Mathematical modelling of cancer cell invasion of tissue: Local and non-local models and the effect of adhesion

A. Gerisch\textsuperscript{a,}\textsuperscript{*}, M.A.J. Chaplain\textsuperscript{b,1}

\textsuperscript{a}Martin-Luther-Universität Halle-Wittenberg, Institut für Mathematik, Postfach, 06099 Halle (Saale), Germany
\textsuperscript{b}The SIMBIOS Centre, Division of Mathematics, University of Dundee, Dundee DD1 4HN, Scotland, UK

Received 23 August 2007; received in revised form 11 October 2007; accepted 12 October 2007

Abstract

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 may ultimately lead to treatments being developed which can localise cancer and prevent metastasis. In this paper we formulate a novel continuum model of cancer cell invasion of tissue which explicitly incorporates the important biological processes of cell-cell and cell-matrix adhesion. This is achieved using non-local (integral) terms in a system of partial differential equations where the cells use a so-called “sensing radius” \( R \) to detect their environment. We show that in the limit as \( R \to 0 \) the non-local model converges to a related system of reaction-diffusion-taxis equations. A numerical exploration of this model using computational simulations shows that it can form the basis for future models incorporating more details of the invasion process.

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Keywords: Cancer invasion; Cell-cell adhesion; Cell-matrix adhesion; Non-local model

1. Introduction

\textit{In vivo} cancer growth is a complicated “multi-scale” phenomenon involving many inter-related biochemical and cellular processes at many different spatial and temporal scales. Although there are many different types of cancers, solid tumours (e.g. carcinoma, sarcoma) make up a large fraction of all clinically observed cancers and we focus on modelling solid tumours in this paper. The growth of solid tumours occurs in two distinct phases: the initial growth being referred to as the relatively harmless \textit{avascular phase} and the later growth as the \textit{vascular phase}. During the early avascular stage of solid tumour growth there may be an immune response to the cancer from the host, with cells of the immune system, most notably T-lymphocytes, responding to and attacking the cancer cells. However, unfortunately solid tumours do not always remain avascular and localised. The transition from avascular growth to vascular growth depends upon the crucial process of angiogenesis which is necessary for the tumour to attain nutrients and dispose of waste products (Folkman, 1974, 1976). To achieve vascularisation, tumour cells secrete a diffusible substance known as tumour angiogenesis factor (TAF) into the surrounding tissue (Folkman and Klagsbrun, 1987). This has the effect of stimulating nearby capillary blood vessels to grow towards and penetrate the tumour, re-supplying the tumour with vital nutrient. Invasion and metastasis can now take place. Indeed, invasion, the ability of cancer cells to break out of tissue compartments and spread locally, gives solid tumours a defining deadly characteristic (Hanahan and Weinberg, 2000). The first step of invasion is the over-expression of proteolytic enzymes, such as the urokinase-type plasminogen activator (uPA) and matrix metalloproteinases (MMPs), by the cancer cells. Degradation of the matrix then enables the
cancer cells to proliferate and migrate through the tissue and to spread to secondary sites in the body (metastasis). Unravelling and better understanding the processes involved in cancer cell invasion of tissue is therefore of the utmost importance for gaining a deeper insight into tumour growth and development, and the design of future anti-cancer strategies.

Over the last 10 years or so, increasingly complex models of cancer cell invasion of tissue have appeared in the research literature, cf. Gatenby (1995), Gatenby and Gawlinski (1996), Perumpanani et al. (1996), Anderson et al. (2000), see also the book Preziosi (2003). Each of these models adopted a continuous approach, using systems of partial differential equations (PDE) of a generic chemotaxis/haptotaxis nature. More recently, a discrete (individual cell based) approach has been adopted, acknowledging the fact that certain processes can be more easily and effectively modelled in this way (Anderson et al., 2000). Both approaches have been combined in a hybrid modelling technique (Anderson, 2005). Individual-based models also allow for the straightforward integration of different (cancer) cell phenotypes of increasing aggressiveness (Anderson et al., 2006), cf. Schofield et al. (2005). The main drawbacks of individual-based and also hybrid models are their high computational simulation effort and their, in general, resistance to rigorous analysis, see, however, Dormann et al. (2001). That it is possible to include more details of importance to the invasion process in a continuous modelling framework has been demonstrated by coupling the uPA-system dynamics to a model of cancer cell invasion (Chaplain and Lolas, 2005, 2006; Chaplain et al., 2007). The latter paper also includes a brief discussion and simulation results for a model involving two cancer cell phenotypes. In a series of papers (Marchant et al., 2000, 2001, 2006) models of cancer cell invasion similar in spirit to those of Anderson et al. (2000) but extending in various directions are proposed. An important part of their work deals with travelling wave analysis for these models and for a simplified model, obtained using a quasi-steady state assumption, the existence of travelling shock waves is established.

The models mentioned so far are all based on the assumption that cells move in response to chemotactic and/or haptotactic cues. This movement, however, is facilitated by the binding and unbinding of cell surface molecules to other cells and/or the extracellular matrix (ECM) leading to cell-cell and cell-matrix adhesion, respectively. The adhesion molecules are transmembrane proteins, for example, cadherins in cell-cell adhesion and integrins in cell-matrix adhesion. The strength and number of such binding processes are mediated by chemical cues present in the cell’s microenvironment and subsequently lead to the observed cell movement due to chemotaxis and haptotaxis. So on a more fundamental, yet still phenomenological level, cell movement is caused by cell-cell and cell-matrix adhesive properties modulated by the cell’s microenvironment. Recently, a continuum description of cell motility due to cell-cell adhesion has been introduced by Armstrong et al. (2006). This is achieved by including a non-local interaction term accounting for adhesion in a PDE model. The cases of single and of multiple interacting cell populations are considered. In the application we have in mind, we have a non-motile ECM “population” and one (or potentially more) population of cancer cells whose motion is driven by adhesive effects between the cancer cell population itself (self-adhesion i.e. cell-cell adhesion) and between the cancer cell population and the ECM (cross-adhesion i.e. cell-matrix adhesion). We also note that a generic model of Keller–Segel type but with a non-local chemotaxis term is studied and analysed in Hillen et al. (2007).

Other models of (cancer) cell invasion of tissue also exist, using slightly different approaches. For instance, Hillen (2006) and Painter (2007) study the process of cell invasion into the ECM and consider a mesoscopic model where the cell and matrix densities are functions of time, space, and orientation. The dependence on orientation allows for a considerably more detailed modelling of specific cell migration strategies. This approach is applied to cancer cell invasion in Painter (2007).

In the work of Byrne and Chaplain (1996) a model of cancer growth and invasion is put forward employing ideas from crystal growth processes and Hele–Shaw flow, developing an earlier idea of Greenspan (1976). Birth and death processes in the cancer cell population are assumed to generate a cell velocity field which is then related to an internal pressure field (via Darcy’s law). Cell-cell adhesion is modelled by incorporating a surface tension force at the tumour surface (cf. Gibbs–Thomson relation) which then controls the evolution of the tumour shape during growth. This work has been taken up and extended in recent models (Cristini et al., 2003; Macklin and Lowengrub, 2007). These surface tension models account for cell-cell adhesion in a phenomenological way but, as yet, do not include cell-matrix adhesive effects.

In this paper, we present a novel continuum model for cancer cell invasion of tissue developing the ideas of Armstrong et al. (2006). The objectives of the current paper are as follows:

1. Formulate a basic PDE model of cancer cell invasion where directed cell migration is governed by haptotaxis, Section 2.1. This model will be based on the model proposed by Anderson et al. (2000).
2. Modify this model to include non-local terms explicitly accounting for cell-cell and cell-matrix adhesion, Section 2.2, and relate the non-local model to the local model by considering an appropriate limit, Section 2.3.
3. Implement numerical schemes (1D and 2D) for the efficient simulation of the local and the non-local model, see Appendix A.
4. Computationally study the differences in simulation outcomes between both models in one and two space dimensions, see Sections 3 and 4, respectively.
2. A basic mathematical model of cancer cell invasion of tissue

The basis of the models discussed in this paper is the PDE model introduced in Anderson et al. (2000). We modify and extend this model as is detailed below. As in Anderson et al. (2000), all models discussed in this paper have three time- and space-dependent variables:

- $c(t, x)$: the cancer cell density,
- $v(t, x)$: the density of the extracellular matrix (ECM), and
- $m(t, x)$: the concentration of a generic matrix-degrading enzyme (MDE).

Here, time $t \in [0, T_{\text{end}}]$ and the $d$-dimensional spatial variable $x \in \Omega \subset \mathbb{R}^d$, where $\Omega$ is a bounded domain. We consider the cases $d = 1$ and 2 in this work. For a compact notation we define the vector of these three functions as $y(t, x) := (c(t, x), v(t, x), m(t, x))^T$.

2.1. A local continuum model based on haptotaxis

For the local continuum model we assume that the motion of the cancer cells is governed by random motility and a haptotactic response to ECM gradients. The latter implies that cancer cells are inclined to move up gradients in the ECM density. Furthermore, we assume that cancer cells proliferate and we model this using a logistic growth law. Based on a conservation of mass argument for the cancer cell density, we then arrive at the following equation:

$$\frac{\partial c}{\partial t} = \nabla \cdot [D_1 c \nabla c - \chi c \nabla v] + \mu_1 c(1 - \beta_1 c - \beta_2 v). \quad (1a)$$

The cell random motility coefficient $D_1$ and the haptotactic function $\chi$ are both assumed to be non-negative and can, in general, be functions of time $t$, space $x$, and the solution at the current point $y(t, x)$. In fact recent experimental work (Zaman et al., 2006) has shown that cancer cell motility depends not only on ECM gradients (haptotaxis) but also on ECM density (haptokinesis), i.e. $D_1 = D_1(v)$, in a bi-phasic manner. However, since our main aim here is to focus on gradient-driven migration, throughout the remainder of this paper we assume that $D_1$ is a constant, i.e. we effectively choose to ignore the dependence of the cancer cell motility on the ECM density in the absence of ECM gradients (this matter is discussed in more detail in the concluding section of the paper). Also, as will be seen later, the estimated size of the (non-dimensionalised) value for $D_1$ is small in comparison with the adhesion parameters of the new non-local model that we introduce in Section 2.2. Note, however, that choosing the haptotactic function $\chi(\cdot)$ to be a constant can lead to an aggregation of cancer cells beyond any bound. This is biologically not feasible, corresponds mathematically to a blow-up situation, and can also pose a considerable difficulty for the numerical simulation of the model equations. For these reasons we consider something more elaborate than a constant for $\chi$ and spatial restrictions lead the way. In our model, the physical space is taken up by the cancer cells and the ECM, although they do not need to occupy all space. The space occupied by the MDE is assumed to be negligible or subsumed in the space occupied by the ECM. Assume that cancer cells at unit density occupy a fraction $\beta_1$ of one unit volume of physical space and ECM at unit density occupies a fraction $\beta_2$ of one unit volume of physical space. Then the total fraction of (locally) occupied space, $f_{\text{tot}}$, is given by

$$f_{\text{tot}} := \beta_1 + \beta_2 v. \quad (1b)$$

For a sensible model $0 \leq f_{\text{tot}} \leq 1$ holds for all space and time points. In order to account for increased crowding, the haptotactic function should decrease with increasing fraction of occupied space, $f_{\text{tot}}$, and be zero for $f_{\text{tot}} = 1$. This is achieved by choosing

$$\chi(\cdot) = \chi_{12}(1 - \beta_1 c - \beta_2 v) \quad (1b)$$

with a haptotactic constant $\chi_{12}$. This functional form is also considered in papers by Hillen and Painter (2001), Painter and Hillen (2002) for chemotactic movement with prevention of overcrowding (volume filling). Their ansatz for one species occupying the physical space is generalised here to the case of two such species. In Hillen and Painter (2001) global existence of solutions for such a model is established. With the same reasoning concerning physical space in mind we do not have a simple logistic growth law $\mu_1 c(1 - c)$ in the model equation but consider the locally available space fraction $1 - f_{\text{tot}}$ as proliferation rate limiting. With this, all terms in Eq. (1a) modelling the evolution of the cell density are explained in sufficient detail and we proceed to the evolution of the ECM density.

The ECM is considered as non-motile matter and changes in its distribution are solely due to its local degradation by MDEs upon contact at a rate $\gamma$ and to its remodelling by cancer and other cells. For the latter process we assume a constant rate of matrix remodelling, $\mu_2$, adjusted to respect the physical limitations of space. This is the simplest possible term which allows the ECM density to remodel back to a normal, healthy level while still respecting spatial limitations. Other functional forms for this term may be used, allowing for a more elaborate description of ECM regeneration but we do not consider them here. We also note that except for the simulations in Figs. 10 and 11, we always use $\mu_2 = 0$, i.e. there is no ECM remodelling. Altogether, this yields the following equation for the ECM density evolution:

$$\frac{\partial v}{\partial t} = -\gamma mv + \mu_2 (1 - \beta_1 c - \beta_2 v). \quad (1c)$$
Finally, the MDEs are assumed to diffuse freely in the spatial domain, they are released at a constant rate \( \dot{m} \) by the cells and are removed from the system at rate \( \lambda \). Removal of those enzymes takes place due to natural decay and also by deactivation of the enzymes. The evolution equation for the MDE concentration hence has the form

\[
\frac{\partial m}{\partial t} = \nabla \cdot [D_3(\cdot) \nabla m] + \dot{m} - \lambda m. \tag{1d}
\]

As for \( D_1 \), also the MDE diffusion coefficient \( D_3 \) can, in general, be a functions of \( t, x, \) and \( \vec{u}(t, x) \). For what follows, we assume that \( D_3 \) is a constant.

We non-dimensionalise system (1) by letting

\[
\tilde{t} = \frac{t}{\tau}, \quad \tilde{x} = \frac{x}{L}, \quad \tilde{c}(\tilde{t}, \tilde{x}) = \frac{c(t, x)}{c},
\]

\[
\tilde{m}(\tilde{t}, \tilde{x}) = \frac{m(t, x)}{\bar{m}}.
\]

We use a characteristic length scale \( L \) in the range of 0.1–1 cm. This corresponds to the maximum invasion distance at the early stage of tumour invasion considered (Anderson et al., 2000). The reference time scale \( \tau = L^2/D \), where \( D \) is a characteristic diffusion coefficient \( D \sim 10^{-6} \text{cm}^2 \text{s}^{-1} \), see e.g. Bray (1992). Following Anderson (2005) and references cited there, we use a typical tumour cell volume of \( 1.5 \times 10^{-8} \text{cm}^3 \) per cell, which defines the parameter \( \bar{v} \). The reference cell density \( \bar{c} \) is then defined by the reciprocal value \( \bar{c} \sim \frac{1}{\bar{v}} \). Following Terranova et al. (1985), Anderson et al. (2000) and Anderson (2005) we use a reference matrix density \( \bar{c} = 10^{-13} \text{nM} \) and define the parameter \( \bar{c} \sim \frac{1}{\bar{v}} \). As in Anderson (2005), we leave the reference MDE concentration unspecified due to difficulties in obtaining suitable experimental values. Summarising, we specify the following non-dimensionalisation constants:

\[
\tau = \frac{L^2}{D}, \quad \tau = 10^4 \text{s}, \quad L = 0.1 \text{cm},
\]

\[
\bar{c} = \frac{1}{\bar{v}}, \quad \bar{c} = 6.7 \times 10^7 \text{cell cm}^{-3}, \quad \bar{c} = 10^{-1} \text{nM}.
\]

The model parameters now scale as given in Table 1. The non-dimensionalisation leads, upon dropping the tildes from all parameters and dependent and independent variables, to the following non-dimensional system

\[
\frac{\partial c}{\partial t} = \nabla \cdot [D_1(\cdot) \nabla c] - \chi_{12}(1 - c - v)c \nabla v + \mu_1 c(1 - c - v), \tag{2a}
\]

\[
\frac{\partial v}{\partial t} = -\gamma mv + \mu_2(1 - c - v), \tag{2b}
\]

\[
\frac{\partial m}{\partial t} = \nabla \cdot [D_3 \nabla m] + \dot{m} - \lambda m. \tag{2c}
\]

This system corresponds to the continuous PDE model given in Anderson et al. (2000) except for (i) the logistic growth terms in the first two equations which are missing in Anderson et al. (2000) and (ii) the solution-dependent (volume filling) haptotactic coefficient function \( \chi(\cdot) \) which is simply a constant in Anderson et al. (2000).

The initial conditions (ICs) for the system are an initial cancer cell mass concentrated around the origin, which has released already some MDEs, which have already locally degraded part of the ECM. In non-dimensional form, we use the following set of ICs:

\[
c(0, \chi) = \exp(-|\chi|^2/0.01), \quad v(0, \chi) = 1 - c(0, \chi),
\]

\[
m(0, \chi) = 0.5c(0, \chi). \tag{3}
\]

The IC for the ECM given here differs slightly from that prescribed in Anderson et al. (2000) where \( c(0, \chi) = 1 - 0.5c(0, \chi) \) is used. We introduced the change to ensure that \( c + v \leq 1 \) at \( t = 0 \), i.e. initially the physical space is not overcrowded. In the 2D numerical experiments we will also use a heterogeneous initial ECM density, see Section 4.

In all our experiments we use a spatial domain \( \Omega = (-4, 4) \) in 1D and \( \Omega = (-1.5, 1.5) \) in 2D and prescribe periodic boundary conditions (BCs). The spatial region of interest is \((-1, 1)\) and we have verified that for our numerical experiments the size of \( \Omega \) is large enough to ensure that the BCs have no significant influence on the

<table>
<thead>
<tr>
<th>( \rho )</th>
<th>Unit</th>
<th>( \dot{\rho} )</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \rho_1 )</td>
<td>( \text{cm}^2 \text{s}^{-1} )</td>
<td>( \frac{D_1}{D} )</td>
<td>Cancer cell motility coefficient (( 10^{-10} - 10^{-9} \text{cm}^2 \text{s}^{-1} )), cf. Bray, 1992; Anderson et al., 2000; Anderson, 2005</td>
</tr>
<tr>
<td>( \rho_{12} )</td>
<td>( \text{cm}^{-2} \text{s}^{-1} \text{nM}^{-1} )</td>
<td>( \frac{D_2}{D_{12}} )</td>
<td>Haptotactic coefficient (( 2.6 \times 10^{-6} \text{cm}^2 \text{s}^{-1} \text{nM}^{-1} )), cf. Anderson et al., 2000</td>
</tr>
<tr>
<td>( \rho_\mu_1 )</td>
<td>( \text{s}^{-1} )</td>
<td>( \rho_\mu_1 )</td>
<td>Cancer cell proliferation rate</td>
</tr>
<tr>
<td>( \rho_\gamma )</td>
<td>( \text{nM}^{-1} \text{s}^{-1} )</td>
<td>( \rho_\gamma )</td>
<td>ECM degradation rate</td>
</tr>
<tr>
<td>( \rho_\mu_2 )</td>
<td>( \text{nM}^{-1} \text{s}^{-1} )</td>
<td>( \rho_\mu_2 )</td>
<td>ECM remodeling rate</td>
</tr>
<tr>
<td>( \rho_\beta_1 )</td>
<td>( \text{cm}^3 \text{cell}^{-1} )</td>
<td>( \frac{D_3}{D} )</td>
<td>MDE diffusion coefficient (( 10^{-10} - 10^{-9} \text{cm}^2 \text{s}^{-1} )), cf. Anderson et al., 2000; Anderson, 2005</td>
</tr>
<tr>
<td>( \rho_x )</td>
<td>( \text{s}^{-1} )</td>
<td>( \frac{\bar{c}_x}{\bar{c}} )</td>
<td>Rate of MDE release by cancer cells</td>
</tr>
<tr>
<td>( \rho_\lambda )</td>
<td>( \text{s}^{-1} )</td>
<td>( \bar{\lambda} )</td>
<td>MDE degradation rate</td>
</tr>
</tbody>
</table>
solution. We furthermore use the following baseline set \( \psi_l \) of parameters for the local model (2):

\[
D_1 = 10^{-3}, \quad b_{12} = 0.005, \quad \mu_1 = 0, \quad \gamma = 10,
\]

\[
\mu_2 = 0, \quad D_3 = 10^{-3}, \quad \alpha = 0.1, \quad \varepsilon = 0. \tag{\Psi_l}
\]

This corresponds to those used in Fig. 1 of Anderson et al. (2000) and reflects a situation without cancer cell proliferation, without ECM remodelling, and without MDE decay. Note, however, that the non-dimensional haptotaxis constant \( b_{12} \) in the baseline parameter set is considerably smaller than the non-dimensional value 0.26 obtained by using the dimensional estimate as given in Table 1; we nevertheless stick to the small value as it is used in the numerical experiments of Anderson et al. (2000) and we plan to compare with their results.

2.2. A non-local continuum model based on adhesion

Model (2) includes random motility and haptotaxis as the mechanisms which drive cancer cell migration. Here we now replace the local haptotaxis flux term \(-b_{12}(1 - c - v)\psi_c\) by the non-local flux term \(-c\mathcal{A}[g(t, \cdot)]\) modelling cell–cell and cell–matrix adhesion in the cancer cell equation. The notation suggests that the non-locality is in space but not in time; its precise form is given and discussed below. With this term the non-dimensional non-local model takes the form

\[
\frac{\partial c}{\partial t} = \nabla \cdot \{ D_1 \nabla c - c\mathcal{A}[g(t, \cdot)] \} + \mu_1 c(1 - c - v), \tag{4a}
\]

\[
\frac{\partial v}{\partial t} = -\gamma mv + \mu_2 (1 - c - v), \tag{4b}
\]

\[
\frac{\partial m}{\partial t} = \nabla \cdot \{ D_3 \nabla m \} + \alpha c - \beta m. \tag{4c}
\]

The IC (3) remains unchanged and as for the local model we use the spatial domain \( \Omega = (-4, 4) \) in 1D and \( \Omega = (-1.5, 1.5)^2 \) in 2D and periodic boundary conditions. The baseline set of parameters for the non-local model (4), \( \Psi_n \), is given at the end of this section.

The non-local term \( \mathcal{A}[g(t, \cdot)] \) is referred to as the adhesion velocity. It is a function of \( x \in \Omega \) and, for a 1D spatial domain, takes the form (cf. Armstrong et al., 2006)

\[
\mathcal{A}[g(t, \cdot)](x) = \frac{1}{R} \int_0^R \sum_{k=0}^{1} \eta(k) \cdot \Omega(\gamma)(g(t, x + r \eta(k))) \, dr,
\]

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

\[
\mathcal{A}[g(t, \cdot)](x) = \frac{1}{R} \int_0^{2\pi} \int_0^R \eta(\theta) \cdot \Omega(\gamma)(g(t, x + r \eta(\theta))) \, d\theta \, dr,
\]

with \( \eta(\theta) = (\cos \theta, \sin \theta)^T \) denoting the unit outer normal vector corresponding to angle \( \theta \). So in \( d \) spatial dimensions, the integral is over a \( d \)-dimensional ball with radius \( R > 0 \) centred in \( x \), the sensing region at \( x \). The parameter \( R > 0 \) of the non-local term is the so-called sensing radius. The integrand is a product of two functions, \( \Omega \) and \( g \), weighted with the corresponding unit normal vector \( \eta \). The first factor, which we will refer to as the radial dependency function, \( \Omega(r) \), depends on the distance \( r \geq 0 \) from \( x \) and the second factor, \( g(\gamma) \), on the vector of concentrations \( \gamma \) at time \( t \) and point \( x + r \eta \). This non-local term represents the velocity of cancer cells at time \( t \) and spatial point \( x \) due to their adhesion to themselves and the ECM sampled over the sensing region at \( x \). The above form of the non-local term has been 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 \( x \) is in the direction where cells can form the most bonds within the sensing region at \( x \).

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 \( \Omega \). We use the following form (converting back to the \( (c, v, m) \) notation) for the function \( g \):

\[
g(c, v) = (S_{cc} c + S_{cv} v) \cdot (1 - c - v)^+.
\]

In the above, \((\cdot)^+ = \max[0, \cdot]\), \( S_{cc} \) is the cell–cell adhesion coefficient and \( S_{cv} \) is the cell–matrix adhesion coefficient. As in the haptotaxis and the logistic growth terms, the factor \((1 - c - v)^+\) 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. \( 1 - c - v < 0 \), then it also has no influence. This way unbound aggregation is avoided. Such a functional form is also considered in Armstrong et al. (2006). The function \( \Omega(r) \) describes how strong the adhesion velocity \( \mathcal{A}[g(t, \cdot)](x) \) is influenced by points of the sensing region at \( x \) depending on their distance \( r \) from \( x \). It should, however, not alter the magnitude of the adhesion velocity. For this reason we require that \( \Omega(r) \) is normalised 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 normalisation also implies that \( \mathcal{A}[g(t, \cdot)](x) \) is a weighted average of \( g \) around \( x \). We consider two qualitative forms for \( \Omega(r) \). First, a form independent of \( r \), which leads to

\[
\Omega_1(r) = \frac{1}{2R} \quad \text{and} \quad \Omega_2(r) = \frac{1}{\pi R^2},
\]

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

\[
\Omega_1(r) = \frac{1}{R} \left(1 - \frac{r}{R}\right) \quad \text{and} \quad \Omega_2(r) = \frac{3}{\pi R^2} \left(1 - \frac{r}{R}\right).
\]
in 1D and 2D, respectively. The first form $\Omega_1$, but without normalisation, was used in Armstrong et al. (2006). It implies that all points within the sensing region have an equal influence whereas the second form $\Omega_2$ implies that the influence decays with increasing distance from the centre.

We use the following baseline set $\mathcal{B}_nl$ of parameters in the non-local model (4):

$$D_1 = 10^{-3}, \quad \mu_1 = 0, \quad \gamma = 10, \quad \mu_2 = 0, \quad D_3 = 10^{-3},$$

$$\lambda = 0.1, \quad \kappa = 0, \quad R = 0.1, \quad S_{cc} = 0, \quad S_{cv} = 0.1. \quad (\mathcal{B}_nl)$$

This parameter set is the same as set $\mathcal{B}_l$ except for the missing haptotactic coefficient $\chi_{12}$ which is not present in the non-local model and for the addition of the three parameters $R$, $S_{cc}$, and $S_{cv}$ of the non-local term. By the default choice of parameters, the non-local term accounts for cell–matrix adhesion but not for cell-cell adhesion. Experimental values for the parameters of the non-local term are not readily available, and hence we have chosen non-dimensional values which lead to reasonable computational simulation results. In Sections 3.2 and 3.3 we investigate the effect of the key adhesion parameters (both cell–matrix and cell–cell) on the speed of invasion.

2.3. Model analysis: relating the non-local model to the local model

In Hillen and Painter (2001) an analysis of a taxis model with volume-filling taxis term (for one population) is presented. This analysis shows global existence of bounded solutions. Such an analysis for our local and non-local models is beyond the scope of this work. Instead, in this section, before presenting computational simulation results of the model, we undertake a mathematical analysis where we derive local models which approximate the non-local model for a small sensing radius $R>0$ and for $R$ tending to zero. This task amounts to relating the non-local adhesion term $\mathcal{A}(g(t, \cdot))(x)$ to a local taxis-type term. For simplicity we first present the spatially 1D case and later consider the more complicated 2D case.

We consider the spatially 1D case now and to indicate this we denote the spatial coordinate $x$ simply by $x$. Under suitable smoothness assumptions on $g$ and $v$, we can then expand $g(u(t, x + r))$ into a Taylor series around $x$ for $|r|$ small up to the $K$th term, where $K$ is even for reasons which will become clear below. This yields

$$g(u(t, x + r)) = \sum_{k=0}^{K} \frac{r^k}{k!} \frac{\partial^k}{\partial x^k} g(u(t, x)) + O(r^{K+1}).$$

Extending $\Omega(r)$ as an odd function for $r<0$, we then obtain upon inserting the expansion into the non-local term for $R \to 0$

$$\mathcal{A}(\mu(t, \cdot))(x) = \frac{1}{R} \int_{-R}^{R} \Omega(r)g(u(t, x + r)) \, dr$$

$$= \sum_{k=0}^{K} \frac{r^k}{k!} \frac{\partial^k}{\partial x^k} g(u(t, x))A_k(R) + O(R^K),$$

where the values

$$A_k(R) := \frac{1}{R} \int_{-R}^{R} \frac{r^k}{k!} \Omega(r) \, dr.$$

Since $\Omega(r)$ is an odd function, we have $A_k(R) = 0$ for all even $k$. On the other hand, when $k$ is odd we obtain a non-zero value for the integral, leading to

$$A_k(R) = \begin{cases} 0 & \text{for } k \text { even}, \\ \frac{2}{R} \int_{0}^{R} \frac{r^k}{k!} \Omega(r) \, dr & \text{for } k \text { odd}. \end{cases}$$

The normalisation condition for $\Omega(r)$ in 1D implies $A_k(R) = \mathcal{C}(R^{k-1})$ for odd $k$. For the two functions $\Omega_1(r)$ and $\Omega_2(r)$ we obtain in particular

$$A_k(R) = \frac{2}{R} \int_{0}^{R} \frac{r^k}{k!} \Omega_1(r) \, dr = \frac{R^{k-1}}{(k+1)!}$$

and

$$A_k(R) = \frac{2}{R} \int_{0}^{R} \frac{r^k}{k!} \Omega_2(r) \, dr = \frac{2R^{k-1}}{(k+2)!}$$

respectively, for $k = 1, 3, \ldots$. This implies that for both functions $\Omega(r)$ considered in this work we have $A_1(R) = \text{const.}$

and this constant is independent of the value of $R$, and $A_K(R) \to 0$ for $R \to 0$ for $k = 3, 5, 7, \ldots$

Hence, for $R \to 0$, we obtain

$$\mathcal{A}(\mu(t, \cdot))(x) \to A_1 \frac{d}{dx} g(u(t, x)) = A_1 \nabla g(u(t, x)) \cdot \mu(t, x).$$

We now consider two specific choices of the function $g(y)$, namely $g(y) = S_{cc}c + S_{cv}v$ and $g(y) = (S_{cc}c + S_{cv}v)(1 - c - v)^+$. The latter is the same form as used in the main part of this work including the factor which accounts for space filling.

In the first case, $g(y) = S_{cc}c + S_{cv}v$, we arrive at

$$A_1 \nabla g(u(t, x)) \cdot \mu(t, x) = A_1(S_{cc}c + S_{cv}v).$$

This implies that, in the limit $R \to 0$, we recover the sum of two standard taxis terms with constant taxis coefficients $A_1S_{cc}$ and $A_1S_{cv}$. It is now clearly seen that the first term models cell–cell adhesion and the second term models cell–matrix adhesion. Intuitively one can now see that depending on the relative magnitudes of $S_{cc}$ and $S_{cv}$, we can expect the formation of a more compact tumour in the case where $S_{cc} > S_{cv}$ and a more spread-out, invasive tumour for $S_{cc} < S_{cv}$. This will be confirmed by numerical simulations of the model which we present in a subsequent section. One drawback of the model in the limit $R \to 0$ is
that it also allows for unbounded build-up of tumour mass (blow-up). However, upon examining the model for small $R > 0$, additional higher-order terms $A_k(S_{cc} c^k_c + S_{cv} c^k_v)$ for odd $k$ are present in the expansion of $\mathcal{A}[g(t, \cdot)]$. In particular, the term $A_1 S_{cv} c^3_v$ leads to a fourth-order term in the corresponding PDE model and has a dampening effect. Following the reasoning in Armstrong et al. (2006), it can hence be expected that the non-local term $\mathcal{A}[g(t, \cdot)]$ allows for aggregation but also prevents blow-up, i.e. solutions remain bounded with this choice of $g$.

In the second case, $g_\infty = (S_{cc} c + S_{cv} v)(1 - c - v)^{r_+}$, we obtain under the assumption $1 - c - v \geq 0$

$$ A_1 \nabla g(t, \cdot) \cdot g_\infty \cdot (t, x) $$

$$ = [S_{cc} c(1 - c - v) - (S_{cc} c + S_{cv} v)] c_x + [S_{cv} (1 - c - v) - (S_{cc} c + S_{cv} v)] v_x. $$

Here, $S_{cc} c(1 - c - v)$ and $S_{cv} (1 - c - v) v_x$ are volume-filling taxis terms accounting for cell-cell and cell-matrix adhesion, respectively, and they correspond to the taxis terms $S_{cc} c_x$ and $S_{cv} v_x$, respectively, present in the simpler form of $g$ considered above. The remaining terms $- (S_{cc} c + S_{cv} v) c_x + v_x$ additionally counteract unbounded aggregation by directing cells down the gradient of $c$ and $v$. So, in the limit $R \to 0$ again a strong connection between the non-local model and a sensible local model can be made. In the case of small $R > 0$ additional and complicated higher-order terms enter the picture but these are not discussed here.

We can proceed similarly, although with increased complexity, in two spatial dimensions. Here we expand $g_\infty (r, \chi + r \eta$ and $f(r) = g((r))$ in a Taylor series around $r = 0$

$$ f(r) = \sum_{k=0}^{\infty} \frac{d^k f(r)}{dr^k} \bigg|_{r=0} r^k \frac{k!}{k!}. $$

The above series expansion requires smooth functions $g$ and $g_\infty$ if this smoothness is not given then the sum should be terminated at a suitable $k = K$ and a remainder term should be added. For a compact presentation of the following analysis, we assume that approximate smoothness conditions on $g$ and $g_\infty$ hold and we proceed as follows. We write the derivative terms in the series expansion in a form which is more appropriate for the following steps. We obtain for $k = 0$

$$ \frac{d^k f(r)}{dr^k} \bigg|_{r=0} = f(r(0)) = g(t, \chi), $$

and for $k = 1$

$$ \frac{d^k f(r)}{dr^k} \bigg|_{r=0} = \nabla f(r(0)) \cdot \eta \eta_1 = \sum_{i=1}^{2} A_i^{[1]}(\chi) \eta_1. $$

where

$$ [A_1^{[1]}, A_2^{[1]}](\chi) = \nabla f(r(\eta_1)) \eta = \nabla g(t, \eta_1) \eta_1. $$

Now the form of higher-order derivatives, $k > 2$, follows by induction

$$ \frac{d^k f(r)}{dr^k} \bigg|_{r=0} = \sum_{i_1, i_2, \ldots, i_k=1}^{2} \frac{d^k f(r)}{dr^k} \bigg|_{r=0} A_{i_1, i_2, \ldots, i_k}^{[k-1]}(\eta_1, \eta_2, \ldots, \eta_k) \cdot \nabla g(t, \chi), $$

Note that the functions $A_{i_1, i_2, \ldots, i_k}^{[k]}(\chi)$ depend on derivatives of $g$ and $g_\infty$ evaluated at $g(\chi)$ and $(\chi, \chi)$, respectively, but are independent of $\eta$. We now insert this expansion in the non-local term and obtain

$$ \mathcal{A}[g(t, \cdot)](\chi) $$

$$ = \frac{1}{R} \int_0^R \int_0^{2\pi} \Theta(r) \int_0^{2\pi} \frac{\eta(\theta) \Omega(r) \d \theta}{\Omega(r) \d \theta} \frac{d^k f(r(\theta))}{dr^k} \bigg|_{r=0} \frac{\eta_1}{\eta^k} \d \theta \d r $$

$$ = \sum_{k=1}^{\infty} \sum_{i_1, i_2, \ldots, i_k=1}^{2} \frac{d^k f(r(\theta))}{dr^k} \bigg|_{r=0} A_{i_1, i_2, \ldots, i_k}^{[k-1]}(\chi) \frac{1}{R} \int_0^R \frac{\eta_1 \eta_2 \ldots \eta_k \d \theta \d r}{\eta^k} $$

Here we have taken out the term for $k = 0$. For the remaining terms in the sum, the integral over $\theta$ is always bounded and for many combinations $(i_1, i_2, \ldots, i_k)$ it will be zero. Furthermore, the integral over $r$, including its pre-factor $1/R$, can be evaluated and we obtain for the two considered radial dependency functions

$$ A_k(\Omega) = \frac{1}{R} \int_0^\frac{R}{k} \frac{\eta^{k+1}}{k!} \Omega(r) \d r $$

$$ = \frac{R^{k-1}}{(2 + k) \pi k!} \Omega = \Omega_1, $$

$$ \frac{2}{3} \frac{k^{k-1}}{(6 + 5k + k^2) \pi k!} \Omega = \Omega_2. $$

This shows that, for the two cases considered here, we have

$$ A_1(\Omega) = \text{const.} $$

and $A_k(\Omega) \to 0$ for $R \to 0$ and $k > 1$.

The normalisation of $\Omega(r)$ ensures that $A_k(\Omega) = C(R^{k-1})$ independent of the particular $\Omega(r)$.
In the special case \( k = 1 \), the integrals over \( \theta \) are

\[
\int_0^{2\pi} \sin^2(\theta) \, d\theta = \int_0^{2\pi} \cos^2(\theta) \, d\theta = \pi
\]

and

\[
\int_0^{2\pi} \sin(\theta) \cos(\theta) \, d\theta = 0.
\]

Taking into account the earlier derived form of \( [A^1_{b1}, A^1_{b2}]((x)) \), we arrive in the limit \( R \to 0 \) at

\[
\mathcal{S} [u(t, \cdot)]((x)) \to \pi A_1 \nabla_x \theta(t, \cdot) \cdot \nabla_x u(t, \cdot).
\]

This form resembles that obtained in the spatially 1D case, except that here \( \nabla_x u(t, \cdot) \) has replaced \( f_{\delta}(t, x) \). So in particular, the same conclusions as in the spatially 1D case can be drawn.

3. Computational results: numerical simulations in 1D

In this section numerical simulations of the local invasion model (2) are presented in Section 3.1 and those of the non-local invasion model (4) with only cell–matrix adhesion in Section 3.2 and with cell–cell and cell–matrix adhesion in Section 3.3. All simulations are performed on a spatial domain \( \Omega = (-4, 4) \), with periodic BCs, and initial values as given in (3). The size of the domain is chosen such that the BCs have no or no significant effect on the solution in the numerical experiments described below. In fact, unless stated otherwise, for the time points and parameter sets considered below, the numerical solution outside \( x \in [-1, 1] \) is virtually unchanged from the initial data. Furthermore, unless stated otherwise, the numerical solutions are symmetric around \( x = 0 \). For those reasons we in general display the numerical solutions for \( x \in [0, 1] \) only.

All model simulations have been performed using the MATLAB® system. The numerical scheme follows the method of lines by first discretising the local or non-local model in space, yielding an initial value problem for a large system of ordinary differential equations. This system is then solved using the time integration scheme ROWMAP (Weiner et al., 1997), implemented in a Fortran subroutine and called from MATLAB®. For the discretisation in space we use a second-order finite volume approach which makes use of flux-limiting for an accurate discretisation of the taxis/adhesion term. A key to efficiency for the spatial discretisation of the non-local model is an accurate approximation of the non-local term and its efficient evaluation using FFT techniques. More details of the numerical scheme are outlined in Appendix A and for further details of the treatment of the non-local terms we also refer the interested reader to Gerisch (2007).

3.1. Local model—effect of volume-filling taxis

In order to have a suitable point of departure for the exploration of our models, we first repeat the numerical experiment shown in Fig. 1 of Anderson et al. (2000). That is we use Eq. (2) together with parameter set \( \beta_1 \). There are three differences between the experiment for Fig. 1 of Anderson et al. (2000) and the one performed here

1. we use the volume-filling taxis coefficient \( \chi(\cdot) = \chi_{12} (1 - c - v) \) instead of the constant taxis coefficient \( \chi(\cdot) = \chi_{12} \),
2. we use our IC (3), i.e. a modified initial matrix density, and
3. we simulate the model on the domain \( \Omega = (-4, 4) \) with periodic BCs as opposed to (0, 1) and no-flux boundary conditions.

The results of our numerical experiment are shown in Fig. 1. The solutions are in good qualitative and quantitative agreement with those shown in Fig. 1 of Anderson et al. (2000). Hence, our Fig. 1 can be regarded as a reproduction of Fig. 1 of Anderson et al. (2000). We note, however, that the invasion of the ECM by the cancer cells takes place marginally slower in our simulations. This difference is primarily due to using the volume-filling taxis coefficient instead of the constant taxis coefficient. The modified ICs and BCs have a negligible influence on the solution. This is demonstrated by additional computational experiments not shown here.

The solutions obtained in Fig. 1 are rather smooth and it is appropriate to assess the accuracy of the spatial discretisation of our numerical scheme. To this end, a series of simulations with decreasing spatial grid width \( h = 1/N \) was performed. The observed absolute errors, for each of the three individual solution components, at time \( t = 20 \) and in the \( L_2 \)-norm vs. the spatial grid width \( h \) are shown in Fig. 2. The errors are computed with respect to a reference solution as obtained on the finest grid (\( N = 900 \)). Cubic spline interpolation is used to transfer the solutions from coarser grids to that fine grid. The plots show that the spatial discretisation converges with order two. We observe that, in this case, a rather coarse grid with \( N = 100 \) or 200 is sufficient to obtain a suitably high spatial accuracy.

Numerical convergence tests like the one discussed have also been performed for other simulations presented below but are not discussed in detail below. The outcome of these tests, however, guided the selection of suitable spatial grid widths \( h \).

However, for different parameter values, the introduction of the volume filling taxis coefficient into the model of Anderson et al. (2000) can have a significantly stronger impact on the solution behaviour than can be seen in the first numerical test. To demonstrate this, we undertake a second numerical simulation of the model with the haptotactic parameter \( \chi_{12} \) and the MDE diffusion coefficient \( D_1 \) increased by a factor of 100 (equivalent to the results of Fig. 4 (bottom) of Anderson et al., 2000). In the left plot of Fig. 3 we show the solution at \( t = 0.5 \) as obtained from model (2) with the volume-filling taxis coefficient and in the right plot that from model (2) but with the constant taxis coefficient as used in Anderson et al. (2000). Again, our Fig. 3 (right) can be considered a reproduction of Fig. 4 (bottom) of Anderson et al. (2000); for minor differences see the following remark.
Remark 1. In this remark we compare in more detail Fig. 3 (right) with the bottom plot of Fig. 4 of Anderson et al. (2000). In our plot, the peak of the cancer cell density is almost exactly at $x = 0.4$ whereas in the simulation results of Anderson et al. (2000) that peak has advanced slightly beyond $x = 0.4$ at $t = 0.5$. This slightly increased speed of propagation in their numerical simulation could be caused by the different numerical schemes employed or by the difference in boundary conditions. (Repeating the numerical experiment for the right plot of Fig. 3 but using the precise ICs of Anderson et al., 2000, simulation results not shown here, causes an even slightly lower speed of propagation for the invading cancer cells compared to Fig. 3 (right) and an expected increase of the ECM density around the origin, but no qualitative differences.) In our simulations we do not observe a dependence of the speed of propagation of the peak on the spatial grid parameter $h$ for $h \to 0$, so that we are confident about the correctness of the peak’s position as computed with our numerical approach.

Comparing the left and right plot of Fig. 3 we observe some striking differences. With the volume-filling taxis coefficient, firstly, the cancer cell density remains bounded above by one; secondly, the cancer cell invasion proceeds much more slowly and the peak of the invading cancer cells does not “enter” the space filled with ECM before that is sufficiently degraded and there is physically space to move into; and thirdly, the profile of the cancer cell peak has changed from a symmetric profile to one which has a less steep leading edge but an almost vertical trailing edge. These steep slopes necessitate the use of a fine spatial grid. In fact, whereas for the simulations shown in Fig. 1 a value of $h = \frac{1}{100}$ or $\frac{1}{200}$ is appropriate, we require now values of $h = \frac{1}{400}$ or even $\frac{1}{500}$ to resolve the peak accurately. Convergence tests also reveal that the choice of $h$ should be guided by the steepness of the slopes in the cancer cell density since the spatial errors for the ECM density and the MDE concentration are considerably smaller for the same value $h$.

The simulation results presented in Fig. 3 illustrates that the introduction of the volume-filling taxis term into the model of Anderson et al. (2000) has a significant influence on the simulation outcome for certain parameter choices.

3.2. Non-local model with cell–matrix adhesion

We now consider the non-local model (4) of cancer cell invasion incorporating cell–matrix adhesion but no
cell–cell adhesion. The haptotaxis term in model (2) models active migration of cells due to density changes (gradients) of the ECM. Physiologically, this is achieved by binding and unbinding of integrins located on the cancer cell surface to ECM molecules, hence through a spatial modulation of cell–matrix adhesion. According to this observation a cell–matrix adhesion term in our model should be able to replace the haptotaxis term. The results of a first investigation into that possibility are displayed in Fig. 4. We show numerical simulations results of the non-local model (4) with parameter set $\beta_{nl}$ but values of $S_c$, as given in the legends. In the left plot $\Omega(t) = \Omega_1(t)$ and in the right plot $\Omega(t) = \Omega_2(t)$. The thin lines give the cancer cell density $c(t, x)$ and the thick grey lines the ECM density $\phi(t, x)$. For both plots, the spatial grid width $h = \frac{1}{400}$.

Fig. 4. Plots showing the solution profiles of the cancer cell and ECM density at time $t = 20$ from a simulation of model (4) with parameter set $\beta_{nl}$ but values of $S_c$, as given in the legends. In the left plot $\Omega(t) = \Omega_1(t)$ and in the right plot $\Omega(t) = \Omega_2(t)$. The thin lines give the cancer cell density $c(t, x)$ and the thick grey lines the ECM density $\phi(t, x)$. For both plots, the spatial grid width $h = \frac{1}{400}$.

In order to investigate more fully the effect and influence of the cell–matrix adhesion term, we next vary the radius of sensitivity $R$. In addition to the simulation results with $R = 0.1$, we show in Fig. 5 results of the same numerical experiment but with fivefold reduced (top row) and fivefold increased (bottom row) value of $R$.

Comparing the simulation results using the small radius of sensitivity $R = 0.02$ with that using $R = 0.1$, we observe that a smaller radius of sensitivity leads to a slightly stronger peak of invading cancer cells. In particular, the trailing edge becomes steeper. Besides this, there are hardly any differences.

However, the situation is different when $R$ is increased fivefold to $R = 0.5$. This increase of the sensitivity radius implies that cancer cells in $[0, 1]$ sense the ECM increasing from 0 to 1 in the $[-1, 0]$ part of the domain (not shown) for a much longer time. This leads to a stronger “adhesive pull” towards the left and subsequently results in a reduced adhesive velocity and speed of invasion, at least initially. Again, this is more pronounced for $\Omega_1(t)$ whereas for $\Omega_2(t)$ at $t = 20$ a more pronounced peak has already formed.

The appearance of the cancer cell peak can be attributed to the form of the integrand in the non-local term and the magnitude of $R$. First the factor $S_{nc}(1-c-v)^+ \phi(t, x)$ means that only spatial regions where the ECM density $\phi$ is strictly between zero and one have an influence on the integral, and further away from the centre of the non-local term in the former case.
second, the form of the radial dependence function $\Omega_1(r) = \text{const}$ means that the adhesion strength at any one point depends equally on its surrounding within the sensing radius $R$ and is independent from anything else (similar for $\Omega_2(r)$). Taken together, this means that after the time point at which the ECM has been degraded in $x \in [-R/2, R/2]$ and forms a $1 \to 0$ interface around $x = -R/2$ and a $0 \to 1$ interface around $x = R/2$, cancer cells near to one of those interfaces are pulled more strongly towards that interface because the other one “leaves” the sensing radius; the other one has reduced cancer cell migration before that time point. Subsequently the peaks at $x \approx \pm R/2$ develop and then “travel” with the ECM interface. Prior to this point in time, both ECM interfaces are within the sensing radius of the cells and the adhesion is more “symmetric”. This explanation implies that the cancer cell peak will appear earlier in time with decreasing sensing radius $R$. Numerical experiments confirm this, as long as $R$ is not getting too small when the non-local term effectively turns local.

We finally undertake some computational experiments to examine how the speed of invasion varies with the cell–matrix adhesion parameter. In Fig. 6 we show the cancer cell density at $t = 20$ for $S_{vw}$ in the range [0.02, 5]. We note that the cell random motility coefficient has been set to zero, i.e. $D_1 = 0$, and so the spatial rearrangement of the cancer cells is solely due to adhesive effects. The sensitivity radius is $R = 0.1$. We have marked the leading and the trailing position of the peak of invading cancer cells as well as the position of the maximum value of the peak by additional lines in the plot. Note the logarithmic scale of $S_{vw}$. From this plot we can draw the following conclusions: (i) peak width and height increase with $S_{vw}$ and lead to the disappearance of cancer cells around $x = 0$ for larger values of $S_{vw}$ and (ii) although the speed of invasion continues to increase with increasing $S_{vw}$, the increments become smaller for larger $S_{vw}$. Note also the form of the peak for large $S_{vw}$: a rather gentle slope in the front and a sharp, almost vertical slope in the back.

![Fig. 5. Plots showing the simulation results at time $t = 20$ of model (4). The parameters are the same as in Fig. 4 but $R = 0.02$ (top row) and $R = 0.5$ (bottom row).](image)

![Fig. 6. Plot showing the cancer cell density $c(t, x)$ at time $t = 20$ obtained from simulations of model (4) with parameter set $\mathcal{A}_2$ but no cell random motility, i.e. $D_1 = 0$ and values of $S_{vw}$ ranging over [0.02, 5]. Note the logarithmic scale along the axis for the cell–matrix adhesion coefficient $S_{vw}$. In the plot the foremost, highest, and hindmost position of the peak of cancer cells are connected by additional lines (blue, red and green respectively). The spatial grid width $h = 600$.](image)
Besides increasing the cell–matrix adhesion coefficient $S_{cm}$, there are other parameters that affect (increase/decrease) the speed of invasion, e.g.

- increase/decrease the MDE diffusion coefficient $D_3$,
- increase/decrease the MDE release rate $a$ (resp. reduce/increase the MDE degradation rate $\lambda$), and
- increase/decrease the ECM degradation rate $\gamma$.

We do not investigate these mechanisms here since our focus is on the effects and potentials of the non-local adhesion term. In the following section we do, however, investigate numerically how the cell–cell adhesion coefficient $S_{cc}$ (which so far has been set to zero) affects the speed of invasion.

From the figures presented in this section it is evident that with increasing cell–matrix adhesion coefficient $S_{cm}$ we observe an increased and more strict formation of a separate cluster of cancer cells which migrates within the layer of ECM being degraded. We have further noted that the speed of cancer cell invasion increases with $S_{cm}$ for the radii $R$ of sensitivity considered. The choice of $R$ can considerably change the qualitative nature of the model solution. For sufficiently small values of $R>0$, however, the solution appears to be almost unaffected by the value of $R$. This is in agreement with the theoretical predictions of Section 2.3.

We obtain good agreement between the solutions of the non-local model (4) with cell–matrix adhesion using parameter set $\mathcal{B}_{nl}$, as considered in this section, and the local model (2) with the haptotaxis term using parameter set $\mathcal{B}_{l}$, as considered in the previous section.

Both the non-local cell–matrix adhesion term as well as the local volume filling haptotaxis term prevent cancer cells invading tissue space which is already crowded. However, there is one difference: the model with the non-local adhesion term can detect regions—within its radius of sensitivity—having suitable low ECM density to move into. This is not possible for the model with haptotaxis because in this case the ECM is sampled locally only. So we should expect (further) differences between both models in heterogeneous environments. Numerical experiments indicate this and we present results from 2D simulations with a heterogeneous ECM density in Section 4.

### 3.3. Non-local model with cell–cell and cell–matrix adhesion

In the previous section we have shown that cell–matrix adhesion modelled by a non-local term can indeed reproduce behaviour which has been observed for model (2) with the haptotaxis term for cancer cell migration. Cell–matrix adhesion is, however, not the only adhesion taking place in a tissue. Cancer cells also adhere to themselves and we are now going to numerically explore the effects of adding cell–cell adhesion to our model, i.e. $S_{cc} > 0$.

Compared to the experiments in the previous section we now also switch on the MDE degradation term by setting $\lambda = 0.5$. This avoids unbounded build-up of the MDE concentration. The parameter value is taken from Anderson et al. (2000); these authors also tested different functional forms of the MDE removal term but observed no significant dependence of the cancer cell density evolution on that form. For the non-local term we consider the biologically more plausible radial dependence function $\Omega(r) = \Omega_2(r)$. We will also fix, unless otherwise stated, the sensitivity radius to $R = 0.1$ and the cell–matrix adhesion coefficient to $S_{cm} = 0.1$, that is the values listed in parameter set $\mathcal{B}_{nl}$.

The simulation results at four time points and using a cell–cell adhesion coefficient $S_{cc} = 0.1$ are shown in Fig. 7.
The most striking difference is that we now have, firstly, a true detachment of a cluster of cancer cells which progressively degrades the ECM and migrates within the area of ECM degradation; secondly, a population of cancer cells staying behind at around $x = 0$ and attaining a rather steady profile there; and thirdly, an incomplete degradation of the ECM (within the time span under consideration) between the cluster of cancer cells around $x = 0$ and the outward moving peak of cells. The cancer cell profile around $x = 0$ shows another feature caused by the non-local cell–cell adhesion term. This is the hump at the right end of the plateau of the cancer cell density before it drops down to small values (there is a corresponding hump also at the left end of the plateau for $x < 0$). These humps are caused by the non-local term because in the surrounding of the ends of the plateau there is more physical space available than in the surroundings in the centre of the plateau and hence cells are driven into the former area but without leaving the tumour mass due to cell–cell adhesion. This can also be viewed in the sense that the model allows for local overcrowding as long as there is no overcrowding on average within the sensing radius; see also Britton (1989, 1990) on a similar related issue. Finally, we note that switching off the MDE degradation in the model by letting $\lambda = 0$ leads to an increased speed of cancer cell invasion but qualitatively there is no difference in the evolution of the cancer cell density. However, we have a considerable build-up of MDE around $x = 0$ spreading out into the domain and also causing the complete degradation of the ECM between the static and the invading cancer cell cluster.

We next investigate how increasing and decreasing the cell–cell adhesion coefficient by a factor of five changes the solution. The results for the same four time points as before are shown in the plots of Fig. 8. Decreasing the cell–cell adhesion coefficient to $S_{cc} = 0.02$ results in a behaviour similar to that observed with the simulations using no cell–cell adhesion at all, $S_{cc} = 0$, cf. Section 3.2. In particular, comparing with the simulations with the default value $S_{cc} = 0.1$, we observe no formation of a cluster of cancer cells around $x = 0$ but an increased speed of invasion. In fact, at $t = 56$, the invading peak of cancer cells has already left the spatial region shown in the plot. On the contrary, increasing the cell–cell adhesion coefficient to $S_{cc} = 0.5$ results in a non-invasion of cancer cells. Visually all cells remain confined to a small region around $x = 0$. Nevertheless, we observe a degradation of the ECM. This is caused by the diffusing MDE produced by the cancer cells. This ECM degradation can, for instance, be reduced by increasing the MDE decay rate $\lambda$.

We next consider how changing the adhesion parameters $S_{sv}$ and $S_{cv}$ affects the invasion of tissue by the cancer cells. As in Fig. 6, we set $D_l = 0$ and vary one of the adhesion parameters in the range $[0.02, 5]$ while the other is kept fixed at 0.5. The results are shown in Fig. 9. In the case

![Fig. 8. Plots showing the cancer cell and ECM density profiles at four time points obtained from simulations of model (4) with parameter set $\mathcal{R}_0^C$ but MDE degradation rate $\lambda = 0.5$ and cell–cell adhesion coefficient $S_{cc} = 0.02$ (top), $S_{cc} = 0.1$ (middle), and $S_{cc} = 0.5$ (bottom). The thin lines give the cancer cell density $c(t, x)$ and the thick grey lines the ECM density $\phi(t, x)$. The radial dependency function $\Omega(r) = \Omega_2(r)$ and the spatial grid width $h = \frac{1}{600}$.](image)
where $S_{cc} = 0.5$ (left plot in Fig. 9), we observe that for $S_{sc} < 0.5$ a steady tumour profile around $x = 0$ is established. Also note that a small amount of cells is able to break off and to invade the tissue/ECM. For increasing values of the cell–matrix adhesion coefficient $S_{sc} > 0.5$ we observe that an increasing proportion of cancer cells breaks off the central tumour mass and invades the ECM with increasing speed. Eventually, for $S_{sc} \approx 5$, no cancer cells remain at $x = 0$. In the case where $S_{cc} = 0.5$ (right plot in Fig. 9), we observe that for small $S_{cc} < 0.5$ cells break off the initial tumour around $x = 0$ and invade the ECM at constant speed (dictated by $S_{cc} = 0.5$); some cells always stay behind around $x = 0$. When $S_{cc} < 0.5$ approaches 0.5, the speed of invasion is reduced gradually and the tumour cell cluster around $x = 0$ becomes bigger. For $S_{cc} > 0.5$ it appears that no cells escape the central tumour mass. In summary, these experiments indicate that $S_{cc} > S_{sc}$ characterises an invasive tumour and $S_{cc} < S_{sc}$ characterises a tumour which remains compact.

We note that the location of the cell cluster around $x = 0$ in Fig. 8 (bottom) might move to the left or right due to some asymmetries introduced numerically and the space

made available after the ECM is degraded (the model includes no mechanism to fix that cluster at $x = 0$). Also for this reason, we chose not to simply increase the MDE decay rate to stop progressive ECM degradation in the model but rather to switch on the ECM remodelling term by letting $\beta_3 = 0.1$. The model now accounts for the production of ECM molecules by cells embedded in the ECM, e.g. fibroblasts, which are not modelled explicitly here. This newly adjusted non-local model now attains a spatially non-homogeneous steady state with a population of cancer cells around $x = 0$ and ECM surrounding it. This situation corresponds to an avascular tumour in a dormant state. The steady state is illustrated in Fig. 10, where we show the numerical solutions for the three variables of the non-local model at times $t = 10, 11, \ldots, 100$ simultaneously. We clearly see a (numerically) stable spatially non-homogeneous steady state.

The spatially non-homogeneous steady state as shown in Fig. 10 serves a good IC for further numerical experiments simulating changes in the tumour (and subsequent changes in its micro-environment) which may occur due to the accumulation of mutations in the tumour cells. It is for instance known that more tumourigenic cells exhibit less
cell–cell adhesion. Reducing the corresponding parameter $S_{cc}$ in our model after establishment of the steady state at $t = 20$ to smaller values 0.1, 0.05 and 0.02 shows further invasion, even an almost break-up of the tumour mass into two parts for the two smallest values of $S_{cc}$. However, invasion stops after some time, the cell clusters are pulled together again and after time a new steady state appears to be established which looks similar to that shown in Fig. 10 but with a wider and less dense cluster of cancer cells in the centre. A reduction of the matrix remodelling rate $\mu_2$ does not change this behaviour qualitatively. In conclusion, for continued invasion of cancer cells with the model under consideration it appears to be necessary to increase the number of cancer cells with time, that is, to include cancer cell proliferation, i.e. letting $\mu_1 > 0$. Then, for instance using $\mu_2 = 0.1$ and changing at $t = 20$ the cell–cell adhesion coefficient $S_{cc}$ from 0.5 to 0.02 and the cell proliferation rate $\mu_1$ from 0 to 0.05, turns the spatially inhomogeneous steady state into a permanently invading front of cancer cells. The cancer cell density is non-monotone—more precisely there is a peak in the invading region, but closer to $x = 0$ the cell density approaches one with increasing $t$. The simulation result is visualised in Fig. 11.

### 4. Computational results: numerical simulations in 2D

In this section we present the results of computational simulations of the non-local invasion model (4) with cell–cell and cell–matrix adhesion on a 2D spatial domain. Specifically we consider the spatial domain $\Omega = (-1.5, 1.5)^2$ and use periodic boundary conditions. The size of the domain is chosen such that the BCs have no significant effect on the solution in the numerical experiments described below. We only display the central part $(-1, 1)^2$ of the domain in the solution plots. Again, as in the 1D case, we use a method of lines approach to simulate the model equations. Details of the approach, in particular concerning the approximation and efficient evaluation of the non-local term using FFT, are outlined in Appendix A.

First of all we carried out numerical experiments in two spatial dimensions with initial values as given in (3). As is to be expected, our 2D simulation results are analogous to the 1D results obtained in Section 3. We do not reproduce these results here.

The main focus of this section is to explore in some detail our non-local model (4) in a 2D domain with a heterogeneous ECM density environment. To this end, we use the initial data for the cancer cell density and MDE concentration as given in (3) but prescribe a heterogeneous initial ECM density similar to that used in the 2D experiments of Anderson et al. (2000). This initial ECM density is visualised in Fig. 12 (centre row, left plot).

Figs. 12 and 13 show the results of our computational simulations. The scenario which we study here is similar to the 1D scenario shown in Fig. 11, i.e. an initial set of parameters is chosen allowing a steady state to be reached, and then two key parameters are changed thus enabling subsequent invasion to take place. We start off with the...
parameter set $B_{nl}$ but $\lambda = 0.5$ and $S_{cc} = 0.5$. We do not allow for matrix remodelling here but use $m_2 = 0$ because otherwise the heterogeneity of our initial data would get lost. This parameter regime is used up to time $t = 30$ and the corresponding simulation results at times $t = 0, 10, 20, 30$ are shown in Fig. 12. What we observe once again is that the initial cancer cell density accumulates due to strong cell–cell adhesion and attains a steady distribution around a time $t = 30$. The effect of the heterogeneous matrix on the cancer cell dynamics can be seen as the cancer cells approach their steady distribution: at about time $t = 10$, the cancer cell cluster is elongated and the axis...
of elongation is in the direction where there is some ECM present and where the cancer cells can make adhesive contacts: by a similar reasoning, the cancer cells do not move preferentially in the directions where there is little ECM due to the fact that there are too few bonds that they can establish there. After some time, however, the strong cell–cell adhesion pulls the cancer cells back into the central cluster and a round cluster of cells has formed at \( t = 30 \), which essentially would remain steady if we were not to change the model parameters.

At time \( t = 30 \), we decrease cancer cell–cell adhesion substantially and set \( S_{cc} = 0.02 \). We also introduce a modest amount of cancer cell proliferation and set \( \mu_1 = 0.1 \). The computational simulation results at times \( t = 32, 40, 50 \) and 60 are displayed in Fig. 13. The consequence of allowing the cancer cells to become more invasive (e.g. implicitly modelling a series of acquired genetic mutations which result in a more aggressive phenotype) can be seen clearly in the sequence of plots. We observe once again that cancer cells do not preferentially move into space with little or no ECM, as can be seen from the snap shots at \( t = 40 \) and 50. However, the cells also do not move into crowded space, which can be seen in the lower and upper end of the domain at time \( t = 60 \). Here cancer cells accumulate in front of the high density ECM, produce MDEs which degrade the ECM barrier and once there is physically space available, the cancer cells then continue to invade. We note that the cancer cells (i.e. cancer cell density) interact in a carefully orchestrated manner with themselves and also their immediate physical neighbourhood. This results in an asymmetric invasion pattern which is not observed in any simulations carried out with a homogeneous ECM.

In summary, these initial computational simulation results in 2D with a heterogeneous ECM density show that our non-local model (4) is capable of generating rich spatio-temporal dynamics.

5. Discussion and conclusions

The ability of cancer cells to invade tissue is one of the defining characteristics of the disease. A more detailed knowledge of the processes involved in cancer invasion is therefore of the utmost importance for gaining a deeper understanding of tumour growth and development, and for the design of future anti-cancer strategies. In this paper we have formulated and developed a novel continuum model of cancer cell invasion of tissue which explicitly accounts for cell–cell and cell–matrix adhesion and interactions. This has been achieved through the inclusion of non-local terms in a system of PDEs.

In order to solve the equations computationally we developed an efficient numerical technique based on the method of lines. The crucial aspect of the numerical scheme was in the implementation of a fast evaluation of the quadrature rule to deal with the non-local terms in the equations. This allowed for 2D simulations to be carried out with high spatial accuracy within reasonable computation times, e.g. the simulations presented in Figs. 12 and 13 required CPU time of about 70 min on a standard laptop\(^2\)—approximately a 15-fold reduction compared to a typical approach for evaluating the non-local term. Comprehensive details of the numerical technique are given in Appendix A and in Gerisch (2007).

Initially we developed a basic invasion model consisting of cancer cells, matrix (ECM) and matrix degrading enzymes (MDEs). Cancer cell invasion was governed largely by haptotaxis in response to ECM gradients generated by the MDEs. This model contained no non-local cell–cell or cell–matrix adhesion terms and was similar in approach and structure to previously published work. The main reason for developing this basic invasion model was to then compare computational simulation results with our new non-local model. In Section 3 the results of the computational simulations of the non-local model were compared with those from the basic haptotaxis-based model. Qualitatively similar solutions were obtained in certain circumstances, with cancer cells invading the tissue in a travelling-wave like manner. For certain parameter sets, in both cases, the cancer cells “split” into two sub-populations, with one sub-population actively invading the tissue, the other sub-population remaining close to the initial spatial location. However, other parameter sets produce very different results between the two models. A key difference of the non-local model is its ability to generate spatially heterogeneous steady-state solutions, where there is a balance of cell–cell adhesion and cell–matrix adhesion, as seen in Fig. 10. This type of solution is not observed with the basic model (2). By letting the sensing radius \( R \) tending to zero, we have shown a clear connection of the local and non-local models considered in this work. This analysis further highlighted the corresponding differences between both models for finite \( R > 0 \).

Last, but not least, the results of our work demonstrate that the non-local term, as proposed by Armstrong et al. (2006) for the modelling of differential adhesion in mixtures of different cell types (cell sorting), is suitable for application in a more general context.

One may draw the general conclusion that the tumour microenvironment (Sutherland, 1988; Anderson et al., 2006; Chaplain et al., 2006), i.e. the oxygen/nutrient supply to the tumour, the biomechanical properties of the matrix and cell–cell and cell–matrix adhesion have a major impact on invasion. Our novel approach complements existing previous work in the area going back to the seminal paper of Greenspan (1976) and developed theoretically and analytically by Byrne and Chaplain (1996, 1997) and computationally by Lowengrub and co-workers (Cristini et al., 2003; Macklin and Lowengrub, 2007). In these models, cell–cell adhesion is modelled by incorporating a surface tension force at the tumour surface which then controls the evolution of the tumour shape during growth.

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\(^2\)Intel® CoreTM2 T5500 1.66 GHz, 1 GB memory.
Future work will consider several developments and extensions of the current model. Firstly, we will consider a more accurate and realistic treatment of the cancer cell random motility function \( D_1(v) \). As noted previously, recent experimental work by Zaman et al. (2006) has shown that cancer cell motility depends on ECM density (haptotaxis), i.e. \( D_1 = D_1(v) \), in a bi-phasic manner. We note that this type of behaviour was modelled by Dickinson and Tranquillo (1993) in a general model of adhesion-mediated cell migration and has also been included in previous models of cell migration (Olsen et al., 1997; Perumpanani et al., 1997). A possible functional form for \( D_1(v) \) may therefore be given by \( D_1(v) = D_0v(K^2 + v^2)^{-1} \) with parameters \( D_0 \geq 0 \) and \( K > 0 \), cf. Olsen et al. (1997), accounting for the fact that cancer cells cannot move in the absence of ECM (\( D_1 = 0 \) when \( v = 0 \)), have reduced movement when the ECM becomes denser, and have maximal rate of random motility at some intermediate value of ECM. This functional form can further be combined with thresholding such that above a certain ECM density no cell random motility is present. Furthermore, the random motility function may also depend on other variables as well, e.g. the uPA system and incorporate intra-cellular mechanisms such as heat shock proteins, known to play a regulatory role in adhesion, using a multi-scale approach. Furthermore, incorporating a realistic nutrient source and different cell populations, e.g. necrotic cells and live tumour cells of various degrees of invasiveness, in the model, cf. Sherratt and Chaplain (2001) will increase the applicability of the model for quantitative studies.

Acknowledgement

AG is grateful to the members of the Division of Mathematics, University of Dundee, Scotland, for many stimulating discussions and for making his long-term visit in 2007 possible. The work of MAJC was supported by a Leverhulme Trust Personal Research Fellowship. Both authors would like to thank an anonymous referee for helpful and constructive comments which led to an improvement of the original version of the paper.

Appendix A. Numerical technique

A.1. One spatial dimension

We discretise the (local and non-local) PDE system following the method of lines (MOL) and using a finite volume scheme in space. The spatial domain \((A, B)\) with \(A < B\) and, for simplicity, \(B - A \in \mathbb{N}\) is covered by a uniform spatial grid with grid width \(h \equiv 1/N\) for some user-prescribed positive \(N \in \mathbb{N}\). Grid points are located in the centres of the grid cells (finite volumes), that is \(x_i := A + (i - 0.5)h, \quad i = 1, 2, \ldots, N(B - A)\).

Following the finite volume methodology, we compute approximations to the average of the exact solution of the PDE system for the individual grid cells, that is, for the cancer cell density, we compute approximations \(C_A(t)\)

\[
C_A(t) \approx \frac{1}{h} \int_{x_i - h/2}^{x_i + h/2} c(t, x) \, dx
\]

and accordingly for the other variables of the PDE system. The finite volume spatial discretisation converts the PDE system together with its BCs into an ODE system for the averages \(\{C_A(t), V_A(t), M_A(t) : i = 1, 2, \ldots, N(B - A)\}\), the so-called MOL-ODE. The initial values for this ODE system are taken from the initial values prescribed for the PDE system. Below we briefly explain (i) how we setup the MOL-ODE system and (ii) how we solve the initial value problem for the MOL-ODE numerically.

A.1.1. Spatial discretisation

In general, there are four different terms to discretise in the PDE system: the local taxis, diffusion, and reaction terms and the non-local adhesion term. The discretisation of the local terms has been discussed in detail in Gerisch (2001) and Gerisch and Chaplain (2006) and we give only a brief summary.

- **Reaction:** For grid cell \(i\), the reaction terms are evaluated using the cell averages \(C_A(t), V_A(t),\) and \(M_A(t)\) in grid cell \(i\).
- **Diffusion:** Here we use a conservative discretisation which ensures that mass balances are preserved. In the case of constant diffusion coefficients, this simply leads to the second order central finite difference approximation for the second derivative. For the case of a non-constant diffusion coefficient we refer to the papers cited above.
- **Taxis:** Also here we use a conservative discretisation. However, simply using central differences for the evaluation of the taxis term leads to difficulties for problems with solutions having steep fronts. The most notable effect would be the introduction of wiggles in areas where the solution gradient changes rapidly. These non-physical oscillations can, in particular, lead to negative solution values which, e.g. upon being fed back into the reaction term, may grow in magnitude and lead to numerical solution blow-up in finite time. Using a finer grid in space cannot eliminate this problem satisfactorily. However, the behaviour described can be avoided by using an appropriate upwinding technique together with a nonlinear limiter function. The limiter function depends on the local smoothness of the solution as approximated by a smoothness monitor. The upwinding direction is determined for each cell face (left and right endpoint of each finite volume) by the sign of the local velocity there. In the case of the taxis
term in our model, this local velocity is given \( v \). We approximate this using central differences and, when necessary for the evaluation of the \( v \) function, averaging of neighbouring solution approximations.

The discretisation outlined above leads, in general, to a second order in \( h \) approximation of the PDE system by the MOL-ODE. The “in general” refers to the fact that the taxis discretisation switches back to a first order scheme in regions where the solution gradient changes rapidly. Furthermore, the MOL-ODE can be shown to have a non-negative solution for arbitrary non-negative initial data. This highly desirable property cannot be achieved without the dedicated discretisation of the taxis term.

For the discretisation of the adhesion term we follow the same route as outlined above for the taxis term. The only difference is that the local velocity is now given by the non-local term \( \mathcal{A}[u(t, \cdot)](x) \) instead of the \( v \). In the following we evaluate how we evaluate that non-local term in 2D. The non-local term involves the parameter \( R > 0 \) and we define \( M = \lfloor R/h \rfloor \).

Given the averages \( C_i(t), V_i(t), M_i(t) \) in the grid cells, we construct a piecewise constant reconstruction \( \hat{u}(t, \cdot) \) as an approximation for \( u(t, \cdot) \) and approximate \( \mathcal{A}[\hat{u}(t, \cdot)](x_i + h/2) \approx \mathcal{A}[\hat{u}(t, \cdot)](x_i + h/2) \).

The right-hand side here can then be evaluated exactly for the functions \( \Omega_1(r) \) and \( \Omega_2(r) \) considered in this work. This leads to

\[
\mathcal{A}[\hat{u}(t, \cdot)](x_i + h/2) = \sum_{l=-M}^{M} w_l g(C_{i+l}(t), V_{i+l}(t), M_{i+l}(t)),
\]

where the weights \( w_l \) depend on the choice of \( \Omega(r) \) but not on the index \( i \). In the sum we make use of the periodic BCs for \( u \). The integral evaluation of \( \mathcal{A}[\hat{u}(t, \cdot)](x_i + h/2) \) for all indices \( i \) can be written as a matrix–vector product with a circulant, and in general sparse, matrix and hence can be evaluated efficiently with FFT techniques. The computation of the non-local term by exploiting the sparsity of the matrix but without using FFT techniques considerably increases the CPU time required for evaluation of the right-hand side of the MOL-ODE and accordingly the CPU time required for running simulations of the non-local model. This effect is even more pronounced in the 2D case described further below. It is important to note that with the above process to approximate the non-local term in the model, we do not sample \( \Omega(r) \) but evaluate integrals involving it exactly; this will be different in the approach which we take in 2D. For details on the computation of the weights, on merits of the FFT approach to evaluate the matrix–vector product, and also on higher-order reconstructions, we refer to Gerisch (2007).

\subsection{Time integration of the MOL-ODE}

For the time integration of the MOL-ODE system we use the fourth-order, matrix-free, linearly implicit code ROWMAP (Weiner et al., 1997). This method is designed for the numerical solution of stiff initial value problems of ODEs of large dimension. It uses the iterative full orthogonalisation method (FOM) to solve the linear stage equations employing a multiple Arnoldi process to extend the Krylov space from stage to stage. A particularly nice feature is that the user is not required to provide a Jacobian matrix or Jacobian matrix times vector subroutine—the latter is by default computed efficiently using finite differences by the code itself. ROWMAP implements automatic time step size control and we use a relative and absolute tolerance of \( 10^{-7} \). This leads to numerical results where the temporal error of the discretisation of the MOL-ODE can be neglected in comparison with the spatial error caused by discretising the PDE on the spatial grids under consideration in our numerical computations.

\subsection{Two spatial dimensions}

The 2D domain \( \Omega = (A, B) \times (C, D) \) with \( A < B, C < D \), and, for simplicity, \( B - A, D - C \in \mathbb{N} \) is covered by a uniform spatial grid with grid width \( h = 1/N \) in both directions for a user-prescribed positive \( N \in \mathbb{N} \). The grid points \( x_{i,j} \) are located in the centres of the grid cells (finite volumes), that is

\[
x_{i,j} := \left( x_i + (i - 0.5)h, C + (j - 0.5)h \right),
\]

\[
i,j = 1, 2, \ldots ,
\]

As in the 1D case, we compute approximations to the average of the exact solution of the PDE system for the individual grid cells, that is, for the cancer cell density, we compute approximations \( \mathcal{C}_p(t) \)

\[
\mathcal{C}_p(t) \approx \frac{1}{N^2} \int_{x_{i-1/2}}^{x_{i+1/2}} \int_{y_{j-1/2}}^{y_{j+1/2}} c(t, x, y) \, dx \, dy
\]

and accordingly for the other variables of the PDE system. The finite volume spatial discretisation converts the PDE system together with its BCs into the MOL-ODE system for the averages \( \{ C_i(t), V_i(t), M_i(t) : i,j = 1,2,\ldots \} \). The initial values for this ODE system are taken from the initial values prescribed for the PDE system. The numerical solution of this initial value problem is done as in the 1D case using the time integration scheme ROWMAP. The finite volume discretisation of the local terms in the 2D PDE problem amounts to employing appropriate 1D discretisations along the \( x \)- and \( y \)-directions of the grid.

In the following, we concentrate on the discretisation of the non-local term in 2D.

As in the 1D case, the non-local term \( \mathcal{A}[u(t, \cdot)] \) in 2D involves the parameter \( R > 0 \). The integral in 2D is over a circle of radius \( R \) centred in \( \chi \) and the integrand has two components due to the presence of the normal vector.
We define the vector valued function
\[
\mathbf{f}(\theta; r) = \eta(\theta) \cdot \Omega(r) g(\mathbf{u}(x + r \eta(\theta))),
\]
where \(r\) is regarded as a parameter. Then
\[
\mathcal{A}(\mathbf{u}(t, \cdot))(x) = \frac{1}{R} \int_0^R r \int_0^{2\pi} f(\theta; r) \, d\theta \, dr
\]
\[
= \frac{1}{R} \int_0^R r \, \mathcal{F}(r) \, dr.
\]
We approximate both, the integral \( \int_0^{2\pi} f(\theta; r) \, d\theta \) and the integral \( \frac{1}{R} \int_0^R r \, \mathcal{F}(r) \, dr \) using a composite trapezoidal rule. The grid width in the radial direction is \( h_r = R/N_r \) and the grid width in the angular direction is \( h_\theta = 2\pi/N_\theta \) with positive integers \( N_r \) and \( N_\theta \). The integration grid points are \( r_m = mh_r \) and \( \theta_n = nh_\theta \). This leads to
\[
\mathcal{F}(r) \approx h_\theta \sum_{n=1}^{N_\theta} f(\theta_n; r)
\]
and
\[
\frac{1}{R} \int_0^R r \, \mathcal{F}(r) \, dr \approx h_r \sum_{m=0}^{N_r - 1} r_m \mathcal{F}(r_m).
\]
The double quotes on the second summation symbol indicate that the first and last term of the sum are multiplied by the factor \( \frac{1}{2} \); the first term of the sum in fact vanishes because \( r_0 = 0 \). Due to periodicity of the domain in the first integral these factors are not necessary because we simply start the sum at \( n = 1 \) and not \( n = 0 \). Combining both approximations and going back to the original integrand we obtain the following approximation of the non-local term:
\[
\mathcal{A}(\mathbf{u}(t, \cdot))(x) \\
\approx \frac{h_\theta}{R} \sum_{n=0}^{N_\theta - 1} \sum_{m=0}^{N_r - 1} r_m \eta(\theta_n) \cdot \Omega(r_m) g(\mathbf{u}(x + r_m \eta(\theta_n))).
\]
Note that, contrary to the treatment of the non-local term in 1D, the function \( \Omega(r) \) and also the vector \( \eta(\theta) \) are sampled in points of the integration grid—integrals involving them are hence, in general, not evaluated exactly.

The remaining difficulty is the evaluation of \( g(\mathbf{u}(x + r_m \eta(\theta_n))) \). Here we follow a similar approach as in 1D and use a suitable reconstruction from grid data. We first define in the grid cell centres \( x_{ij} \) the values
\[
G_{ij} := g(C_{ji}, V_{ji}, M_{ji}) \approx g(\mathbf{u}(x_{ij})).
\]
In a second step, we can now approximate \( g(\mathbf{u}(x + r_m \eta(\theta_n))) \) by bilinear interpolation using the four values \( G_{ij} \) corresponding to the four grid cell centres \( x_{ij} \) which surround \( x + r_m \eta(\theta_n) \). Here we make use of periodicity again.

For the discretisation of the PDE, we must evaluate the first component of the approximation of the non-local term for \( x = (x_i + h/2, y_j) \), i.e. located in the centre of the right cell face of a grid cell \((i,j)\) and the second component for \( x = (x_i, y_j + h/2) \), i.e. located in the centre of the upper cell face. Let \( M = \lceil R/h \rceil \) as before. Then these evaluations can be expressed using weights \( w_{ij}^{(1)} \) and \( w_{ij}^{(2)} \), respectively. The weights are independent of the grid cell index \((i,j)\) for which we evaluate the non-local term. Using the periodic BCs to extend the grid values \( G_{ij} \) periodically, the evaluations then take the form
\[
\lbrack \mathcal{A}(\mathbf{u}(t, \cdot))(x_i + h/2, y_j) \rbrack_i = \sum_{k=-M}^{M-1} \sum_{l=-M}^{M-1} w_{ij}^{(1)} G_{ji+k,j+l},
\]
\[
\lbrack \mathcal{A}(\mathbf{u}(t, \cdot))(x_i, y_j + h/2) \rbrack_i = \sum_{k=-M}^{M-1} \sum_{l=-M}^{M-1} w_{ij}^{(2)} G_{ji+k,j+l}.
\]
Evaluating each of these two formulas for all \((i,j)\) of the spatial grid corresponds to a matrix–vector product with a block-circulant matrix with circulant blocks (sparse). A first application of the FFT techniques reduces the matrix to a block-circulant matrix with diagonal blocks but, for the simulations considered in this paper, does not yield an improvement in CPU time compared to an efficient evaluation of the above sums exploiting sparsity. However, reordering of the matrix to a block-diagonal matrix with circulant blocks and an appropriate second application of the FFT cuts down on the CPU time requirements for the evaluation of the matrix–vector product considerably leading to a required CPU time of about 70 min on a standard laptop\(^3\) for a typical simulation of the non-local PDE model in 2D. This is approximately a 15-fold reduction in CPU time compared to an efficient evaluation of the above sums exploiting sparsity. For details we again refer to Gerisch (2007).

References


\(^3\)Intel\textsuperscript{R} Core\textsuperscript{TM}2 T5500 1.66 GHz, 1 GB memory.


