EUROPEAN JOURNAL OF COMPUTATIONAL MECHANICS, 2017
VOL. 26, NO. 4, 430–442
https://doi.org/10.1080/17797179.2017.1306833

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# DRBEM solution of the acid-mediated tumour invasion model with time-dependent carrying capacities

Gülnihal Meral

Department of Mathematics and Computer Science, Ankara Yıldırım Beyazıt University, 06010 Ankara, Turkey

**ABSTRACT**

It is known that the pH level of the extracellular tumour environment directly effects the progression of the tumour. In this study, the mathematical model for the acid-mediated tumour cell invasion consisting of a system of nonlinear reaction diffusion equations describing the interaction between the density of the tumour cells, normal cells and the concentration of $H^+$ protons produced by the tumour cells is solved numerically using the combined application of dual reciprocity boundary element method (DRBEM) and finite difference method. The space derivatives in the model are discretised by DRBEM using the fundamental solution of Laplace equation considering the time derivative and the nonlinearities as the nonhomogenity. The resulting systems of ordinary differential equations after the application of DRBEM are then discretised using forward difference. Because of the highly nonlinear character of the model, there arises difficulties in solving the model especially for two-dimensions and the boundary-only nature of DRBEM discretisation gives the advantage of having solutions with a lower computational cost. The proposed method is tested with different kinds of carrying capacities which also depend on time. The results of the numerical simulations are compared among each case and seen to confirm the expected behaviour of the model.

**ARTICLE HISTORY**
Received 31 October 2016
Accepted 20 February 2017

**KEYWORDS**
DRBEM; acid-mediated tumour cell invasion; time-dependent carrying capacities; reaction-diffusion equations; finite difference method

## 1. Introduction

Cancer cells grow and divide in an uncontrolled manner and form metastasis which is the process of developing a secondary tumour at a distant part of the body. The initial step for metastasis is the invasion of the tissue in which they arise and the pH level of the tumour microenvironment is one of the important factors effecting the cancer invasion. Cancer cells produce energy by glycolysis followed by lactic acid release which leads to an acidic tumour microenvironment in which the cancer cells are able to survive but the normal cells cannot. The normal cells start to die in this altered environment and this creates a free space for tumour cells to migrate. The original model was

**CONTACT** Gülnihal Meral gmeral@ybu.edu.tr

introduced by Gatenby and Gawlinski (1996) and it was given with a system consisting of two reaction-diffusion equations describing the temporal evolution and spatial distribution of the density of tumour cells and the concentration of $H^+$ protons produced by the tumour cells coupled with an ordinary differential equation (ODE) for the normal cell density. Later, Gatenby, Gawlinski, Gmitro, Kaylor, and Gillies (2006) analysed the model from different aspects, e.g. *in silico* using mathematical models and experimental observations, and later (Gatenby & Gillies, 2007) studied therapy strategies. Following these macroscopic models, the mathematical model was extended to include the microscopic effects, i.e. intracellular proton dynamics by Stinner, Surulescu, and Meral (2015) and a treatment approach was made by Meral, Stinner, and Surulescu (2015).

Märkl, Meral, and Surulescu (2013) extended the main model given by Gatenby and Gawlinski (1996) to include the crowding effects in the growth of normal cells and they showed that this extended model has a unique solution; however, the analytical solution for the system is not known. Thus, it is important to have efficient numerical methods for the approximate solution. Due to the nonlinearities seen in the equation for tumour cell density and proton concentration, the above-mentioned mathematical models are not easy to solve numerically, either. The nonlinearity appears as a coefficient in the diffusion term and as an added term in the model. In the literature, the model is often solved using finite difference methods, namely method of lines (e.g. in the papers by Gatenby et al. (2006), Martin, Goffney, Gatenby, and Maini (2010) or nonstandard finite difference method (as in the papers by Märkl et al. (2013), Meral et al. (2015), Stinner et al. (2015). The mentioned methods are easy to implement but as the dimension gets higher one needs more discretisation points which makes the method computationally expensive and stability problems may occur.

In this study, the macro-model for the acid-mediated tumour invasion is extended to include the time-varying carrying capacities and it is solved using the combined application of dual reciprocity boundary element method (DRBEM) and finite difference method (FDM). DRBEM discretises only the boundary of the domain and the solution then can be approximated for the desired interior points. The spatial derivatives in the model system are discretised using DRBEM with the fundamental solution of Laplace equation considering the time derivative and the nonlinearity as nonhomogenity. The nonlinearity in the cancer cell density equation includes a term containing the derivative of the normal cell density which is approximated using finite differences with the updated values obtained from the solution of the ODE for the normal cells which is solved using FDM. The cases with different kinds of carrying capacities, depending on time or constant case are compared. The expected behaviour is obtained using a small number of discretisation points and the numerical results agree well with the experimental facts.

## 2. Model problem

It is known that an acidic pH boosts apoptosis of normal cells and this leads an enhanced growth due to more space becoming available (Gatenby & Gawlinski, 1996; Märkl et al., 2013; Stinner et al., 2015). However, there is a certain threshold of the acidity level and too acidic environment is not suitable also for cancer cells (Stinner et al., 2015). Therefore, the carrying capacity should also depend on the extracellular proton concentration to indicate this fact. Thus the resulting extended macro-model is given by

$$\begin{aligned}\frac{\partial n}{\partial t} &= \omega_n n\left(1-\frac{n}{K_n}-\eta_1\frac{c}{K_c(a)}\right)-d_n a n\\ \frac{\partial c}{\partial t} &= \omega_c c\left(1-\frac{c}{K_c(a)}-\eta_2\frac{n}{K_n}\right)+\nabla\cdot\left(\triangle_c\left(1-\frac{n}{K_n}\right)\nabla c\right)\\ \frac{\partial a}{\partial t} &= \omega_a c-d_a a+\triangle_a\nabla^2 a\end{aligned} \tag{1}$$

where $n, c, a$ denote the normal and tumour cell densities and the concentration of $H^+$ extracellular protons, respectively. The model parameters $\omega_c$, $\omega_n$ and $\omega_a$ denote the production rates for the cancer and normal cells and for the $H^+$ protons, respectively; $\triangle_c$, $\triangle_a$ denote the diffusion coefficients for the cancer cells and $H^+$ protons, respectively, whereas $d_n$ is the death rate of normal cells and $d_a$ is the uptake rate for $H^+$ protons. Moreover, $\eta_1$, $\eta_2$ denote the strength parameters for the competition between the normal and cancer cells; $K_n$ and $K_c$ are the corresponding carrying capacities for the normal cell and cancer cell populations, respectively. For the carrying capacity function $K_c(a)$, three different choices are considered:

$$K_c(a) = \frac{C_0 + bC_0 a}{1+da^2}, \tag{2a}$$

$$K_c(a) = C_0 + fC_0 a \tag{2b}$$

$$K_c(a) = C_0. \tag{2c}$$

The first choice (2a) indicates that a too acidic environment reduces the carrying capacity of cancer cells. The second choice (2b) describes the enhanced growth in an environment becoming more acidic whereas the last choice gives no relationship between acidic environment and the growth of the tumour. Here $C_0$ is a reference carrying capacity for cancer cells and $b$, $d$, $f$ are positive constants.

It is assumed that there is no exchange of cancer cells and protons across the boundary of the problem domain $\Omega$ which leads to the boundary conditions

$$\frac{\partial c}{\partial \nu} = \frac{\partial a}{\partial \nu} = 0 \qquad \text{in } (0,T)\times\partial\Omega \tag{3}$$

with $\nu$ denoting the outward unit normal to $\partial\Omega$ (boundary of $\Omega$).

The initial conditions are given by

$$n(0,\mathbf{x}) = n_0(\mathbf{x}), \quad c(0,\mathbf{x}) = c_0(\mathbf{x}), \quad a(0,\mathbf{x}) = a_0(\mathbf{x}), \quad \text{in } \Omega \tag{4}$$

where the functions $n_0$, $c_0$, $a_0$ are strictly positive functions which are appropriate with the no-flux boundary conditions.

The global existence of the system (1), (3) and (4) with the choices (2a)–(2c) can be obtained using the proof techniques in the papers by Märkl et al. (2013) and Stinner et al. (2015).

Before solving the system numerically, the model system is written in the nondimensionalised form and the transformations

$$\tilde{n} = \frac{n}{K_n}, \quad \tilde{c} = \frac{c}{C_0}, \quad \tilde{a} = a\frac{d_a}{\omega_a C_0}, \quad \tilde{t} = \omega_n t, \quad \tilde{\mathbf{x}} = \sqrt{\frac{\omega_n}{D_a}}\mathbf{x}, \tag{5}$$

are made use of to get the nondimensionalised system

$$\frac{\partial n}{\partial t} = n\left(1 - n - \eta_1 \frac{c}{K_c(a)}\right) - \delta_n a n \tag{6a}$$

$$\frac{\partial c}{\partial t} = \rho_c c\left(1 - \frac{c}{K_c(a)} - \eta_2 \frac{n}{K_n}\right) + \nabla \cdot \left(D_c\left(1-n\right)\nabla c\right) \tag{6b}$$

$$\frac{\partial a}{\partial t} = \delta_a c - \delta_a a + \nabla^2 a \tag{6c}$$

with the parameters

$$\rho_c = \frac{\omega_c}{\omega_n}, \quad D_c = \frac{\Delta_c}{\Delta_a}, \quad \delta_a = \frac{d_a}{\omega_n}, \quad \delta_n = \frac{d_n \omega_a C_0}{d_a \omega_n}.$$

## 3. Discretisation of the model

For the spatial discretisation of the model problem (6), DRBEM is used following the book of Partridge, Brebbia, and Wrobel (1992). Before the spatial discretisation of Equations (6b) and (6c), the ODE (6a) for normal cell density is solved at the space discretisation points using an explicit–implicit scheme. This scheme is a combination of the forward and the backward Euler methods and the method handles the degradation term $\delta_n a n$ implicitly for $n$ (the values for $a$ are still evaluated at the same time level) while it calculates the proliferation term $\left(n\left(1 - n - \eta_1 \frac{c}{K_c(a)}\right)\right)$ explicitly in time:

$$n_{ij}^{m+1} = \frac{1}{1 + \Delta t \delta_n a_{ij}^m}\left(n_{ij}^m + \Delta t n_{ij}^m\left(1 - n_{ij}^m - \eta_1 \frac{c_{ij}^m}{K_c(a_{ij}^m)}\right)\right) \tag{7}$$

where $m$ is the time level, $\Delta t$ is the length of the time interval, $i, j = 1, 2, \ldots N+L$ with $N$ and $L$ denoting the number of boundary and interior nodes, respectively.

For the discretisation of the space derivatives in (6b) and (6c) with DRBEM, the equations are weighted by the fundamental solution $u^* = \frac{1}{2\pi} \ln \frac{1}{r}$ of Laplace equation:

$$\int_\Omega \nabla^2 c u^* \mathrm{d}\Omega = \int_\Omega b_1 u^* \mathrm{d}\Omega \tag{8}$$

$$\int_\Omega \nabla^2 a u^* \mathrm{d}\Omega = \int_\Omega b_2 u^* \mathrm{d}\Omega \tag{9}$$

where the nonhomogenities $b_1$ and $b_2$ can be approximated using radial basis functions $f_j(x, y)$ as

$$\begin{aligned} b_1\left(c, n, \frac{\partial c}{\partial t}, \frac{\partial c}{\partial x}, \frac{\partial c}{\partial y}, \frac{\partial n}{\partial x}, \frac{\partial n}{\partial y}\right) &= \frac{1}{D_c(1-n)}\left[\frac{\partial c}{\partial t} - \rho_c c\left(1 - \frac{c}{K_c(a)} - \eta_2 n\right)\right. \\ &\quad \left. + D_c\left(\frac{\partial n}{\partial x}\frac{\partial c}{\partial x} + \frac{\partial n}{\partial y}\frac{\partial c}{\partial y}\right)\right] \\ &\approx \sum_{j=1}^{N+L} \alpha_j(t) f_j(x, y) \end{aligned} \tag{10}$$

$$b_2\left(a, c, \frac{\partial a}{\partial t}\right) = \frac{\partial a}{\partial t} - \delta_a c + \delta_a a \approx \sum_{j=1}^{N+L} \beta_j(t) f_j(x, y) \tag{11}$$

resulting with a linear system of equations

$$\left[F\right]\{\alpha\} = \{b_1\} \tag{12}$$

$$\left[F\right]\{\beta\} = \{b_2\} \tag{13}$$

with $N$ and $L$ being the number of boundary and selected interior nodes, $F$ is the $(N + L) \times (N + L)$ matrix of distance functions $f_j$ related to other distance functions $\hat{u}_j(x, y)$ through $\nabla^2 \hat{u}_j = f_j$ .

Application of Green's second identity to both sides of Equations (8) and (9) yields to

$$\left[H\right]\{c\} - \left[G\right]\left\{\frac{\partial c}{\partial \nu}\right\} = \left(\left[H\right]\left[\hat{U}\right] - \left[G\right]\left[\hat{Q}\right]\right)\{\alpha\} \tag{14}$$

$$\left[H\right]\{a\} - \left[G\right]\left\{\frac{\partial a}{\partial \nu}\right\} = \left(\left[H\right]\left[\hat{U}\right] - \left[G\right]\left[\hat{Q}\right]\right)\{\beta\} \tag{15}$$

with the $(N + L) \times (N + L)$ matrices $[G]$ and $[H]$ containing the integrals of the fundamental solution and its normal derivative, respectively, over the boundary. Because of the non-flux boundary conditions, the second terms on the left-hand

side of Equations (14) and (15) vanish and back substitution of $\{\alpha\}$ and $\{\beta\}$ gives

$$D_c[H]\{c(1-n)\} = [C]\left(\left\{\frac{\partial c}{\partial t}\right\} - \rho_c\left\{c\left(1-\frac{c}{K_c(a)}-\eta_2 n\right)\right\} + D_c\left(\left[\frac{\partial F}{\partial x}\right][F]^{-1}\left\{\frac{\partial n}{\partial x}c\right\} + \left[\frac{\partial F}{\partial y}\right][F]^{-1}\left\{\frac{\partial n}{\partial y}c\right\}\right)\right)\right) \tag{16}$$

$$[H]\{a\} = [C]\left(\left\{\frac{\partial a}{\partial t}\right\} - \{\delta_a c\} + \{\delta_a a\}\right) \tag{17}$$

where

$$[C] = \left([H][\hat{U}] - [G][\hat{Q}]\right)[F]^{-1}. \tag{18}$$

Rearranging Equation (16) and applying the same explicit–implicit scheme as in the time discretisation in Equation (7) with the updated $n$ values at the time level $m+1$, the time-discretised equation for the density of cancer cells is obtained as

$$\frac{\left\{c^{m+1}\right\} - \{c^m\}}{\Delta t} = \rho_c\left\{c^m\left(1-\frac{c^m}{K_c(a^m)}-\eta_2 n^{m+1}\right)\right\} + \left([C]^{-1}\{h\} - \left[\frac{\partial F}{\partial x}\right][F]^{-1}\{d_1\} - \left[\frac{\partial F}{\partial y}\right][F]^{-1}\{d_2\}\right)\left\{c^{m+1}\right\}. \tag{19}$$

After using Backward Euler method for the time discretisation of Equation (17) with the updated values of $c$ at the time level $m+1$ from Equation (19) , the final discretised equation for the concentration of $H^+$ protons is:

$$\frac{\left\{a^{m+1}\right\} - \{a^m\}}{\Delta t} = [C]^{-1}[H]\left\{a^{m+1}\right\} - \delta_a\left\{a^{m+1}\right\} + \delta_a\left\{c^{m+1}\right\} \tag{20}$$

with $\{d_1\} = D_c\left\{\frac{\partial n}{\partial x}\right\} = D_c\left\{\frac{n_{i+1,j}^{m+1} - n_{ij}^{m+1}}{\Delta x}\right\}$,

$\{d_2\} = D_c\left\{\frac{\partial n}{\partial y}\right\} = D_c\left\{\frac{n_{i,j+1}^{m+1} - n_{ij}^{m+1}}{\Delta y}\right\}, i,j = 1,2,\ldots N+L$ and

$\{h\} = D_c[H]\{1-n\}$.

Hence in order to solve the model for the time level $m+1$ with the numerical method described here, one should first solve Equation (7) starting with the initial condition and then should use these updated values for the normal cell density together with the initial condition for solving the equation for cancer cells, then should use the updated values for cancer cells in order to obtain the $H^+$ proton concentration at the discretisation points.

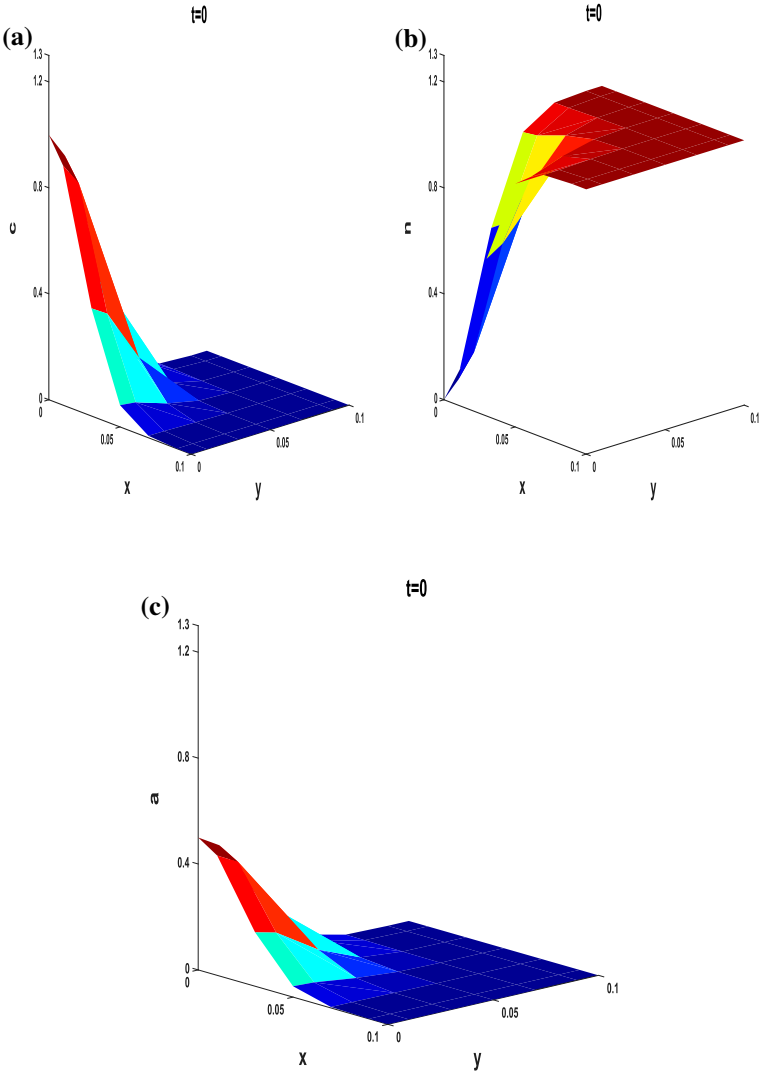


**Figure 1.** Initial conditions.

## 4. Numerical results

The numerical simulations are performed in the square $[0, 0.1] \times [0, 0.1]$ with $N = 20$ boundary nodes and $L = 25$ interior nodes. The time step is taken to be $\Delta t = 0.1$ . The boundary conditions for $c$ and $a$ are given by (3). The initial profiles are given by Figure 1. For the initial conditions, cancer cells are assumed to penetrate a short distance while the space is occupied mainly by the normal cells and the $H^+$ proton concentration is proportional to the cancer cell density.

In the simulations, the following parameter values are fixed (Gatenby & Gawlinski, 1996):

$$\delta_a = 110,\ D_c 4 \times 10^{-5},\ \rho_c = 1.$$

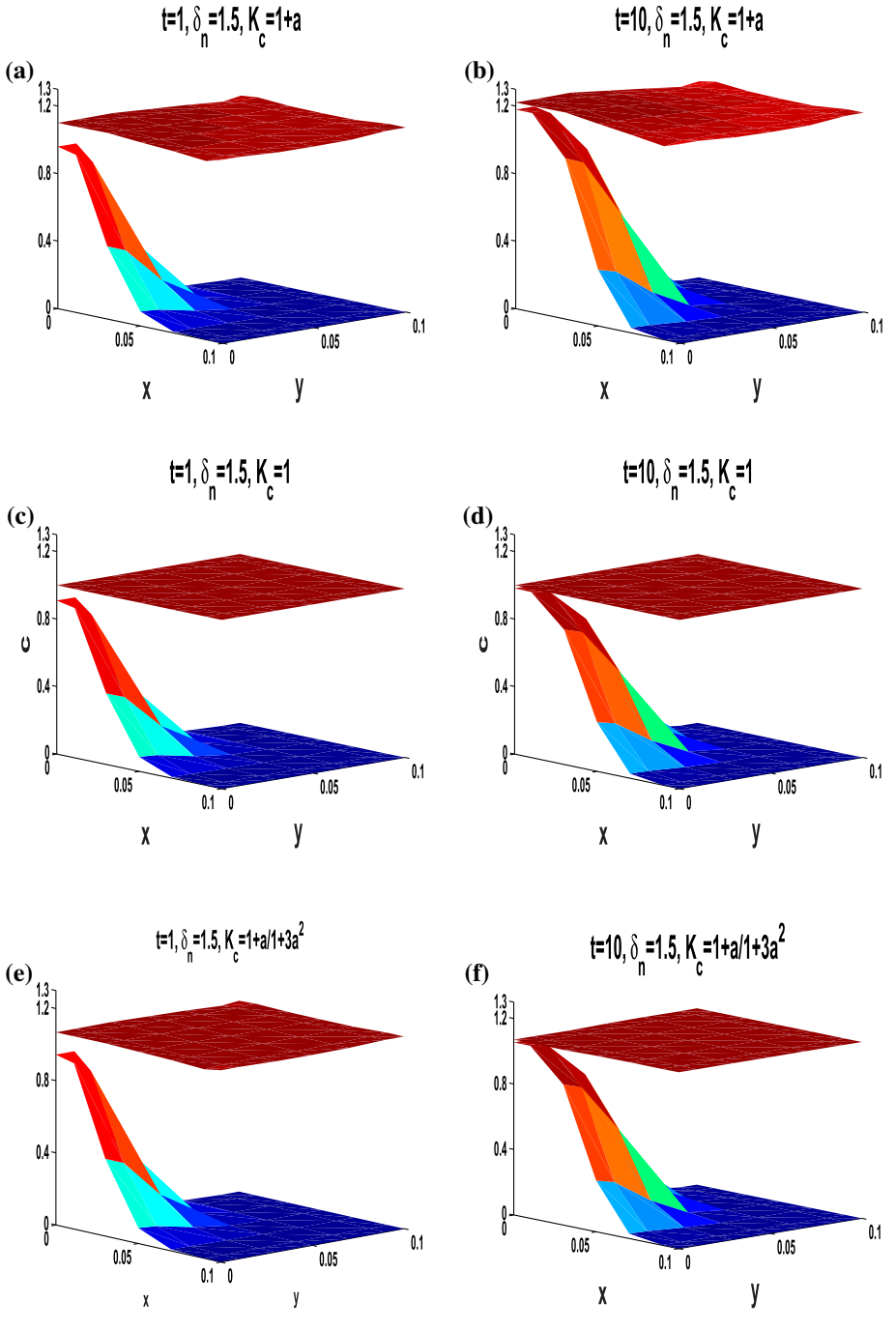


**Figure 2.** Evolution of the cancer cell density with different carrying capacities.

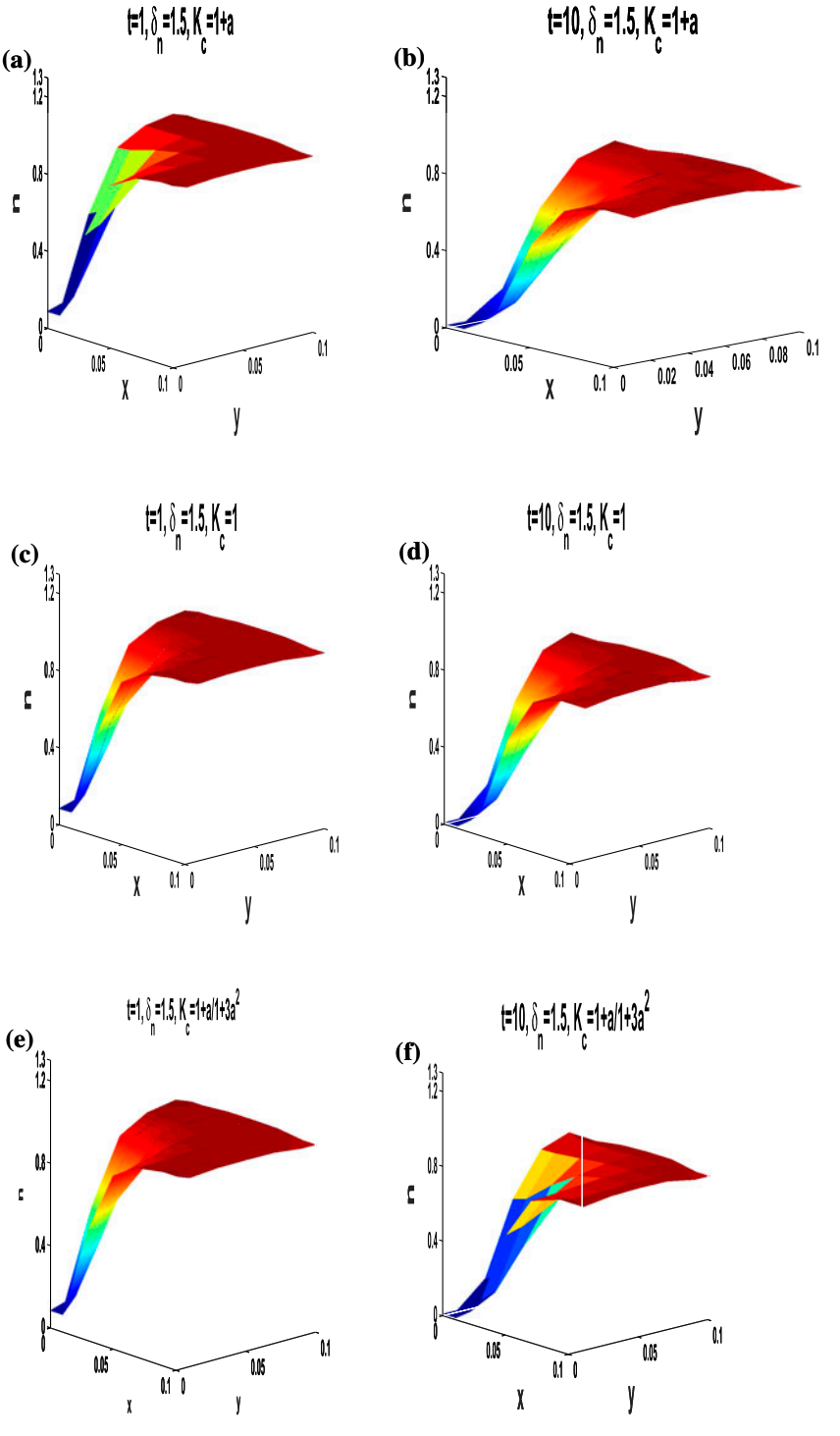


**Figure 3.** Evolution of the normal cell density with different carrying capacities.

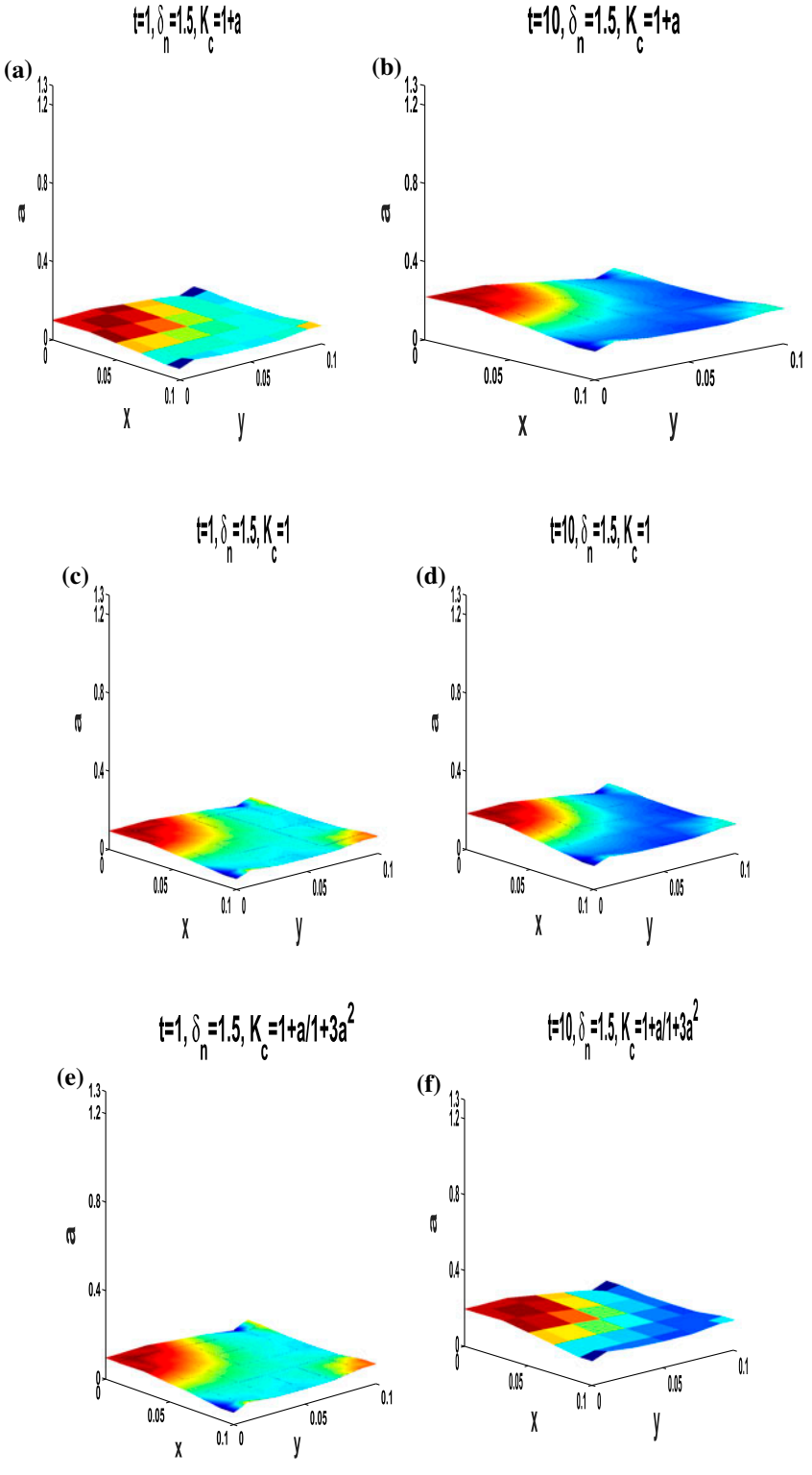


**Figure 4.** Evolution of the acid concentration with different carrying capacities.

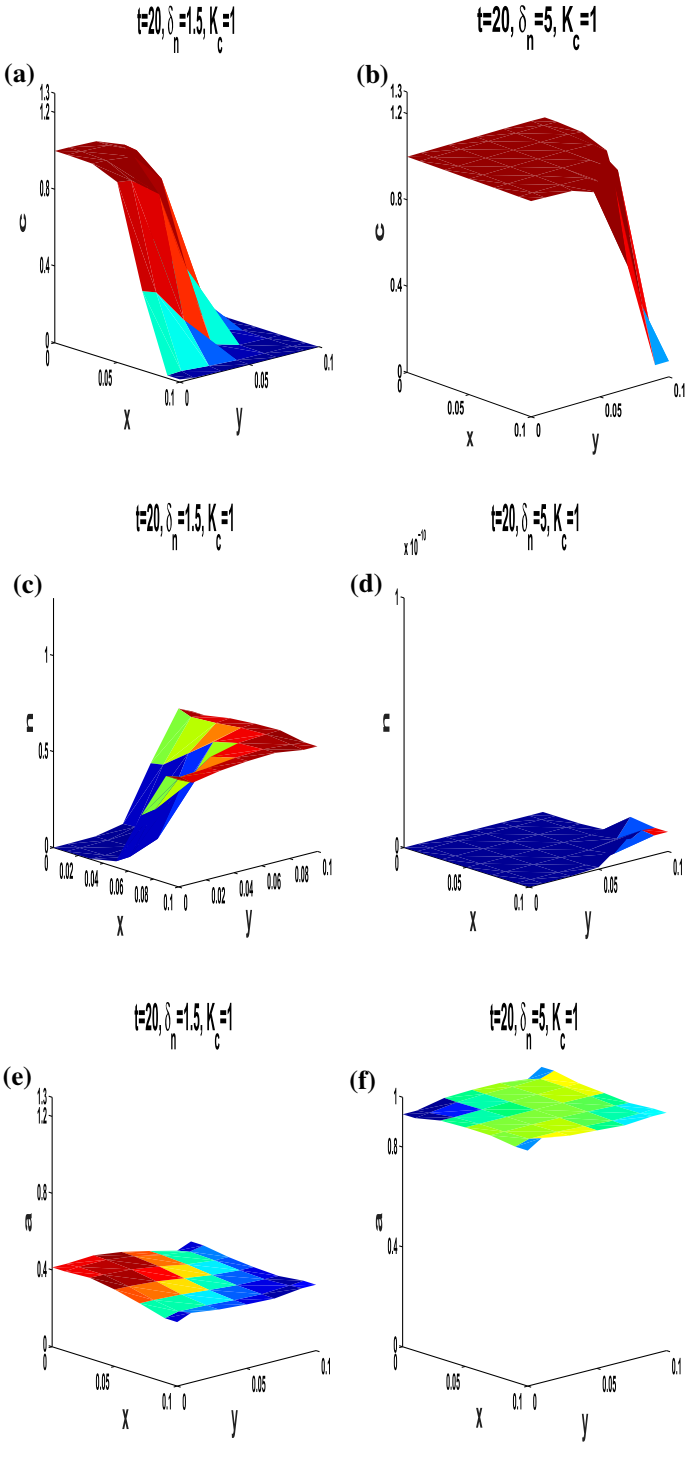


**Figure 5.** Effect of aggresivity parameter on the invasivity of the cancer cells.

Throughout the simulations, different carrying capacities and their effects on the invasion are compared. Moreover, the effect of the parameter $\delta_n$ (in Equation (6a) is analysed in the second part. The parameter $\delta_n$ is called the aggressivity parameter and the linear stability analysis in Gatenby and Gawlinski (1996) shows that it has a direct effect on the invasiveness of the cancer cells.

### 4.1. Simulations with different carrying capacities for cancer cells

In this part, three different carrying capacity functions (in the nondimensionalised form) are considered:

$$K_c(a) = \frac{1+a}{1+3a^2}, \quad K_c(a) = 1 + a, \quad K_c(a) = 1 \tag{21}$$

In the figure sets (2–4), we see the change in the densities of cancer and normal cells and the change in the concentration of $H^+$ protons with a fixed aggressivity parameter $\delta_n = 1.5$ for two different times, $t = 1$ and $t = 10$. For each case in Figure 2, the cancer cells have the same invasive behaviour and their density is tending the corresponding carrying capacity ,while one can easily observe the decays in the normal cell density in Figure 3. Figure 4 shows also that the concentration of the $H^+$ protons is proportional to the cancer cell density.

The first choice $K_c(a) = \frac{1+a}{1+3a^2}$ considers the effect of higher acidic levels on the tumour cells. It is known that cancer cells are far more resistant to the higher acidic levels; however, there is a certain threshold that also the cancer cells are affected. The second choice in Equation (21) considers the positive effect of acidity of the extracellular environment. Thus, the expectation with this choice of carrying capacity is that as the concentration of the protons gets higher, the normal cells die and cancer cells show enhanced growth comparing to the other cases (Figure 2).

The last choice in Equation (21) is nothing but the constant choice which does not consider effect of increased acidity of the environment on carrying capacity of the cancer cells.

### 4.2. Effect of the parameter $\delta_n$ on the invasiveness of the tumour

In this part, the effect of the aggressivity parameter $\delta_n$ is considered. In Figure 5, the behaviour of the cancer and normal cells and the concentration of $H^+$ protons are analysed for a later time $t = 20$ with $\delta_n = 1.5$ and 5.0. The figures show that a more aggressive tumour is more invasive and they occupy almost all the space at $t = 20$ and the concentration of the protons is proportional to the density of cancer cells as expected.

## 5. Conclusion

In this study, a numerical method is proposed for an acid-mediated tumour cell invasion model which includes the effect of the acidity of environment

on the carrying capacity of cancer cells. The model consists of a system of nonlinear reaction–diffusion equations for the density of cancer and normal cells and for the concentration of $H^+$ protons. For the discretisation of the system, DRBEM and FDM are used in space and in time, respectively. DRBEM has the advantage of discretising only the boundary and therefore uses small number of discretisation points comparing to other discretisation methods. The comparison of the different carrying capacities and the effect of the aggressivity parameter are tested by the proposed method. The results are consistent with the expected behaviour of the model that if one considers the positive effect of the acidity on the cancer cells, the enhanced growth is observed and when the aggressivity parameter is larger, then the tumour is more aggressive.

## Disclosure statement

No potential conflict of interest was reported by the author.

## ORCID

*Gülnihal Meral* http://orcid.org/0000-0003-0072-0609

## References

Gatenby, R. A., & Gawlinski, E. T. (1996). A reaction-diffusion model of cancer invasion. *Cancer Research, 56*, 5745–5753.

Gatenby, R. A., Gawlinski, E. T., Gmitro, A. F., Kaylor, B., & Gillies, R. J. (2006). Acid-mediated tumor invasion: A multidisciplinary study. *Cancer Research, 66*, 5216–5223.

Gatenby, R. A., & Gillies, R. J. (2007). Glycolysis in cancer: A potential target in therapy. *The International Journal of Biochemistry and Cell Biology, 39*, 1358–1366.

Martin, N. K., Goffney, E. A., Gatenby, R. A., & Maini, P. K. (2010). Tumour-stromal interactions in acid-mediated invasion: A mathematical model. *Journal of Theoretical Biology, 267*, 461–470.

Märkl, C., Meral, G., & Surulescu, C. (2013). Mathematical analysis and numerical simulations for a system modeling acid-mediated tumor cell invasion. *International Journal of Analysis, 2013*, 1–15.

Meral, G., Stinner, C., & Surulescu, C. (2015). A multiscale model for acid-mediated tumor invasion: Therapy approaches. *Journal of Coupled Systems and Multiscale Dynamics, 3*, 135–142.

Partridge, P. W., Brebbia, C. A., & Wrobel, L. C. (1992). *The dual reciprocity boundary element method*. Southampton, Boston: Computational Mechanics Publications.

Stinner, C., Surulescu, C., & Meral, G. (2015). A multiscale model for pH-tactic invasion with time varying carrying capacities. *IMA Journal of Applied Mathematics, 80*, 1300–1321.