

Multiscale mathematical modelling in biology and medicine

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Cancer is one of the major causes of death in the world (particularly the developed world), with around 11 million people diagnosed and around 7 million people dying each year. The World Health Organization predicts that current trends show around 9 million people will die in 2015, with the number rising to 11.5 million in 2030. Cancer growth is a complicated complex phenomenon involving many interrelated processes across a wide range of spatial and temporal scales, and in spite of many advances, it is still difficult to treat and cure as the previous statistics show. New approaches are necessary if further progress in curing the disease is to be made. The description of most biological processes in the human body involves many different but interconnected phenomena, which occur at different spatial and temporal scales. From the modelling viewpoint, there are three natural scales of interest: subcellular, cellular and tissue. The modelling described in this paper has a common theme of quantitative predictive mathematical modelling, analysis and computational simulation of key aspects of cancer growth and treatment. The long-term goal is to build a ‘virtual cancer made up of different but connected mathematical models at the different biological scales (from genes to tissue to organ)’. The development of quantitative predictive models (based on sound biological evidence and underpinned and parameterized by biological data) will no doubt have a positive impact on patients suffering from diseases such as cancer through improved clinical treatment.

Keywords: multiscale mathematical modelling; cancer; metastasis; invasion.

1. Introduction

The past 10–15 years have witnessed enormous advances in our understanding of the molecular basis of cell structure and function. Scientists, as well as the lay public, are cognizant of the spectacular success of the human genome project and the consequent burgeoning interest in the related field of proteomics. Biochemists and cell biologists have made similarly impressive strides in elucidating the mechanisms mediating cell signalling and its consequences for the control of cell proliferation, motility and gene expression. It is, however, abundantly clear that reductionist logic using this impressive subcell level information base is not sufficient to deduce an understanding of phenomena operative at the next higher level of biological organization: the tissue. Employing a literary analogy, the vast omic databases of catalogued genes and proteins, taken together with our growing understanding of the inner workings of individual cells, provide a dictionary and a grammatical syntax required for the next great challenge, i.e. understanding the sentences and paragraphs characteristic of emergent tissue-level phenomena.

The description of most biological processes in the human body involves many different but interconnected phenomena, which occur at different spatial and temporal scales. From the modelling viewpoint, there are three natural scales of interest: subcellular, cellular and tissue. This paper has a common theme of quantitative predictive mathematical modelling, analysis and computational simulation of key aspects of cancer growth and invasion. The paper is focussed around three aspects of cancer growth and

development each dealing with a specific scale (spatial/temporal/both) and an important biological system (i) intracellular signal transduction pathways, (ii) the biomechanics of individual cell adhesion and movement and (iii) cancer cell migration and invasion of tissue. The projects are linked to one another in various ways and at various different biological scales (from intracellular to tissue level) and the overall common theme of the project may be termed as *multiscale mathematical modelling* or, from a biological perspective, *quantitative systems biology* or *quantitative integrative biology*. To use the literary analogy of the previous paragraph, the long-term goal is to build a mathematical book of the cell composed of individual chapters made from the sentences and paragraphs of the specific models.

In the longer term, the development of quantitative predictive models (based on sound biological evidence and underpinned and parameterized by biological data) will no doubt have a positive impact on patients suffering from diseases such as cancer through improved clinical treatment.

2. Modelling overview

The ability to invade tissue is one of the hallmarks of cancer. Cancer cells achieve this through the secretion of matrix degrading enzymes, cell proliferation, loss of cell–cell adhesion, enhanced cell–matrix adhesion and active migration. Invasion of tissue by the cancer cells is one of the key components in the metastatic cascade, whereby cancer cells spread to distant parts of the host and initiate the growth of secondary tumours (metastases). A better understanding of the complex processes involved in cancer invasion will ultimately lead to treatments being developed, which can localize cancer and prevent metastasis. A crucial aspect of cancer invasion is *adhesion*—both cell–cell adhesion and cell–matrix adhesion. The common thread running through the modelling is the role of adhesion at an intracellular level, cellular level and tissue level.

2.1 *The intracellular scale: cadherin– β -catenin interactions*

At the intracellular scale, we consider the dynamics of E-cadherin and N-cadherin interacting with β -catenin in the cytoplasm and at the cell membrane using a system of nonlinear ordinary differential equations. Cadherins are cell–cell adhesion proteins that form part of multiprotein complexes at the cell membrane to bind neighbouring cells and determine the tissue architecture. Cell adhesion may be regulated by interactions between E-cadherin and β -catenin and the control of cell adhesion may be related to cell migration, to the epithelial–mesenchymal transition and to invasion in populations of eukaryotic cells. E-cadherin mediates cell–cell adhesion and plays a critical role in the formation and maintenance of junctional contacts between cells. Loss of E-cadherin-mediated adhesion is a key feature of the epithelial–mesenchymal transition. β -Catenin is an intracellular protein associated with the actin cytoskeleton of a cell. E-cadherins bind to β -catenin to form a complex that can interact both with neighbouring cells to form bonds and with the cytoskeleton of the cell. When cells detach from one another, β -catenin is released into the cytoplasm, targeted for degradation and downregulated. In this process, there are multiple protein complexes involved that interact with β -catenin and E-cadherin. There is evidence that cytoplasmatic E-cadherin translocates to the membrane after binding to β -catenin at the *endoplasmic reticulum*. For technical reasons, we assume that the complexes are formed in the cell membrane. The model considers three possible states of the cadherins within the cell: (i) in the cytosol in cadherin-coated vesicles (E_c), (ii) free at the membrane (E_m) and (iii) forming bonds at an intermembrane position after forming a complex with the scaffolding protein β -catenin (E/β) (shown in Fig. 1, left diagram).

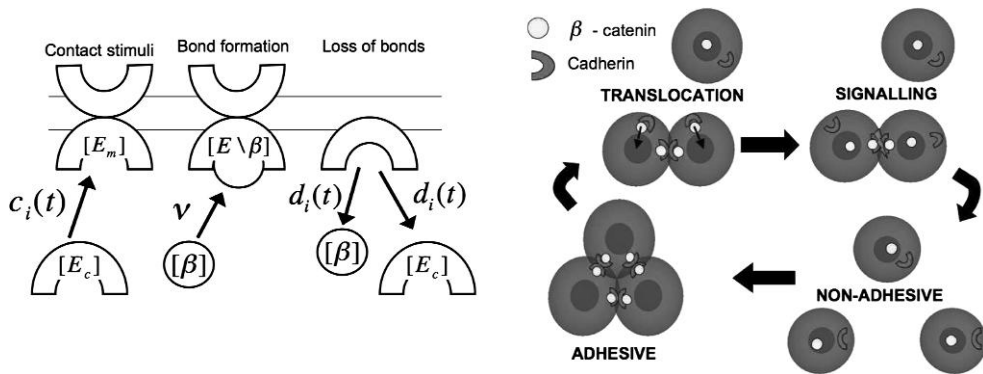


FIG. 1. The left-hand figure shows the three states of E-cadherin, which we consider in our individual-based model: (i) E-cadherin free in the cytoplasm E_c , (ii) E-cadherin that has just arrived at the cell membrane E_m and (iii) E-cadherin that forms bonds in a multiprotein complex. The right-hand figure shows the effect of differing levels of intracellular E-cadherin on the adhesive state of individual cells.

2.2 The cellular scale: cell–cell adhesion dynamics

Each cell is modelled as an isotropic elastic object capable of migration and division and parameterize it by cell kinetic, biophysical and cell biological parameters that can be experimentally measured. Full details of the governing equations are given in the following section and in Ramis-Conde *et al.* (2008a, 2009). Figure 1 (right diagram) gives a schematic picture of the cellular scale modelling, which is coupled to the intracellular cadherin– β -catenin dynamics.

2.3 The tissue scale: cell–matrix interactions

The final scale at which the multiscale mathematical model operates on is the tissue scale. Along with the intracellular signal transduction pathways (e.g. cadherin–catenin dynamics) within each cell and neighbouring cell–cell interactions, the total number of cell–cell interactions across a domain representing a specific tissue is considered. Computational simulations of the multiscale model in these domains then enables us to monitor the spatiotemporal dynamics of cadherin, β -catenin and cell adhesivity throughout the entire tissue domain while at the same time being able to monitor the model variables in individual cells. Figure 2 shows possible tissue structures that can be considered. The top left tissue structure represents a sheet of cells (e.g. epithelium) and can be used to investigate how cancer cells in a connected sheet break through their basement membrane and invade the surrounding tissue (cf. epithelial–mesenchymal transition). The top right tissue structure (tube) represents a vessel and can be used to investigate how invasive cancer cells *intravasate* and *extravasate*—crucial processes during metastasis. The bottom figure shows a generic structure of cells of arbitrary shape demonstrating the flexibility of the modelling approach to consider realistic tissue geometries and structures. The diagram also illustrates the multiscale modelling approach, with intracellular dynamics being modelled within each individual cell, then individual cells interacting locally with one another and finally everything combining at the tissue scale.

2.4 Tissue scale: modelling the urokinase plasminogen activation system

The ability of cancer cells to break out of tissue compartments and invade locally gives solid tumours a defining deadly characteristic. The first step of invasion is the overexpression by the cancer cells of

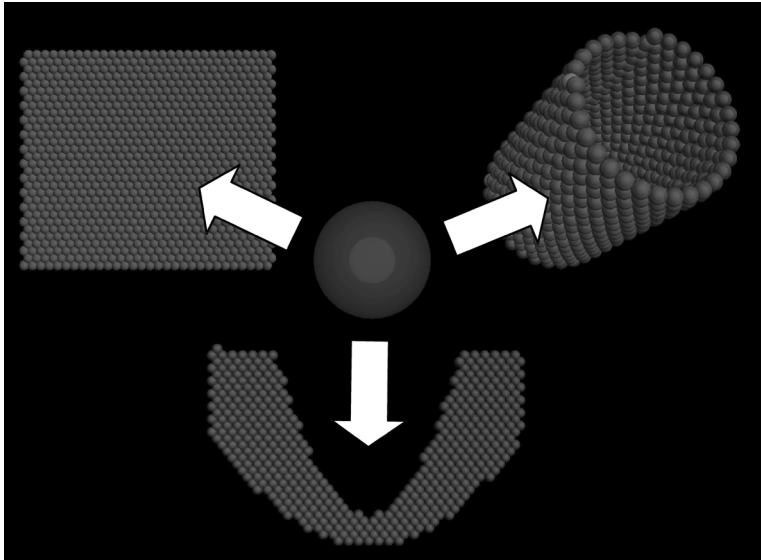


FIG. 2. Schematic diagram showing a variety of tissue structures representing different biological scenarios, which can be considered by the modelling approach.

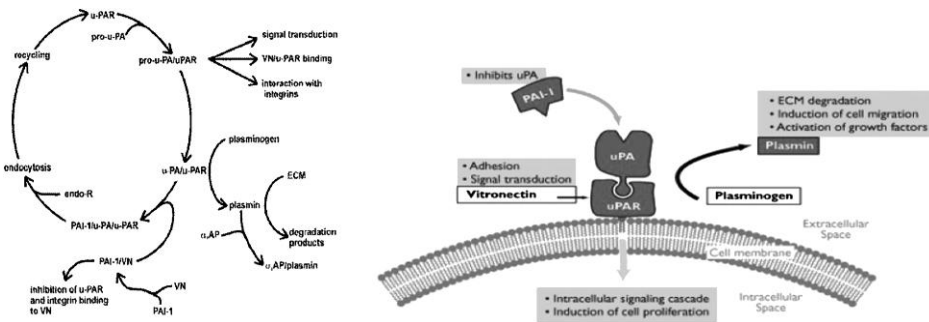


FIG. 3. Schematic diagrams showing the key features of the uPA system. Secretion and binding to cell surface receptors, competition with PAI-1, activation of plasmin, matrix degradation and recycling of receptors.

proteolytic enzymes, such as the urokinase-type plasminogen activator (uPA) and matrix metalloproteinases (MMPs). Degradation of the matrix then enables the cancer cells to migrate through the tissue and subsequently to spread to secondary sites in the body (metastasis). In this development of the modelling, a mathematical model of the uPA system is incorporated (see Fig. 3). The model consists of a system reaction–diffusion–taxis partial differential equations describing the interactions between the cancer cells, uPA, uPA inhibitors, plasmin and the host tissue. The spatiotemporal dynamics of the uPA system is coupled to the cancer cells through chemotaxis and haptotaxis.

3. Multiscale mathematical modelling

Cancer is characterized by multiple mutations in a single cell leading to a loss of control in cell replication accompanied by an uncontrolled growth of the total cell mass, eventually leading to the formation of

an *in situ* solid tumour. After the tumour reaches a certain size, genetic instability in the cancer cells may lead to further dedifferentiation within the malignant cell mass. These secondary mutations are relevant in order for the tumour to gain advantage over neighbouring cells and to invade further the local tissue and organs. In the transition from a normal cell to a malignant cell, the modification of intracellular pathways related to cell–cell adhesion and cell–matrix adhesion is important and determines the compactness of the tumour surface and the invasiveness of the tumour (Chaplain *et al.*, 2006). Indeed, the ability to invade tissue is one of the hallmarks of cancer. Cancer cells achieve this through the secretion of matrix degrading enzymes, cell proliferation, loss of cell–cell adhesion, enhanced cell–matrix adhesion and active migration. Invasion of tissue by the cancer cells is one of the key components in the metastatic cascade, whereby cancer cells spread to distant parts of the host and initiate the growth of secondary tumours (metastases). A better understanding of the complex processes involved in cancer invasion will ultimately lead to treatments being developed, which can localize cancer and prevent metastasis. A crucial aspect of cancer invasion is *adhesion*—both cell–cell adhesion and cell–matrix adhesion. Cadherins are cell–cell adhesion proteins, which form part of multiprotein complexes at the cell membrane to bind neighbouring cells and determine the tissue architecture. Of particular interest is E-cadherin, sometimes considered as a tumour suppressor protein due to its functionality in maintaining the compactness of the epithelium. The role of E-cadherin in the malfunction of cell–cell adhesion observed in colorectal cancer and in the β -catenin degradation system after mutations that affect the wnt-pathway belongs to the most studied examples (Natke, 2004; Hardy *et al.*, 2000). More than 80% of colorectal tumours show malfunctions in APC, a key protein in the wnt-pathway related also to intracellular interactions where E-cadherin plays a main role. These mutations are correlated with higher cancer invasion and therefore poorer prognosis.

Mathematical modelling of cell adhesion has been approached by different strategies including continuum models (Byrne & Chaplain, 1996, 1997; Armstrong *et al.*, 2006; Gerisch & Chaplain, 2008) (for a general review of mathematical continuum models of cancer, see Araujo & McElwain, 2004), individual-based, lattice-free models (Galle *et al.*, 2005; Schaller & Meyer-Hermann, 2005; Drasdo & Hoehme, 2005; Ramis-Conde *et al.*, 2008a,b, 2009) and lattice-based models where each lattice site can at most be occupied by one single cell (Anderson, 2005; Drasdo, 2005; Block *et al.*, 2007) (for general reviews of individual-based models, see Moreira & Deutsch, 2002; Alber *et al.*, 2002; Drasdo, 2003; Anderson *et al.*, 2007). Although all these different approaches have shown the importance of cell adhesion to keep tumour compactness and prevent invasion, there is still a wide field to explore linking the intracellular dynamics of signalling pathways to the adhesion molecules at the cell surface and the extracellular consequences in invasive tumours.

3.1 Intracellular modelling

When a cell adheres to adjacent neighbours, the E-cadherin molecules are situated in an intermembrane position, forming bonds with local neighbours at the intercellular space. The cytoplasmic tail of the E-cadherin molecule binds to the proteins of the catenin family: p120-catenin, α -catenin and β -catenin. The α -catenin and β -catenin then form a complex to link the actin filaments of the cytoskeleton and the E-cadherins. When bonds are released, caused by intracellular signalling or the effect of mechanical stress, the multiprotein complex is broken and the E-cadherins are internalized, i.e. transported into the cytoplasm by the endocytosis apparatus within cadherin-coated vesicles. It is not well known yet if, after being endocytosed, E-cadherins are degraded or if they are kept by the vesicles for later recycling.

When the bond is broken, β -catenin is released in a phosphorylated state. In this form, it is ready to interact with other molecules and can be recognized and degraded in the proteasome systems.

Intracellular control of β -catenin concentration is important in preserving the tissue architecture. Upregulation of free β -catenin (also known as soluble β -catenin) is related to cell migration and the epithelial–mesenchymal transition, a process where a well-ordered and polarized layer of cells changes into an unstructured configuration to facilitate collective cell migration. Sufficiently large concentrations of soluble β -catenin then move from the cytoplasm into the nucleus, where it interacts with transcription factors, which modify cell behaviour—for example by promoting cell proliferation. Although the precise mechanisms which relate the β -catenin nuclear translocation to cell migration are not yet very well known, it has been observed that invasive cells show a higher nuclear accumulation of soluble β -catenin.

The first step in this paper is to develop a mathematical multiscale model describing how cell adhesion may be regulated by interactions between E-cadherin and β -catenin and how the control of cell adhesion may be related to cell migration, to the epithelial–mesenchymal transition and to invasion in populations of eukaryotic cells. E-cadherin mediates cell–cell adhesion and plays a critical role in the formation and maintenance of junctional contacts between cells. Loss of E-cadherin-mediated adhesion is a key feature of the epithelial–mesenchymal transition. β -Catenin is an intracellular protein associated with the actin cytoskeleton of a cell. E-cadherins bind to β -catenin to form a complex that can interact both with neighbouring cells to form bonds and with the cytoskeleton of the cell. When cells detach from one another, β -catenin is released into the cytoplasm, targeted for degradation and downregulated. In this process, there are multiple protein complexes involved that interact with β -catenin and E-cadherin.

This problem is approached by using a multiscale, individual-based, lattice-free model that accounts for the intracellular dynamics of the E-cadherin– β -catenin interactions and the physical forces on the cells. First, the model of the intracellular β -catenin dynamics is presented and the importance of this regulation system on the E-cadherin system is shown. The single-cell model is then described and it is shown how the intracellular dynamics are coupled to the cell biophysical and cell biological single-cell parameters.

3.1.1 The β -catenin kinetics. It is not completely known how E-cadherin is transported from the cytosol to the intermembrane position to form bonds. However, there is some evidence that cytoplasmatic E-cadherin translocates to the membrane after binding to β -catenin at the *endoplasmic reticulum*. For simplicity, it is assumed that the complexes are formed in the cell membrane.

This is translated into the model by considering three possible different states of the E-cadherins: catenin free in the cytoplasm ($[E_c]$), catenin free at the cell membrane ($[E_m]$) and the complex E-cadherin– β -catenin forming bonds at the cell membrane ($[E/\beta]$). As one cell comes into contact with another cell, the cadherin in the cytoplasm moves to the cell surface. Here, the assumption is made that the amount of cadherin stimulated to move is proportional to the contact area so that the surface density of β -catenin–E-cadherin receptors is constant. At the cell membrane, the cadherin binds to β -catenin and the cell forms bonds with its neighbouring cells. On the other hand, if cell detachment occurs, then the β -catenin–E-cadherin complex is ruptured, the β -catenin becomes soluble β -catenin and E-cadherin is sequestered into the cytoplasm by endocytosis. Furthermore, it is assumed that E-cadherin can be recruited to form bonds again. In this way, the total E-cadherin concentration ($E_T = 100$ nM) can be considered to be constant:

$$E_T = [E_c] + [E_m] + [E/\beta]. \quad (3.1)$$

The other reactions described above can be written as follows:





Figure 1 summarizes the intracellular interactions of the different forms of E-cadherin. It is assumed that the production of β -catenin occurs at a constant rate ($k_m = 0.01 \text{ nM min}^{-1}$). The degradation process takes place after forming a complex with the proteasome. In the framework of the model, this *proteasome* variable should be understood as a complex of proteins which after different biochemical interactions degrade soluble β -catenin, i.e.



where $[P]$ denotes the concentration of proteasome, $[C]$ is the concentration of β -catenin–proteasome complex and ω is the final product of the degradation process. The important wnt-pathway is taken into account within this degradation process in a very simple way: if wnt is activated, and therefore β -catenin cannot bind to actin and be marked for degradation, degradation is at low levels that in the model is equivalent to $k^+ \approx 0$. If wnt is not activated, β -catenin can be degraded and therefore down-regulated.

In a similar way to the E-cadherin concentration, it is assumed that the proteasome total concentration remains constant ($P_T = 0.33514 \text{ nM}$) and therefore

$$P_T = [C] + [P]. \tag{3.6}$$

Using mass conservation, the following system of reaction equations is obtained from the above chemical reactions for each individual cell i :

$$\begin{aligned} d_t[E_c] &= -c_i(t)[E_c] + d_i(t)[E/\beta], \tag{3.7} \\ d_t[E/\beta] &= \nu(E_T - [E_c] - [E/\beta])[\beta] - d_i(t)[E/\beta], \\ d_t[\beta] &= -\nu(E_T - [E_c] - [E/\beta])[\beta] + d_i(t)[E/\beta] - k^+[\beta](P_T - [C]) + k^-[C] + k_m, \\ d_t[C] &= k^+[\beta](P_T - [C]) - k^-[C] - k_2[C], \tag{3.8} \end{aligned}$$

where $\nu = 100 \text{ min}^{-1}$ is the rate at which the complex $[E/\beta]$ is produced and $k^+ = 100 \text{ min}^{-1}$ and $k^- = 19 \text{ min}^{-1}$ are the β -catenin–proteasome association and dissociation rates, respectively. The functions $c_i(t)$ and $d_i(t)$ measure the amount of cadherin stimulated to form bonds by physical contact with neighbouring cells. The function $c_i(t)$ is defined as follows:

$$c_i(t) = \sum_{\text{newcontacts}} a_{c,j}(t)\rho_c,$$

where $a_{c,j}(t)$ models the area of the newly formed cell–cell contact of cell i with its local neighbour j , $\rho_c = 200 \text{ min}^{-1}$ is the rate at which E-cadherin concentration translocates from cytoplasm to the intermembrane position when induced by cell–cell contact stimuli. The function $d_i(t)$ describes the equivalent effect if detachment occurs, i.e.

$$d_i(t) = \sum_{\text{new detachments}} a_{d,j}(t)\rho_d,$$

where $a_{d,j}(t)$ models the contact area lost by the detachment of cell i from cell j at time t . $\rho_d = 200 \text{ min}^{-1}$ is the rate at which E-cadherin concentration translocates from the intermembrane to the cytoplasm after cell–cell detachment.

The functions $a(t)_{c,j}$ and $a(t)_{d,j}$ determine the area stimulated to interchange the cadherin from the cytosol to the membrane and from the membrane to the cytosol, respectively. These functions are defined as follows:

$$a_{c,j}(t) = \begin{cases} \frac{\partial}{\partial t} \hat{a}(t)_j, & \text{if } \frac{\partial}{\partial t} \hat{a}(t)_j > 0, \\ 0, & \text{otherwise,} \end{cases}$$

and

$$a_{d,j}(t) = \begin{cases} \left\| \frac{\partial}{\partial t} \hat{a}(t)_j \right\|, & \text{if } \frac{\partial}{\partial t} \hat{a}(t)_j < 0, \\ 0, & \text{otherwise,} \end{cases}$$

where $\hat{a}(t)_j$ is the approximated area in contact with the cell j at time t calculated by the spherical caps in contact (this approximation has also been used in [Galle *et al.*, 2005](#)).

Hence, both attachment and detachment of cells lead to an exchange of E-cadherin between the membrane in the contact zone of the interacting cells. It is assumed that (3.8) and (3.8) determine the concentrations of β -catenin and β -catenin–E-cadherin only as long as the soluble β -catenin concentration is below a threshold c_T . In the case $[\beta] > c_T$, we consider the soluble β -catenin in cytoplasm to be large enough and as a consequence, it is free to enter the nucleus and interact with transcription factors causing the cell to migrate. As a necessary step of migration, cell detachment occurs. To model the active detachment process, it is assumed that for $[\beta] > c_T$,

$$\begin{aligned} d_i[E/\beta] &= -(\alpha + d_i(t))[E/\beta], \\ d_i[\beta] &= (\alpha + d_i(t))[E/\beta] - k^+[\beta](P_T - [C]) + k^-[C] + k_m \end{aligned} \quad (3.9)$$

replace the original equations (3.8) and (3.8), respectively. α is the rate at which the complex is dissociated once the migration decision has been made.

Since the molecular kinetics of β -catenin and its interaction varies between different cells, each cell within the model is considered as an individual entity whose intracellular dynamics are governed by the previous equations. Motivated by the observations that cells in isolation tend to aggregate, it is assumed that an invasive cell changes into a non-invasive state again if it comes into contact with other cells to which it can attach to. In this case, (3.8) and (3.8) are recovered.

3.2 Cell level modelling: the biophysical model of a single cell

Each cell is modelled as an isotropic elastic object capable of migration and division and parameterize it by cell kinetic, biophysical and cell biological parameters that can be experimentally measured. The key features of this modelling approach are now described below.

3.2.1 Cell–cell shape. It is assumed that an individual cell in isolation is spherical and the cell shape of a spherical cell is characterized by its radius R .

3.2.2 *Cell division.* In the model, the cell cycle will be subdivided into two phases—the mitotic phase where a cell divides into two daughter cells and the interphase, the period of time between two mitotic events. It is assumed that during interphase, the cell doubles its mass and model the process of cell division by replacing two cells of size R by two daughter cells of radius $R/2^{1/3}$ which then gradually grow during interphase to their original radius R . This radius value to determine the size of the new daughter cells was taken in according to the experiments performed by [Galle et al. \(2005\)](#), where they reproduced realistic tumour growth curves using an individual force-based model of similar characteristics to ours.

3.2.3 *Cell–cell interaction.* With decreasing distance between the centres of two cells (e.g. upon compression), both their contact area and the number of adhesive contacts increase, resulting in an attractive interaction. On the other hand, if cells are spheroidal in isolation, a large contact area between them significantly stresses their cytoskeleton and membranes. Furthermore, experiments suggest that cells only have a small compressibility (i.e. the Poisson numbers are close to 0.5). In this instance, both the limited deformability and the limited compressibility give rise to a repulsive interaction. The combination of the repulsive and attractive energy contributions is modelled by a modified Hertz model ([Galle et al., 2005](#); [Schaller & Meyer-Hermann, 2005](#)) where the potential V_{ij} between two cells of radius R_i and R_j is given by

$$V_{ij} = \underbrace{(R_i + R_j - d_{ij})^{5/2} \frac{1}{5\tilde{E}_{ij}} \sqrt{\frac{R_i R_j}{R_i + R_j}}}_{\text{repulsive forces}} + \underbrace{\epsilon_s}_{\text{adhesive forces}}. \tag{3.10}$$

The first term of the equation models the repulsive interaction and the second term the adhesive interaction and \tilde{E}_{ij} is defined by

$$\tilde{E}_{ij} = \frac{3}{4} \left(\frac{1 - \sigma_i^2}{E_i} + \frac{1 - \sigma_j^2}{E_j} \right). \tag{3.11}$$

Here, E_i and E_j are the elastic moduli of the cells i, j , σ_i, σ_j the Poisson ratios of the spheres. $\epsilon_s \approx \varrho_m A_{ij} W_s$, where $W_s \approx 25k_B T$ (T is temperature and k_B is Boltzmann constant) is the energy of a single bond, A_{ij} the contact area between cells i, j and ϱ_m is the density of surface adhesion molecules in the contact zone, in this case the density of E-cadherin. The interaction force results from deriving the potential function

$$\underline{F}_{ij} = -(\partial V_{ij} / \partial d_{ij})(d(d_{ij})/dx, d(d_{ij})/dy, d(d_{ij})/dz). \tag{3.12}$$

The modified Hertz model approximates a cell as an elastic sphere and superimposes the repulsive force that emerge in case of a deformation or compression of the sphere with an attractive contribution due to cell–cell adhesion. In some cancer cell lines, a hysteresis effect has been observed, i.e. the attachment and detachment of cells occur at different distances between the cell centres. However, [Drasdo et al. \(2007\)](#) have been shown that the effect of the hysteresis is only a delay in the detachment, while the qualitative behaviour of the detachment process does not depend on the existence of the hysteresis. The advantage of the modified Hertz model is that both the interaction energy and the force can be represented as an analytical expression, while for models that represent the hysteresis effect such as the Johnson–Kendall–Roberts model, the force has to be calculated numerically from an implicit equation ([Drasdo & Hoehme, 2005](#)).

3.2.4 *Cell movement.* The direct use of equations of motion for the cells permits one to include more easily the limiting case of very small (or no) noise and is more intuitive. In this approach, cells move under the influence of forces and a random contribution to the locomotion which results from the local exploration of space. Moreover, in some of the scenarios explained below, a chemoattractant chemical generates a force-like term in the Langevin equation as suggested in [Stevens \(2000\)](#):

$$\underbrace{\underline{\underline{\Gamma}}_{is}^f \underline{v}_i}_{s\text{-friction}} + \sum_{j \text{ nn } i} \underbrace{\underline{\underline{\Gamma}}_{ij}^f (\underline{v}_i - \underline{v}_j)}_{\text{cell-cell friction}} = \underbrace{\sum_{i \text{ nn } j} \underline{E}_{ij}}_{\text{forces}} + \underbrace{\underline{f}_i(t)}_{\text{noise}} + \underbrace{\chi \underline{\nabla} Q(t)}_{\text{chemotaxis}}. \quad (3.13)$$

Inertia terms are neglected due to the high friction of cells with their environment, and the existence of any memory term as in [Galle *et al.* \(2005\)](#) is not considered. \underline{v}_i is the velocity of the cell i at time t , \underline{E}_{ij} is the force of cell j on cell i (previously calculated from the implicit equations (3.10) and (3.11) and the sums are over the nearest neighbours in contact with cell i . The *s-friction* term determines the friction with the substrate and the *cell-cell friction* determines the friction with the nearest neighbours. The tensors $\underline{\underline{\Gamma}}_{ij}^f$ and $\underline{\underline{\Gamma}}_{is}^f$ denote cell-cell friction and cell-substrate friction, respectively. In the model, cells are considered to be spherical and to be surrounded by a homogeneous and an isotropic environment, either a gel or a homogeneous intracellular matrix, depending on the experimental situation under consideration. Under these assumptions, the cell-substrate friction tensor takes the form

$$\underline{\underline{\Gamma}}_{is}^f = \gamma \underline{I},$$

where \underline{I} denotes the identity matrix and γ is the friction coefficient of the medium. The cell-cell friction is described by the tensor ([Drasdo *et al.*, 2007](#))

$$\underline{\underline{\Gamma}}_{ij}^f = \gamma_{\parallel}^{(ij)} \underline{n}_{ij} \underline{n}_{ij} + \gamma_{\perp}^{(ij)} (\underline{I} - \underline{n}_{ij} \underline{n}_{ij}).$$

\underline{x}_i and \underline{x}_j are the position of the centre of mass of the cells and $\underline{n}_{ij} = \frac{\underline{x}_j - \underline{x}_i}{|\underline{x}_j - \underline{x}_i|} \cdot \underline{n}_{ij} \underline{n}_{ij}$ here denotes the dyadic product, i.e. it is a 3×3 matrix. $\gamma_{\parallel}^{(ij)}$ and $\gamma_{\perp}^{(ij)}$ are the parallel and perpendicular friction constants, respectively. The *force* term is the force that cell i exerts on the other cells in contact with it. The *noise* term models the random component in the cell movement (the micromotility) and is chosen to be uncorrelated as explained in [Galle *et al.* \(2005\)](#) and [Drasdo *et al.* \(2007\)](#), i.e.

$$\langle \underline{f}(t) \underline{f}(t') \rangle \approx 2 \hat{\underline{\underline{\Gamma}}} \delta(t - t')$$

and zero mean

$$\langle \underline{f}(t) \rangle = 0.$$

$\hat{\underline{\underline{\Gamma}}}$ denotes the amplitude of the autocorrelated noise. Here, we approximate $\hat{\underline{\underline{\Gamma}}} \approx 2\gamma^2 D \underline{I}$. D is the diffusion constant and characterizes the free random movement of isolated cells in the medium. Typically, $D \approx 10^{-12} \text{ cm}^2/\text{s}$.

The *chemotaxis* term is the chemotactic/haptotactic response towards a gradient of morphogen $Q(t)$ and χ is the cell sensitivity to the chemical. This last term is included in specific computational simulation scenarios of cancer cell invasion of blood vessels which initiate metastatic spread.

3.3 Coupling of cell parameters to intracellular molecule concentrations

In the model, the adhesion forces between cells are controlled by the density of E-cadherin in the cell membrane within the cell–cell contact zone. A value for the adhesion energy per unit of area of $W_s \varrho_m = 100 \mu \text{ Nm}^{-1}$ is used (cf. Galle *et al.*, 2005), so that the surface receptor density is $\varrho_m = 100 \mu \text{ Nm}^{-1} W_s^{-1}$. This value is used as a maximum density of the cadherin– β -catenin complex in the membrane and so the actual density is defined by

$$\varrho = \frac{[E/\beta]}{E_T} \varrho_m.$$

For our computational simulations, all cadherin concentrations are non-dimensionalized by E_T , so that the non-dimensional concentrations of free E-cadherin in the cytoplasm and in the membrane and of E-cadherin within E-cadherin– β -catenin complexes are all in the interval $[0, 1]$.

By modifying the intracellular concentration of β -catenin, the cells can control the concentration of $[E\text{erin}/\beta]$ complexes and thereby the strength of the intercellular adhesion force. The active decision of a cell to migrate can be triggered in different ways, all of them involving an upregulation of the soluble β -catenin which overcomes the critical threshold c_T . One case happens if the cytoplasmic concentration of β -catenin is upregulated due to a failure in the *proteasome* system. A further case happens if the detachment of local neighbours upregulates the soluble β -catenin concentration. In both cases, β -catenin enters the nucleus and triggers cell migration. One way that this could cause rupture of the cell–cell contacts is by physical forces that a cell that starts to migrate exerts on the cadherin bonds in the cell–cell contact area to its neighbours. In the simulations presented here, we have chosen the last term in (3.13) that represents chemotaxis so large that the cells at the tumour surface were not able to detach by breaking the cell–cell contacts but they need to downregulate their adhesion molecules. However, detachment could also be triggered by an increase of the intrinsic random movement component of a cell represented by the *noise* term, which is not considered here.

Computational simulation results from this model are given in Ramis-Conde *et al.* (2008b, 2009) where applications of the model to growing and developing cancers are investigated. In Fig. 4, we present the computational simulation results of an application of the model to the intravasation of a cancer cell into a blood vessel. As can be seen from the plots, the individual cancer cell (red) approaches the blood vessel (composed of individual endothelial cells) under the influence of a chemotactic field. When contact is made, the cancer cell interacts with several individual endothelial cells and disrupts their adhesive bonds sufficiently to enable it to penetrate into the blood vessel. Intravasation is the first and most crucial stage of metastatic spread of cancer.

3.4 Tissue level modelling

In addition to modelling at a tissue level by undertaking computational simulations of the individual cell model, it is also possible to develop continuum models of systems of nonlinear partial differential equations. The first model of this type that is described here considers three key variables active in cancer invasion: cancer cells n , matrix degrading enzymes m and tissue v . This relatively simple but novel model will consider cancer cell random migration, cell–cell adhesion, cell–matrix adhesion, matrix

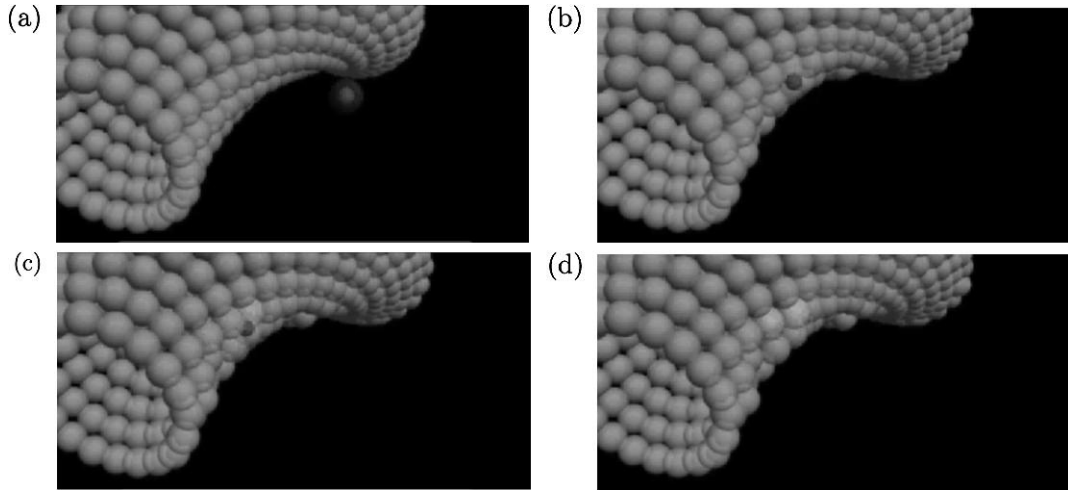


FIG. 4. Plots (a)–(d) showing the progression over time of an individual cancer cell as it approaches a blood vessel under the influence of a chemotactic field. When contact is made, the cancer cell interacts with several individual endothelial cells and disrupts their adhesive bonds sufficiently to enable it to penetrate into the blood vessel.

degrading enzyme secretion/production, diffusion and decay and tissue degradation as follows:

$$\frac{\partial n}{\partial t} = \nabla \cdot [D_1 \nabla n - n \mathcal{A}\{\underline{u}(t, \cdot)\}] + \mu_1 n(1 - n - v), \quad (3.14a)$$

$$\frac{\partial v}{\partial t} = -\gamma m v + \mu_2(1 - n - v), \quad (3.14b)$$

$$\frac{\partial m}{\partial t} = \nabla \cdot [D_3 \nabla m] + \alpha c - \lambda m, \quad (3.14c)$$

with appropriate initial conditions and periodic boundary conditions in domains $\Omega = (-4, 4)$ in 1D and $\Omega = (-1.5, 1.5)^2$ in 2D.

The non-local term $\mathcal{A}\{\underline{u}(t, \cdot)\}$ is referred to as the *adhesion velocity*. It is a function of $\underline{x} \in \Omega$ and, for a 1D spatial domain, takes the form

$$\mathcal{A}\{\underline{u}(t, \cdot)\}(\underline{x}) := \frac{1}{R} \int_0^R \sum_{k=0}^1 \underline{\eta}(k) \cdot \Omega(r) g(\underline{u}(t, \underline{x} + r \underline{\eta}(k))) dr,$$

with right and left unit outer normal vector $\underline{\eta}(k) = (-1)^k$, $k = 0, 1$. For a 2D spatial domain, the adhesion velocity is defined by

$$\mathcal{A}\{\underline{u}(t, \cdot)\}(\underline{x}) := \frac{1}{R} \int_0^R r \int_0^{2\pi} \underline{\eta}(\theta) \cdot \Omega(r) g(\underline{u}(t, \underline{x} + r \underline{\eta}(\theta))) d\theta dr,$$

with $\underline{\eta}(\theta) = (\cos \theta, \sin \theta)^\top$ denoting the unit outer normal vector corresponding to angle θ . So in d spatial dimensions, the integral is over a d -dimensional ball with radius $R > 0$ centred in \underline{x} , the *sensing region* at \underline{x} . The parameter $R > 0$ of the non-local term is the so-called *sensing radius*. The integrand is a product of two functions, Ω and g , weighted with the corresponding unit outer normal vector $\underline{\eta}$.

The first factor, which we will refer to as the *radial dependency function*, $\Omega(r)$, depends on the distance $r \geq 0$ from \underline{x} and the second factor, $g(\underline{u})$, on the vector of concentrations \underline{u} at time t and point $\underline{x} + r\eta$. This non-local term represents the velocity of cancer cells at time t and spatial point \underline{x} due to their adhesion to themselves and the extracellular matrix (ECM) sampled over the sensing region at \underline{x} . The above form of the non-local term was originally put forward by [Armstrong et al. \(2006\)](#) as a model for adhesion between single and multiple species of cells. In simplified terms, it can be said that the adhesion velocity of cells at \underline{x} is in the direction where cells can form the most bonds within the sensing region at \underline{x} .

Here, we are concerned with adhesion between the cancer cells themselves (self-adhesion, cell–cell adhesion) and cancer cells and ECM (cross-adhesion, cell–matrix adhesion). To complete the definition of the non-local term, it remains to specify the functions g and Ω . We use the following form for the function g

$$g(n, v) = (S_{nn}n + S_{nv}v) \cdot (1 - n - v)^+.$$

In the above, $(\cdot)^+ := \max\{0, \cdot\}$, S_{nn} is the cell–cell adhesion coefficient and S_{nv} is the cell–matrix adhesion coefficient. As in the haptotaxis and the logistic growth terms, the factor $(1 - n - v)^+$ ensures that a space point (or region) which is already densely filled with cells and/or ECM does not contribute to determine the direction of migration due to adhesion; if the physical space at this point is overcrowded already, i.e. $1 - n - v < 0$, then it also has no influence. This way unbounded aggregation is avoided. The function $\Omega(r)$ describes how strong the adhesion velocity $\mathcal{A}\{\underline{u}(t, \cdot)\}(\underline{x})$ is influenced by points of the sensing region at \underline{x} depending on their distance r from \underline{x} . It should, however, not alter the magnitude of the adhesion velocity. For this reason, we require that $\Omega(r)$ is normalized in the sense that its integral over the sensing region is one. For problems in 1D and 2D space, this amounts to

$$\int_0^R 2\Omega(r) dr = 1 \quad \text{and} \quad \int_0^R 2\pi r \Omega(r) dr = 1,$$

respectively. This normalization also implies that $\mathcal{A}\{\underline{u}(t, \cdot)\}(\underline{x})$ is a weighted average of g around \underline{x} . We consider two qualitative forms for $\Omega(r)$. First, a form independent of r , which leads to

$$\Omega_1(r) = \frac{1}{2R} \quad \text{and} \quad \Omega_1(r) = \frac{1}{\pi R^2},$$

in 1D and 2D, respectively. For the second form, we assume that $\Omega(r)$ decays linearly to $\Omega(R) = 0$. This leads to

$$\Omega_2(r) = \frac{1}{R} \left(1 - \frac{r}{R}\right) \quad \text{and} \quad \Omega_2(r) = \frac{3}{\pi R^2} \left(1 - \frac{r}{R}\right)$$

in 1D and 2D, respectively. The first form Ω_1 implies that all points within the sensing region have an equal influence, whereas the second form Ω_2 implies that the influence decays with increasing distance from the centre.

Computational simulation results from this model are given in [Gerisch & Chaplain \(2008\)](#) and [Chaplain et al. \(2011\)](#) where a rich range of dynamic heterogeneous solutions are found and the roles of cell–cell and cell–matrix adhesion are explored in some detail.

3.5 The role of the uPA system

The prognosis of a cancer is primarily dependent on its ability to invade and metastasize, and a crucial component of these processes is the degradation of ECM. A major component of ECM are proteins

and their directed degradation by cellular enzymes (proteolytic enzymes or *proteases* for short) is called *proteolysis*. Many steps that occur during tumour invasion and the formation of metastasis (as well as in a number of distinct physiological events in the healthy organism) require the regulated turnover of ECM macromolecules. A more localized degradation of matrix components is required when cells migrate through a basal lamina. In any case, it is now widely believed that the breakdown of these barriers is catalysed by proteases released from the invading cancer cells. Most of these proteases belong to one of two general classes: MMPs or *serine proteases*. Proteases give cancers their defining deadly characteristic—the ability of malignant cells to break out of tissue compartments.

The enzymatic system we will focus on in this project is the *uPA system*, which consists of

- uPA, the urokinase plasminogen activator,
- uPAR, the urokinase plasminogen activator receptor,
- VN, the ECM protein vitronectin and
- PAI-1, the plasminogen activator inhibitor type-1.

uPA is an extracellular serine protease. Cells secrete its enzymatically inactive form pro-uPA into the extracellular space. pro-uPA is activated by plasmin to its active form uPA. In the model below, we do not distinguish between pro-uPA and uPA, which both bind to uPA receptors (uPARs) located on the cell membrane. Two major functional domains make up the uPA molecule: the protease domain and the growth factor domain (not discussed here). The protease moiety in uPAR-bound uPA activates the proenzyme plasminogen to its active form plasmin. Plasminogen is a ubiquitous protein produced mainly in the liver and present in the blood and the ECM. Plasmin itself is a broadly acting serine protease that, either directly or through the activation of other proteases, catalyses the breakdown of many of the known ECM and basement membrane molecules, such as vitronectin (VN), fibronectin, fibrin, laminin, thrombospondin and collagens. Plasmin also can affect the activity of cytokines and growth factors, notably transforming growth factor- β , which influences the composition of the extracellular milieu. Thus, the unrestrained generation of plasmin from plasminogen by the action of uPA is potentially hazardous to cells. Therefore, to maintain tissue *homeostasis* and to avoid unrestrained tissue damage, the process of plasminogen activation in a healthy organism is strictly controlled through the availability of uPA, localized activation and interaction with specific inhibitors (PAIs). One of these inhibitors, PAI-1, is believed to be the most abundant fast acting inhibitor of uPA *in vivo*. In other words, for cells to protect themselves, they must secrete a surplus of inhibitors to guarantee restraint of pericellular proteolysis. Indeed, secreted uPA is often associated with PAI-1 and remains inactive. PAI-1 has a high affinity to the ECM constituent VN and VN-bound PAI-1 remains in an active conformation for prolonged periods of time.

These facts suggest to us that the four molecules uPA, PAI-1, uPAR and VN (an example of one ECM macromolecule) constitute the core of an integrated dynamical system, which allows spatial and temporal rearrangements of its components at cell surfaces during cell migration and invasion. Moreover, it has become clear that this system has a multifunctional role in cancer biology. The system seems to function not only in cancer cell migration and invasion but also in remodelling of the tissue surrounding the cancer cells, which may contribute decisively to the overall process of metastasis.

In the model now considered here, we combine the model of Gerisch & Chaplain (2008) and consider the interactions of cancer cells, matrix and l chemicals described by a system of $l + 1$ non-local

taxis–diffusion–reaction equations of the form

$$\partial_t n = D_n \Delta n - \nabla \cdot \left(n \sum_{j=1}^l p_j(n, \underline{c}) \nabla c_j + n \mathcal{A}\{\underline{c}(t, \cdot)\} \right) + f(n, \underline{c}), \tag{3.15a}$$

$(t, \underline{x}) \in (0, T] \times \Omega.$

$$\partial_t \underline{c} = \mathbf{D} \Delta \underline{c} + \underline{g}(n, \underline{c}), \tag{3.15b}$$

where the time (t) and space (\underline{x}) dependent concentrations of the chemical species are denoted by the vector-valued function $\underline{c}(t, \underline{x})$ and the density of the cancer cells by $n(t, \underline{x})$,

$$\underline{c} : [0, T] \times \bar{\Omega} \rightarrow \mathbb{R}^l \quad \text{and} \quad n : [0, T] \times \bar{\Omega} \rightarrow \mathbb{R}.$$

Here, $\Omega \subset \mathbb{R}^d$, $d = 1$ or $d = 2$, is a bounded domain and $[0, T]$ is the time interval of interest. Furthermore, the cancer cell random motility coefficient $D_n \geq 0$ and the diagonal matrix $\mathbf{D} \geq 0$ of chemical diffusion coefficients, the taxis functions p_j , $j = 1, \dots, l$, associated with each chemical c_j , as well as the reaction terms f and g are given. The temporal derivative is denoted by ∂_t , the spatial gradient operator by ∇ and the Laplace operator by Δ . The partial differential equation system (3.15) is supplied with appropriate initial and boundary conditions.

Denoting the uPA concentration by $u(t, \underline{x})$, the PAI-1 concentration by $p(t, \underline{x})$, the plasmin concentration by $m(t, \underline{x})$ and the VN concentration by $v(t, \underline{x})$. An appropriate initial mathematical model, in a non-dimensionalized form, is given by

$$\partial_t v = - \underbrace{\delta v m}_{\text{degradation}} + \underbrace{\phi_{21} u p}_{\text{uPA/PAI-1}} - \underbrace{\phi_{22} v p}_{\text{PAI-1/VN}} + \underbrace{\mu_2 v (1 - n - v)}_{\text{remodelling}}, \tag{3.16a}$$

$$\partial_t u = \underbrace{D_u \Delta u}_{\text{diffusion}} - \underbrace{\phi_{31} p u}_{\text{uPA/PAI-1}} - \underbrace{\phi_{33} n_i u}_{\text{uPA/uPAR}} + \underbrace{\alpha_{31} n_i}_{\text{production}}, \tag{3.16b}$$

$$\partial_t p = \underbrace{D_p \Delta p}_{\text{diffusion}} - \underbrace{\phi_{41} p u}_{\text{PAI-1/uPA}} - \underbrace{\phi_{42} p v}_{\text{PAI-1/VN}} + \underbrace{\alpha_{41} m}_{\text{production}}, \tag{3.16c}$$

$$\partial_t m = \underbrace{D_m \Delta m}_{\text{diffusion}} + \underbrace{\phi_{52} p v}_{\text{PAI-1/VN}} + \underbrace{\phi_{53} u n_i}_{\text{uPA/uPAR}} - \underbrace{\phi_{54} m}_{\text{degradation}}. \tag{3.16d}$$

Figure 5 shows the computational simulation results of an application of the model to the cancer cell invasion of ECM. The parameter values have been chosen to model a highly malignant cancer with reduced cell–cell adhesion. As can be seen from the figures, the cancer cells have penetrated into the ECM in a very heterogeneous manner, with some groups of cancer cells breaking off from the main mass and spreading quite deeply into the ECM. This type of heterogeneous invasive penetration makes complete surgical removal of a cancer very difficult. Full details of the model and parameter values chosen can be found in [Andasari et al. \(2011\)](#).

4. Discussion

Who of us would not be glad to lift the veil behind which the future lies hidden; to cast a glance at the next advances of our science and at the secrets of its development during future centuries? What particular goals will there be toward which the leading mathematical

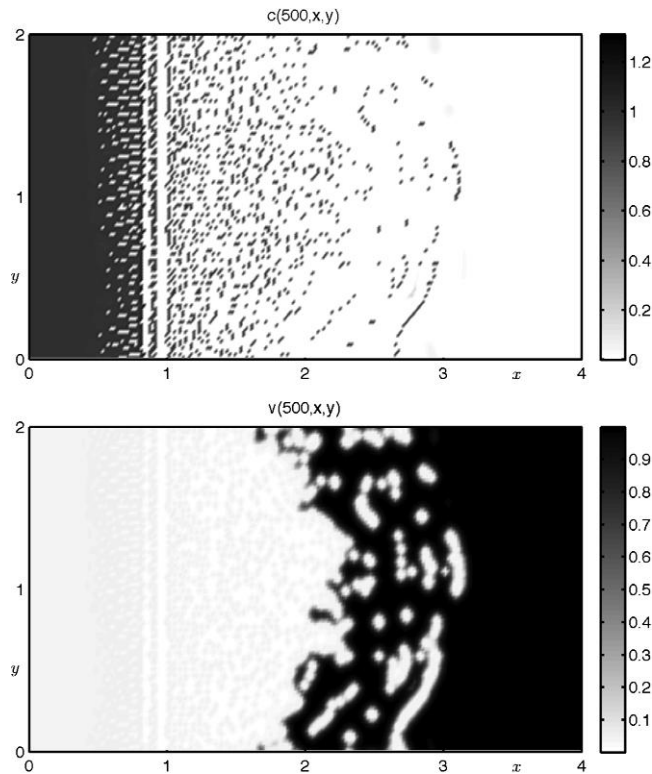


FIG. 5. Plots showing the invasion of ECM by an aggressive malignant cancer with reduced cell–cell adhesion. The upper figure shows the distribution of the cancer cell density, while the lower figure shows the corresponding distribution of the ECM.

spirits of coming generations will strive? What new methods and new facts in the wide and rich field of mathematical thought will the new centuries disclose?

D. Hilbert, opening of his speech to the 1900 Mathematics Congress in Paris

A century on, the words of David Hilbert still ring true, resonating particularly strongly when considering mathematics applied to the life sciences in our brave new postgenomic world. Elucidating the complex interplay of factors regulating higher-order tissue-level phenomena via cell–cell and cell–matrix interactions has emerged as a major scientific challenge in the postgenomic era. Progress in this endeavour and its effective translation into improved clinical practice and commercial competitiveness, with all the concomitant societal benefits, is now recognized to require an integrated multidisciplinary approach bringing together scientists and clinicians from diverse backgrounds. Mathematics has a central role to play in all of this.

The past 20 years have witnessed enormous advances in our understanding of the molecular basis of cell structure and function. Scientists, as well as the lay public, are cognizant of the spectacular success of the human genome project and the consequent burgeoning interest in the related field of proteomics. Biochemists and cell biologists have made similarly impressive strides in elucidating the mechanisms mediating cell signalling and its consequences for the control of cell proliferation, motility and gene expression. It is, however, abundantly clear that reductionist logic using this impressive subcell level

information base is not sufficient to deduce an understanding of phenomena operative at the next higher level of biological organization: the tissue. Employing a literary analogy, the vast omic databases of catalogued genes and proteins, taken together with our growing understanding of the inner workings of individual cells, provide a dictionary and a grammatical syntax required for the next great challenge, i.e. understanding the sentences and paragraphs characteristic of emergent tissue-level phenomena.

The description of most biological processes in the human body involves many different but interconnected phenomena, which occur at different spatial and temporal scales. From the mathematical modelling viewpoint, there are three natural scales of interest: subcellular, cellular and tissue. Using techniques from modern applied mathematics and computational science, in the last few years, novel multiscale mathematical models have been developed, which are now beginning to describe in more detail complex biomedical systems such as wound healing, cancer growth and spread, embryonic development, heart physiology, drug delivery and tissue engineering.

The development of quantitative predictive multiscale models by applied mathematicians (based on sound biological evidence and underpinned and parameterized by biological data) is now beginning to have a positive impact on patients suffering from debilitating diseases through improved clinical treatment.

Biology is the new physics and cancer may one day be cured with calculus.

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