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Finite Difference Schemes to Nonlinear Parabolic System of Cancer Invasion and Interaction of Cancer Cell with Surrounding Tissues

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ABSTRACT

The development of a primary solid tumour (e.g., a carcinoma) begins witha single normal cell becoming transformed as a result of mutations in certain key genes. The invasiveness of tumors, however, requires a change in the concept to include cellular motility in addition to proliferative growth. In this article we review some of the recent developments in mathematicalmodeling of tumors. We consider a nonlinear parabolic system of equations that describes interactions between tumor cells and micro environmental factors such as extracellular matrix and matrix degradative enzymes. Given the application, conservation of nonnegativity and conservation or evolution laws of totalvcell 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.

Key words: Finite Difference Scheme, Extra Cellular Matrix, Matrix DegradativeEnzymes

1. INTRODUCTION

Cancer is a complex, dynamic disease with underlying processes occurring over the full range of biological scales from genetic, through proteomic, cellular, tissue, organ, to organism and sometimes even the whole population level. The first detectable (palpable) symptoms are almost always macroscopic, but differences are also present a priori at the cellular level, and these in turn originate from changes in the individual's DNA. Perhaps one of the most difficult questions of modern medicine is how to intervene and manipulate the complex system of the patient's body to affect changes in dynamics, which can bring it back from a state of disease to either full remission or stabilization. Given the complexity of the system,

one way to answer that question should be sought by complementing the traditional clinical methods with mathematical and computational modelling and simulations. However, while developing "good" predictive models one should remember a few important points. The most crucial seems to be the consideration of one of the key features of the disease, if not the key feature, i.e. its multiscale character.

The tumour cells first secrete angiogenic factors which in turn induce endothelial cells in a neighbouring blood vessel to degrade their basal lamina and begin to migrate towards the tumour. Endothelial cell migration through the extracellular matrix is driven by a chemotactic response to the angiogenic factors and a haptotactic response to components in the matrix such as fibronectin and collagen. The complete process of metastasis involves several sequential steps, each of which must be successfully completed by cells of the primary tumour before a secondary tumour (a metastasis) is formed. Referring also to Chapters 8 and 9 (Anderson, A.R.A. and Chaplain, M.A.J.,) a summary of the key stages of the metastatic stage is as follows:[2]

A crucial part of the angiogenic response of the endothelial cells and the invasive/ metastatic process is the ability of the cancer cells to degrade the surrounding tissue or extracellular matrix (ECM) [31,32,41,52]. (see Figure 10.1).

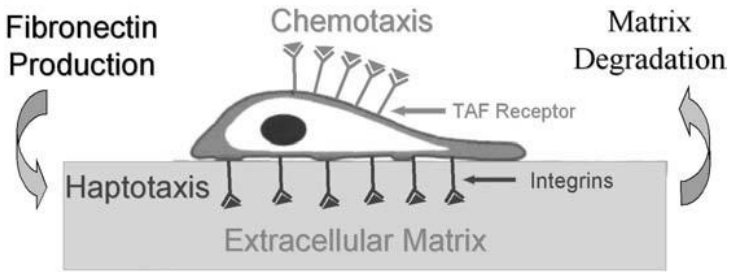

Figure 10.1 Schematic diagram of the tissue response unit.

The extracellular matrix (tissue) itself is a complex mixture of proteins and proteoglycans within and on which the normal cells of solid organs are situated. The matrix is highly dynamic, at any one time being actively secreted and degraded. It has become increasingly clear that the matrix has more than a passive structural role; it can sequester growth factors and indeed be degraded to release fragments which themselves have growth-promoting activity. Thus, while ECMmay have to be physically removed in order to allow a tumour to spread or intra- or extra-vasate, its degradation may in addition have biological effects on the tumour cells themselves. A number of matrix degradative enzymes (MDEs) such as the plasminogen activator (PA) system and the large family of matrix metalloproteases (MMPs) have been described [34,36,55]. Both PAs and the MMPs have been repeatedly implicated in all of the above steps of tumour invasion and metastasis [1,7,9,12,25,26,29,40,47, 53,58]. Regulation of matrix-degradative activity is highly complex. In both these enzyme systems (PAs/MMPs) there exist several endogenous

inhibitors [8,28,54], and the enzymes are often secreted as inactive precursors which must themselves be partially degraded to reach full activity. More than one cell type may be involved in the activation of any one enzyme [28].

2. MATHEMATICAL MODEL

We will base our mathematical model on generic solid tumour growth, which for simplicity we will assume is at the avascular stage. While most tumours are asymptomatic at this state, it is still possible for cells to escape and migrate to the lymph nodes and for the more aggressive tumours to invade. In principle, our model can be extended to include such interactions and the general form of our model will be the same for both invading vascular and avascular tumours. In the initial model we consider the following key variables: tumour cell density (denoted by$n$), MDE concentration (denoted by m), ECM density (denoted by f), and endogeneous inhibitor (e.g., tissue inhibiting metalloproteases, TIMPs) concentration (denoted by m). Each of the variables (n, f and m)is a function of the spatial variable x and time t.

MDEs are important at many stages of tumour growth, invasion, and metastasis, and the manner in which they interact with endogenous inhibitors, growth factors, and tumour cells is very complex. In our model we assume that the tumour cells produce MDEs which degrade the ECM locally and that the ECM responds by producing endogenous inhibitors (e.g., TIMPs). The ECM degradation, as well as making space into which tumour cells may move by simple diffusion, results in the production of molecules which are actively attractive to tumour cells (e.g., fibronectin) and which then aid in tumour cell motility. We refer to the movement of tumour cells up a gradient of such molecules as haptotaxis. To describe the random motility of the tumour cells we assume a flux of the form

$$J_{random} = -D(f, m)\nabla n$$

Where $D(f, m)$ may be a constant or a function of either the MDE or ECM concentration, the latter cases representing a chemokinetic response i.e., increased random motility will be observed for regions of high MDE/ECM concentration. We take the haptotactic flux to be

$$J_{hapto} = \gamma\, n\, \nabla f$$

The conservation equation for the tumour cell density n is therefore given by

$$\frac{\partial n}{\partial t} + \nabla \cdot (J_{random} + J_{hapto}) = 0$$

Hence these work devoted to mathematical and numerical analysis of the following model of cancer invasion.

$$\frac{\partial n}{\partial t} = D_n \frac{d^2 n}{dx^2} - \gamma \frac{\partial}{\partial x}\left(n \frac{\delta f}{\delta x}\right)$$

$$\frac{\partial f}{\partial t} = -\eta m f \qquad (1)$$

$$\frac{\partial m}{\partial t} = D_m \frac{d^2 m}{dx^2} + \alpha n - \beta m$$

The unknown functions $n = n(x,t), f = f(x,t), m = m(x,t)$ depend on the space variable x belonging to the scaled domain $\Omega = [0,1]$ of tissue, and time t.

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 [11] and applied to experimental data for prostate cancer growth in [12].

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

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

$$m(1,t) = 0 \quad n(1,t) = 0 \qquad (3)$$

or the zero-flux boundary condition

$$\frac{dn}{dt}(1,t) = \frac{\gamma}{d_n} n(1,t) \frac{\delta f}{\delta x}(1,t), \qquad \frac{\partial m}{\partial x}(1,t) = 0 \qquad (4)$$

and initial conditions

$$n(x,0) = n_0(x), \qquad f(x,0) = f_0(x), \qquad m(x,0) = m_0(x), \qquad (5)$$

We assume that $n_0(x), f_0(x), m_0(x) \geq 0$

It is known (cf: [9,10]) 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 [9, 10], one obtains,

$n(x,t), f(x,t), m(x,t) \geq 0, (x,t) \in Q_T \equiv [0,1] \times [0,T)$

3. FINITE-DIFFERENCE SCHEMES

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

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

$$x_i = (i - 0.5\,h), \hat{x}_i = (i-1)\,h), \quad i = 1,2,\ldots,I+1, \quad Ih = 1$$

Grid points over [0,T] are defined by

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

Where the time increment $\tau_j > 00$ will be determined later.We consider approximation of $n(x,t)$ and $m(x,t)$on $x_i, t_i$and $(\hat{x}_i, \hat{t}_j)$respectively. Thus, we would like to find $n^j \approx n(x_i, t_j)$and $m_i^j \approx n(\hat{x}_i, \hat{x}_j)$

Let introduce the vectors

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

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

Scheme for solving m^j

We introduce

$$\hat{n}_i^j = \begin{cases} n_1^j, & i = 1 \\ \frac{1}{2}(n_{i+1}^j + n_i^j) & i = 1, \ldots., I \\ n_{I+1}^j & i = I+1 \end{cases}$$

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

$$\frac{m_i^{j+1} - m_i^j}{\tau_j} = \sigma d_m \frac{m_{i-1}^{j+1} - 2m_i^{j+1} + m_{i+1}^{j+1}}{h^2} + (1-\sigma) d_m \frac{m_{i+1}^j - 2m_i^j + m_{i-1}^j}{h^2} + \alpha \hat{n}_i^j - \beta m_i^j, \qquad (9)$$

wherem_0^j and $m_{N+2}^j$are eliminated by the boundary conditions

$$m_0^j = m_2^j, \quad m_{N+2}^j = m_N^j, \qquad j = 1, \ldots.. J+1 \qquad (10)$$

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

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

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

$$\mathbf{A} = \begin{bmatrix} 2 & -2 & 0 & \cdots & \cdots & 0 \\ -1 & 2 & -1 & & & \\ & & \cdots & \cdots & & \\ & -1 & 2 & -1 & & \\ & & & & \cdots & \cdots \\ & & & & -2 & 2 \end{bmatrix}$$

$$\mathbf{g}^j = \alpha \hat{m}^j - \beta n^j,$$

Scheme for solving n^j

The key point is to introduce a reasonableapproximation of the flux$W$ by applying upwind technique. We set

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

$$b_i^j = \frac{\hat{F}(m_i^j) - \hat{F}(m_{i-1}^j)}{h}(2 \le i \le I+1),\quad b^j = (b_1^j, \ldots\ldots, b_{I+1}^j)^T$$

Further, we set

$$b_i^{j,+} = \max[0, b_i^j] \quad and \quad b_i^{j,-} = \max[0, -b_i^j]$$

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 $\hat{x}_i$of flowsand$-b_{i+1}^{j-1}$, respectively.

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

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

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

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

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

$$W_1^j = 0, \quad W_{I+1}^j = 0, \quad \widehat{W}_i^j = 0, \quad \widehat{W}_{I+1}^j = 0$$

Then our proposed scheme is as follows:

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

with boundary condition (13).

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

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

Where

$$\mathbf{H} = \begin{bmatrix} 1 & -1 & 0 & \cdots & \cdots & 0 \\ -1 & 2 & -1 & \cdots & \cdots & \cdots \\ \vdots & \ddots & \ddots & \ddots & \cdots & \cdots \\ \vdots & -1 & 2 & -1 & \cdots & \cdots \\ \vdots & \cdots & \ddots & \ddots & \cdots & \cdots \\ 0 & \cdots & \cdots & \cdots & -1 & 1 \end{bmatrix}$$

$$\mathbf{B^j} = \begin{bmatrix} b^j_{1,+} & -b^j_{2,-} & 0 & \cdots & \cdots & 0 \\ -b^j_{1,+} & b^j_{2,+} + b^j_{2,-} & -b^j_{3,+} & & & \\ & & \cdots & \cdots & & \\ & -b^j_{i-1,+} & b^j_{i,+} + b^j_{i,-} & b^j_{i+1,+} & & \\ & & & \cdots & \cdots & \\ & & & -b^j_{I,+} & b^j_{I+1,-} & \end{bmatrix}$$

4. NUMERICAL SIMULATIONS

This system is considered to hold on some spatial domain (a region of tissue) with appropriate initial conditions for each variable. We assume that the tumor cells, and consequently the MDEs, and the inhibitors all remain within the domain of tissue under consideration and therefore no-flux boundary conditions are imposed on $\delta\Omega$, the boundary of Ω.

In order to solve the system numerically, we first nondimensionalise the equations in the standard way. We rescale distance with an appropriate length scale L (e.g., maximum invasion distance of a cancer cell), time with $\tau = L^2/D$ (where D is a reference chemical diffusion coefficient $\sim 10^{-6} cm^2 s^{-1}$), tumour cell density with n_0, ECMdensity withf_0, andMDE concentration$m$ with (where n_0, f_0, and m_0 are appropriate reference variables). Therefore setting

$$\tilde{n} = \frac{n}{n_0}, \tilde{f} = \frac{f}{f_0}, \tilde{m} = \frac{m}{m_0}, \tilde{\mathrm{x}} = \frac{\mathrm{x}}{L}, \tilde{t} = \frac{t}{\tau}, d_n = \frac{D_n}{D}, d_m = \frac{D_m}{D} \qquad (19)$$

in Equation (1) and dropping the tildes for notational convenience, we obtain the scaled system of equations:

$$\begin{aligned} \frac{\partial n}{\partial t} &= d_n \nabla^2 n - \gamma\, \nabla(n\, \nabla f) \\ \frac{\partial f}{\partial t} &= -\eta m f \qquad (20) \\ \frac{\partial m}{\partial t} &= d_m \nabla^2 m + \alpha n - \beta m \end{aligned}$$

The considered model has to be closed by appropriate initial conditions (8). In one space dimension, the scaled domain is the unit interval$[0,1]$, while in two space dimensions, the scaled domain is the unit square$[0,1] \times [0,1]$. 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. 2 and are defined as follows, where ε is a positive constant.

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

$$f(x,0) = 1 - 0.5\,n(x,0), \qquad m(x,0) = 0.5\,n(x,0), \quad \forall x \in [0,1]$$

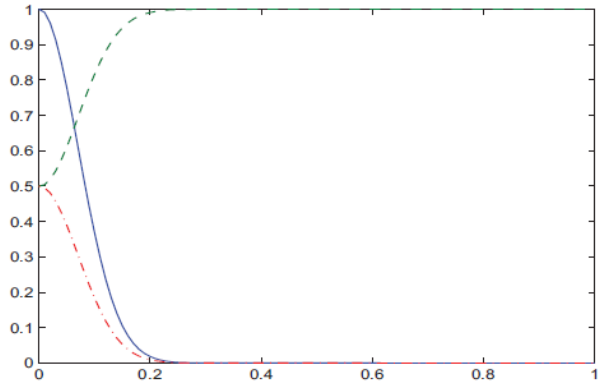

FIGURE 1. The initial distribution of cancer cell density (solid), ECM density (dashed), and MDE concentration (dashdot).

5. RESULT

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 fortumor 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 $-\gamma\Delta(n\Delta f)$of the model (1). For low values of parameter *dn*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.Cancer cell migration and interactions between the cancer and the surrounding tissue: cancer cell density (solid), ECM density (dashed), and MDE concentration (dashdot).

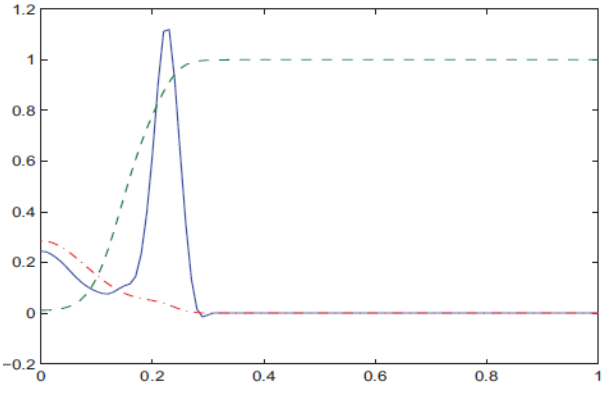

FIGURE 2. Solutions to (1), (2), (4), (5) with the parameter value d_n = 0.001 at time t = 1.

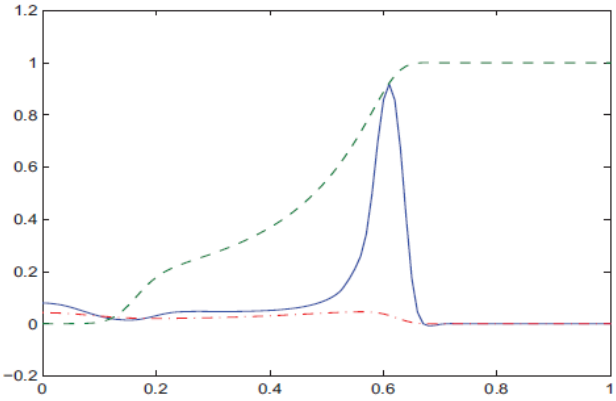

FIGURE 3. Solutions to (1), (2), (4), (5) with the parameter value $d_n = 0.001$ at time $t = 5$

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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 thetumor 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 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 non-negativity 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}.

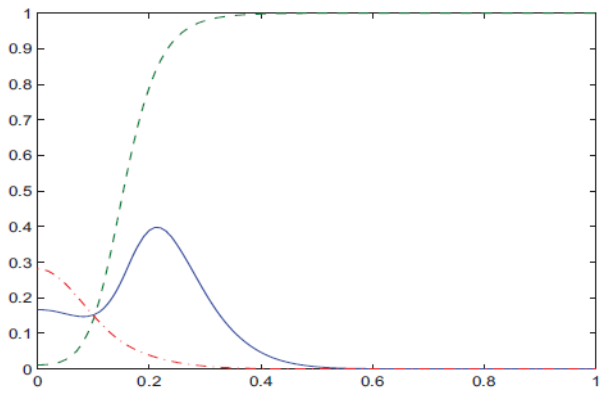

FIGURE 4. Solutions to (1), (2), (4), (5) with the parameter values $d_n = 0.01$ at time $t = 1$.

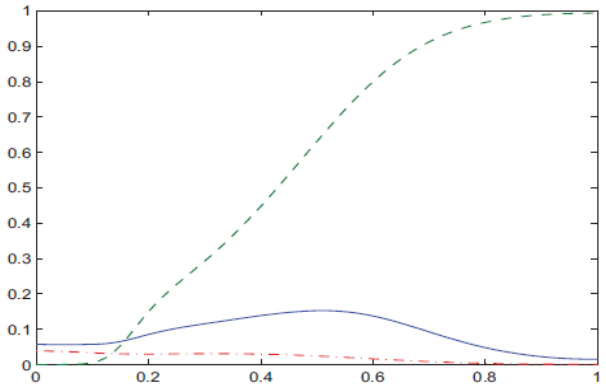

FIGURE 5. Solutions to (1), (2), (4), (5) with the parameter values $d_n = 0.01$ at time $t = 5$.

6. CONCLUSIONS

We have proposed finite difference schemes, which preserve the non-negativity as well as the conservation properties of the solution to a model of tumor invasion. This work presents a mathematical model for tumour invasion using a novel blend of continuum, deterministic modelling in one space dimensions. The continuum model consists of a system of nonlinear partial differential equations and examines how tumour cells respond to ECM gradients via haptotaxis, created both by the tumour cells through MDE degradation of the matrix and those already in existence within the matrix. The results from the one dimensional continuum model simulations demonstrate the impact of interactions between tumour cells and the ECM on possible metastasis. In particular if tumour cells move via random migration and haptotaxis and the intensity of the random movements is dependent upon MDE concentration then a small cluster of cells can easily break away from the main body of the tumour

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