Mathematical modelling of cancer cell invasion of tissue

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Abstract

Cancer cell invasion of tissue is a complex biological process during which cell migration through the extracellular matrix, facilitated by the secretion of degradative enzymes, is a central process. Cells can deform their cytoplasm to produce pseudopodia, anchor these pseudopodia to neighbouring spatial locations in the tissue and detach earlier bonds, to enable them to move and therefore migrate in a specified direction. Genetic mutations, chemoattractant gradients or a lack of nutrients in their current location can stimulate cell motility and cause them to migrate. When cancer cells migrate they degrade the surrounding extracellular matrix, thereby invading new territory. In this paper we propose a hybrid discrete-continuum two-scale model to study the early growth of solid tumours and their ability to degrade and migrate into the surrounding extracellular matrix. The cancer cells are modelled as discrete individual entities which interact with each other via a potential function, while the spatio-temporal dynamics of the other variables in the model (extracellular matrix, matrix degrading enzymes and degraded stroma) are governed by partial differential equations.

Keywords: Cancer invasion; matrix degradation; hybrid model; discrete-continuum

1 Introduction

The formation of a tumour begins with failure in the replication of a cell's DNA which leads to the uncontrolled division of the cell. This initial failure in DNA replication occurs at a molecular level in the cell nucleus. The result of such cellular instability are new daughter cells which interact with the environment in a two-scale, physical-chemical framework. At the cellular level, dynamics have in general a much longer space-scale and a slower time-scale than events at the molecular level. For example, a reaction such as the enzymatic degradation of a substrate can occur in milliseconds whereas the replication of a cell can take about one day. This difference in space- and time-scales is evident at the edge of a cancerous cell mass as it tries to penetrate the extracellular matrix (ECM) and thereby invade surrounding territory or spread to other locations. At a molecular level cells need to produce those reactions that facilitate their migration through the ECM, a process which often involves the degradation of this matrix [1] [2]. The pathways involved in tumour-growth can be classified as: intracellular, such as the formation of actin filaments to produce pseudopodia; extracellular, for example the reorganization of the collagen filaments of the ECM; and certain others that connect intracellular dynamics with the extracellular stroma, for instance the uptake of growth factors released from the remodelled ECM, which promote cell mitosis [3]. From a cellular perspective, physical interactions with the ECM are crucial in determining the nature of the tumour's invasion-front [4].

Invasion of surrounding tissue normally occurs after the tumour has reached a certain size and the peripheral rim of cells has started to disaggregate. At this point the cells on the tumour surface initiate different invasion mechanisms including the fingering process, Indian lines, cluster detachment, etc. All these processes are characterized by a loss of compactness at the tumour surface and are the hallmarks of metastasis. This loss of compactness differentiates malignant and benign tumours and seems to be a biological process similar to the epithelial-mesenchymal transition in embryogenesis [5] [6] where a well organized and bipolar layer of cells becomes more diffuse and semidetached. In this transition, cell adhesion plays an important role in maintaining the compactness of the tissue [7]. For a tumour to become especially harmful and to invade distant organs in the body, a loss of compactness is crucial. This dictates that cell-cell bonds must be able to detach. In many tumours mutations related to the cells' adhesive system have been

found [8] [9]. These abnormalities are often related to other intracellular biological pathways that may promote further abilities related to invasion, e.g. cell-cycle progression and increased cellular motility. For instance, the beta catenin pathway is thought to be related to tumour invasion: Up-regulation of beta-catenin in the cytoplasm is linked to a poor prognosis for cancer patients [10] [8]. This increased invasive ability can be associated with cell-cycle progression or increased cellular motility but, in addition, the beta catenin pathway is closely related to the intracellular domain of the E-cadherin adhesive system [11]. Even if increased cell motility and proliferation contribute greatly to the invasive ability of the tumour, in order for metastasis to occur the detachment of intercellular bonds is necessary.

Cancer cells employ different methods of invasion both individually and in combination to allow tumours to grow. Before a tumour becomes invasive, the rough-nature of its surface is caused by variations in how groups of peripheral cells degrade the ECM they are in contact with. This degradation is achieved by the tumour cells secreting matrix-degrading enzymes, mainly of the type Matrix Metalloproteinases (MMPs) and Urokinase Plasminogen Actovators (uPAs). Cancer-induced degradation leads to the reorganization of the protein network that forms the ECM and, in many cases, to the production of chemicals that promote cell migration and proliferation. For instance, certain ECM protein-complexes like vitronectin, fibronectin, laminin, type-I collagen, type-IV collagen, and thrombospondin stimulate tumour cells into migration. Both haptotaxis and chemotaxis are induced by different types of degradation of these proteins [12] [13].

Modelling aspects of cancer growth has been approached using a wide range of mathematical models [14] [15] [16] [17] [18]. Specific models of cancer cell invasion have been both discrete, where cells are consider as individual identities [4] [19], continuum using reaction diffusion equations [20] [21] [22] [23] [24], or hybrid models [25] [26] [27], and have been used to explain the diverse aspects of tumour growth dynamics. A good survey of mathematical models of cancer growth and development can be found in the excellent book [28], and an excellent survey of the range of mathematical and computational modelling techniques used for biological problems on different scales can be found in the book [29]. Even if some cellular automata approaches have shown the irregularities of the cells' invading front ([26] [30]), in general the invasion process has not been deeply studied. Continuum models using PDEs are usually too "large" scale and are inappropriate when the problem focusses on a relatively small number of individual cancer cells. This is a key issue in

invasion since it is created by single cell-matrix interactions which lead the tumour front to invade healthy tissue.

In this paper we propose a model for studying the interactions of cancer cells with the ECM. To do this we set an in-silico experiment where we let proliferate a cell on the surface of an imaginary petri dish filled with artificial ECM, we solve the system numerically to show the qualitative behaviour of invasion patterns and, in section 3, we simplify the system to 1 spatial dimension, and give an analytical solution in Fourier series where we study the matrix degradation by a single cell.

2 The Hybrid Model

Here we introduce a hybrid discrete-continuum model for studying patterns of cancer invasion. We use a two-scale approach where intracellular pathways are related to the cells' extracellular interactions with the ECM.

The continuum part of the model describes the interaction of the chemicals with the ECM whereas the individual-based part models the individual cells. In order to capture the dynamics linking the intracellular and the extracellular environments, every cell can act as a source and a sink of specified molecular components.

Cells are considered to be discrete particles that interact with each other physically via a potential function and with the surrounding environment reacting to the contact with the ECM. We assume that the amount of molecules interacting is large enough to use a continuum system of partial differential equations to model the chemicals and the ECM (cf. [25] [26]).

2.1 Chemicals and the ECM

In our model we will assume that the invasion process is triggered by contact between peripheral cancer cells and the ECM [1] [2] [3]. We use the variable M to denote the ECM density. Cancer cells which are in contact with the protein network of the ECM release MMPs which modify the ECM by degrading it. We use the variable E to denote the concentration of these matrix metalloproteinases. The resulting new configuration of the adjacent stroma, denoted by the variable A, stimulates cells to migrate via chemotaxis and haptotaxis. Once the ECM has been degraded, the new configuration of its protein network can interact with the cells. This interaction results in

mitosis, via the cells absorbing the growth factors present in the degraded medium, as well as migration. Cell migration occurs because of the chemotactic and haptotactic gradients that arise in the degraded ECM.

The equations that govern the enzymes' interactions with the adjacent stroma are

$$\frac{\partial}{\partial t}E(\underline{x},t) = \underbrace{\lambda N(\underline{x},t)M(\underline{x},t)}_{1} + \chi_e \triangle E(\underline{x},t) - \mu_e E(\underline{x},t), \tag{1}$$

$$\frac{\partial}{\partial t}M(\underline{x},t) = -\beta E(\underline{x},t)M(\underline{x},t),$$

$$\frac{\partial}{\partial t}A(\underline{x},t) = \gamma E(\underline{x},t)M(\underline{x},t) + \chi_a \triangle A(\underline{x},t) - \mu_a A(\underline{x},t),$$

where $\underline{x} \equiv (x,y)$. $E(\underline{x},t)$ is the concentration of MMPs/uPAs, $M(\underline{x},t)$ is the density of the ECM and $A(\underline{x},t)$ represents the density of degraded ECM in which cells can absorb growth factors. $N(\underline{x},t)$ is the number of cells at time t in a specified neighbourhood of $\underline{x}$ such that

$$N(\underline{x},t) = \sum_{i=1}^{i=N} I_{B_\epsilon(\underline{x})}(\underline{x_i})$$

where $I_{B_\epsilon(\underline{x})}$ is the Heavyside function

$$I_{B_\epsilon(\underline{x})} = \begin{cases} 1 \text{ if } \underline{x_i} \in B_\epsilon(\underline{x}) \\ 0 \text{ Otherwise} \end{cases}$$

and $B_\epsilon(\underline{x})$ is the ball of radius ϵ, centered at $\underline{x}$. N is the total number of cells in the tumour and $\underline{x_i}$ is the position of the i^{th} cell. The term "1" in the first PDE above describes the instantaneous local production of enzymes by the cells. Definitions of the parameters in our equations are presented in the table in the numerics section.

2.2 Modelling the Cells

To model the cells, we consider them to be free particles, existing in two-dimensional space, that interact with one another. To describe cell-cell adhesion, we introduced what are effectively adhesive bonds on the cells' surfaces by including a potential function (see Figure 1). In our model, two cells

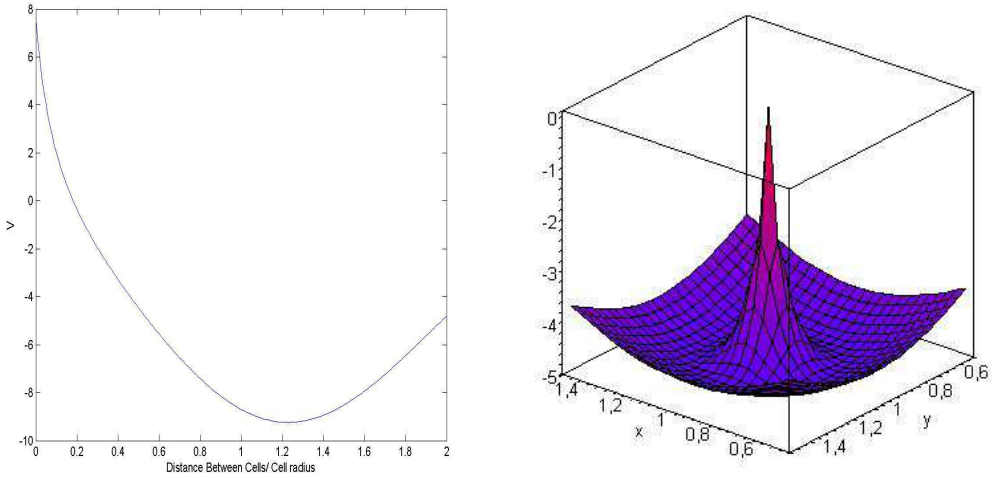

Figure 1: The potential function we use to model intercellular adhesion is graphed in one- and two-dimensional space. The left-hand image shows the interaction energy between two cells which are separated by a distance x which is scaled relative to the radius of an average cancer cell vs the potential energy $y = V(x)$. The image on the right shows the interaction energy between two cells located in a two-dimensional domain.

interact via the potential function if they are separated by a distance that is less than ϵ, which is normalized to be approximately double the radius of an average cancer cell.

2.2.1 Potential function

We take as potential energy in the bond between two cells at time t is given by

$$V(\underline{x_i}, t) = I_{B_\epsilon(\underline{x_i})} \left(\frac{1}{d(\underline{x_i}, \underline{x_j}) + e_\infty} - he^{-(d(\underline{x_i}, \underline{x_j}) - \frac{\epsilon}{2})^2} \right) \tag{2}$$

where $d(\underline{x_i}, \underline{x_j})$ is the distance between the two cells, h represents their capacity to bond, e_∞ is the maximum energy.

In an analogous way, to represent the bonds connecting a set of cells, we employ the function

$$V(\underline{x_i}, t) = \sum_{\underline{x_j} \in B_\epsilon(\underline{x_i})} \frac{1}{d(\underline{x_i}, \underline{x_j}) + e_\infty} - he^{-(d(\underline{x_i}, \underline{x_j}) - \frac{\epsilon}{2})^2},$$

where $B_\epsilon(\underline{x_i})$ is a neighbourhood centred on $\underline{x_i}$ with a radius ϵ, the maximum intercellular interaction distance.

2.2.2 Movement

In the absence of any kind of attractant or interaction with the extracellular matrix, cells will move in the direction that minimizes the potential function between them, i.e. their motion would solely be governed by

$$D = - \bigtriangledown V(\underline{x_i}, t).$$

Because our potential function is only a means of determining the direction in which a cell will move, we specify that our cells move at a constant speed rather than imposing more complicated rules of motion. Depending on the energy involved, cells may move towards one another due to the atractive forces generated by the bonds or towards an area offering more free space due to the repulsive forces caused by the cell compression.

In terms of the cell interactions with the environment, when the ECM is degraded and chemoattractant gradients have been established, cells will respond by travelling up these gradients. We model this response using the following chemotaxis equation [31] which biases the direction of the cells' motion.

$$D = \overbrace{\nabla(-V(\underline{x}, t))}^{\text{direction driven by the potential}} + \overbrace{r\nabla A(\underline{x}, t)}^{\text{Direction driven by chemotactic gradient}}$$

where r denotes the cells' sensitivity to the chemoattractant.

2.2.3 Cell Mitosis

In our model cell mitosis can occur for two reasons. The first possibility is uncontrolled cell-cycle progression due to an autocrine stimulus while the

second results from cells interacting with growth factors released by the degraded ECM.

$R(\underline{x_i}, t)$ is the mitosis rate of the i^{th} cell at time t. It is a probability function that depends on the interaction of cells with growth factors. At each time step a cell will duplicate with probability

$$R(\underline{x_i}, t) = f(A(\underline{x}, t)) + p_0,$$

where

$$f(A(\underline{x}, t)) = \left(\frac{\tau A(\underline{x}, t)}{\tau A(\underline{x}, t) + 1} \right) P.$$

At low values of degraded ECM, $R(\underline{x_i}, t) \to p_0$ which is the mitosis rate of a cell experiencing only an autocrine stimulus. The function $f(A(\underline{x}, t))$ models the mitosis probability resulting from the cells being externally stimulated due to the absorbtion of growth factors from the medium. This function saturates at high values of $A(\underline{x}, t)$ where $p_0 + P$ is the maximum mitosis probability allowed at each time step. This models the fact that, when cancer cells experience high growth factor concentrations, receptors in the cell surface saturate. The parameter τ is the instantaneous [growth factor]-[growth factor receptor] reaction rate. If we examine the temporal derivative of $f(x)$

$$\dot{f}(x) = \frac{\tau}{1 + \tau x} - \frac{\tau^2 x}{(1 + \tau x)^2}$$

we see that as $x \to 0$ the derivative $\to \tau$ and so we can consider τ to be the instantaneous rate at which receptors bind to growth factors. Consequently, the more growth factor receptors that are being stimulated, the higher the probability of cell duplication up to the point at which the cell-surface receptors become saturated.

3 Mathematical Analysis

The dynamics of hybrid models are usually complex to study due to the interactions of every single with its local neighbours and the underlying PDE system. In this section we simplify the system and set a basic in-silico experiment to study interactions of a single cell with the adjacent ECM. We consider the analogous situation to place a single cell on the surface of a petri dish with constant density of an artificial ECM. We do not include the

process of migration or proliferation but we just approach the degradation and diffusion of the degraded matrix. In this way we develop an analytical solution in Fourier series which helps to understand how cells behave.

Our initial model

$$\frac{\partial}{\partial t}E(\underline{x},t) = \lambda N(\underline{x},t)M(\underline{x},t) + \underbrace{\chi_e \triangle E(\underline{x},t)}_{2} - \mu_e E(\underline{x},t), \tag{3}$$

$$\frac{\partial}{\partial t}M(\underline{x},t) = -\beta E(\underline{x},t)M(\underline{x},t),$$

$$\frac{\partial}{\partial t}A(\underline{x},t) = \gamma E(\underline{x},t)M(\underline{x},t) + \chi_a \triangle A(\underline{x},t) - \mu_a A(\underline{x},t),$$

includes the minimal variables to describe the process of cell migration through the ECM: matrix contact, matrix degradation and directed movement. In particular, term 2 describes the diffusion of the enzymes in the sourrounding environment of the cell. There exists evidence of how this matrix degradation is confined to the contact zones of the cells with the matrix. Rather than a diffusion effect, matrix degradation is a kind of cut off of the fibers that impede cell migration[1]. Therefore enzyme dynamics can be model using a slow diffusion as we do in our system or just allowing to degrade the part of the matrix where the cells are in contact with. This two approaches have similar dynamics. Then, in order to analyse our model we can drop the first equation and consider the simpler system

$$\frac{\partial}{\partial t}M(x,t) = -\beta M(x,t)N(x,t), \tag{4}$$

$$\frac{\partial}{\partial t}A(x,t) = \gamma M(x,t)N(x,t) + \chi_a \triangle A(x,t) - \mu_a A(x,t),$$

which is more suitable to make a mathematical analysis and it captures the same biological interactions. For the simplest case we study the interactions of one cell in one spatial dimension which interacts with the surrounding matrix. In the appendix section we solve this system getting that the extracellular matrix is ruled by

$$M(x,t) = e^{-\beta t} I_{[x_o-\epsilon, x_o+\epsilon]} + I_{\overline{[x_o-\epsilon, x_o+\epsilon]}},$$

and the degraded stroma

$$A(x,t) = \sum_{n=1}^{n=\infty} [\frac{2\gamma cos(\frac{n\pi x}{l})|_{x_o-\epsilon}^{x_o+\epsilon}(e^{-\beta t} - e^{-(\chi_a(\frac{n\pi}{l})^2+\mu)t})}{n\pi(\chi_a(\frac{n\pi}{l})^2 + \mu - \beta)} sin(\frac{n\pi x}{l})].$$

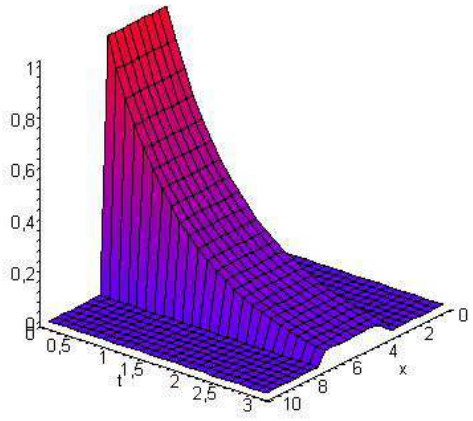

Figure 2: Plot showing the evolution of the ECM density as it is degraded by a single cell placed on a petri dish. The cell is centred at $x = 5$ with a radius of size 2. The cell is not allow to move and therefore it only degrades the part of the matrix is in contact with.

These equations show how a single cell degrades the ECM once it get in contact with it and at the same time is producing a wave of chemoattractants, and growth factors that diffuses in the adjacent space. Figure 2 shows the degradation of ECM by a single cell and Figure 3 shows the spatio-temporal evolution of attractant concentration profiles in the case of one and two cells respectively.

4 Numerical Simulations

In order to perform our in-silico experiment we consider as initial conditions what would be a very common in-vitro experiment: a single cell is placed on the surface of a petri dish filled with artificial ECM. The initial density of ECM is considered to be constant equal to 1. There is no enzyme on the surface of the plate at the moment when the cell is placed and therefore there is no degraded matrix in the system. For solving the PDE system we used centered differences with appropriate time and space scales. Since the cellular

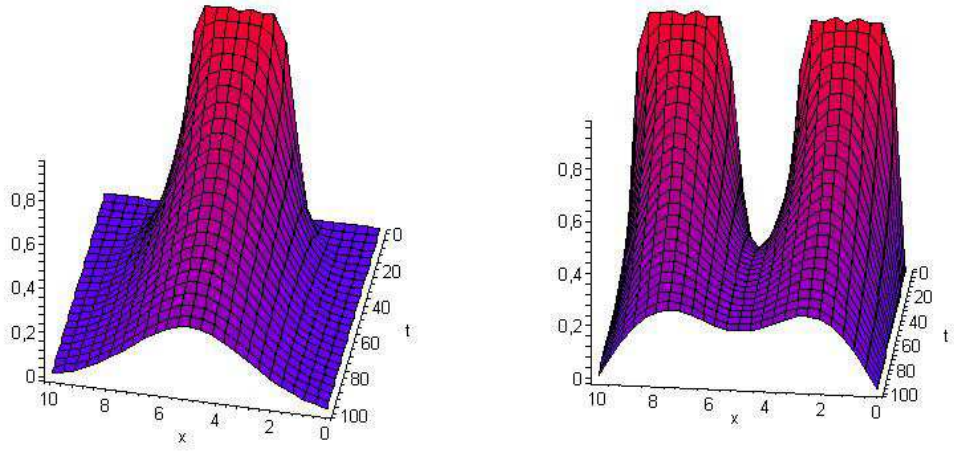

Figure 3: Plots showing the concentration profile over time of chemoattractants and growth factors as they are released from the degraded ECM. Figure at the left hand side shows the profile created by a single cell on the surface of a petri dish. Figure at the right hand side shows the profiles for two nearby cells.

dynamics have in general a much longer space-scale and a slower time-scale than events at the molecular level, we chose to use a 20 times slower time-step for solving the molecular scale equations than the one used for the cellular scale dynamics. As well we used smaller space dynamics compared to the cell size ($\epsilon/4$) for the PDE grid space step. Simulations were run for both Dirichlet and Newmann conditions producing the same type of dynamics and invasion patterns. The values of the parameters used in the computational simulations are given in the following table:

Parameter	Definition	value
λ	Production rate of enzymes by a single cell	0.5
χ_e	Diffusion coefficient of the enzymes	0.01
μ	Decay rate of the enzymes in the medium	0.05
β	Digestion rate of the ECM	1
γ	Production rate of attractants	0.5
χ_A	Diffusion coefficient of the digested ECM	0.01
μ_A	Decay rate of the digested ECM	0.01
p_0	Autocrine mitosis rate	0.0315
P	Maximum stimulated mitosis rate	0.04
τ	Instantaneous [growth factor]-[growth factor receptor] reaction rate	0.5

Results from our simulations mirror biological reality. In Figure 4 we see the tumour growing outwards as a result of the continual process of cell-line formation and collapse which occurs at its periphery. Cells on the tumour's edge are in contact with the ECM and are responsible for its degradation. As expected, mitosis occurs more rapidly when the cells are highly stimulated by growth factors. Although we only model a small number of cells, we still observe the characteristic linear morphology of the cells as they degrade the ECM at the tumour's edge. In reality, degradation of the ECM is almost exclusively confined to where cancer cells are in direct contact with it. In Figure 5 we present the temporal evolution of the enzyme wave that accompanies the tumour's outward expansion.

We observe that enzyme concentration is highest in areas where cell-ECM contact is highest. High enzyme concentrations, which cause maximum degradation of the ECM, in turn lead to a rise in the concentration of attractants and growth factors that are released by the degraded ECM. The

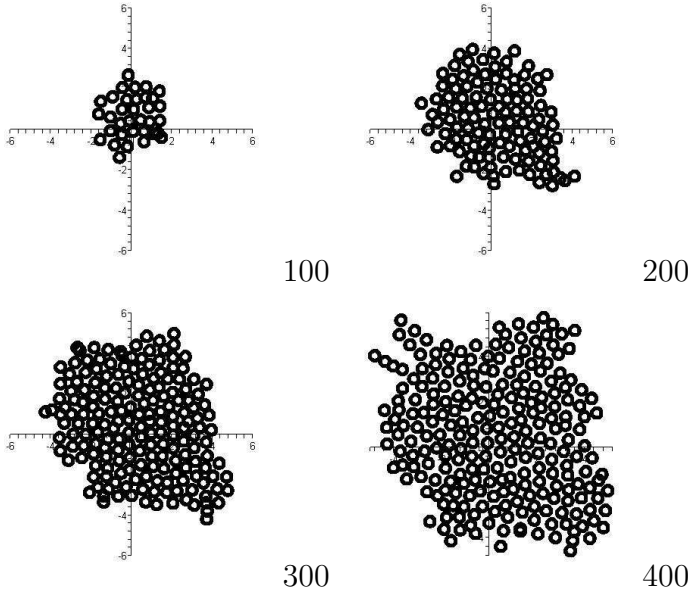

Figure 4: Plots of the spatio-temporal evolution of the cancer cells as they invade the ECM. The tumour grows by extending finger-like cell-structures, which are composed of a small number of cells, from its periphery into the ECM. These fingers then recede and spread on to the tumour's surface resulting in its heterogeneous outwards expansion.

outward propagating wave of chemoattractants and growth factors at the periphery of the tumour causes cells in this region to migrate outwards and to proliferate. In Figure 6 we show the temporal evolution of the enzyme-induced degradation of the ECM. The associated wave of growth factors and chemoattractants is presented in Figure 7.

5 Conclusions and Discussion

In this paper we have presented a hybrid discrete-continuum mathematical model for cancer invasion. Cancer cells are treated as individual entities, interacting through a potential function which is an attempt to model adhesive forces. The cancer cells proliferate, secrete matrix degrading enzymes and then move in a directed manner in response to chemical and matrix gradi-

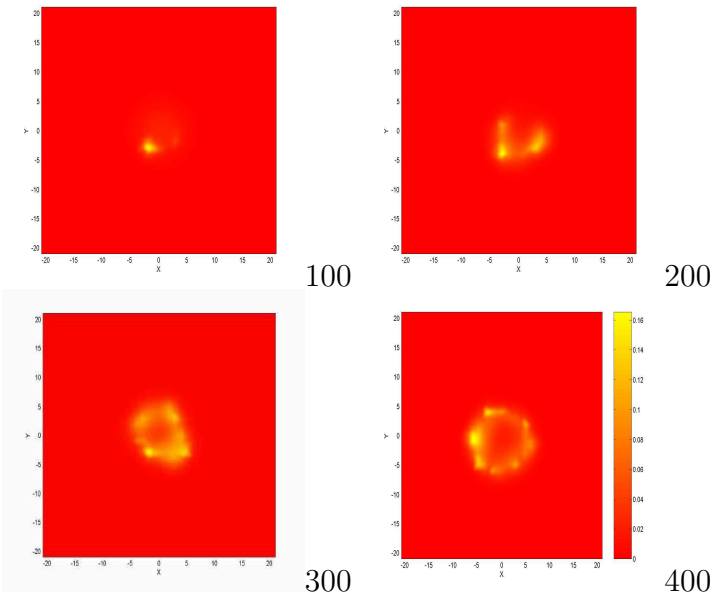

Figure 5: Plots showing the spatio-temporal evolution of the matrix degrading enzyme concentration. Cancer cells in contact with the extracellular matrix release enzymes, mainly matrix metalloproteinases and urokinase plasminogen activators, creating a wave of ECM-degrading chemicals that precedes the growing tumour. Lighter zones correspond to areas of higher cell density which are in contact with the matrix. The heterogeneity of the enzyme wave front is caused by the heterogeneous morphology of the tumour's surface.

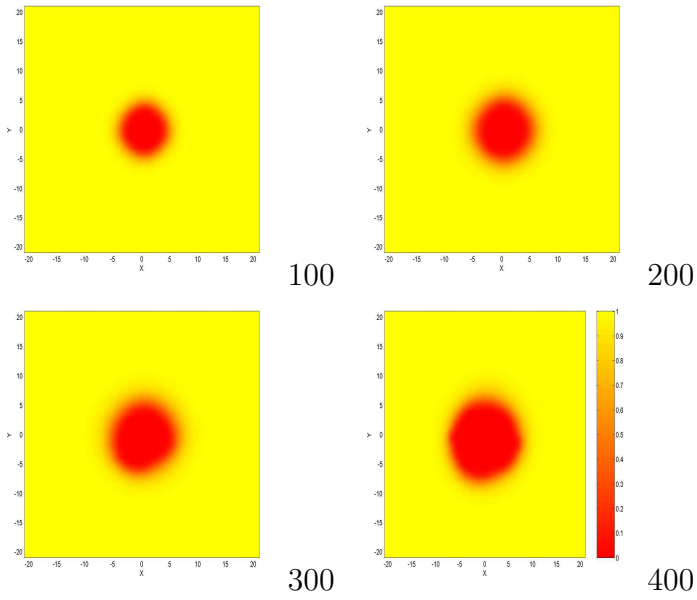

Figure 6: plots showing the spatio-temporal evolution of the ECM density. The extracellular matrix is degraded by the enzymes produced by the cancer cells that are in contact with it. Therefore, degradation of the extracellular matrix mirrors the tumour's growth. The dark area represents the degraded ECM.

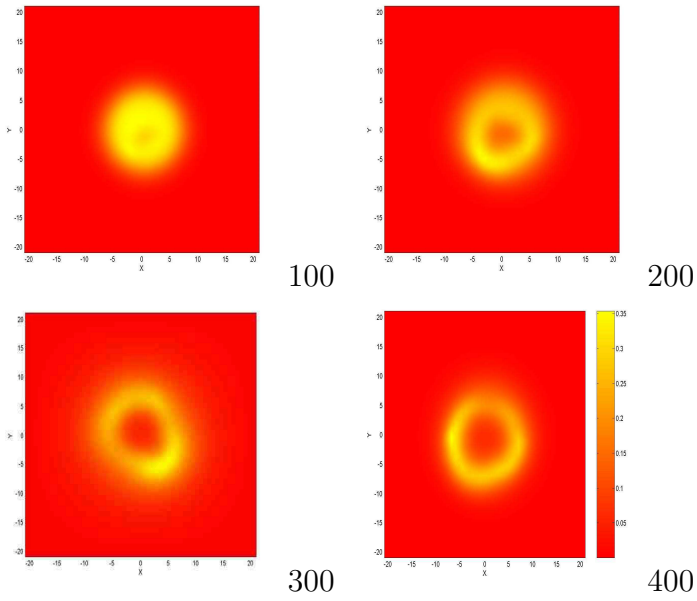

Figure 7: Plots of the spatio-temporal evolution of the degraded matrix density. A wave of chemoattractants and growth factors (light areas represent high concentrations) arises from the degraded extracellular matrix. This leads cells to proliferate and migrate which, in turn, continues the stimulation of enzyme production and the corresponding degradation of the ECM. As a result, a migration feedback loop is established.

ents. Our model highlights the importance of chemoattractant gradients in the invasion process. The results of computational simulations of the model are able to reproduce local invasion strategies of a small number of cancer cells. This is in contrast with what continuum models can produce. This process sees leading cells on the tumour's edge boring tunnel-like channels of degradation into the ECM. This is not only produced by the general expansive tumour growth of the whole cancer mass, but also by a combination of proliferation and migration at the contact zone with the ECM. In these degraded areas of the ECM, chemoattractant concentrations are high which results in cells following the "leaders" and forming invasion fingers which extend from the tumour's periphery. This suggests the importance of a possible feedback loop of degradation between the protein network and invasion promotion.

Acknowledgments

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Appendix

Here we show the mathematical analysis done in order to find the solutions of the 1 spatial dimension simplified system of section 3

$$\frac{\partial}{\partial t}M(x,t) = -\beta M(x,t)N(x,t), \tag{5}$$

$$\frac{\partial}{\partial t}A(x,t) = \gamma M(x,t)N(x,t) + \chi_a \triangle A(x,t) - \mu_a A(x,t).$$

We consider the cell as an object centered at position x_o and of radius ϵ. Then $N(x,t)$ is nothing but a Heaviside function $I_{[x_o-\epsilon,x_o+\epsilon]}$.

Solution of equation (4) is of the form

$$M(x,t) = Ce^{-\beta t} I_{[x_o-\epsilon, x_o+\epsilon]} + g(x),$$

which for one cell and initial matrix density equals to 1 leads to

$$M(x,t) = (Ce^{-\beta t} - (C+1)) I_{[x_o-\epsilon, x_o+\epsilon]} + I_{\overline{[x_o-\epsilon, x_o+\epsilon]}},$$

where the bar denotes the complementary set. Since in absence of cells on the petri dish the ECM density is 1 we can take without lost of generality $C = 1$ and $g(x) = 0$.

Then we can look for solutions for the second equation of the simplified system. For this we set firstly the problem with Dirichlet conditions:

$$\frac{\partial}{\partial t} A(x,t) = \gamma e^{-\beta t} I_{[x_o-\epsilon, x_o+\epsilon]} + \chi_a \triangle A(x,t) - \mu_a A(x,t), \tag{6}$$

$$A(x,0) = h(x),$$

$$A(0,t) = 0,$$

$$A(l,t) = 0$$

where $x \in [0,l]$ and $t \in [0,T]$.

The homogeneous associated problem can be solved using separation of variables. The equality on time variable has solution of the form of a exponential function in time dependent variable

$$T(t) = Ce^{kt}.$$

In our particular problem, at $t = 0$, when the cell is just placed on the surface of the petri dish, the ECM it has not been degraded yet. Therefore $h(x) = 0$, this leads to

$$T(0) = 0 = C$$

and then the solution for the homogeneous associated is the trivial solution $A_h(x,t) = 0$.

For the non-homogeneous part of the system we look for solutions of the form

$$A(x,t) = \sum_{n=0}^{\infty} u_n(t) sin(\frac{n\pi x}{l}).$$

In order to find the coefficients $u_n(t)$, firstly, we expand the non-homogeneous term in *sin* series

$$\gamma e^{-\beta t} I_{[x_o-\epsilon, x_o+\epsilon]} = \sum_{n=0}^{\infty} a_n(t) sin(\frac{n\pi x}{l}),$$

then

$$a_n(t) = \frac{2}{l}\int_0^l \gamma e^{-\beta t} I_{[x_o-\epsilon, x_o+\epsilon]} sin(\frac{n\pi x}{l}) dx$$

Which leads to

$$a_n(t) = \frac{2\gamma e^{-\beta t} cos(\frac{n\pi x}{l})|_{x_o-\epsilon}^{x_o+\epsilon}}{n\pi}$$

Now we can substitute this fourier series in the equation (5) to get an expression involving all the coefficients

$$0 = \sum_{n=0}^{\infty} [-\frac{d}{dt}u_n(t) + \frac{2\gamma e^{-\beta t} cos(\frac{n\pi x}{l})|_{x_o-\epsilon}^{x_o+\epsilon}}{n\pi} - \chi_a u_n(t)(\frac{n\pi}{l})^2 - \mu_a u_n(t)] sin(\frac{n\pi x}{l}).$$

Multiplying both sides by $sin(\frac{n\pi x}{l})$ and using orthogonality we get the set of ODEs that will determine the value of the coefficients

$$\begin{gathered} \frac{d}{dt}u_n(t) = \frac{2\gamma cos(\frac{n\pi x}{l})|_{x_o-\epsilon}^{x_o+\epsilon}}{n\pi} e^{-\beta t} - \chi_a u_n(t)(\frac{n\pi}{l})^2 - \mu_a u_n(t), \\ u_n(0) = h_n, \end{gathered}$$

where h_n are the coefficients of the initial data

$$h_n = \frac{2}{l}\int_0^l h(x) sin(\frac{n\pi x}{l}) dx$$

Then rearranging and using as integrant factor $e^{(\chi_a(\frac{n\pi}{l})^2+\mu)t}$ we get the following expression

$$\frac{d}{dt}(u_n e^{(\chi_a(\frac{n\pi}{l})^2+\mu)t}) = \frac{2\gamma cos(\frac{n\pi x}{l})|_{x_o-\epsilon}^{x_o+\epsilon}}{n\pi} e^{(\chi_a(\frac{n\pi}{l})^2+\mu-\beta)t}$$

which leads to the solution

$$u_n = \frac{2\gamma cos(\frac{n\pi x}{l})|_{x_o-\epsilon}^{x_o+\epsilon}}{n\pi}(\frac{e^{-\beta t}}{\chi_a(\frac{n\pi}{l})^2 + \mu - \beta} - Ke^{-(\chi_a(\frac{n\pi}{l})^2+\mu)t})$$

where K is a constant to be determined.

If we consider the cell has been just placed on the surface of a flat petri dish with initial concentration of ECM equal to 1 and no degraded ECM, we have $h(x) = 0$ and therefore $u_n(0) = 0$. For this initial setup of the experiment we get

$$u_n = \frac{2\gamma cos(\frac{n\pi x}{l})|_{x_o-\epsilon}^{x_o+\epsilon}(e^{-\beta t} - e^{-(\chi_a(\frac{n\pi}{l})^2+\mu)t})}{n\pi(\chi_a(\frac{n\pi}{l})^2 + \mu - \beta)}.$$

Observe that the general solution of the homogeneous system vanishes for $A(x, 0) = h(x) = 0$. Therefore, the general solution of the non-homogeneous system is

$$A(x,t) = \sum_{n=1}^{n=\infty}[\frac{2\gamma cos(\frac{n\pi x}{l})|_{x_o-\epsilon}^{x_o+\epsilon}(e^{-\beta t} - e^{-(\chi_a(\frac{n\pi}{l})^2+\mu)t})}{n\pi(\chi_a(\frac{n\pi}{l})^2 + \mu - \beta)} sin(\frac{n\pi x}{l})].$$

References

[1] K. Wolf and P. Friedl, Tumour cell invasion and migration: diversity and escape mechanisms, Nature Cancer Reviews 3 (2003) 362-374.

[2] K. Wolf and P. Friedl, Functional imaging of pericellular proteolysis in cancer cell invasion, Biochimie 87 (2005) 315-320.

[3] L. Trusolino and P.M. Comoglio, Scatter factor and semaphorin receptors: Cell signalling for invasive growth, Nature Cancer Reviews 2 (2002) 290-300.

[4] D. Drasdo, R. Kree and J.S. McCaskill, Monte Carlo approach to tissue-cell populations, Phys. Rev. 52 (1995) 6635-6657.

[5] E.W. Thompson and D. F. Newgreen, Carcinoma invasion and metastasis: A role for epithelial-mesenchymal transition?, Cancer Res. 65 (2005) 5991-5995.

[6] J.P. Thiery, Epithelial-Mesenchymal transitions in tumour progression, Nature Cancer Reviews 2 (2002) 442-454.

[7] K. Kikuchi and S. Yasumoto, Retention of cell adhesion and growth capability in human cervical cancer cells deprived of cell anchorage, J. Cancer Res. 90 (1999) 867-873.

[8] A. Wong and M. Gumbiner, Adhesion independent mechanism for suppression of tumour cell invasion by e-cadherin, J. Cell Biol. 161 (2003) 1191-1203.

[9] I. Hart and N. Hogg (Eds). Cancer Surveys 24 Cold Spring Harbor Laboratory Press (1995).

[10] C. Gottardi, E. Wong and B. Gumbiner, E-cadherin suppresses cellular transformation by inhibiting beta-catenin signalling in adhesion independent manner, J. Cell Biol, 153 (2001) 1049-1060.

[11] F. Fagotto, N. Funayama, U. Gluck and B. Gumbiner, Binding to cadherins antagonizes the signalling during axis formation in xenopus, J. Cell Biol. 132 (1996) 1105-1114.

[12] T. Bogenrieder, M. Herlyn, Axis of evil: Molecular mechanisms of cancer metastasis, Oncogene 22 (2003) 6524-653.

[13] A.J. Perumpanani, D.L. Simmons, A. Gering, K.M. Miller, G. Ward, J. Norbury, M. Schneemann and J. Sherratt, Extracellular matrix mediated chemotaxis can impede cell migration, Proc. Roy. Soc. Lond. 265 (1998) 2347-2352.

[14] N. Bellomo, A. Bellouquid and M. Delitala, Mathematical topics on the modelling complex of multicellular systems and tumour immune cells competition, Math. Modell. Meth. Appl. Sci. 14 (2004) 1683-1733.

[15] N. Bellomo, E. De Angelis and L. Preziosi, Multiscale modelling and mathematical problems related to tumour evolution and medical therapy, J. Theor. Med. 5 (2004) 111-136.

[16] N. Bellomo and L. Preziosi, Modelling and mathematical problems related to tumour evolution and its interaction with the immune system, Math. Comput. Modell. 32 (2000) 413-452.

[17] M.A.J. Chaplain, L. Graziano and L. Preziosi, Mathematical modelling of the loss of tissue compression responsiveness ans its role in solid tumour development, Math. Med. Biol. 23 (2006) 197-222.

[18] H.M. Byrne and L. Preziosi, Modelling solid tumour growth using the theory of mixtures, Math. Med. Biol. 20 (2004) 341-366.

[19] D. Drasdo and S. Hohme. A single-cell-based model of tumour growth in vitro: Monolayers and spheroids, Phys. Biol. 2 (2005) 133-147 .

[20] H.M. Byrne, M.A.J. Chaplain, G.J. Pettet and D.L.S. McElwain, A mathematical model of trophoblast invasion, J. Theor. Med. 1 (1999) 275-286.

[21] R.A. Gatenby and E.T. Gawlinsky, A reaction diffusion model of cancer invasion, Cancer Res. 56 (1997) 5745-5753.

[22] M.A.J. Chaplain and B.D. Sleeman, Modelling the growth of solid tumours and incorporating a method for their classification using nonlinear elasticity theory, J. Math. Biol. 31 (1993) 431-479.

[23] M.A.J. Chaplain and G. Lolas, Mathematical modelling of cancer cell invasion of tissue: The role of the urokinase plasminogen activation system, Math. Modell. Meth. Appl. Sci. 15 (2005) 1685-1734.

[24] A.J. Perumpanani, J.A. Sherratt, J. Norbury and H.M. Byrne, Biological inferences from a mathematical model for malignant invasion, Invas. Metast. 16 (1996) 209-221.

[25] A.R.A. Anderson, M.A.J. Chaplain, E.L. Newman. R.J.C. Steele and A.M. Thompson, Mathematical modelling of tumour invasion and metastasis, J. Theor. Med. 2 (2000) 129-154.

[26] A.R.A. Anderson, A hybrid mathematical model of solid tumour invasion: the importance of cell adhesion, Math. Med. Biol. 22 (2005) 163-186.

[27] S. Dorman and A. Deutsch, Modelling of self organized avascular tumour growth with a hybrid automaton, In Silico Biology 2 (2002) 1-35.

[28] L. Preziosi (Ed) Cancer Modelling and Simulation, Chapman & Hall/CRC (2003).

[29] W. Alt, M.A.J. Chaplain, M. Griebel and J. Lenz (Eds), Polymer and cell dynamics: Multiscale modelling and numerical simulations, Birkhauser Verlag, Basel (2003).

[30] S. Turner and J. A. Sherratt, Intercellular adhesion and cancer invasion: A discrete simulation using the extended potts model, J. theor. Biol. 216 (2002) 85-100.

[31] A. Stevens, The derivation of chemotaxis equations a limit dynamics of moderately interacting stochastic many particles systems, SIAM J. Appl. Math. 61 (2000) 183-212.