MATHEMATICAL MODELLING OF CANCER INVASION OF TISSUE: THE ROLE AND EFFECT OF NONLOCAL INTERACTIONS

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In this paper we consider a mathematical model of cancer cell invasion of tissue (extracellular matrix). Two crucial components of tissue invasion are (i) cancer cell proliferation, and (ii) over-expression and secretion of proteolytic enzymes by the cancer cells. The proteolytic enzymes are responsible for the degradation of the tissue, enabling the proliferating cancer cells to actively invade and migrate into the degraded tissue. Our model focuses on the role of nonlocal kinetic terms modelling competition for space and degradation. The model consists of a system of reaction-diffusion-taxis partial differential equations, with nonlocal (integral) terms describing the interactions between cancer cells and the host tissue. We first of all prove results concerning the local existence, uniqueness and regularity of solutions. We then prove global existence. Using Green's functions, we transform our original nonlocal equations into a coupled system of parabolic and elliptic equations and we undertake a numerical analysis of this equivalent system, presenting computational simulation results from our model showing the effect of the nonlocal terms (travelling waves we observed have the shape closely linked to the nonlocal terms). Finally, in the discussion section, concluding remarks are made and

open problems are indicated.

Keywords: cancer invasion of tissue; haptotaxis; nonlocal interactions; existence, uniqueness, regularity of solutions; computational simulations; travelling waves

AMS Subject Classification: 35A05, 35A07, 35K55, 35K57, 35Q80, 65M99, 92C17

1. Introduction

In many biological and physical processes it is very important and highly relevant to take into account nonlocal (i.e. other than point-wise) interactions. It is already well known that elliptic equations (e.g. those describing chemotaxis) can be transformed to equivalent nonlocal PDEs (that are related to the solutions of Poisson-like equations (see Ref. 31)). However, in this paper our purpose is different and here we seek to model certain biological processes which possess a nonlocal character. The specific model we will develop in this paper refers to the process of tumour invasion, but the method of investigation is general and therefore can be applied to many other different processes.

The prognosis of a cancer is primarily dependent on its ability to invade the surrounding tissue and spread to distant secondary sites i.e. metastasize. The crucial process of invasion consists of four main steps: cancer cell adhesion (binding) to the extracellular matrix (ECM), secretion of the matrix degrading enzymes (extracellular matrix degradation), the movement or migration of the cancer cells through the extracellular matrix and finally cell proliferation. Cancer cells encounter a variety of factors which may influence their directed migration at different stages in the process of tumour invasion and metastasis. Such factors can promote the directed movement of tumour cells by a mechanism termed **haptotaxis**. This is defined as directed cellular locomotion in response to a concentration gradient of a bound, non-diffusible molecule (cf. chemotaxis, where cells respond to a concentration gradient of a diffusible chemical substance) such as those present within the components of the extracellular matrix e.g. collagen, fibronectin, vitronectin[13]. Such adhesive molecules can be present in spatially varying amounts within extracellular matrix. A cell that is constantly making and breaking adhesions with such molecules will move from a region of low concentration to an area where that adhesive molecule is more highly concentrated.

In this paper we develop a new mathematical model of cancer cell invasion. The model we propose is relatively simple, because rather than taking into account all the very complex details of the invasion process, we concentrate on modelling nonlocal interactions involved there. In order to achieve this we develop an integro-differential equation model involving cancer cells and the extracellular matrix. The modelling of the degradation of tissue is achieved through the incorporation of a spatial kernel modelling the degradative interactions between cancer cells and the tissue. In the following section we formulate and describe the mathematical model which consists

of two coupled, nonlinear parabolic partial integro-differential equations. In Section 3 using the theory of linear semigroups we first of all prove results concerning the local existence, uniqueness and regularity of solutions of our system of nonlinear PDEs. In Section 4, we prove global existence, uniqueness and regularity of the solutions. Using Green's functions, in Section 5 we transform our original nonlocal equations into a coupled system of parabolic and elliptic equations. We undertake a numerical analysis of this equivalent system, presenting computational simulation results from our model showing travelling waves of cancer cells degrading, invading and replacing the tissue. We then compare our computational results in two distinct cases: (i) the situation when the non-local effect is strong (i.e. the kernel support is relatively big) and, (ii) the situation when the non-local effect is weak (i.e. the case close to local one) and we discuss the differences between them. Finally, concluding remarks are made in the Discussion section (Section 6).

2. The Mathematical Model

Cancer is a very complex and multi-faceted disease. Therefore there is a genuine need for theoretical approaches and studies that may help to better understand various aspects of this phenomenon. The literature concerning the mathematical modelling of many of the key aspects of cancer growth, spread and treatment is now quite extensive (see e.g. Refs. 6, 30).

Previous mathematical models for cancer invasion and metastasis can be found in, for example, Refs. 2, 3, 15, 16, 23. Many of these papers examine how cancer cells respond to ECM gradients via haptotaxis. The gradients are created through the degradation of the extracellular matrix (ECM) by matrix degrading enzymes (MDEs). In this paper, we will base our mathematical model on generic solid tumour growth, which for simplicity we assume is at an avascular stage, focussing initially solely on the interactions between the cancer cells and the surrounding tissue (ECM together with the healthy cells). We develop a mathematical model consisting of two coupled partial differential equations (PDEs) describing the evolution in time and space of the system variables and including nonlocal (integral) terms. The key physical variables are taken to be the cancer cell density (denoted by u) and the tissue density (denoted by v). The focus of the model is on examining different key features of the system separately *i.e.* cell random motility, haptotaxis, proliferation and extracellular matrix degradation.

We now describe the way in which the cancer cell density $u(t, x)$ and the tissue density $v(t, x)$ are involved in invasion and derive partial differential equations governing the evolution of each variable.

(a) ***Cancer Cells:***

The degradation of the extracellular matrix by cancer cell associated enzymes allows cancer cells to invade surrounding tissues and gain access to the circulation.

In addition, invasive cells *in vivo* adhere to surrounding ECM molecules via specific receptors and produce and secrete several types of matrix degrading enzyme (MDE). The consequent digestion of ECM allows the cells to move into the spaces thereby created and also sets up tissue gradients, which the cells then exploit to move forwards[4,5,12,24,25,37]. Movement up concentration gradients of ECM has been reported as a mechanism enabling movement through tissues by a variety of cell types. Tumour cell motility toward high concentrations/densities of substratum-bound insoluble components has been termed "**haptotaxis**". Along with random motility (cf. diffusion), we assume that these two key mechanisms govern cancer cell migration and in our model, we model these phenomena using standard terms (for details see: Ref. 14 and the references given therein).

Individual cells proliferating within the overall tumour cell mass have to compete for nutrients, oxygen and space. So even cancer cells under some conditions are suppressed in their proliferation e.g. cells in the interior of a solid tumour do not divide as quickly as the cells on the surface. When describing cell growth we therefore have to take into account this phenomenon. It is possible to do this by using a logistic growth term, for instance. However, assuming ordinary logistic growth may well be a crude over-simplification, since it means that proliferation of the cells depends on the cells and the tissue density at given point, whereas the proliferation probably actually depends on the cell and tissue density in a local neighbourhood. The immediate surrounding of a cell influences its ability to divide and therefore we include a nonlocal term[8] describing a neighbourhood of a cell that inhibits its proliferation in the model and we adopt the following proliferation term in our model:

$$\mu_1\, u(t,x)\Big(1 - \int\limits_{\Omega} k_{1,1}(x,y)\, u(t,y)\,\mathrm{d}y - \int\limits_{\Omega} k_{1,2}(x,y)\, v(t,y)\,\mathrm{d}y\Big), \tag{2.1}$$

where Ω is a bounded domain in $\mathbb{R}^d$ $(d \geq 1)$ with smooth boundary $\partial\Omega$, μ_1 represents the cancer cell proliferation rate, and $k_{1,1}$, $k_{1,2}$ are given spatial kernels. The kernels that are used in the present paper describe the short-range cell-cell and cell-matrix interactions (through cell-cell signalling via inter-cellular junctional complexes, and cellular protrusions e.g. filopodia) in a standard way. The precise forms of the kernels are given in Section 5 (see Fig. 1). The terms

$$u(t,x) \int\limits_{\Omega} k_{1,1}(x,y)\, u(t,y)\,\mathrm{d}y \tag{2.2}$$

and

$$u(t,x) \int\limits_{\Omega} k_{1,2}(x,y)\, v(t,y)\,\mathrm{d}y\,, \tag{2.3}$$

describe the inhibition of cell proliferation caused by the density of surrounding cancer cells and tissue respectively.

Therefore, incorporating both the migration terms (random motility and haptotaxis) and the non-local proliferation terms, the equation describing the spatio-temporal dynamics of the cancer cells reads

$$\partial_t u(t,x) = D\Delta u(t,x) - \nabla \cdot \big(\chi(v)\, u(t,x)\, \nabla v(t,x)\big)$$
$$+\mu_1\, u(t,x)\Big(1 - \int_\Omega k_{1,1}(x,y)\, u(t,y)\, \mathrm{d}y - \int_\Omega k_{1,2}(x,y)\, v(t,y)\, \mathrm{d}y\Big) \qquad (2.4)$$

where $\chi(v)$ is the haptotaxis sensitivity function and $D > 0$ is the coefficient of linear diffusion. In summary, the equation for cancer cells consists of linear diffusion together with a standard haptotaxis transport term[2,3,14,15,18,29] and a non-local "source term" given by expression (2.1) i.e. a (parabolic) reaction-diffusion-taxis equation. However, we note that different assumptions regarding cell migration may lead to hyperbolic models as documented in 7, 20.

(b) ***Extracellular Matrix***

We now turn attention to the extracellular matrix (ECM). This is known to contain many macromolecules such as vitronectin, laminin and fibronectin which can be degraded by several matrix degrading enzymes.

Since extracellular matrix (ECM) is "static", we neglect any diffusion. We focus solely on its degradation by the cancer cells. As mentioned above, matrix degradation *in vivo* is achieved either through re-binding of MDE to receptors on the cancer cell surface or by MDE-activation of other degrading components in the matrix. This has the effect of producing a region of degradation that is restricted to a small distance around the leading edge of the invading cancer cells. Therefore, in our model we assume that cancer cells themsleves degrade the ECM upon contact in a highly controlled and restricted manner, and use an integral term to capture this, thus simplifying our model slightly by not explicitly modelling the MDE. We also assume that ECM components are re-established or re-modelled by other cells present in the tissue e.g. fibroblasts. These cells are assumed to be proliferating and competing for space with the invasive cells in a manner similar to that describing cancer cell proliferation. Thus, in the absence of cancer cells, we assume that the extracellular matrix is remodelled in a logistic manner, representing a return to the normal, healthy "uninvaded" state. On the other hand, the presence of cancer cells leads to competition for space between the cancer cells and the ECM which again we model by incorporating a crowding term into the logistic equation. Using a modified logistic growth with rate constant μ_2 to describe the ECM production, and taking γ to represent the rate of degradation, we have the following equation

for the extracellular matrix:

$$\partial_t v(t,x) = -\gamma\, v(t,x) \int\limits_\Omega k(x,y)\, u(t,y)\,\mathrm{d}y$$
$$+\mu_2\, v(t,x)\Big(1 - \int\limits_\Omega k_{2,1}(x,y)\, u(t,y)\,\mathrm{d}y - \int\limits_\Omega k_{2,2}(x,y)\, v(t,y)\,\mathrm{d}y\Big), \qquad (2.5)$$

where γ, μ_2 are given non-negative parameters (ECM degradation rate and ECM production rate, respectively) and $k_{2,1}$, $k_{2,2}$ and k are non-negatively defined functions, kernels, once again describing the short-range cell-matrix interactions in a standard way. The precise forms of the kernels are given in Section 5 (see Fig. 1).

The complete system of equations describing the interactions between the tumour cells and extracellular matrix is therefore:

$$\begin{aligned}
\partial_t u(t,x) &= D\Delta u(t,x) - \nabla\cdot\big(\chi(v)\, u(t,x)\,\nabla v(t,x)\big) \\
&\quad +u(t,x)\mu_1\Big(1 - \int\limits_\Omega k_{1,1}(x,y)\, u(t,y)\,\mathrm{d}y \\
&\quad - \int\limits_\Omega k_{1,2}(x,y)\, v(t,y)\,\mathrm{d}y\Big) \\
\partial_t v(t,x) &= -\gamma\, v(t,x) \int\limits_\Omega k(x,y)\, u(t,y)\,\mathrm{d}y \\
&\quad +v(t,x)\mu_2\Big(1 - \int\limits_\Omega k_{2,1}(x,y)\, u(t,y)\,\mathrm{d}y \\
&\quad - \int\limits_\Omega k_{2,2}(x,y)\, v(t,y)\,\mathrm{d}y\Big)\,,
\end{aligned} \qquad (2.6)$$

where D, μ_1, μ_2, γ (the cancer cell linear diffusion coefficient, cancer cell proliferation rate, ECM production rate and ECM degradation rate, respectively) are given nonnegative parameters, k, $k_{i,j}$ $(i,j=1,2)$ are given spatial kernels and χ is the haptotaxis function that depends on v. We assume that

$$k\,, k_{i,j} \in L^\infty(\Omega\times\Omega)\,, \qquad \nabla k\,, \nabla k_{2,j} \in (L^\infty(\Omega\times\Omega))^d\,, \qquad i,j=1,2\,, \qquad (2.7)$$

$$k \geq 0 \qquad k_{i,j} \geq 0 \qquad i,j=1,2, \qquad (2.8)$$

$$\begin{gathered}
\chi \in C^2(\mathbb{R})\,, \qquad \chi \geq 0 \\
\text{and } \chi,\ \chi' \text{ are globally Lipschitz continuous.}
\end{gathered} \qquad (2.9)$$

Mathematically these are very weak assumptions and it is easy to see that the kernels that we use in Section 5 do indeed satisfy (2.7) and (2.8).

The system (2.6) may be rewritten in the following compact version:

$$\begin{aligned}
\partial_t u &= D\Delta u - \nabla\cdot\Big(u\chi(v)\nabla v\Big) + \mu_1 u\,\Big(1 - k_{1,1}\circledast u - k_{1,2}\circledast v\Big)\,, \\
\partial_t v &= -\gamma\, v\, k\circledast u + \mu_2\, v\,\Big(1 - k_{2,1}\circledast u - k_{2,2}\circledast v\Big)\,,
\end{aligned} \qquad (2.10)$$

where $k\circledast u(x) = \int\limits_\Omega k(x,y)u(y)\mathrm{d}y$.

Remark 2.1. If instead of Ω we consider $\mathbb{R}^d$ or $d-$dimensional torus $\mathbb{T}^d$ (periodic boundary conditions), then it is natural to use the convolution $\star$ instead of $\circledast$.

Boundary Conditions: We assume that there is no-flux of cancer cells on the boundary of the domain,

$$u\chi(v)\frac{\partial v}{\partial \nu} - D\frac{\partial u}{\partial \nu} = 0 \qquad \text{on} \quad]0,T[\times\partial\Omega\,, \tag{2.11}$$

where ν is the outward normal vector to $\partial\Omega$.

Initial Conditions: We consider the initial data

$$\big(u(0,x)\,,\,v(0,x)\big) = \big(u_0(x)\,,\,v_0(x)\big)\,. \tag{2.12}$$

3. Local existence

The question of local existence was studied for a similar model in Ref. 26. However it should be noted that the proof of local existence given here differs from the one given in Ref. 26. We note that in Ref. 26 the author uses a classical setting, while here we adopt the approach using the theory of semigroups.

Denote the norm of $L^p(\Omega)$ by $\|\,.\,\|_p$ and the norm of the Sobolev space $W^{l,p}(\Omega)$ by $\|\,.\,\|_p^{(l)}$. Let

$$p > d\,. \tag{3.1}$$

For a fixed $T > 0$ let

$$|||u|||_p = \sup_{t\in[0,T]} \|u(t)\|_p\,, \qquad |||u|||_p^{(l)} = \sup_{t\in[0,T]} \|u(t)\|_p^{(l)}\,.$$

For simplicity of notation, and without loss of generality, we can assume

$$D = \gamma = \mu_1 = \mu_2 = 1\,. \tag{3.2}$$

We note that although the constants do not play a role in the proof, they do play a role in the derivation of the model that is postulated here. We therefore stress that although putting all the constants equal to one is useful for the proof, any analysis of the model (e.g. computational simulations) must consider the relative values of these parameters. Indeed, quantitative estimates of the parameters are given in Section 5.

Now we introduce the new variable (see Ref. 18 and references therein)

$$w(t,x) = \frac{u(t,x)}{z(t,x)}\,, \qquad z(t,x) = \exp\Big(\int_0^{v(t,x)} \chi(s)\,\mathrm{d}s\Big). \tag{3.3}$$

In the new variables the equation reads

$$\begin{aligned}\partial_t w &= \Delta w + \chi(v)\nabla v\cdot\nabla w + w\Big(1 - k_{1,1}\circledast(w\,z) - k_{1,2}\circledast v\Big)\\ &\quad +\chi(v)\,w\,vk\circledast(w\,z) - \chi(v)\,w\,v\Big(1 - k_{2,1}\circledast(w\,z) - k_{2,2}\circledast v\Big)\\ \partial_t v &= -vk\circledast(wz) + v(1 - k_{2,1}\circledast(wz) - k_{2,2}\circledast v\Big)\end{aligned} \tag{3.4}$$

on $]0,T[\times\Omega$, with the boundary conditions

$$\frac{\partial w}{\partial\nu} = 0\,, \qquad (t,x)\in]0,T[\times\Omega\,, \tag{3.5}$$

and the initial data

$$(w,v)(0,x) = (w_0,v_0)(x)\,, \qquad x\in\Omega\,. \tag{3.6}$$

In order to show local existence of solutions to (3.4)–(3.6), we apply the theory of linear semigroups. Let A_p denote the sectorial operator defined by

$$A_p u = -\Delta u\,, \qquad u\in D(A_p) = \left\{\xi\in W^{2,p}(\Omega)\,:\quad \frac{\partial\xi}{\partial\nu} = 0 \text{ on } \partial\Omega\right\}.$$

Since $Re\,(\sigma(A_p+1))\geq 1>0$, where $\sigma(A_p+1)$ is the spectrum of A_p+1, the operator A_p+1 possesses the fractional powers $(A_p+1)^\beta$, $\beta\geq 0$. Let $X_p^\beta = D((A_p+1)^\beta)$. Then we have the following embedding properties Ref. 22 (Theorem 1.6.1)

$$\begin{aligned} &X_p^\beta\hookrightarrow W^{k,q}(\Omega) && \text{for } \ k-\tfrac{d}{q} < 2\beta - \tfrac{d}{p}\,, \quad q\geq p>d\\ &X_p^\beta\hookrightarrow C^\kappa(\overline{\Omega}) && \text{for } \ 0\leq\kappa<2\beta-\tfrac{d}{p}\,,\end{aligned} \tag{3.7}$$

where C^κ is the space of $[\kappa]$–times continuously differentiable functions with the $[\kappa]$–order derivative satisfying the Hölder condition with exponent $\kappa-[\kappa]$.

Since A_p+1 is a sectorial operator then $\{e^{-t(A_p+1)}\}_{t\geq 0}$ defines an analytical semigroup. Moreover for $u\in L^p(\Omega)$, we have (see Ref. 22)

$$\big\|(A_p+1)^\beta e^{-t(A_p+1)}u\big\|_p \leq ct^{-\beta}e^{-\delta t}\big\|u\big\|_p\,, \tag{3.8}$$

where $\delta\in]0,1[$.

Let $p>d$ be fixed. We denote by $\|\,.\,\|$ the norm in $W^{1,p}(\Omega)$. Given $T>0$, let

$$Y = C^0\Big([0,T]\,;\,W^{1,p}(\Omega)\Big)\,, \qquad Y^{1,\infty} = C^0\Big([0,T]\,;\,W^{1,\infty}(\Omega)\Big).$$

with the norms denoted by $|||\,.\,|||$ and $|||\,.\,|||_\infty^{(1)}$, respectively.

Now the local existence theorem can be formulated:

Theorem 3.1. *Let initial data (3.6) be such that $(w_0,v_0)\in W^{1,p}(\Omega)\times W^{1,\infty}(\Omega)$. If assumptions (2.7), (2.9) are satisfied, then there exists $T>0$ such that problem (3.4)–(3.6) has a unique solution (w,v) in $Y\times Y^{1,\infty}$ and*

$$\begin{aligned} w &\in C^1\Big(]0,T[\,;W^{1,p}(\Omega)\Big)\cap C^0\Big(]0,T[\,;W^{2,p}(\Omega)\Big)\,,\\ v &\in C^1\Big(]0,T[\,;W^{1,\infty}(\Omega)\Big)\,.\end{aligned} \tag{3.9}$$

Moreover, if $w_0\,,\ v_0 \geq 0$, *then*

$$w(t) \geq 0\,, \quad v(t) \geq 0\,, \qquad t \in\ [0,T]\,. \tag{3.10}$$

Let $T_{\max}$ *be the maximal existence time. If there is a continuous function* $\omega\ :\ ]0,\infty[\to]0,\infty[$ *such that, for each* $\tau > 0$,

$$\big\|w(t)\big\| \leq \omega(\tau), \qquad \big\|v(t)\big\|_\infty^{(1)} \leq \omega(\tau) \qquad 0 < t < \min\Big\{\tau, T_{\max}\Big\}\,, \tag{3.11}$$

then $T_{\max} = +\infty$.

Proof. Let B_R, for some $R > 0$, be the ball

$$B_R = \Big\{(w,v) \in Y \times Y^{1,\infty}\ :\quad \big|\!\big|\!\big|w\big|\!\big| + \big|\!\big|\!\big|v\big|\!\big|_\infty^{(1)} \leq R\Big\}$$

and $J = (J_1, J_2)$ be the operator

$$\begin{aligned} J_1(w,v) = e^{-t(A_p+1)}w_0 + \int\limits_0^t e^{-(t-s)(A_p+1)}\Big(&\chi(v)\nabla v\cdot\nabla w + 2w \\ &-w\,k_{1,1}\circledast(wz) - w\,k_{1,2}\circledast v + \chi(v)\,w\,vk\circledast(w\,z) \\ &-\chi(v)\,w\,v\big(1 - k_{2,1}\circledast(w\,z) - k_{2,2}\circledast v\big)\Big)\,\mathrm{d}s \\ J_2(w,v) = v_0 + \int\limits_0^t\Big(&-v\,k\circledast(w\,z) \\ &+v\,\big(1 - k_{2,1}\circledast(w\,z) - k_{2,2}\circledast v\big)\Big)\,\mathrm{d}s\,. \end{aligned} \tag{3.12}$$

Fix $R > K\|w_0\| + \|v_0\|_\infty^{(1)}$ where

$$K := \sup_{t\in[0,T]} \|e^{-t(A_p+1)}\|_{\mathcal{L}(W^{1,p}(\Omega),W^{1,p}(\Omega))}.$$

We first prove that B_R is invariant under J if $T > 0$ is sufficiently small. Using $(3.7)_1$ with $k = 1$, $p = q$ and $\beta \in]\,\frac{1}{2}\,,\,1\,[$ as well as (3.8) we obtain

$$\begin{aligned} \big\|J_1\big\| \leq\ K\|w_0\| + \text{const}\int\limits_0^t (t-s)^{-\beta}e^{-\delta(t-s)}\Big(&\big\|\chi(v)\big\|_\infty\big\|\nabla w\big\|_p\big\|\nabla v\big\|_\infty \\ &+2\big\|w\big\|_p + \big\|w\big\|_p\big\|k_{1,1}\circledast(w\,z)\big\|_\infty + \big\|w\big\|_p\big\|k_{1,2}\circledast v\big\|_\infty \\ &+\big\|\chi(v)\big\|_\infty\big\|w\big\|_p\big\|v\big\|_\infty\Big(\big\|k\circledast(w\,z)\big\|_\infty + 1 \\ &+\big\|k_{2,1}\circledast(w\,z)\big\|_\infty + \big\|k_{2,2}\circledast v\big\|_\infty\Big)\Big)\,\mathrm{d}s\,. \end{aligned} \tag{3.13}$$

Then by (2.7), assuming that $(w,v) \in B_R$, we obtain

$$\big|\!\big|\!\big|J_1(w,v)\big|\!\big|\!\big| \leq K\|w_0\| + \frac{\text{const}}{1-\beta}\,T^{1-\beta}\,, \tag{3.14}$$

where the constant indicated by "const" depends on R.

In the same manner, by (2.7) and (2.9), we obtain

$$\left\|\left\| J_2(w,v)\right\|\right\|_\infty^{(1)} \leq \|v_0\|_\infty^{(1)} + \text{const}\, T\,, \tag{3.15}$$

where the constant indicated by "const" depends on R. Hence we can choose T sufficiently small to assert that $J(B_R) \subset B_R$.

Similar arguments show that

$$\left\|\left\| J_1(w_1,v_1) - J_1(w_2,v_2)\right\|\right\| \leq \frac{\text{const}}{1-\beta} T^{1-\beta}\Big(\left\|\left\| w_1 - w_2\right\|\right\| + \left\|\left\| v_1 - v_2\right\|\right\|_\infty^{(1)}\Big) \tag{3.16}$$

and

$$\left\|\left\| J_2(w_1,v_1) - J_2(w_2,v_2)\right\|\right\|_\infty^{(1)} \leq \text{const}\, T\,\Big(\left\|\left\| w_1 - w_2\right\|\right\| + \left\|\left\| v_1 - v_2\right\|\right\|_\infty^{(1)}\Big)\,, \tag{3.17}$$

where the constants indicated by "const" depend on R.

Hence, given T small enough we obtain the contractivity of the operator J in B_R. Thus local existence and uniqueness follow.

Now, we proceed with the proof of (3.9). Let $t_0 \in]0,T[$ fixed, then (see Ref. 22, Lemma 3.5.2) entails

$$\frac{d}{dt} w(t_0,\cdot) \in W^{1,p}(\Omega).$$

Next, we rewrite the first equation of (3.4) in the following form

$$-\Delta w - b\cdot\nabla w + w = f - \frac{\partial w}{\partial t},$$

where $b = \chi(v)\nabla v \in (L^\infty(\Omega))^N$ and

$$f = w\Big(2 - k_{1,1}\circledast(wz) - k_{1,2}\circledast v) + \chi(v) w v (k\circledast(wz) - 1 + k_{2,1}\circledast(wz) + k_{2,2}\circledast v\Big) \in L^p(\Omega).$$

Therefore, from elliptic estimates we get $w(t_0) \in W^{2,p}(\Omega)$, ending the proof of (3.9).

From (2.7), (2.9) and the regularity of our solutions we obtain

$$\Big(1 - k_{1,1}\circledast(wz) - k_{1,2}\circledast v + \chi(v) v (k\circledast(wz) - 1 + k_{2,1}\circledast(wz) + k_{2,2}\circledast v)\Big) \in L^\infty(]0,T[\times\Omega).$$

Consequently the non–negativity of w follows from maximum principle arguments. Next we observe that the equation for v can be written as

$$v_t = v f,$$

with $f = 1 - k\circledast(wz) - k_{2,2}\circledast v - k_{2,1}\circledast(wz)$. Thus,

$$v(x,t) = v_0(x) e^{\int_0^t f(x,s)ds},$$

concluding the non–negativity of v.

The last statement follows by prolongation arguments (see Ref. 22, Theorem 3.3.4). This finishes the proof.

□

Corollary 3.1. *Let $(u_0, w_0) \in W^{1,p}(\Omega) \times W^{1,\infty}(\Omega)$. Assume (2.7), (2.9) then there exists $T > 0$ such that the problem (2.10), (2.11), (2.12) has a unique solution*

$$\begin{aligned} u &\in C^0\Big([0,T]\,;W^{1,p}(\Omega)\Big) \cap C^1\Big(]0,T[\,;W^{1,p}(\Omega)\Big) \cap C^0\Big(]0,T[\,;W^{1,\infty}(\Omega)\Big)\,,\\ v &\in C^0\Big([0,T]\,;W^{1,\infty}(\Omega)\Big) \cap C^1\Big(]0,T[\,;W^{1,\infty}(\Omega)\Big)\,. \end{aligned}$$

Proof. Since $u_0 \in W^{1,p}(\Omega)$ and $v_0 \in W^{1,\infty}(\Omega)$ then $w_0 \in W^{1,p}(\Omega)$. Therefore, we can apply Theorem 3.1. Finally, taking into account that $u = wz$, the corollary easily follows. □

4. Global existence

It is well known that for various systems describing cell motions and chemotaxis (see 29 chapter 5 and references given therein), the solutions may blow up in finite time. Here we prove that the solutions to the nonlocal equation (2.6) exist globally in any space dimension d without imposing any kind of smallness conditions on the initial conditions.

In this section we assume that (u, v) is a nonnegative solution to Eq. (2.6), (2.11), (2.12) given by Theorem 3.1 — see Remark 3.1 — on the time interval $[0, T]$, with $T > 0$. We start with some simple lemmas that provide *a priori* estimates.

Lemma 4.1.

$$v(t,x) \le v_0(x)\, e^T\,, \qquad t \in [0,T]\,, \quad x \in \Omega\,. \tag{4.1}$$

Proof. The statement is a consequence of the nonnegativity of u and v, the assumption (2.8) as well as the inequality

$$\partial_t v \le v\,, \tag{4.2}$$

that follows from Eq. (2.6). □

Lemma 4.2.

$$\big|\!\big|\!\big|u\big|\!\big|\!\big|_1 \le \big\|u_0\big\|_1\, e^T\,, \qquad \big|\!\big|\!\big|w\big|\!\big|\!\big|_1 \le \big\|u_0\big\|_1\, e^T\,. \tag{4.3}$$

Proof. Integrating Eq. $(2.6)_1$ we obtain

$$\begin{aligned} \big\|u(t,\,.\,)\big\|_1 = \int\limits_\Omega u(t,x)\,\mathrm{d}x \le \int\limits_\Omega u_0(x)\,\mathrm{d}x + \int\limits_0^t \int\limits_\Omega u(t',x)\,\mathrm{d}x\,\mathrm{d}t'\\ \big\|u_0\big\|_1 + \int\limits_0^t \big\|u(t',\,.\,)\big\|_1\,\mathrm{d}t'\,. \end{aligned} \tag{4.4}$$

Hence, by Gronwall's lemma

$$\big|\!\big|\!\big|u\big|\!\big|\!\big|_1 \le \big\|u_0\big\|_1\, e^T\,. \tag{4.5}$$

Taking into account the fact that $w = \frac{u}{z}$ and $z^{-1} \le 1$ yields (4.1).

□

Lemma 4.3. *We have*

$$\left|\!\left|\!\left| v \right|\!\right|\!\right|_{\infty}^{(1)} \leq \mathfrak{c}_1 \left(\left\| v_0 \right\|_{\infty}^{(1)} + \mathfrak{c}_2 \right), \tag{4.6}$$

where the constants $\mathfrak{c}_1$ *and* $\mathfrak{c}_2$ *depend on* T, $\left\| u_0 \right\|_1$ *and* $\left\| v_0 \right\|_\infty$.

Proof. By Eq. $(3.4)_2$ we have

$$\begin{aligned} \partial_t \nabla v = & -\nabla v \, k \circledast u - v \, (\nabla_1 k) \circledast u \\ & + \nabla v \left(1 - k_{2,1} \circledast u - k_{2,2} \circledast v \right) \\ & + v \left((\nabla_1 k_{2,1}) \circledast u - (\nabla_1 k_{2,2}) \circledast v \right), \end{aligned} \tag{4.7}$$

where by ∇_1 we indicate the gradient with respect to the first variable x.
Therefore, by (2.7), we obtain

$$\begin{aligned} |\nabla v(t,x)| \leq & \, |\nabla v_0(x)| + \text{const} \int_0^t \left\| v(s) \right\|_\infty \left(\left\| u(s) \right\|_1 + \left\| v(s) \right\|_\infty \right) \\ & + \text{const} \int_0^t |\nabla v(s,x)| \left(1 + \left\| u(s) \right\|_1 + \left\| v(s) \right\|_\infty \right) . + \left\| v_0 \right\|_\infty \Big) . \end{aligned} \tag{4.8}$$

By (4.1) and (4.3) it follows

$$\begin{aligned} |\nabla v(t,x)| \leq & \left(|\nabla v_0(x)| + \text{const} \, T e^T \left\| v_0 \right\|_\infty \left(\left\| u_0 \right\|_p + \left\| v_0 \right\|_\infty \right) \right) \\ & \times \exp \left(\text{const} \, T \, e^T (1 + \left\| u_0 \right\|_p + \left\| v_0 \right\|_\infty \right) . \end{aligned} \tag{4.9}$$

This completes the proof. □

Lemma 4.4. *We have*

$$\left|\!\left|\!\left| w \right|\!\right|\!\right| \leq \mathfrak{c}_3 \left\| w_0 \right\|, \tag{4.10}$$

where the constants $\mathfrak{c}_3$ *depends on* T, $\left\| u_0 \right\|_1$ *and* $\left\| v_0 \right\|_\infty$.

Proof. Estimates similar to that in (3.13) show

$$\begin{aligned} \left\| w(t) \right\| \leq & \, \text{const} \, t^{-\beta} e^{-\delta t} \left\| w_0 \right\|_p + \text{const} \int_0^t (t-s)^{-\beta} e^{-\delta(t-s)} \left\| w \right\| \\ & \times \Bigg(1 + \left\| \chi(v) \right\|_\infty \left\| \nabla v \right\|_\infty + \left\| k_{1,1} \circledast u \right\|_\infty + \left\| k_{1,2} \circledast v \right\|_\infty \\ & + \left\| v \right\|_\infty \left\| \chi(v) \right\|_\infty \Big(\left\| k \circledast u \right\|_\infty + 1 \\ & + \left\| k_{2,1} \circledast u \right\|_\infty + \left\| k_{2,2} \circledast v \right\|_\infty \Big) \Bigg) \, \mathrm{d}s \, . \end{aligned} \tag{4.11}$$

Thus, by (2.7)

$$\begin{aligned}\big\|w(t)\big\| \leq \text{const}\, t^{-\beta} + \text{const} \int_0^t (t-s)^{-\beta} \big\|w(s)\big\| \\ \times \Bigg(1 + \Big(\big\|v(s)\big\|_\infty^{(1)} + \chi_0 \Big) \big\|v(s)\big\|_\infty^{(1)} + \big\|u(s)\big\|_1 + \big\|v(s)\big\|_\infty \\ + \Big(\big\|v(s)\big\|_\infty + \chi_0 \Big) \big\|v(s)\big\|_\infty \Big(\big\|u(s)\big\|_1 + 1 + \big\|v(s)\big\|_\infty \Big) \Bigg) \, \mathrm{d}s \,. \quad (4.12)\end{aligned}$$

By Theorem 7.1.1 of Ref. 22 as well as (4.1), (4.3) and (4.6) we conclude that

$$\big\|w\big\| \leq \text{const}\ t^{-\beta}, \quad (4.13)$$

for $0 < t \leq T$. Finally, taking into account the local existence and (4.13) we finish the proof.

□

By (4.6), (4.10) and Theorem 3.1 we obtain the main global result:

Theorem 4.1. *Let initial data (3.6) be such that* $(w_0, v_0) \in W^{1,p}(\Omega) \times W^{1,\infty}(\Omega)$. *If assumptions (2.7), (2.9) are satisfied, then for any* $T > 0$ *problem (3.4)–(3.6) has a unique solution* (w, v) *in* $Y \times Y^{1,\infty}$ *and*

$$\begin{aligned} w &\in C^1\Big( ]0,T[\,; W^{1,p}(\Omega)\Big) \cap C^0\Big( ]0,T[\,; W^{2,p}(\Omega)\Big)\,, \\ v &\in C^1\Big( ]0,T[\,; W^{1,\infty}(\Omega)\Big)\,. \end{aligned} \quad (4.14)$$

Moreover, if $w_0\,,\ v_0 \geq 0$, *then*

$$w(t) \geq 0\,, \quad v(t) \geq 0\,, \qquad t \in\ [0,T]\,. \quad (4.15)$$

□

Arguing as in the previous section we have:

Corollary 4.1. *Let* $(u_0, w_0) \in W^{1,p}(\Omega) \times W^{1,\infty}(\Omega)$. *Assume (2.7), (2.9) then for every* $T > 0$ *the problem (2.10), (2.11), (2.12) has a unique solution*

$$\begin{aligned} u &\in C^0\Big([0,T]\,; W^{1,p}(\Omega)\Big) \cap C^1\Big( ]0,T[\,; W^{1,p}(\Omega)\Big) \cap C^0\Big( ]0,T[\,; W^{1,\infty}(\Omega)\Big)\,, \\ v &\in C^0\Big([0,T]\,; W^{1,\infty}(\Omega)\Big) \cap C^1\Big( ]0,T[\,; W^{1,\infty}(\Omega)\Big)\,. \end{aligned}$$

Remark 4.1. The regularity of the solutions is strictly related to the regularity of the initial conditions and the regularity of the kernels. In particular, under suitable regularity assumptions on the kernels and on the initial data, we may obtain for any $T > 0$

$$\begin{aligned} w &\in C^0\Big([0,T]; W^{1,p}(\Omega)\Big) \cap C^{1,2}\Big( ]0,T[\times\Omega\Big)\,, \\ v &\in C^0\Big([0,T]; C^{1+\alpha}(\overline{\Omega})\Big) \cap C^1\Big( ]0,T[\,; C^{1+\alpha}(\overline{\Omega})\Big)\,, \end{aligned} \quad (4.16)$$

for $0 < 1 + \alpha < 2\beta - d/p$.

5. Numerical Analysis and Computational Simulations

In this section we undertake computational simulations of a non-dimensionalised version of the system of non-local equations (2.6) describing cancer cell invasion of the ECM. We recall that in one space dimension, the system of equations (2.6) can be written as:

$$\begin{aligned}
\partial_t u(t,x) &= D\partial_x^2 u(t,x) - \partial_x\big(\chi(v)\, u(t,x)\, \nabla v(t,x)\big) \\
&\quad + u(t,x)\mu_1\Big(1 - \int_\Omega k_{1,1}(x,y)\, u(t,y)\,\mathrm{d}y - \int_\Omega k_{1,2}(x,y)\, v(t,y)\,\mathrm{d}y\Big) \\
\partial_t v(t,x) &= -\gamma\, v(t,x) \int_\Omega k(x,y)\, u(t,y)\,\mathrm{d}y \\
&\quad + v(t,x)\mu_2\Big(1 - \int_\Omega k_{2,1}(x,y)\, u(t,y)\,\mathrm{d}y - \int_\Omega k_{2,2}(x,y)\, v(t,y)\,\mathrm{d}y\Big)\,,
\end{aligned} \tag{5.1}$$

where D, μ_1, μ_2, γ (the cancer cell linear diffusion coefficient, cancer cell proliferation rate, ECM production rate and ECM degradation rate, respectively) are given nonnegative parameters, k, $k_{i,j}$ $(i,j = 1,2)$ are given spatial kernels and χ is the haptotaxis function that depends on v. Ω is now the interval $[0, L]$ for some $L > 0$.

Without loss of generality, we now assume that $k_{1,2} = k_{2,2}$ and $k_{2,1} = k_{1,1}$ and we can now rewrite system (5.1) as

$$\begin{aligned}
\partial_t u &= D\partial_x^2 u - \partial_x\Big(u\chi(v)\partial_x v\Big) + \mu_1 u\,\Big(1 - k_{1,1} \circledast u - k_{2,2} \circledast v\Big) \\
\partial_t v &= -\gamma\, v\, k \circledast u + \mu_2\, v\,\Big(1 - k_{1,1} \circledast u - k_{2,2} \circledast v\Big)\,,
\end{aligned} \tag{5.2}$$

The above system of integro-partial-differential equations presents challenges from a numerical analysis point of view. In order to make progress in this direction and to enable the implementation of an efficient numerical scheme, we adopt the approach taken in Refs. 10, 11, 21.

We let $p \geq 1$ and fix $t \in [0, T]$. Then for each $g(t, \,.\,) \in L^p(\Omega)$ we consider the linear operator $G : L^p(\Omega) \to W^{2,p}(\Omega)$, where $G(g)$ is the unique solution to the equation

$$\begin{aligned}
&-\partial_x^2 f + \theta^2 f = \theta^2 g \text{ in } \Omega\,, \\
&\frac{\partial f}{\partial \nu} = 0 \qquad\qquad \text{on } \partial\Omega\,,
\end{aligned} \tag{5.3}$$

for some $\theta \in \mathbb{R} > 0$. It is then straightforward to see that[40]

$$f(x) = G(g)(x) = \int_\Omega k(x,y) g(y)\,\mathrm{d}y. \tag{5.4}$$

Using this approach, it is now easily seen that with $k_{1,1}$, $k_{2,2}$ and k defined by equations (5.3)–(5.4) for $\theta = \lambda_{1,1},\ \lambda_{2,2},\ \lambda$ respectively, our system (5.1) can be

re-written as:

$$\begin{aligned}
\partial_t u(t,x) &= D\,\partial_x^2 u(t,x) - \partial_x\big(\chi(v)\,u(t,x)\,\partial_x\,v(t,x)\big)\\
&\quad + \mu_1 u(t,x)\Big(1 - f_{1,1}(t,x) - f_{2,2}(t,x)\Big)\\
\partial_t v(t,x) &= -\gamma\,v(t,x)f(t,x) + \mu_2 v(t,x)\Big(1 - f_{1,1}(t,x) - f_{2,2}(t,x)\Big)\\
\lambda^2 u(t,x) &= -\partial_x^2 f(t,x) + \lambda^2 f(t,x)\\
\lambda_{1,1}^2 u(t,x) &= -\partial_x^2 f_{1,1}(t,x) + \lambda_{1,1}^2 f_{1,1}(t,x)\,,\\
\lambda_{2,2}^2 v(t,x) &= -\partial_x^2 f_{2,2}(t,x) + \lambda_{2,2}^2 f_{2,2}(t,x)\,.
\end{aligned} \tag{5.5}$$

The above set of equations is now a system of coupled elliptic-parabolic PDEs which can be solved using standard numerical techniques (in our case finite elements). In order to close the system, we assume no-flux boundary conditions i.e.

$$u\,\chi(v)\,\partial_x v - D\partial_x u = \partial_x f = \partial_x f_{1,1} = \partial_x f_{2,2} = 0\,, \qquad \text{on} \quad]0,T[\times\partial\Omega\,. \tag{5.6}$$

and initial data:

$$\big(u(0,x)\,,\,v(0,x)\big) = \big(u_0(x)\,,\,v_0(x)\big)\,, \tag{5.7}$$

where

$$\begin{aligned}
&u_0(x) = \exp(\frac{-x^2}{\epsilon}),\ x\ \in\ \Omega\ \text{and}\,\epsilon = 0.01 > 0,\\
&v_0(x) = 1,\ x\ \in\ \Omega.
\end{aligned} \tag{5.8}$$

Before proceeding with our computational simulations, we state the following corollary:

Corollary 5.1. *The system of equations (5.5) with boundary conditions (5.6) and initial data given by (5.7), (5.8) has a unique solution*

$$(u,v) \in C^0\Big([0,T]\times[0,L]\Big)\cap C^\infty\Big(]0,T[\times]0,L[\Big), \tag{5.9}$$

for any $T > 0$.

Proof Keeping in mind the properties of the operator G, we may repeat the arguments of Section 3 and obtain the local existence and uniqueness theorem. The additional regularity comes from a standard parabolic and elliptic regularization. In order to obtain global existence we repeat the arguments before Lemma 4.2 and we also need the following lemma:

Lemma 5.1. *The solution given by Corollary 5.1 is such that*

$$\big\|\!\big|u\big|\!\big\|_2 \le \mathfrak{c}_4, \tag{5.10}$$

where $\mathfrak{c}_4$ depends on T and $\big\|w_0\big\|_2$.

Proof. Following the notation of Section 3 we have

$$\begin{aligned}
z\partial_t w = \nabla(z\nabla w) + zw\Big(1 - k_{1,1}\circledast(wz) - k_{1,2}\circledast v\Big)\\
+z\chi(v)wvk\circledast(wz) - z\chi(v)wv\Big(1 - k_{2,1}\circledast(wz) - k_{2,2}\circledast v\Big).
\end{aligned} \tag{5.11}$$

Multiplying Eq. (5.11) by w and itegrating in the space we get

$$\frac{1}{2}\frac{d}{dt}\int\limits_{\Omega}(zw^2) = \frac{1}{2}\int\limits_{\Omega} z\chi(v)w^2v_t + zw^2\Big(1 - k_{1,1} \circledast (wz) - k_{1,2} \circledast v\Big)$$
$$+z\chi(v)w^2vk \circledast (wz) - z\chi(v)w^2v\Big(1 - k_{2,1} \circledast (wz) - k_{2,2} \circledast v\Big). \quad (5.12)$$

Taking into account (4.1), (4.3) and (2.7), (2.9) we obtain

$$\frac{d}{dt}\int\limits_{\Omega} zw^2 \leq -\int\limits_{\Omega} z|\nabla w|^2 + c\int\limits_{\Omega} zw^2. \quad (5.13)$$

This yields

$$\int\limits_{\Omega} zw^2 \leq \text{const}, \quad (5.14)$$

where the constant "const" depends on T and $\left\|z_0w_0^2\right\|_2$ and the statement of Lemma 5.1 follows.

□

By Lemma 5.1 and by the Sobolev Embedding Theorem (see Ref. 1), we may repeat the arguments from Section 4 and obtain the statement of Corollary 5.1. □

We are now in a position to solve our system of equations (5.5), (5.6), (5.7) numerically. In order to do this, we first of all non-dimensionalise the equations. The variables and parameters in the system of equations and their associated boundary conditions are transformed into dimensionless quantities using the following reference variables:

(1) a reference length scale, L, (*e.g.* the maximum invasion distance of the cancer cells at this early stage of invasion $0.1 - 1cm$),
(2) a reference time unit, $\tau = \dfrac{L^2}{D_c}$, where D_c is a reference chemical diffusion coefficient *e.g.* $10^{-6}cm^2s^{-1}$ (see Ref. 9) Therefore, we deduce that τ varies between $10^4 - 10^6 sec$.
(3) a reference tumour cell density u_0, extracellular matrix density v_0 (where u_0, v_0 are appropriate reference variables).

For the numerical calculations presented here, we assume $\chi(v)$ to be a constant χ, and we thus define the non-dimensional variables:

$$\tilde{t} = \frac{t}{\tau}, \tilde{x} = \frac{x}{L}, \tilde{u} = \frac{u}{u_0}, \tilde{v} = \frac{v}{v_0}.$$

and new parameters via the following scaling:

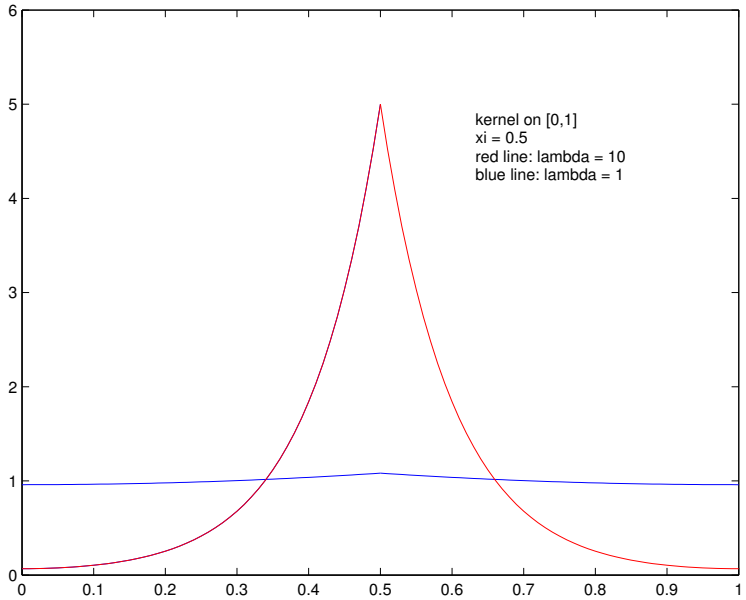

Fig. 1. Plot of the finite kernel (Green's function) on [0,1], $y = 0.5$, for the two cases $\lambda = 1, 10$.

$$\tilde{D} = \frac{D}{D_c}, \tilde{\chi} = \chi \frac{v_0}{D_c},$$

$$\tilde{\mu}_1 = \mu_1 \tau, \tilde{\mu}_2 = \mu_2 \tau, \tilde{\gamma} = \gamma u_0 v_0 \tau.$$

Henceforth we omit the tildes for notational simplicity.

As was mentioned previously, we work on a one-dimensional domain $[0, L]$. In this case, it is straightforward to calculate explicitly the Green's Function (and hence the spatial kernel) for our problem (see, for example, Ref. 40). Thus we have

$$k(x; y) = \begin{cases} \dfrac{\lambda \cosh \lambda x \cosh \lambda (L - y)}{\sinh \lambda L}, \ 0 < x < y \\ \dfrac{\lambda \cosh \lambda (L - x) \cosh \lambda y}{\sinh \lambda L}, \ y < x < L \end{cases}$$

A plot of the above kernel for different values of λ is given in Figure 1 and we note the role played by the parameter λ — the smaller λ is, the greater the nonlocal effect and, conversely, if $\lambda \to \infty$ the nonlocal term becomes local. Therefore, the quantity $\dfrac{1}{\lambda}$ can be considered as a measure of the spatial scale over which the

nonlocal term acts. Thus for system (5.5), $\frac{1}{\lambda}$ is a measure of the size of the spatial domain over which degradation acts, $\frac{1}{\lambda_{1,1}}$ is a measure of the size of the spatial domain over which cancer cells compete with other cells for space/resources, and $\frac{1}{\lambda_{2,2}}$ is a measure of the size of the spatial domain over which components or cells of the ECM compete with others for space/resources.

Before presenting the results of our computational simalutions, we first of all give estimates for as many of the parameters of the model as is possible.

5.1. *Estimation of Parameters*

Whenever possible parameter values are estimated from available experimental data. However, given the large number of parameters in the model to be determined, it is perhaps not surprising that several remain unquantified. In the cases where no experimental data could be found, parameter values were chosen to give the best qualitative numerical simulation results. This is in line with previous papers successfully simulating tumour invasion and angiogenesis[2,28].

Estimation of the Reference Diffusion Coefficients D_c, D

We introduce D_c a reference chemical diffusion coefficient *e.g.* $D_c \sim 10^{-6} cm^2 s^{-1}$,[9]. Estimates for the cell random motility coefficient vary depending on the cell type: $3 \times 10^{-9} cm^2 s^{-1}$ - $5.9 \times 10^{-11} cm^2 s^{-1}$ for epidermal cells[34]; $(7.1 \pm 2.7) \times 10^{-9} cm^2 s^{-1}$ for endothelial cells[36]; also, Bray estimated the random motility coefficient of animal cells to be $\sim 5 \times 10^{-10} cm^2 s^{-1}$,[9]. In light of these data, our choice for the cell random motility coefficient D will vary betweeen $10^{-9} cm^2 s^{-1}$ and $10^{-11} cm^2 s^{-1}$, and so our nondimensional value $D_c \in [10^{-5}, 10^{-3}]$.

The haptotactic coefficient χ

Stokes *et al.* estimated the chemotaxis sensitivity of ECs migrating in a culture containing αFGF, to be $2600 cm^2 s^{-1} M^{-1}$ (see Ref. (36)). In the absence of reliable empirical data, we chose the haptotaxis sensitivity χ to be in the range from 2.5×10^{-3} to $2.5 \times 10^{-1}\, cm^2 s^{-1} M^{-1}$. Therefore, considering the fact that the vitronectin blood plasma concentration is around $4 \mu M$,[17] leads to a dimensionless estimate of the haptotaxis coefficient χ in the range between 0.001 and 1. A value of v_0 vary between $0.38 \times 10^{-9} M$ and $0.38 \times 10^{-12} M$ what is consistent with experimental measurements.

Proliferation rate constant μ_1

Yu *et al.* estimated the doubling time of human epidermoid carminoma cells (HEp3) from *in vitro* proliferation experiments time to be $24h$[38]. By taking the proliferation

rate as the reciprocal of the cell-cycle time we get $\tilde{\mu}_1 \sim 0.042h^{-1}$. For our numerical simulations we will choose the proliferation rate to be between $0.02h^{-1}$ and $0.72h^{-1}$, and thus obtain the dimensionless parameter μ_1 in the range from 0.05 to 2.

Parameters $\lambda,\ \lambda_{1,1},\ \lambda_{2,2}$

As noted previously, $1/\theta$, with $\theta = \lambda$, $\lambda_{1,1}$, or $\lambda_{2,2}$ can be considered as a measure of the spatial scale over which the nonlocal term acts. In our simulations, we used values of $\lambda_{1,1} \in [1, 10]$ in dimensionless units. Although the cancer cells have rather non-regular shape we estimate that an average diameter of a cancer cell is equal to 10 microns. The above range for $\lambda_{1,1}$ is therefore equivalent to the assumption that the non-local effect varies from 1 cell diameter to up to 10 cell diameters. Similarly we used values of $\lambda_{2,2} \in [10, 50]$ and $\lambda \in [1, 10000]$.

Remaining Parameters

Not all parameters in the model were able to be estimated. Therefore, we chose these remaining parameter values in line with previous models of cancer invasion[15,16].

A summary of all parameter value ranges used in the computational simulations is given in the table below:

Parameter	**Description**	**Value**
D	cell diffusion coefficient	$[10^{-5}, 10^{-3}]$
χ	haptotactic sensitivity	$[10^{-3}, 1]$
μ_1	proliferation rate of cancer cells	$[5 \cdot 10^{-2}, 2]$
μ_2	matrix re-modelling rate	$[1.5 \cdot 10^{-1}, 2.5]$
γ	matrix degrading rate	$[1, 2 \cdot 10]$
$\lambda_{1,1}$	cancer cell non-local effect	$[1, 10]$
$\lambda_{2,2}$	ECM non-local effect	$[1, 50]$
λ	degradation non-local effect	$[1, 10000]$

5.2. *Computational Simulations*

We now present some computational results from numerical simulations of the system of equations (5.5) which was solved numerically using the Femlab finite element package (Lagrange quadratic elements were used as basis functions and the backward Euler time-stepping method was implemented to integrate the equations).

Figures 2 and 3 show the computational simulation results where the parameters $\lambda_{1,1}, \lambda_{2,2}$ and λ have the following values: $\lambda_{1,1} = 10, \lambda_{2,2} = 50$ and $\lambda = 10000$. The choice of parameter $\lambda = 10000$ means in effect that the degradation term of the second equation of (5.5) is almost local i.e. $\approx -\gamma uv$. We chose this value for λ in

order to focus on the effect of nonlocal proliferation. As can be seen from the plots in figures 2 and 3, the initial profile of cancer cells develops into a travelling wave which invades the ECM, degrading the ECM as it invades. Eventually all the ECM is degraded and we are left with the cancer-only steady state of $(1, 0)$.

Figures 4 and 5 show the computational simulation results where the parameters $\lambda_{1,1}, \lambda_{2,2}$ and λ have the following values: $\lambda_{1,1} = 1, \lambda_{2,2} = 5$ and $\lambda = 10000$. As can be seen from both sets of plots, once again the initial profile of cancer cells develops into a travelling wave which invades the ECM, degrading the ECM as it invades. However, in this case we note that there is an "overshoot" in the cancer cell density at the front of the travelling wave, where the maximum cancer cell density reaches a value of approximately 1.5. This is due to the influence of the nonlocal proliferation terms whose effects have been enhanced due to the choice of parameters $\lambda_{1,1} = 1, \lambda_{2,2} = 5$. Once again, the wave of cancer cells invades the ECM, degrading the ECM as it invades. Eventually all the ECM is degraded and we are left with the cancer-only steady state of $(1, 0)$. We note that in this case, the cancer cells penetrate less deeply into the ECM - at $t = 60$ the leading edge of the cancer cells has reached the point just beyond $x = 0.7$, while in figure 2 at $t = 60$ the leading edge of the cancer cells has reached approximately $x = 0.625$.

The results presented in figures 2 , 3 and 4 , 5 illustrate the effect of the nonlocal proliferation terms. The cancer cells degrade the surrounding ECM and then invade this degraded region of tissue by a combination of diffusion and haptotaxis. This is seen as the travelling wave solution connecting the cancer-free state with the cancer-only state. In the model we assume that cancer cells are competing for nutrient (e.g. oxygen) with other cells at different spatial locations. In the one-dimensional domain considered here this means that the cancer cells competing both with those cells in front and with those cells behind. In an invasion of a region of tissue where there were no cancer cells, those cells at the front of the invasion wave (mathematically, at the point where the travelling front is steepest) will find there are essentially no cancer cells ahead of them. This means that essentially these cells are only in competition with the cells behind. This gives them an "invasive advantage" and allows the cell numbers there to get above the carrying capacity level (the maximum level that can be sustained in the long term), but only in the neighbourhood of the front of the invading cells (see Ref. 21, where a different, simpler model was considered). As a result we see an "overshoot" in the front profile.

6. Discussion

In this paper we have presented a mathematical model of cancer cell invasion of tissue and investigated the effect of nonlocal reaction kinetics. The model was formulated as a system of partial differential equations (integro-differential equations) with the nonlocal terms modelling competition for nutrient between the cancer cells and tissue re-modelling. Additionally, we incorporated a nonlocal degradation term. Certain important analytical results were proved and computational results

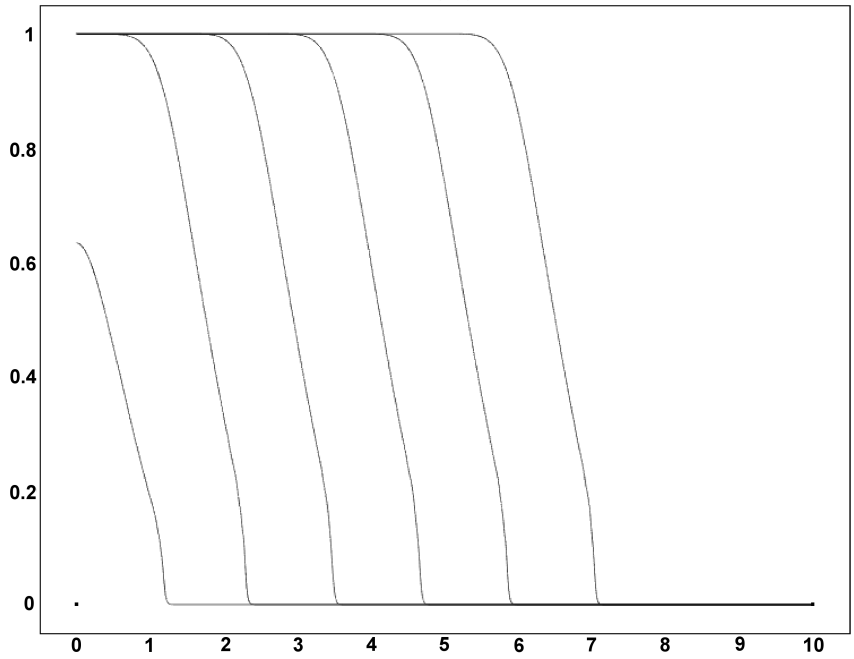

Fig. 2. Plot showing profile of the density of cancer cells at times $t = 10, 20, 30, 40, 50, 60$. Figure shows the travelling wave of invasion of cancer cells invading the ECM. Parameters $\lambda_{1,1} = 10, \lambda_{2,2} = 50, \lambda = 10000$, $D = 0.001$, $\chi = 0.075$, $\mu_1 = 1$, $\mu_2 = 0.15$ and $\gamma = 1$.

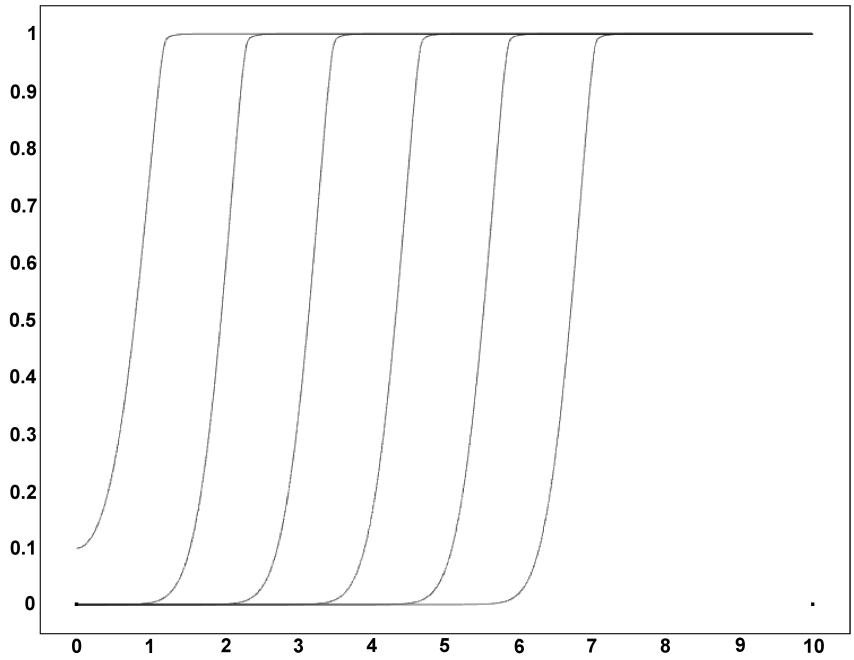

Fig. 3. Plot showing the corresponding profile of the density of ECM at times $t = 10, 20, 30, 40, 50, 60$. Figure shows ECM being degraded by the cancer cells as they invade.

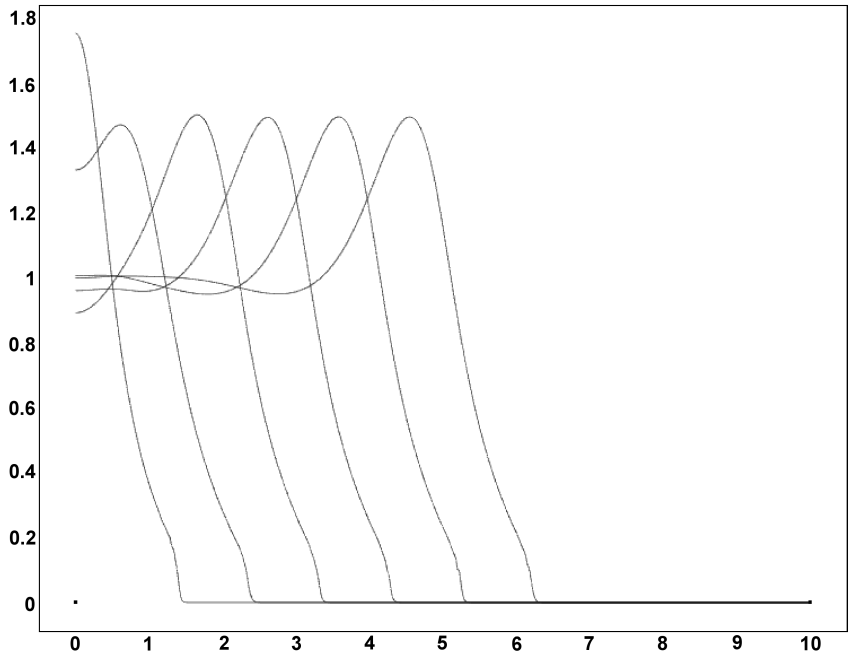

Fig. 4. Plot showing profile of the density of cancer cells at times $t = 10, 20, 30, 40, 50, 60$. Figure shows the travelling wave of invasion of cancer cells invading the ECM. Parameters $\lambda_{1,1} = 1, \lambda_{2,2} = 5, \lambda = 10000$, $D = 0.001$, $\chi = 0.075$, $\mu_1 = 1$, $\mu_2 = 0.15$ and $\gamma = 1$.

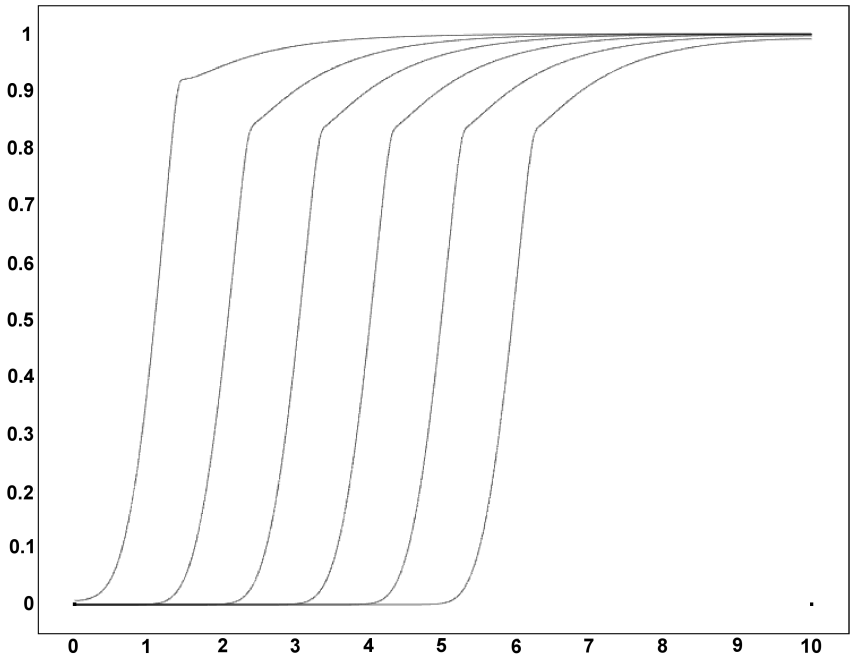

Fig. 5. Plot showing the corresponding profile of the density of ECM at times $t = 10, 20, 30, 40, 50, 60$. Figure shows ECM being degraded by the cancer cells as they invade.

of numerical simulations of our model were given.

In Section 3 we presented a mathematical analysis of the model and proved the local existence results for the solution of our equations using the theory of linear semigroups. In Section 4 we proved that the solutions to the nonlocal equations exist globally and are unique in any space dimension d without imposing any kind of smallness conditions in the initial conditions. Finally, we showed that the regularity of the solutions is strictly related to the regularity of the initial conditions and the regularity of the kernels and proved some results related to this.

In Section 5 we presented the computational results of numerical simulations of our basic model. These simulations showed the effect of the nonlocal terms[21]. Travelling waves of invading cancer cells were observed, and the shape of the travelling wave was closely linked to the nonlocal terms and the size of the parameters $\lambda,\ \lambda_{1,1},\ \lambda_{2,2}$. The invasive waves were either "regular" or had an "overshoot" at the front, indicating a region of high cancer cell density. From a biological perspective these results indicate the important role that competition for nutrient (e.g. oxygen) and space may play during cancer cell invasion. The numerical simulations indicate that cancer cells at the leading edge of an invasive front are only in competition with the cells behind, giving them an "invasive advantage" over cells futher behind. This may have implications for the depth of penetration into the ECM.

The numerical simulations that we have carried out suggest various interesting open mathematical and analytical questions that will be studied in future work, such as a rigorous proof of the existence of travelling waves and the derivation of an upper bound for the wave speed.

Future work will also consider extending the current model. Firstly, we will consider a more realistic treatment of the cancer cell random motility function $D(\cdot)$. Although in this paper we have considered this to be a constant (i.e. linear diffusion), from a physical point of view, migration of the cancer cells through the ECM is more like movement in a porous medium and so we may consider the cell random motility to be a function of the cancer cell density i.e. $D \equiv D(u)$. Specifically $D(u) = u^{\alpha}, \alpha \geq 1$.

Recent experimental work[39] has shown that the cancer cell motility also depends on ECM density (haptokinesis), i.e. $D \equiv D(v)$, with a possible form[27] $D(v) = D_0 v(K^2 + v^2)^{-1}$ with parameters $D_0 \geq 0$ and $K > 0$, accounting for the fact that cancer cells cannot move in the absence of ECM ($D = 0$ when $v = 0$), have reduced movement when the ECM becomes denser, and have maximal rate of random motility at some intermediate value of ECM.

Finally, we may also consider extending the current model to explicitly include the effect of matrix degrading enzymes[14,15,16]. In this instance, the cancer cell motility may also depend upon the matrix degrading enzyme (MDE) concentration (chemokinesis). In this case, we would consider $D \equiv D(u, v, m)$, where m is the MDE concentration. Considering such cases of nonlinear diffusion of the cancer cells naturally leads to a finite wave speed of propagation[19,32,33] (given initial data with compact support).

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