Mathematical Modelling of Cancer Invasion: A Review

Nikolaos Sfakianakis and Mark A.J. Chaplain

Abstract A defining feature of cancer is the capability to spread locally into the surrounding tissue, with cancer cells spreading beyond any normal boundaries. Cancer invasion is a complex phenomenon involving many inter-connected processes at different spatial and temporal scales. A key component of invasion is the ability of cancer cells to alter and degrade the extracellular matrix through the secretion of matrix-degrading enzymes. Combined with excessive cell proliferation and cell migration (individual and collective), this facilitates the spread of cancer cells into the local tissue. Along with tumour-induced angiogenesis, invasion is a critical component of metastatic spread, ultimately leading to the formation of secondary tumours in other parts of the host body. In this paper we present an overview of the various mathematical models and different modelling techniques and approaches that have been developed over the past 25 years or so and which focus on various aspects of the invasive process.

1 Introduction

In their ground-breaking paper *The Hallmarks of Cancer*, Hanahan and Weinberg [2000] identified six essential alterations in cell physiology that distinguish cancer cells/tissue from normal cells/tissue. Tissue invasion and metastasis was one of these key "hallmarks". Although the first use of the term "metastasis" can be traced

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back to Jean Claude Recamier in his 1829 book *"Recherches sur le traitement du cancer sur la compression méthodique simple ou combinée et sur l'histoire générale de la meme maladie"* [Recamier, 1829], tissue invasion by cancer cells goes back to classical antiquity, with the phenomenon recognised by Hippocrates and Galen (among others). The word cancer itself derives from the Latin *cancer, -cri (m)* meaning crab, in turn derived from the Greek καρκίνος [cf. *carcinoma*] also meaning crab. The physicians of classical antiquity already recognised the distinctive spreading pattern of an invasive cancer, with cellular projections into the surrounding tissue like the arms of a crab.

An excellent historical overview of the biology of cancer metastasis can be found in the article by Talmadge and Fidler [Talmadge and Fidler, 2010], while an overview of the core aspects of invasion can be found in the articles of Hanahan and Weinberg [Hanahan and Weinberg, 2000, 2011] and the review article of Friedl and Wolf [Friedl and Wolf, 2003].

The mathematical modelling of cancer invasion, part of the broader topic of mathematical oncology, may have a somewhat shorter history than its biological/pathological counterpart, but nonetheless mathematical models of cancer cell migration and invasion have the potential to shed light on this complex phenomenon and can play a role in improving treatment protocols. The purpose of this review paper is to give an overview of the key developments in the mathematical modelling of cancer invasion starting in the mid-1990s. Before embarking on this task, we first of all give a brief description of the main cellular processes involved in cancer invasion.

2 Biological background

Cancer invasion is a complex process involving numerous interactions between the cancer cells and the *extracellular matrix* (ECM) (cf. the tumour microenvironment) facilitated by matrix degrading enzymes. Along with active cell migration (both individual and collective) and increased/excessive proliferation, these processes enable the local spread of cancer cells into the surrounding tissue. Any encounter with blood or lymphatic vessels (cf. tumour-induced angiogenesis, lymph-angiogenesis) in the tumour microenvironment initiates the spread of the cancer to secondary locations in the host, i.e., metastasis or metastatic spread.

Critical steps in the invasion-metastatic cascade include the following:

- metastatic cells arise within a population of neoplastic/tumourigenic cells as a result of genomic instabilities;
- vascularization of the primary solid tumour through tumour-induced angiogenesis;

- detachment of any metastatic-competent cells that have already evolved;
- migration of the metastatic cells;
- local invasion of cancer cells into the surrounding tissue, requiring adhesion to and subsequent degradation of ECM components;
- transport of metastatic cells either travelling individually or as emboli composed of tumour cells (homotypic) or of tumour cells and host cells (heterotypic);
- metastatic cells survive their journey in the circulation system;
- adhesion/arrest of the metastatic cells at the secondary site, cells or emboli arrest either because of physical limitations (i.e. too large to traverse a lumen) or by binding to specific molecules in particular organs or tissues;
- escape from the blood circulation (extravasation);
- proliferation of the metastatic tumour cells;
- growth of the secondary tumour in the new organ.

Further details of the invasion-metastasis process (and also extensive biological/clinical references) can be found in the papers of Hanahan and Weinberg [2000, 2011], Friedl and Wolf [2003], Valster et al. [2005], Nyström et al. [2005], Talmadge and Fidler [2010].

In the next section we present a number of mathematical models which have been developed since the mid-1990s, exploring a range of issues associated with cancer invasion and using a range of different mathematical approaches and techniques.

3 Mathematical Models of Cancer Invasion

3.1 Early ODE and PDE models

We start with the seminal paper of Gatenby [1995] where he proposes a macroscopic mathematical model in which the tumour is viewed as a dynamic community of malignant cells, rather than a collection of individual cells, interacting and competing for resources with the normal tissue. This allows for an analytical insight in the mechanisms by which an initially small malignancy grows to replace a much larger and stable population of normal cells. In particular the author proposes the following model

$$\begin{cases} \dfrac{dN_1}{dt} = r_1 N_1 \dfrac{K_1 - N_1 - a_{12} N_2}{K_1} \\ \dfrac{dN_2}{dt} = r_2 N_2 \dfrac{K_2 - N_2 - a_{21} N_1}{K_2} \end{cases} \tag{1}$$

where N_1, N_2 represent the populations of cancer and normal cells respectively, r_1, r_2 the intrinsic growth rates of each population, and K_1, K_2 the carrying capacities or maximum numbers of cells from each population which can occupy the tissue and be supported by the environment. Furthermore a_{12}, a_{21} are the competition coefficients that measure the effects on the population N_2 (respectively N_1) from the presence of N_1 (respectively N_2).

Further to the fundamental formulations introduced in (1), Gatenby and Gawlinski [1996] made the modelling assumption that tumour-induced alteration of microenvironmental pH provides a mechanism for cancer invasion. In particular they propose the following reaction-diffusion system:

$$\begin{cases} \dfrac{\partial N_1}{\partial t} = \nabla \cdot (D_{N_1}[N_2]\nabla N_1) + r_1 N_1 \left(1 - \dfrac{N_1}{K_1} - a_{12}\dfrac{N_2}{K_2}\right) - d_1 L N_1 \\ \dfrac{\partial N_2}{\partial t} = \nabla \cdot (D_{N_2}[N_1]\nabla N_2) + r_2 N_2 \left(1 - \dfrac{N_2}{K_2} - a_{21}\dfrac{N_1}{K_1}\right) \\ \dfrac{\partial L}{\partial t} = D_3 \nabla^2 L + r_3 N_2 - d_3 L \end{cases} \tag{2}$$

where N_1, N_2 represent the density of the normal and neoplastic tissue respectively, and L the excess concentration of H^+ ions. $d_1 L$ is the death rate of the normal tissue due to excess acid concentration.

Investigations of the structure and dynamics of the proposed model demonstrate a transition from benign to malignant growth analogous to the adenoma-carcinoma progression. Accordingly, the authors conclude that their model predicts crossover behaviour that is consistent with clinical observations on the growth of *in-situ* tumours before the development of an invasive phenotype. Their model moreover predicts a variable interfacial structure, including a previously unrecognised hypocellular interstitial gap in some malignancies, and show some evidence in support of this prediction in both clinical observations and in vitro experiments.

In a follow-up paper, Gatenby et al. [2006] consider a direct simplification of the model (2). Namely, they consider a healthy tissue that is well organised and regulated in an organ and will therefore be immovable i.e. $D_{N_1}[N_2] = 0$; and the diffusivity of the cancer cells $D_{N_2}[N_1] = D_2\left(1 - \frac{N_1}{K_1}\right)$ attains the value D_2 in the absence of healthy tissue and the value zero when the density of the healthy tissue N_1 is at carrying capacity K_1.

This simpler model allows the authors to perform numerical simulations that provide testable predictions concerning the morphology of cellular and extracellular dynamics at the interface between tumour and host. On the other hand, *in-vivo* experiments confirm the presence of peritumoral acid gradients as well as cellular toxicity and ECM degradation in the normal tissue exposed to the acidic microenvironment. They conclude that their acid-mediated invasion model (2) can provide a description

mechanism to link altered glucose metabolism with the ability of cancer cells to form invasive tumours.

Along similar lines of modelling, Perumpanani et al. [1996] proposed a cancer invasion model that accounts for the competition between the invasive cancer cells, the non-invasive cancer cells, the normal tissue, and the ECM. They moreover account for the proteases responsible for the degradation of the ECM and the product of proteolysis.

In particular, the model they propose reads as:

$$\begin{cases} \dfrac{\partial n}{\partial t} = k_1 n\,(k_2 - n - m - u) + \dfrac{\partial}{\partial x}\left[\Theta(c)\left(\Gamma_n(u,m,n)\dfrac{\partial u}{\partial x}\right)\right] \\ \dfrac{\partial m}{\partial t} = k_4 m\,(k_5 - n - m - u) + \dfrac{\partial}{\partial x}\left[\Theta(c)\left(\Gamma_n(u,m,n)\dfrac{\partial m}{\partial x}\right)\right] \\ \dfrac{\partial u}{\partial t} = k_4 u\,(k_5 - n - m - u) \\ \qquad + \dfrac{\partial}{\partial x}\left[\Theta(c)\left(\Gamma_u(u,m,n)\dfrac{\partial u}{\partial x} - k_{17}u\dfrac{\partial c}{\partial x} - k_{16}u\dfrac{\partial s}{\partial x}\right)\right] \\ \dfrac{\partial c}{\partial t} = -k_8 pc \\ \qquad + \dfrac{\partial}{\partial x}K\left[c\,\Theta(c)\left(\Gamma_n\left(\dfrac{\partial u}{\partial x} + \dfrac{\partial m}{\partial x}\right) + \Gamma_u\dfrac{\partial u}{\partial x} - k_{17}u\dfrac{\partial c}{\partial x} - k_{16}u\dfrac{\partial s}{\partial x}\right)\right] \\ \dfrac{\partial s}{\partial t} = k_{21}pc + D_s\dfrac{\partial^2 s}{\partial x^2} \\ \dfrac{\partial p}{\partial t} = k_1 uc - k_{12}p - k_{13}pu - k_{14}pc + D_p\dfrac{\partial^2 p}{\partial x^2} \end{cases} \tag{3}$$

where n represents the concentration of the normal cells, m the non-invasive cancer cells, u the invasive cancer cells, c a generic ECM protein (e.g. *collagen*, *vitronectin* or other), s the product of the ECM proteolysis, and p a generic protease. Moreover, Θ is the ramp function

$$\Theta(c) = \begin{cases} k_{26}, & 0 < c < k_{27} \\ \dfrac{k_{28} - c}{k_{28} - k_{27}}, & k_{27} < c < k_{28} \\ 0, & k_{28} < c \end{cases} \tag{4}$$

and

$$\Gamma_n = k_3 \frac{k_{18}}{k_{19} + k_{25}\,(k_{25}n + k_{25}m + k_{20}u)} \tag{5}$$

$$\Gamma_u = k_6 \frac{k_{18}}{k_{19} + k_{20}\,(k_{25}n + k_{25}m + k_{20}u)} \tag{6}$$

In a follow-up work, Perumpanani et al. [1998] investigate further the degradation of the ECM. During the invasion, a gradient of ECM fragments is established counter to the direction of the invasion. This results in anti-invasive chemotactic attraction which opposes the haptotaxis migration of the cancer cell towards higher ECM concentrations. They then conclude that the invasion potential of the cancer cells depends on the action of *matrix metalloproteinases* (MMPs) in "a biphasic manner"; excessive degradation of the ECM can lead to the opposite than the invasion effect.

For u, c, p, s representing the concentrations of HT1080 cells, intact *fibronectin*, MMP-2, and the MMP-2-digested soluble *fibronectin* respectively, the model reads as

$$\begin{cases} \dfrac{\partial u}{\partial t} = k_1 u(k_2 - u) - \dfrac{\partial}{\partial x}\left(k_3 \psi(s) u \dfrac{\partial s}{\partial x} - k_4 \chi(c) u \dfrac{\partial c}{\partial x}\right) \\ \dfrac{\partial c}{\partial t} = -k_5 pc \\ \dfrac{\partial s}{\partial t} = k_5 k_6 pc + h(p,s) + D_s \dfrac{\partial^2 s}{\partial x^2} \\ \dfrac{\partial p}{\partial t} = k_7 uc - k_8 pu - k_9 p + D_p \dfrac{\partial^2 p}{\partial x^2} \end{cases} \tag{7}$$

where k_i, s are positive constants and the functions $\psi(s)$, and $\chi(c)$ represent the extend of chemo- and haptotaxis respectively. The proteolysis of the *fibronectin* is represented by $-pc$ and $h(p,s)$ the continued action of the proteases.

Furthermore, Perumpanani et al. [1999] develop and analyse a model for malignant invasion, that combines proteolysis and haptotaxis; a common feature of these two mechanisms is that they can be produced by contact with the ECM. Namely, the model they study reads:

$$\begin{cases} \dfrac{\partial u}{\partial t} = f(u) - k_3 \dfrac{\partial}{\partial x}\left(u \dfrac{\partial c}{\partial x}\right) \\ \dfrac{\partial c}{\partial t} = -g(c,p) \\ \dfrac{\partial p}{\partial t} = h(u,c) - Kp \end{cases} \tag{8}$$

where u, c, and p represent the concentrations of the invasive cancer cells, the ECM, and the matrix degrading proteases, and where

$$f(u) = k_1\, u(k_2 - u), \quad g(c,p) = k_4\, pc, \quad h(u,c) = k_5\, uc,$$

with $k_1, \ldots, k_5, K \geq 0$.

Compared with the previous works of these authors, i.e. Perumpanani et al. [1996, 1998], special characteristic of the model (8) is the absence of cancer cell diffusion. In the search for travelling wave solutions, the model (8) is reduced to a system of

ordinary differential equations (ODEs) which the authors then study using phase plane analysis. They are able to demonstrate that the model admits a family of travelling waves with speeds depending on the ECM concentration, and hence identify an expected qualitative property on behalf of cancer invasion.

Following the steps laid in Perumpanani et al. [1996], Marchant et al. [2000, 2001] address a haptotaxis model that accounts for three variables: the concentration u of the invasive cells, the connective tissue c, and of the proteases p. In the non-dimensional form the model they study takes the form:

$$\begin{cases} \dfrac{\partial u}{\partial t} = u(1-u) - \dfrac{\partial}{\partial x}\left(u\dfrac{\partial c}{\partial x}\right) \\ \dfrac{\partial c}{\partial t} = -pc \\ \dfrac{\partial p}{\partial t} = \dfrac{1}{\varepsilon}(uc - p) \end{cases}, \tag{9}$$

where $0 < \varepsilon$ represents the relative timescale of the dynamics of the protease p versus the cell growth dynamics. The time variable t is scaled so that u grows as $O(1)$ to the carrying capacity of unity; the space variable x is scaled so that the rate of haptotaxis is of the same order, p is scaled so that c dissolves on the same timescale and, c is scaled so that p and uc are of the same order in the p-equation. This implies that the p timescale is relatively much faster, so that $0 < \varepsilon << 1$ is small. This allows the authors to re-model the proteases dynamics, i.e. p-equation in (9), into

$$p = uc$$

and accordingly (9) recasts to:

$$\begin{cases} \dfrac{\partial u}{\partial t} = u(1-u) - \dfrac{\partial}{\partial x}\left(u\dfrac{\partial c}{\partial x}\right) \\ \dfrac{\partial c}{\partial t} = -uc^2 \end{cases} \tag{10}$$

The authors were then able to identify a host of travelling wave solutions in the system (10), among which (discontinuous) shock waves. The latter being of a particularly high interest as, according to the authors, the sharpness of the invading profile better approximates the sharp invasion front observed experimentally in cancer growth.

In a follow-up work Marchant et al. [2006] adopted the sequence of models (3), (7), and (8) to obtain the following haptotaxis invasion model

$$\begin{cases} \dfrac{\partial u}{\partial t} = ru(1 - \dfrac{u}{U_0}) - kuc - \chi \dfrac{\partial}{\partial x}\left(u \dfrac{\partial c}{\partial x}\right) \\ \dfrac{\partial c}{\partial t} = -\alpha pc \\ \dfrac{\partial p}{\partial t} = \beta uc - \gamma p \end{cases} \tag{11}$$

where u represents the concentration of tumour cells; c the concentration of the ECM, and p the concentration of a matrix-degrading protease.

With arguments similar as in the case of (9), the authors were able to reduce the model (11) to a two-equation system similar to (10) that exhibits discontinuous solutions, and is able to reproduce the biphasic behaviour first seen in (3).

In a different approach, still though within the general modelling of cancer invasion, Swanson et al. [2000], develops further a mathematical model of *glioma* growth—the most common type of brain tumour—previously proposed in a series of papers by Cruywagen et al. [1995], Tracqui et al. [1995], and Woodward et al. [1996].

The proposed model describes the time evolution of of the glioma cell population based solely on proliferation and diffusion. It is comprised of a single equation, namely,

$$\frac{\partial c}{\partial t} = \nabla \cdot (D(\mathbf{x})\nabla c) + \rho c \tag{12}$$

where $c(\mathbf{x}, t)$ represents the density of the glioma cells, and where the Fickian diffusivity depends on the local tissue

$$D(\mathbf{x}) = \begin{cases} D_g, & \mathbf{x} \in \text{grey matter} \\ D_w, & \mathbf{x} \in \text{white matter} \end{cases}, \quad D_w > D_g.$$

The authors argue that, although the linear proliferation term ρc lacks a saturation effect (like e.g. a logistic term) that would make it more accurate, still it is adequate for the time scale of the experiment considered. The previously observed fit of the model predictions with *in-vivo computerised tomography* (CT) scan measurements, is further investigated under the availability of information regarding the local composition of the brain in grey and white matter.

In a follow up work Swanson et al. [2003] introduce chemotherapy in the model (12), administered in the form of a time dependent decay of the tumour cell population c. Namely, the authors propose the model

$$\frac{\partial c}{\partial t} = \nabla \cdot (D(\mathbf{x})\nabla c) + \rho c - G(t)c \tag{13}$$

where the therapy schedule G is given by

$$G(t) = \begin{cases} k, & \text{during administration periods} \\ 0, & \text{otherwise} \end{cases}$$

Besides chemotherapy though, the authors consider the effect of surgical resection in the treatment of high- and low-grade gliomas. The mathematical approach they followed has allowed them to demonstrate that any local treatment of a diffusely invading glioma will fail, since the invasion is still more peripheral than any localizable treatment can reach.

In a follow-up work, Swanson [2008] studied further the model (12) discussed in Swanson et al. [2000, 2003], and compared its predictions against *in vitro* experimental measurement data.

The authors then argue that the model sufficiently describes the key dynamics of gliomas *in-vitro* and that these results provide a foundation for using this model for more complicated scenarios *in-vivo*. In any case, they argue, that they have obtained with their model a better understanding of glioma cell behaviour since the model provides a means for quantification of experimental observations.

3.2 A hybrid continuum-discrete model

In the next milestone in the evolution towards hybrid invasion models, Anderson et al. [2000] propose a blend of continuum deterministic modelling and discrete stochastic modelling in 1- and 2- space dimensions.

The continuum model they study examines the migratory response of cancer cells to self-generated haptotaxis gradients. Namely, the authors consider cancer cell mediated production and activation of *matrix degrading enzymes* (MDEs), the ensuing degradation of the ECM, and the subsequent haptotaxis response of the cancer cells to the induced gradient of the matrix. The model itself reads as follows

$$\begin{cases} \dfrac{\partial n}{\partial t} = D_n \nabla^2 n - \chi \nabla \cdot (n \nabla f) \\ \dfrac{\partial f}{\partial t} = -\delta m f \\ \dfrac{\partial m}{\partial t} = D_m \nabla^2 m + \mu n - \lambda m \end{cases} \tag{14}$$

where n, f, m, denote the densities of the cancer cells, the ECM, and the MDEs respectively, and D_n, D_m and χ the diffusion and haptotaxis coefficients respectively.

They can verify with their model that the cancer cells are split in two groups: those driven primarily by diffusion that form a propagating front and degrade the matrix, and those driven by haptotaxis that follow the gradient formed in the ECM. The self-

generated haptotaxis effect is still present when a heterogeneous ECM is considered, although not clearly seen due to the pre-existing ECM gradients.

The authors formulate also a discrete model which tracks the positions of migratory cancer cells while accounting for the extracellular stimuli (haptotaxis in this instance). The model reads as follows:

$$\begin{cases} n_{l,m}^{q+1} = P_0 n_{l,m}^q + P_1 n_{l+1,m}^q + P_2 n_{l-1,m}^q + P_3 n_{l,m+1}^q + P_4 n_{l,m-1}^q \\ P_0 = 1 - \dfrac{4kD}{h^2} - \dfrac{k\gamma}{h^2}\left(f_{l+1,m}^q + f_{l-1,m}^q - 4f_{l,m}^q + f_{l,m+1}^q + f_{l,m-1}^q\right), \\ P_1 = \dfrac{kD}{h^2} - \dfrac{k\gamma}{4h^2}\left(f_{l+1,m}^q - f_{l-1,m}^q\right) \\ P_2 = \dfrac{kD}{h^2} + \dfrac{k\gamma}{4h^2}\left(f_{l+1,m}^q - f_{l-1,m}^q\right) \\ P_3 = \dfrac{kD}{h^2} - \dfrac{k\gamma}{4h^2}\left(f_{l,m+1}^q - f_{l,m-1}^q\right) \\ P_4 = \dfrac{kD}{h^2} + \dfrac{k\gamma}{4h^2}\left(f_{l,m+1}^q - f_{l,m-1}^q\right) \end{cases} \tag{15}$$

where $P_0, \cdots, P_4$ are termed directional transition rates. In the above k, h represent the the time- and space-step of the discretisation method.

This discrete version allows the authors to track individual cells as they move in the two-dimensional tissue. They can then make remarks on the migration of the cancer cells which have important implications in metastasis.

The authors also combine the discrete and continuum versions of their models, acting in different scales of the cancer invasion, and compare the model predictions with clinical observations of cancer invasion in breast cancer.

3.3 A model of trophoblast invasion

Further in the macroscopic tissue invasion, although not cancerous, Byrne et al. [2000] present a mathematical model that describes the initial stages of placental development during which trophoblast cells begin to invade the uterine tissue as a continuous mass of cells.

The proposed model accounts for the density of the trophoblast cells $n(x,t)$, trophoblast-derived proteases $u(x,t)$, and uterine tissue $\rho(x,t)$, and reads as

$$\begin{cases} \dfrac{\partial n}{\partial t} = D_n \dfrac{\partial}{\partial x}\left(n^2 \dfrac{\partial n}{\partial x}\right) - \chi \dfrac{\partial}{\partial x}\left(n \dfrac{\partial v}{\partial x}\right) + k_1 n(1-n-p) \\ \dfrac{\partial u}{\partial t} = D_u \dfrac{\partial^2 u}{\partial x^2} + k_2 un(1-n) - k_3 uv \\ \dfrac{\partial v}{\partial t} = D_v \dfrac{\partial^2 v}{\partial x^2} + k_4 u\rho - k_3 uv \\ \dfrac{\partial \rho}{\partial t} = k_5 \rho(1-n-\rho) - k_6 u\rho \end{cases} \tag{16}$$

where $D_n,\ D_u,\ D_v > 0$, $\chi > 0$ are the corresponding linear diffusion and haptotaxis coefficients, $k_1,\ k_2,\ k_5 > 0$ the logistic proliferation rates, and $k_3,\ k_4,\ k_6 > 0$ are kinetic rate parameters.

The mathematical analysis of a simpler submodel that the authors undertake, describes the final stages of normal embryo implantation and suggests that as the timescale of interest increases, the dominant migratory mechanism of the trophoblasts switches from chemotaxis to nonlinear random motion. More precisely, the initial invasion of the system is dominated by the chemotactic response of the trophoblast cells to the inhibitor w. In addition, when the protease is relaxing to a uniform steady state, chemotaxis plays an important role in defining the depth of penetration of the trophoblasts while the limiting profile adopted is determined by nonlinear random motility.

3.4 An individual-based cellular Potts model

Switching back to cancer invasion, Turner and Sherratt [2002] develop a discrete model of malignant invasion using a thermodynamic argument. They employ an extension of the Potts model to simulate a population of malignant cells experiencing interactions due to both homotypic and heterotypic adhesion while also secreting proteolytic enzymes and experiencing a haptotactic gradient.

Specifically, the authors consider a square lattice and assign at every point (i, j) a label σ_{ij}. Neighbouring lattice sites with the same value of σ are assumed to lie within the same cell. The interaction between the cell surfaces follows from the coupling constants $J_{\tau(\sigma_{ij}),\tau(\sigma_{i'j'})}$, which account for the energy/strength of the interaction between adjacent points with different values of σ_{ij} (i.e. of different cells). This is described in the first term in the total energy H:

$$H = \sum_{ij} \sum_{i'j'} J_{\tau(\sigma_{ij}),\tau(\sigma_{i'j'})} \left\{1 - \delta_{\sigma_{ij},\sigma_{i'j'}}\right\} + \sum_{\sigma} \lambda \left(u_\sigma - V_T\right)^2 \tag{17}$$

The second term describes the energy required for the growth and mechanical deformation of the cells where v_σ is the volume of the cell σ, V_T is the target volume,

and λ the corresponding Lagrange-multiplier. Furthermore, the model accounts for haptotaxis by attaching in every lattice point a parameter f_{ij} that accounts for the local density of the ECM protein concentration.

The overall energy change is then calculated as

$$\Delta H_{ij} = \Delta H_{1,ij} + \Delta H_{2,ij} + k_H (f_{i'j'} - f_{ij}) \tag{18}$$

where $k_H > 0$ represents the strength of haptotaxis, and where $\Delta H_{1,ij}, \Delta H_{2,ij}$ correspond to the surface and mechanical energy changes between the two conformations H_1 and H_2, given by the corresponding total energy formulas (17).

With this approach the authors demonstrate that the morphology of the invading front is influenced by changes in the adhesiveness parameters, and detail how the invasiveness of the tumour is related to adhesion. Their model suggests that cell-cell adhesion has less of an influence on invasion compared to cell-matrix adhesion, and that increases in both proteolytic enzyme secretion rate and the coefficient of haptotaxis act in synergy to promote invasion. By including cell proliferation, they extend their algorithm for cell division rates that depend on changes in the relative magnitudes of homotypic and heterotypic cell-cell adhesiveness.

3.5 A model of the urokinase-plasminogen uPA system

Further on the macroscopic description, Chaplain and Lolas [2005] present a mathematical model of the invasion of the ECM by cancer cells through the secretion of MDEs. The model focuses specifically on the role of the urokinase plasminogen activation system and is more complex than other mathematical models of invasion, in the sense that it accounts for more key biological components of tissue invasion.

Denoting the cancer cell density by c, the urokinase plasminogen activator (uPA) concentration by u, the plasminogen activator inhibitor-1 (PAI-1) concentration by p, the plasmin concentration by m and the ECM substrate (*vitronectin* in this case) density by v, the model reads as:

$$\begin{cases} \dfrac{\partial c}{\partial t} = D_c \dfrac{\partial^2 c}{\partial x^2} - \dfrac{\partial}{\partial x}\left(\chi_c c \dfrac{\partial u}{\partial x} + \zeta_c c \dfrac{\partial p}{\partial x} + \xi_c c \dfrac{\partial v}{\partial x}\right) + \phi_{13} cu + \mu_1 c \left(1 - \dfrac{c}{c_0}\right) \\ \dfrac{\partial v}{\partial t} = -\delta v m + \phi_{21} up - \phi_{22} vp + \mu_2 v \left(1 - \dfrac{v}{v_0}\right) \\ \dfrac{\partial u}{\partial t} = D_u \dfrac{\partial^2 u}{\partial x^2} - \phi_{31} pu - \phi_{33} cu + a_{31} c \\ [0.2em] \dfrac{\partial p}{\partial t} = D_p \dfrac{\partial^2 p}{\partial x^2} - \phi_{41} pu - \phi_{42} pv + a_{41} m \\ \dfrac{\partial m}{\partial t} = D_m \dfrac{\partial^2 m}{\partial x^2} - \phi_{51} pu - \phi_{52} pv + a_{53} uc \end{cases} \tag{19}$$

where D_c, D_u, D_p, $D_m \geq 0$ and χ_c, ζ_c, $\xi_c > 0$ are the diffusion and taxis coefficients, μ_1, μ_2 the cell proliferation and matrix reconstruction rates, and the rest of the parameters are the kinetic rate parameters.

The main achievement of this model is that fairly simple mathematical representation of the binding interactions of the components of the plasminogen activation system coupled with cell migration were able to capture the main characteristic effects of the system in cancer progression and invasion. The results show a very rich dynamic spatio-temporal behaviour which are in line with recent experimental results, that show that when breast cells become malignant, plasmin is activated on their membrane and their morphology is changed from sheet-like structures to multicellular heterogeneous masses.

3.6 Modelling the role of acidity in invasion

With a series of papers, Smallbone et al. [2005, 2007, 2008] turn their attention to the role of acidity in cancer invasion and connect with the previous works of Gatenby et al. [2006]. Smallbone et al. [2005]. In particular, they develop a simple model of three-dimensional tumour growth to examine the role of *acidosis* in the interaction between normal and tumour cell populations. The tumours under investigation are assumed to be at the first avascular and early vascular stages and in effect, expect the formation of necrotic cores. The model they discuss reads

$$\begin{cases} \dfrac{\partial H}{\partial t} = D_H \nabla^2 H + F_H \\ \dfrac{dR_2^3}{dt} = S\left(R_2^3 - R_1^3\right) - L R_1^3 \end{cases} \tag{20}$$

where H represents the concentration of the acid, $D_H > 0$ represent the diffusion coefficient and F_H the combined rate of acid production and removal from the system. The second equation stems after an assumption of rotational symmetry on

the tumour—which is assumed to be of radius R_2—and the formation of a (rotational symmetric) necrotic core—with radius R_1. The proliferation term $S\left(R_2^3 - R_1^3\right)$ refers solely to the living part of the tumour, the only part of the tumour where proliferation takes place.

With this modelling setting, the authors are able to observe a number of different behaviours. The analysis they perform predicts three regimes of tumour growth. If the rate of acid removal from the tumour is insufficient, there is growth followed by auto-toxicity, resulting in a benign tumour. This is found always to occur in an avascular tumour. A vascular tumour displays sustained growth, and invades the whole of the normal tissue space. If the tumour is sufficiently small, there is no growth as the acid perturbations cannot to induce normal cell death.

3.7 Modelling the role of cell-cell adhesion using PDEs

Armstrong et al. [2006] move away from the interactions between the cancer cells and the tumour microenvironment, and turn their attention to the interactions between the cancer cells themselves. Accordingly, they develop a macroscopic model of cell-cell adhesion by considering the movement of cells in response to the adhesive forces generated through transcellular binding proteins.

Namely, for $u(t,x)$, $v(t,x)$, $t \geq 0$ and $x \in \mathbb{R}$ denoting the population densities of two cell types, the model reads:

$$\begin{cases} \dfrac{\partial}{\partial t}u = \dfrac{\partial^2}{\partial x^2}u - \dfrac{\partial}{\partial x}\left(uK^u(u,v)\right) \\ \dfrac{\partial}{\partial t}v = \dfrac{\partial^2}{\partial x^2}v - \dfrac{\partial}{\partial x}\left(vK^v(u,v)\right) \end{cases} \tag{21}$$

where the adhesion terms K^u, K^v encompass both self- and cross-population adhesion for the u and v cell family respectively, and read:

$$\begin{aligned} K^u(u,v) =& S^u \int_{-1}^{1} g^{uu}\left(u(x+x_0), v(x+x_0)\right)\omega^{uu}(x_0)dx_0 \\ &+ C\int_{-1}^{1} g^{uv}\left(u(x+x_0), v(x+x_0)\right)\omega^{uu}(x_0)dx_0 \\ K^v(u,v) =& S^v \int_{-1}^{1} g^{vv}\left(u(x+x_0), v(x+x_0)\right)\omega^{vv}(x_0)dx_0 \\ &+ C\int_{-1}^{1} g^{vu}\left(u(x+x_0), v(x+x_0)\right)\omega^{uv}(x_0)dx_0 \end{aligned}$$

Here S^u, S^v and C represent the self-adhesive strength of the populations u and v, and the cross-adhesive strength between the populations, respectively. Differences in cell geometry can be modelled through the specific choices of S^u, S^v and C as well as of g^{uu}, g^{uv}, g^{vv} and ω^{uu}, ω^{uv}, ω^{vv}.

The authors employ both analytical and numerical techniques to demonstrate the that (21) can predict the aggregation behaviour of a disassociated adhesive cell populations and can replicate the different types of cell sorting behaviour that is observed experimentally. The authors argue that the resulting aggregation and pattern formation phenomena is a direct consequence of the relative strengths of self-population and cross-population adhesive bonds in the model.

Further on the modelling of cell-cell and cell-matrix interactions, Gerisch and Chaplain [2008] explore the spatio-temporal evolution of cancer invasion by cell-cell adhesion and haptotaxis by accounting for local and non-local contributions in the cell-cell adhesion tensor.

For a single family of cancer cells, the model the authors propose reads as

$$\begin{cases} \dfrac{\partial c}{\partial t} = \nabla \cdot \left(D_1 \nabla c - c \mathcal{A}\left\{ \underline{u}(t,\cdot) \right\} \right) + \mu_1 c \left(1 - c - v\right) \\ \dfrac{\partial v}{\partial t} = -\gamma m v + \mu_2 \left(1 - c - v\right) \\ \dfrac{\partial m}{\partial t} = \nabla \cdot \left(D_3 \nabla m\right) + \alpha c - \lambda m \end{cases} \tag{22}$$

where the non-local cell-cell adhesion term $\mathcal{A}\left\{ \underline{u}(t,\cdot) \right\}$ is defined for $x \in \mathbb{R}$, as:

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

where $\underline{\eta}(k) = (-1)^k$, $k = 0, 1$. In a two dimensional extension, $\mathbf{x} \in \mathbb{R}^2$ the authors define the non-local cell-cell adhesion term to be

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

where $\underline{\eta}(\theta) = (\cos\theta, \sin\theta)^{\mathrm{T}}$ is the unit outer normal vector corresponding to the angle θ.

Furthermore Domschke et al. [2014] extend (22) to a two-cancer-cell species non-local as follows:

$$\begin{cases} \dfrac{\partial c_1}{\partial t} = \nabla \cdot \left(D_{1,1} \nabla c_1 - c_1 \mathcal{A}_1 \left\{ t, x, \underline{u}(t, \cdot) \right\} \right) + \mu_{1,1} c_1 \left(1 - \rho(\mathbf{u}) \right) + M_{1,1}(t, \mathbf{u}) c_1 \\ \dfrac{\partial c_2}{\partial t} = \nabla \cdot \left(D_{1,2} \nabla c_2 - c_2 \mathcal{A}_2 \left\{ t, x, \underline{u}(t, \cdot) \right\} \right) + \mu_{1,2} c_2 \left(1 - \rho(\mathbf{u}) \right) + M_{2,1}(t, \mathbf{u}) c_1 \\ \dfrac{\partial v}{\partial t} = -\gamma m v + \mu_2 \left(1 - \rho(\mathbf{u}) \right)^+ \\ \dfrac{\partial m}{\partial t} = \nabla \cdot (D_3 \nabla m) + \alpha_1 c_1 + \alpha_2 c_2 - \lambda m \end{cases} \tag{23}$$

Another extension that the model (23) introduces to (22) is the possibility for a change of adhesion properties during the growth of the caner; this is achieved through time-dependent cell-cell and cell-matrix adhesion functions.

Numerical experiments of both (22) and (23) demonstrate a range of heterogeneous dynamics which are qualitatively similar to the invasive growth patterns observed experimentally in a number of different types of cancer, such as *tumour infiltrative growth patterns* (INF).

3.8 Multiscale moving boundary models of cancer invasion

Amalgamating the previous ideas of mutliscale interactions between the cancer cells and their microenvironment, Trucu et al. [2013], Peng et al. [2017], Shuttleworth and Trucu [2019a,b,c] formulate in a series of papers a moving boundary two-scale model for cancer invasion of the tissue. Their approach combines the macroscopic dynamics of the distributions of cancer cells and of the surrounding ECM, and microscopic scale dynamics of the MDEs, produced by the individual cancer cells. These microscopic scale dynamics are assumed to take place at the interface of the cancer cells and the ECM and give rise to a moving boundary at the macroscopic scale.

To be more specific, Peng et al. [2017] consider the macroscopic *urokinase* model (19), which was earlier introduced by Chaplain and Lolas [2005]. In its original derivation, the macroscopic equation for the urokinase u reads as

$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} - \phi_{31} p u - \phi_{33} c u + a_{31} c.$$

The approach of the authors amounts to reconsidering the u-equation in, what they call "microscopic regime", as follows:

$$\frac{\partial u}{\partial \tau} = D_u \frac{\partial^2 u}{\partial x^2} - \phi_{31} p u + \left(-\phi_{33} u + a_{31} \right) f_1^{\epsilon Y}(y, \tau)$$

where the "source" $f_1^{\epsilon Y}$ of the urokinase is given in terms of the cancer cell concentration c by:

$$f_1^{\epsilon Y}(y,\tau) = \frac{1}{\lambda\left(B(y,\gamma)\cap\Omega(t_0)\right)}\int_{B(y,\gamma)\cap\Omega(t_0)} c(x,t_0+\tau)dx$$

where λ is the usual Lebesgue measure and γ represents the maximal thickness of the outer proliferating rim, and $\Omega(t_0)$ the physical space occupied by the tumour.

The proposed modelling framework allows the authors to study the changes in the macroscopic scale morphology of the tumour caused by the dynamical urokinase processes occurring in the microscopic scale along the invasive edge of the tumour.

3.9 A framework for modelling the metastatic spread of cancer

Even more recently, the hybrid cancer and tissue modelling led Franssen et al. [2019] to study the metastatic process, and to present a mathematical modelling framework that captures the interconnected processes of invasion and metastatic spread of individual cancer cells in a spatially explicit manner a multigrid, hybrid, individual-based approach. This framework accounts for the spatiotemporal evolution of mesenchymal- and epithelial-like cancer cells, *membrane-type-1 matrix metalloproteinase* (MT1-MMP) and the diffusible *matrix metalloproteinase-2* (MMP-2), and for their interactions with the ECM.

The authors consider a modelling and computational representation of an organism comprised of a number of compartments, each one representing a separate organ. One of the organs is designated as the primary spatial domain—where the initial tumour is located—and assign locations within it to function as entry points into the vasculature. Similarly they impose a spatial map of exit locations from the vasculature to secondary locations organs. This allows cancer cells to use the vasculature and travel from the primary tumour site to the metastatic sites.

Within every organ the authors consider the following dimensional cancer growth/invasion invasion model:

$$\begin{cases} \dfrac{\partial c_E}{\partial t} = d_E\nabla^2 c_E - \phi_E\nabla\cdot(c_E\nabla w) \\ \dfrac{\partial c_M}{\partial t} = d_M\nabla^2 c_M - \phi_M\nabla\cdot(c_M\nabla w) \\ \dfrac{\partial m}{\partial t} = d_m\nabla^2 m + \theta c_M - \lambda m \\ \dfrac{\partial w}{\partial t} = -\left(\gamma_1 c_M + \gamma_2 m\right) w \end{cases} \tag{24}$$

where $c_E(t, x, y), c_m(t, x, y)$ represent the two-dimensional densities of the epithelial-like and mesenchymal-like cancer cells respectively. The MMP-2 concentration is represented by $m(t, x, y)$, and the density of the ECM by $m(t, x, y)$. The diffusion of the epithelial-, mesenchymal-like cancer cells and the diffusible MMPs is assumed ot be linear with diffusivities d_E, d_M and d_m respectively. ϕ_E and ϕ_M are the haptotaxis sensitivities of the epithelial- and mesenchymal-like cancer cells respectively. Finally θ_m, λ_m and γ_1, γ_2 are the production and decay rates of the MMPs, the degradation rates of the ECM.

With a series of numerical experiments, the authors were able to reproduce a number qualitative observations/phenomena and quantitative measurements made in *in vivo* experimental settings in human oral squamous carcinoma cells invasion in myoma tissue.

In a follow up work, Franssen and Chaplain [2020] propose an extension of (24), where besides the multiorgan and metastatic conformation of the two phenotypic states of epithelial- and mesenchymal-like cancer cells, they also consider a partial-EMT phenotype. They allow for the switching between these phenotypic states via EMT (locally) and MET (in the metastatic site) and account for the likelihood of spread of cancer cells to the various secondary sites. They also consider the maladaptation of metastasized cancer cells at the secondary sites and the effect of the immune response by accounting for cancer cell dormancy and death. They achieve this by considering a discrete-continuous approach along the lines proposed by Anderson et al. [2000] and presented here in (14).

3.10 A novel hybrid continuum-discrete multiscale model of invasion

We close this review with most recent and genuinely hybrid modelling of cancer invasion. Sfakianakis et al. [2020] propose a modelling framework to study the combined invasion of the ECM by two types of cancer cells, the epithelial- and the mesenchymal-like cancer cells. The proposed framework is a *genuinely hybrid multiscale model* that treats the epithelial-like cancer cells in a macroscopic and deterministic fashion and the mesenchymal-like cancer cells in an atomistic and stochastic way.

This modelling framework is a coupled system of macroscopic deterministic PDEs and Stochastic Differential Equations (SDEs) for the migration of the individual mesenchymal-like cancer cells.

The macroscopic sub-model—for the time evolution of the macroscopic quantities, such as the ECM, MMPs, and the densities of the epithelial-like cancer cells—reads as follows:

$$\begin{cases} \dfrac{\partial}{\partial t}c^{\alpha}(\mathbf{x},t) = D_{\alpha}\Delta c^{\alpha}(\mathbf{x},t) - \mu_{\alpha}^{\mathrm{EMT}}(\mathbf{x},t)c^{\alpha}(\mathbf{x},t) + \mu_{\beta}^{\mathrm{MET}}(\mathbf{x},t)c^{\beta}(\mathbf{x},t) \\ \qquad\qquad + \rho_{c}^{\alpha}c^{\alpha}(\mathbf{x},t)\left(1 - c^{\alpha}(\mathbf{x},t) - c^{\beta}(\mathbf{x},t) - v(\mathbf{x},t)\right), \\ \dfrac{\partial}{\partial t}m(\mathbf{x},t) = D_{m}\Delta m(\mathbf{x},t) + \rho_{m}^{\alpha}c^{\alpha}(\mathbf{x},t) + \rho_{m}^{\beta}c^{\beta}(\mathbf{x},t) - \lambda_{m}m(\mathbf{x},t) \\ \dfrac{\partial}{\partial t}v(\mathbf{x},t) = -\left(\lambda_{v}^{\alpha}c^{\alpha}(\mathbf{x},t) + \lambda_{v}^{\beta}c^{\beta}(\mathbf{x},t)\right)m(\mathbf{x},t)v(\mathbf{x},t), \end{cases} \tag{25}$$

where $\mu_{\alpha}^{\mathrm{EMT}}(\mathbf{x},t) = \mu_{\alpha}\chi_{\mathcal{E}(t)}(\mathbf{x})$, $\mu_{\beta}^{\mathrm{MET}}(\mathbf{x},t) = \mu_{\beta}\chi_{\mathcal{M}(t)}(\mathbf{x})$, with $\mathcal{E}(t), \mathcal{M}(t) \subset \Omega$, and D_{α}, μ_{α}, $\mu_{\beta}, \rho_{c}^{\alpha} \geq 0$, and D_{m}, ρ_{m}^{α}, ρ_{m}^{β}, $\lambda_{m} \geq 0$ constants. Alternative approaches could also be considered, e.g. an ECM-density dependent production of the MMPs by the cancer cells, and λ_{v}^{α}, $\lambda_{v}^{\beta} \geq 0$ constants. Possible extensions of the model could include non-diffusible MMPs, MC-only matrix degradation, matrix reconstruction, and other biologically relevant processes.

The stochastic submodel—responsible for the migration of the individual mesenchymal-like cancer cells—reads:

$$d\mathbf{X}_{t}^{p} = \mu\left(\mathbf{X}_{t}^{p}, t\right)dt + \sigma\left(\mathbf{X}_{t}^{p}, t\right)d\mathbf{W}_{t}^{p}, \quad \text{for } p \in P, \tag{26}$$

where $\mathbf{X}_{t}^{p}$ represents the position vector of the mesenchymal-cell with index $p \in \{1, \ldots, N(t)\}$, $\mathbf{W}_{t}^{p}$ is a Wiener process with independent components, μ and σ^{2} are the *drift* and *diffusion* coefficients that encode the modelling assumptions made on the directed and random parts of the motion of the mesenchymal-cells.

The coupling between the macroscopic and stochastic submodels (25) and (26) is happening via phase transition operators that connect the isolated cellular description with the density formulation:

$$\left\{(\mathbf{x}_{p}(t), m_{p}),\ p = 1, \ldots, N(t)\right\} \rightleftarrows c(\mathbf{x},t)$$

$$m_{p}(t) = \int_{M_{p}} c(\mathbf{x},t)d\mathbf{x}, \qquad \mathbf{x}_{p}(t) = \text{ the (bary-)centre of } M_{p}$$

This approach allows them to reproduce, in a very natural way, fundamental qualitative features, of the current biomedical understanding of cancer invasion, that are not easily captured by classical modelling approaches, for example, the invasion of the ECM by self-generated gradients and the formation of EC invasion islands outside of the main body of the tumour.

With the atomistic stochastic sub-model, they reproduce a sustainable invasion of the ECM by means of a *self-induced haptotaxis gradient*; this verifies the experimentally invasion behaviour and at the same time it serves as verification of the propagating invasion front seen in numerical simulations of macroscopic deterministic cancer invasion models.

With the full model, they reproduce the spread of the tumour and the invasion of the ECM in the form of invasion "islands". These are well known to appear in many cases of cancer, outside the main body of the tumour, and are quite difficult to reproduce by either macroscopic or atomistic cancer invasion models. With this approach these invasion "islands" are a naturally emerging property of modelling framework, which has very recently been used to model oral squamous cell carcinoma cell migration and invasion in an in vitro organotypic invasion assay experiment [Franssen et al., 2021].

4 Discussion and Conclusion

In a prescient statement from 50 years ago, Judah Folkman (the "father" of tumour-induced angiogenesis and angiogenesis research) stated that the interactions between tumour cells and endothelial cells *"...may constitute a highly integrated ecosystem. In this ecosystem the mitotic index of the two cell populations may depend on each other."* [Folkman, 1971]. This viewpoint was echoed in the 2011 paper of Hanahan and Weinberg, where they note: *"When viewed from this perspective, the biology of a tumor can only be understood by studying the individual specialized cell types within it as well as the "tumor microenvironment" that they construct during the course of multistep tumorigenesis. This depiction contrasts starkly with the earlier, reductionist view of a tumor as nothing more than a collection of relatively homogeneous cancer cells, whose entire biology could be understood by elucidating the cell-autonomous properties of these cells."* [Hanahan and Weinberg, 2011]

The first paper discussed in this review [Gatenby, 1995] considered the interactions of cancer cells with the host tissue precisely from this "ecological" perspective. The subsequent papers reviewed here also take a "holistic approach" to the problem, focussing on the complex dynamic interactions between the (solid) tumour and the tumour microenvironment (between the cancer cells and normal cells of the host tissue). The results of these mathematical modelling efforts (both analytical and computational) have helped to elucidate some of the details of the interplay between cancer cells and normal tissue during invasion across a range of spatial and temporal scales. Insight into how better treatment protocols could be developed have arisen from the results of several models e.g. changing the level of acidity within the tumour or interrupting the hypoxia-glycolysis-acidosis cycle [Smallbone et al., 2005, 2007, 2008], estimating the amount of healthy tissue to resect during breast cancer surgery [Anderson et al., 2000], estimating the depth of invasion and its relation to cell adhesion [Turner and Sherratt, 2002], and estimating the depth of spread of gliomas into brain tissue [Swanson et al., 2000, 2003, Swanson, 2008]. Moreover, the complexity of cancer invasion has necessitated the development of new modelling approaches resulting in advances on the mathematical side over and above the biological insight provided.

While a lot of the insight from the modelling has been qualitative in nature, the recent work of Franssen et al. [2021], focussing on modelling cell invasion in a 3D organotypic assay with a novel hybrid continuum-discrete model, indicates a possible way to combine and include real data from *in vitro* experiments, parameterise the model accurately and robustly, calibrate the model and then use the model to make further predictions on the *in vitro* system, while opening up possible avenues to make use of this as a platform to simulate *in vivo* invasion in a predictive and quantitative manner cf. Brady and Enderling [2019].

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