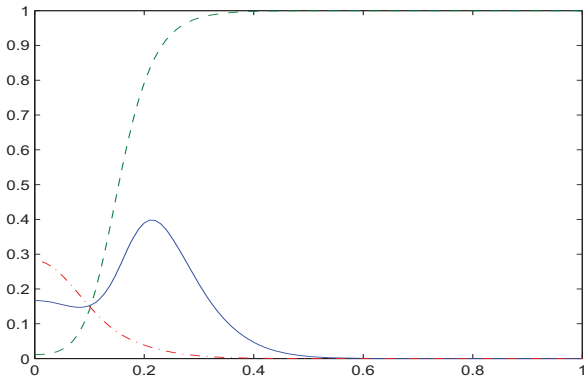

FIGURE 4. Solutions to (1), (2), (4), (5) with the parameter values $d_n = 0.01$ at time $t = 1$.

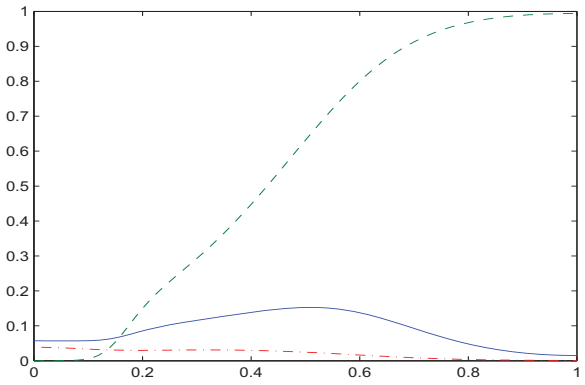

FIGURE 5. Solutions to (1), (2), (4), (5) with the parameter values $d_n = 0.01$ at time $t = 5$.

CONCLUSIONS

In this work, we have proposed finite difference schemes, which preserve the nonnegativity as well as the conservation properties of the solution to a model of tumour invasion. The model evaluation proves the high accuracy of the numerical method and demonstrate an improved efficiency compared to collocation numerical approaches [6]. In future work we plan to address the development of the numerical method for more complicated mathematical models. Also, discrete maximum principle and convergence of the finite difference approximations will be theoretically studied.

ACKNOWLEDGMENTS

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TABLE 1. Differences between theoretical and calculated values for Eqs. 6 - 8.

Figure i	Error for Eq. 6	Error for Eq. 7	Error for Eq. 8
1	0.0006	$2.63 * 10^{-6}$	-0.063
2	0.0002	$-1.19 * 10^{-6}$	-0.073
3	$7.65 * 10^{-7}$	$3.67 * 10^{-8}$	-0.061
4	$1.18 * 10^{-8}$	$2.93 * 10^{-7}$	-0.071

REFERENCES

1. A.R.A. Anderson, M.A.i. Chaplain, E.L. Newman, R.i.C. Steele, and A.M. Thompson, Mathematical modelling of tumour invasion and metastasis, *J. Theor. Med.* **2**, 129–154 (2000).
2. M.A.i. Chaplain, and A.R.A. Anderson, "Mathematical modelling of tissue invasion", in *Cancer modelling and simulation*, edited by L. Preziosi, Chapman & Hall/CRC, Boca Raton, FL, 2003, pp. 269–297.
3. M.A.i. Chaplain, and G. Lolas, Mathematical modelling of cancer cell invasion of tissue: The role of the urokinase plasminogen activation system, *Math. Models Methods Appl. Sci.* **15**, 1685–1734 (2005).
4. M.A.i. Chaplain, and G. Lolas, Mathematical modelling of cancer invasion of tissue: dynamic heterogeneity, *Netw. Heterog. Media* **1** (3), 399–439 (2006).
5. N. Bellomo, N.K. Li and P.K. Maini, On the foundations of cancer modeling, selected topicsm speculations and perspectives. Math. Models Appl. Sci. 18 (2003), 593-646.
6. M. Kolev, and B. Zubik-Kowal, Numerical solutions for a model of tissue invasion and migration of tumour cells, *Computational and Mathematical Methods in Medicine*, **2011**, Article ID 452320, 16 pages, (2011). doi:10.1155/2011/452320.
7. M. Kolev, and B. Zubik-Kowal, Numerical versus experimental data for prostate tumour growth, *i. Biol. Sys.*, to appear.
8. G. Litcanu, and C. Morales-Rodrigo, Asymptotic behavior of global solutions to a model of cell invasion, *Math. Models Methods Appl. Sci.* **20** (9), 1721–1758 (2010).
9. C. Morales-Rodrigo, Local existence and uniqueness of regular solutions in a model of tissue invasion by solid tumor, *Math. Comput. Modelling,* **47**, 604–613, (2008).
10. N. Saito, Conservative difference scheme to a chemotuxis system , *Proceed. of 4-th Int. Conf. FDM: T and A'06 Lozenetz (Bulgaria), Eds. I. Farago, P. Vabishchevich and L. Vulkov, Rousse,* (2007), 294-300. 604–613, (2008).