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REVIEW

Biomechanical modelling of cancer: Agent-based force-based models of solid tumours within the context of the tumour microenvironment

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Abstract

Once cancer is initiated, with normal cells mutated into malignant ones, a solid tumour grows, develops and spreads within its microenvironment invading the local tissue; the disease progresses and the cancer cells migrate around the body leading to metastasis, the formation of distant secondary tumours. Interactions between the tumour and its microenvironment drive this cascade of events which have devastating, if not fatal, consequences for the human host/patient. Among these interactions, biomechanical interactions are a vital component. In this review paper, key biomechanical relationships are discussed through a presentation of modelling efforts by the mathematical and computational oncology community. The main focus is directed, naturally, towards lattice-free agent-based, force-based models of solid tumour growth and development. In such models, interactions between pairs of cancer cells (as well as between cells and other structures of the tumour microenvironment) are governed by forces. These forces are ones of repulsion and adhesion, and are typically modelled via either an extended Hertz model of contact mechanics or using Johnson–Kendal–Roberts theory, both of which are discussed here. The role of the extracellular matrix in determining disease progression is outlined along with important cell-vessel interactions which combined together account for a great proportion of Hanahan and Weinberg's *Hallmarks of Cancer*.

KEYWORDS
agent-based, cancer growth and development, force-based, in silico tumours, tumour microenvironment

1 | INTRODUCTION

The term cancer covers a spectrum of diseases—cancer cells can arise from any type of cell in the body and can grow in or around any tissue or organ making it highly complex. Tumour cells proliferate, occupying whole areas of tissue; they interact with surrounding cells, tissue structures, vasculature and the extracellular matrix (ECM) in a

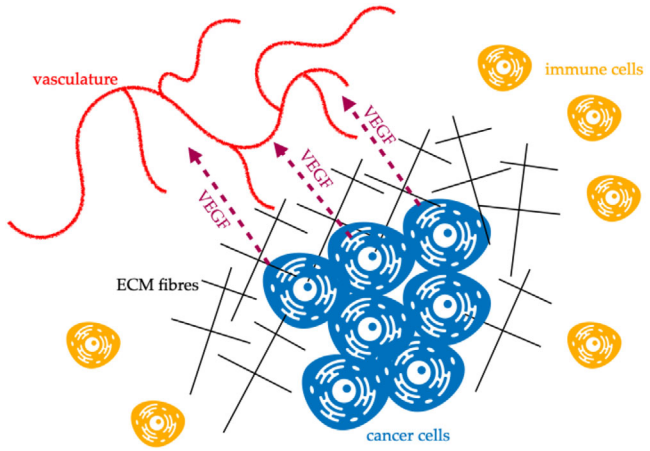


FIGURE 1 Schematic diagram showing several key aspects of the TM: the cancer cells (blue), the ECM fibres (black), the vasculature (red), vascular-endothelial growth factor (VEGF) signalling protein (magenta) and immune cells (orange)

variety of ways. In recent years, mathematical and computational biologists have endeavoured to accurately capture the growth and development of tumours within their local environment through in silico models. By simulating virtual tumours, insight is gleaned which complements traditional biological and experimental approaches to cancer research at limited financial and ethical cost. This review paper will focus on highlighting selected lattice-free agent-based (specifically force-based models) of tumour growth and development. By way of introduction it will be worthwhile to discuss the importance of approaching the problem from a mechanical standpoint, as such, in Section 1.1, the tumour microenvironment (TM) is presented followed by, in Section 1.2, a discussion of the inherent biomechanics of the TM. In Section 1.3, certain other modelling techniques which have been used to study the dynamics of tumour growth and development will be highlighted paying specific attention to where biomechanics have been successfully implemented.

1.1 | The TM

The term *tumour microenvironment* is given to all aspects of the local environment of a tumour, consisting of, but not limited to, the surrounding blood vessels/vasculature, ECM, tumour-associated immune cells and signalling molecules/proteins released by the cancer cells (see schematic in Figure 1). The tumour and the TM are intrinsically linked and there is constant interplay and interactions between them, starting from the point of tumour initiation [1]. Indeed, non-cancerous cells within tissue respond continuously to the external signals of their environment, changing their metabolic state, growth, mitosis, gene expression, differentiation, movement or even undergoing programmed cell death (apoptosis), accordingly. Should the cell fail to correctly transduce or respond to a specific (external) signal it effectively becomes cancerous [2]. A cell with a cancerous phenotype has several distinct *Hallmarks* [2, 3]. For example, cancer cells resist apoptosis and enable replicative immortality; this unchecked proliferation creates a tumour (or neoplasm) within the tissue.

Tumours influence the TM in a variety of different ways. Hypoxic tumour cells, starved of oxygen, are known to release vascular-endothelial growth factor (VEGF) which promotes tumour angiogenesis, supplying the tumour with constant access to vital nutrient [4, 5]. Equally, as the growing tumour vies for space within the tissue, cells release matrix metalloproteinases (MMPs) which degrade the ECM making room for tumour growth and local invasion [6, 7]. Conversely, the TM affects tumour growth and development; the shape and size of a tumour; but also its genetic evolution being determined by properties of the local environment [8, 9]. For example, cells migrate preferentially up gradients of ECM stiffness in a specific type of mechanotaxis called *durotaxis* [10]. Stiff ECMs can promote tumourigenesis through integrin-dependent mechanotransduction at focal adhesions [11] while soft ECMs contribute to phenotypic selection of tumour-repopulating cells (TRCs) [12]. Indeed, the TM has been found to play an active role in the progression of malignancies [13, 14].

One of the *Hallmarks of Cancer* is tissue invasion and metastasis in which tumours spread both locally and non-locally [2, 3]. Malignant tumours aggressively take over large areas of tissue, and, of greater concern, are able to move from primary locations to secondary locations using the body's circulatory system. This is a major issue since it is commonly purported that as many as 90% of all cancer deaths are due to metastatic spread; note that this figure, while widely reported and hypothesised [2, 15], is not yet scientifically proven, although it is true that the majority of cancer fatalities are due to metastases [16]. Nevertheless, agent-based models of tumours typically and vitally should also include aspects of the TM in order to model how cancers invade and metastasise.

1.2 | Biomechanics in the TM

The focus of this paper is towards force-based models, and as such it is important to understand why mechanical interactions are so important. As discussed above there is constant interplay between a tumour and the TM. Indeed, the TM governs how a tumour establishes and develops; the tumour cells respond to mechanical cues actively by

changing shape, state or migrating. For example, Friedl and coworkers have shown how the specific nature of the ECM (it's density, stiffness and geometry) along with aspects of the cancer cell (it's adhesive properties and polarity) determine how a cell (or a collection of cells) migrates through tissue [17–21]. *Durotaxis* was mentioned above but another type of 'taxis' experienced by cells is *haptotaxis* [22] which is motility of cells preferentially up gradients of adhesion within the ECM. More generally, cells are affected by 'mechanotransduction', in which cell-external mechanical stresses provoke cell-internal chemical signals leading to some type of adaptive response [23]. For further discussion of mechanotransduction in cancer, please see the helpful review in [24]. Equally, within the tumour itself, stresses affect development. Homeostatic pressure in which a balance of proliferation and apoptosis results in zero net growth has been found to limit the growth of some solid tumours [25, 26]. Conversely, such mechanical compression (solid stress) may actually drive cancer cells to invade and metastasise [27–30]. Given the intrinsic links between cancer cell behaviour and biomechanics, in order to fully understand how tumours, initiate, grow, invade and metastasise it is vital to include such processes in mathematical and computational models.

1.3 | Other in silico models

Early mathematical modelling of cancer (avascular solid tumours) focused on deterministic or continuum models of solid tumour spheroids developed from the classical Greenspan model [31]. Such models continue to provide insight through the ability to efficiently model large-scale dynamics (typical palpable tumours will contain at least 10^8 cells [32]) and equally since they lend themselves to mathematical analysis. For reviews of deterministic and continuum models, see, for example, [33, 34]. Selected articles in which mechanical stress is modelled using a continuum approach include [1, 35–39] while cell–cell interactions are considered in [40–46], and cell–matrix interactions in [47].

More recently, efforts have been focused on using individual-based models or agent-based models which allow a more direct comparison to the biology through the ability to model at the cell scale and within. In fact, modelling cell behaviour on the individual level is naturally scale bridging allowing at once intracellular (microscopic) and intercellular (mesoscopic) mechanisms to be included even when modelling a large number of cells (macroscopic). Equally, taking an individual approach easily allows the modelling of heterogenous cell populations or, at the very least, variability between cells.

1.3.1 | On lattice models

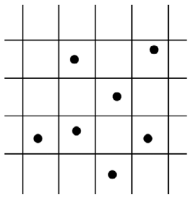
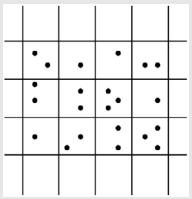
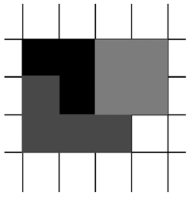
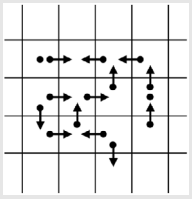
The most simplistic agent-based models are cellular automata models; in general, on-lattice agent based models have dominated the literature, these can be broadly categorised into four distinct types (see Table 1). Note, in the schematics in Table 1 each type is shown on a structured square lattice, however, on-lattice models often now use unstructured lattices such as the Voronoi–Delaunay lattice, for example, which typically results in more biologically realistic shapes, both of cells and cell-masses [49, 76]. On-lattice models may be 3D as in the case of the classic multicellular tumour spheroid (MCTS) models or 2D as in the case of monolayers. On-lattice models lend themselves to efficient large-scale simulations of a great number of cells at little computational cost. Table 1 provides details of some selected references for state-of-the-art on-lattice models of tumour growth, specifying the tumour–TM interactions considered where appropriate. For further discussion of on-lattice models, see, for example, the reviews in [76–82]. On-lattice models typically do not include mechanics which may be necessary to accurately depict the biology (see discussion above). Types I, II and IV rely solely on stochastic processes governing changes of state or position of a cell as well as mitosis. Cellular-Potts (Type III) is the only type to permit the modelling of physical mechanisms by solving an effective energy equation which goes some way to modelling the forces between cells (see, for example, [83–85]). There are several open-source on-lattice computational frameworks which include, notably for cancer, the *CompuCell3D* Cellular-Potts framework [86] and *Chaste* (Cancer, Heart and Soft Tissue Environment) [87, 88].

The remainder of this paper considers lattice-free (or off-lattice) agent-based, specifically, centre-based, force-based models of tumour growth and development. It is structured as follows: in Section 2 the modelling approach is introduced, in Section 3 the specifics of the forces acting between cells are outlined and in Section 4 there is a discussion of selected modelling efforts of other aspects of the TM. Throughout, a sample of results from the literature will be given.

2 | CENTRE-BASED FORCE-BASED MODELLING

Within a lattice-free agent-based model each component (e.g. cell, tissue fibre or vessel segment) is considered explicitly. Let us start by considering the most important aspect of the TM, the tumour cells themselves. Each cancer cell, i, is an individual agent; this paper

TABLE 1 Summary of on-lattice models with some selected references

Schematic	Model description	Selected references
	Type I - Single cell per lattice site	MCTS [48–50]; Allee-effect in tumour growth [51]; cell–vessel interactions [52]; cell–cell interactions [53]; cell adhesion [54–57]; monolayers [58]; phenotypic heterogeneity [59–62]
	Type II - Compartment model. Multiple cells per lattice site	coarse-grained proliferative rim [63, 64]; exclusion processes [65]
	Type III - Single cell covers multiple lattice sites (Cellular-Potts)	MCTS [66]; cell adhesion [67, 68]; angiogenesis [69]; cell–fibre interaction [70]; monolayers [71]
	Type IV - Multiple (or single) cell(s) per lattice site, movement though velocity channels (lattice gas cellular automata)	MCTS [72]; cell–fibre interaction [73]; cell–ECM interaction [74]; Allee-effect in tumour growth [75]

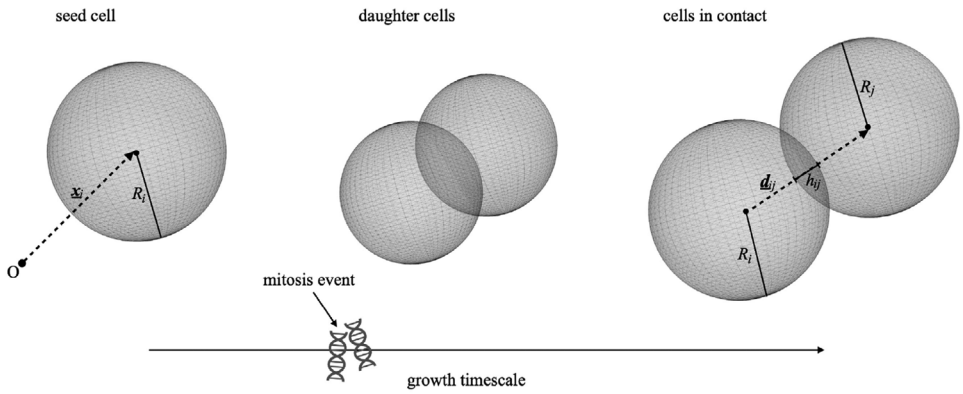


FIGURE 2 Schematic diagram indicating the basic physical properties of cells in centre-based models, showing on the left a single cell in isolation primed for mitosis, in the middle that seed cell having undergone mitosis creating two daughter cells and on the right two mature cells in contact under a balance of forces

focuses on centre-based models (CBM) in which the cell geometry is simplified with each cell considered to be a viscoelastic sphere subject to small deformations, described by the position of its centre, $\underline{\mathbf{x}}_i$, in the domain (hence centre-based) and its radius, R_i, see leftmost image of Figure 2. When growing tumours of significant size it is a reasonable assumption/simplification to make that cells may be represented by spheres. Other tumour models exist in which cells have non-spherical shape or are fully deformable, notably the work of Rejniak and coworkers [89–92]. However, these are not the subject of the review given here.

The behaviour of tumour cells can be broken down into three distinct but linked aspects. Firstly, there are

biological factors such as the cell cycle; each cell has the ability to grow in size and divide, undergoing mitosis. Once a cell has reached maturity (proliferative size) it may split into two daughter cells; mitosis is considered a stochastic event (taking place randomly, indicated by the DNA segments on the growth timescale in Figure 2) with probability inverse to the cell-cycle time. When the mother cell divides the simplest implementation is to have two smaller (volume preserving) daughter cells replace the mother cell (see middle image of Figure 2) [93, 94], more sophisticated models depict the splitting more accurately by deforming the spherical mother cell into a dumbbell shape the ends of which eventually separate into the daughter cells [95, 96]. The daughter cells then grow according to a growth rate until they too reach proliferative size and experience forces imposed by each other (see below and Section 3). Mitosis may be inhibited by external factors such as an excessive compression force due to a high number of neighbouring cells, this is commonly referred to as either contact inhibition [95] or as an exclusion process [97].

Secondly, there are genetic factors; cells may have given phenotypes or genotypes which prescribe their behaviour in some way. For example, cell phenotypic evolution might depend on biophysical processes, or biochemical interactions such as the availability of nutrients. This will be discussed further in Section 4.3.2, in which the traits of cells with a hypoxic phenotype are compared to the *Hallmarks of Cancer*.

Lastly, and particularly key, for force-based models interactions between cells (and indeed other agents in the model) are described by forces or potentials. Typically, each cell is governed by an equation of motion, an ordinary differential equation of the form:

$$\underbrace{\boldsymbol{\Gamma}\dot{\mathbf{x}}_i(t)}_{\text{friction}} + \underbrace{f_i(t)}_{\text{migration}} = \underbrace{\sum \mathbf{F}_i(t)}_{\text{mechanical forces}} . \tag{1}$$

The equation of motion takes into account three main aspects. Firstly, it accounts for friction experienced by the cell (first term in Equation 1, in which $\boldsymbol{\Gamma}$ is a three-dimensional tensor that models the physical structure of the environment)—this may be simply background friction imposed by the tissue but may account for friction imposed on cells by other structures. Secondly, the cell will have some pre-described active migration properties (second term in Equation 1), these may be as simple as random fluctuations/motion as in [93, 94] or may take into account a cells preferred direction (polarity) as in [98] and even effects of the external environment (e.g. chemotaxis where cells are naturally driven up gradients of nutrient, as in [99]). Thirdly, it incorporates mechanical interactions via forces (third term in Equation 1) between a cell and other agents within the model.

For two cells in contact (determined when the distance between their centres is less than the sum of their radii) a force directed along the vector between their centres, $\underline{\mathbf{d}}_{ij}$, is calculated taking into account repulsion and adhesion. Resolving the resulting potential between the two cells in the absence of any migration terms leads to two cells which remain stationary under a balance of forces (see rightmost image of Figure 2). In the following section, we discuss in more detail the repulsion and adhesion forces between cells. Later we will outline interactions of cells with other aspects of the TM (Section 4).

3 | REPULSION AND ADHESION FORCES

Force-based models are naturally governed by forces, specifically, repulsion and adhesion forces. In this section, the repulsion and adhesion forces acting between cancer cells are elucidated. The types of model discussed assume that a cell is spherical in isolation. Thus, any large contact area between a pair of cells (and indeed multiple contact areas between a cell and multiple others) creates a significant stress on the cytoskeleton of the cell(s). The limited ability to deform or indeed compress (with Poisson numbers found by experiments to be between approximately 0.4–0.5 [100]) leads to repulsion between cells. Conversely, cells are naturally adhesive. For cells in contact, binding due to adhesive molecules occurs; as the contact area increases so too do the adhesive bonds. The adhesive molecules at play are Cadherins (calcium-dependent adhesion) and Catenins, together these proteins form complexes called adherens junctions which facilitate cell–cell adhesion. Ramis-Conde and co-authors incorporated the E-Cadherin-β-Catenin pathway explicitly into their individual -based model of tumour development in order to discuss the implications of this pathway on cell migration and cancer invasion [101–104].

The total cell–cell interaction force between two cells, i and j, directed along the vector, $\mathbf{d}_{ij}$, joining their centres (see righthmost image of Figure 2), is given by

$$\mathbf{F}_{i,j} = \left(\mathbf{F}^{\text{rep}}_{i,j} - \mathbf{F}^{\text{adh}}_{i,j}\right)\frac{\mathbf{d}_{ij}}{\|\mathbf{d}_{ij}\|}, \tag{2}$$

where $\mathbf{F}^{\text{rep}}_{i,j}$ is the repulsion force discussed in Section 3.1 and $\mathbf{F}^{\text{adh}}_{i,j}$ is the adhesion force discussed in Section 3.2. In order to calculate the change in position of cell i at each timestep, the sum of all resulting forces between cell i and any cell j with which it is in contact is included in the equation of motion (Equation 1).

TABLE 2 Selected forms of CBM adhesion force with selected references

Adhesive force	Description	References
$\lvert\mathbf{F}_{i,j}^{\text{adh}}\rvert = \alpha S_{ij}$, e.g. $= 2\pi\alpha\left(R_i - \frac{h_{ij}}{4}\right)h_{ij}$	Adhesion directly proportional to contact surface area, S_{ij}. The resulting force can be determined explicitly.	[93, 94, 101, 102, 106]
$\lvert\mathbf{F}_{i,j}^{\text{adh}}\rvert = \frac{4E^*}{3R^*}a^3 - [8\pi\alpha E^* a^3]^{1/2}$	Johnson–Kendal–Roberts (JKR) theory. Contact surface area (with contact radius parameter a) is modified by adhesion. The resulting force must be determined implicitly.	[96, 107, 108]

3.1 | Hertzian repulsion

For two spherical cells, i and j, in contact and subject to small (elastic) deformations, the repulsive force experienced is typically described in the literature by the classical Hertzian contact mechanics repulsion [105]. The form of the repulsion force for two such cells of radii R_i and R_j, is, therefore

$$|\mathbf{F}_{i,j}^{\text{rep}}| = \frac{4}{3}E^* {R^*}^{1/2} {h_{ij}}^{3/2}, \tag{3}$$

where $h_{ij} = R_i + R_j - \|\mathbf{d}_{ij}\|$ describes the length of 'overlap' (or contact area) between the two cells. This repulsion force term includes both an effective radius, $R^* = R_i R_j/(R_i + R_j)$ and an effective Young's Modulus, E^*, which is calculated from

$$\frac{1}{E^*} = \frac{1-\nu_i^2}{E_i} + \frac{1-\nu_j^2}{E_j}, \tag{4}$$

where E_i and E_j are the cells' respective Young's moduli and ν_i and ν_j their Poisson ratios.

Under Hertzian elastic contact alone, the following assumptions must be made: (a) strains on the cells are small and within the elastic limit, (b) the area of contact between the spherical cells is much smaller than their radii, (c) the cell surfaces are continuous and non-conforming and (d) there is no friction between the cells. Moreover, this classical model is strictly non-adhesive. Cells, however, are naturally adhesive, governed by adhesion molecules that travel to the cellular membrane, stimulated by the proximity of a neighbouring cell, forming adhesive bonds. Thus, for those modelling mechanical cell–cell interactions using contact mechanics it is necessary to also include an adhesion force between cells, thus extending or modifying the classical Hertzian model.

3.2 | Adhesion

There are several examples in the literature of cell–cell interaction forces, with differing expressions for the adhesive force, $\mathbf{F}_{i,j}^{\text{adh}}$. Here, we discuss two key variants. These are outlined in Table 2 for quick reference and comparison. In each case, the force takes into account the strength of adhesion, α, which is assumed to be constant among the cell population and considers the contact surface area between cells since as contact surface area increases so too does the number of adhesive bonds.

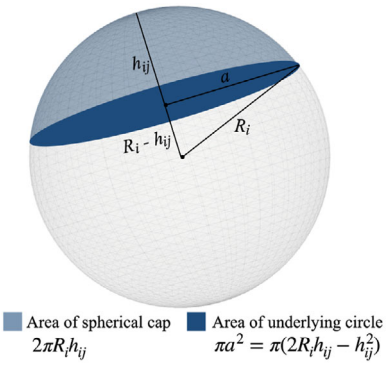


FIGURE 3 Figure showing how the contact area is estimated in [93]

3.2.1 | Explicit adhesion force

In this variant, the adhesion force, $\mathbf{F}_{i,j}^{\text{adh}}$, between two overlapping cells, is assumed be directly proportional to the contact surface between them, S_{ij}. The contact surface area is first calculated which then feeds into the adhesion force. Within the literature, there are different approximations for the contact surface area. In [106], for example, they model the contact surface area of cells in contact as the area of the circle equidistant between the two cells, underlying the spherical cap of height $h_{ij}/2$ (i.e. half the overlap between cells). While in [93] they calculate the area to be the average value between the area of the spherical cap of height the overlap between the cells, h_{ij}, and area of the circle underlying the cap (see Figure 3). In this case, the contact surface is approximated as

$$S_{ij} = \frac{1}{2}\left[2\pi R_i h_{ij} + \pi\left(2R_i h_{ij} - h_{ij}^2\right)\right] = 2\pi R_i h_{ij} + \frac{\pi h_{ij}^2}{2},$$

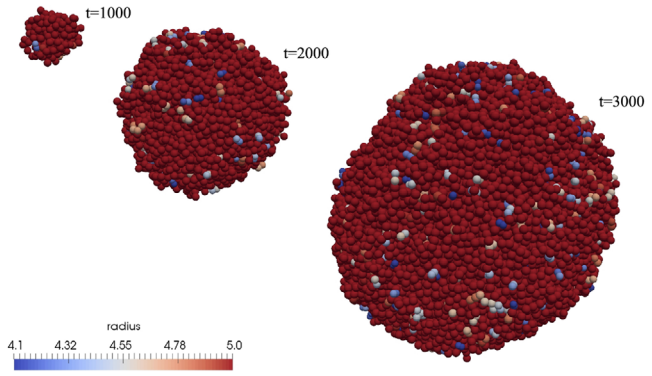


FIGURE 4 Figures showing the results of a computational simulation of the growth over time of an MCTS from the CBM of [94] (unpublished) in which adhesion is incorporated via Equation (5)

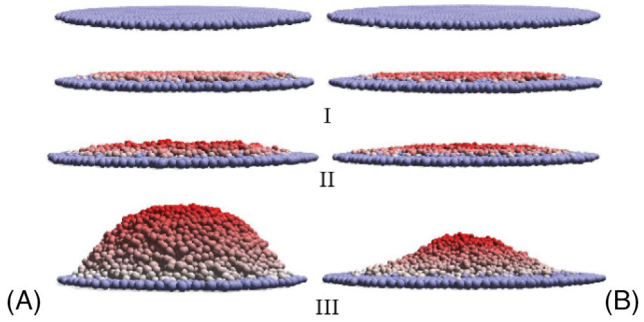


FIGURE 5 Destabilisation of a monolayer using the extended Hertz interaction (A) and the JKR-interaction energy (B). The numbers (I), (II), (III) denote the knocked-outcontrol mechanisms which lead the destabilisation. (I) contact inhibition, (II) anchorage-dependent proliferation (III) anchorage-dependent apoptosis (anoikis). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, *Journal of Statistical Physics*, [108], Copyright (2007)

with the resulting adhesion force given by

$$|\mathbf{F}_{i,j}^{\text{adh}}| = 2\pi\alpha\left(R_i - \frac{h_{ij}}{4}\right)h_{ij}. \tag{5}$$

This approach to modelling adhesion considers a 'suction' effect as a consequence of the increasing density of effective bonds between the cells. In such an approach certain assumptions have been made [106]. Firstly, it is assumed that the adhesion molecules (receptors and ligands) which bind the cells together are distributed homogeneously over the whole cell surface and thus the whole contact surface area. Secondly, that binding takes place instantaneously and furthermore that since adhesion which causes deformations to the cell naturally change the cell surface area it is assumed that this process happens rapidly so that it is not necessary to explicitly consider the cell surface area.

Figure 4 shows the growth of an MCTS over 3000 time-steps (approximately 2 days) in which adhesion is modelled by the explicit adhesion force given by Equation (5). The simulation results shown are derived from the model (along with parameters) given in [94].

3.2.2 | Implicit Johnson–Kendal–Roberts (JKR) adhesion force

The explicit model(s) of adhesion discussed in the previous section, do not take into account the fact that the adhesion (derived from the surface contact area) then affects and modifies the surface contact area. The JKR theory of adhesive contact derives a model for the adhesive force which includes this hysteresis phenomena [109]. In this case, the force is given by

$$|\mathbf{F}_{i,j}^{\text{adh}}| = \frac{4E^*}{3R^*}a^3 - \left[8\pi\alpha E^* a^3\right]^{1/2}, \tag{6}$$

in which E^* and R^* are, once again, the effective Young's modulus and radius, respectively, and a is the contact surface radius (see Figure 3). However, in this case a is not fixed but rather changes and may be calculated from

$$h_{ij} = \frac{a^2}{R^*} - \left[\frac{2\pi\alpha a}{E^*}\right]^{1/2}. \tag{7}$$

Figure 5 is reproduced, with permission, from [108] (their fig. 5) in which they directly compare the behaviour of cells governed by (A) an explicit extended Hertzian model of adhesion (Section 3.2.1) with (B) the JKR theory model (Section 3.2.2). This study of the destabilisation of a monolayer shows clearly how the hysteresis effect between attachment and detachment of cells within the JKR model leads to fewer cells detaching from the substrate over the same timescale when compared with the extended Hertz model. For further details of the model parameters in these simulations, see [108].

For more details and simulation results of tumour growth under either the modified Hertzian or JKR adhesion forces see, for example, the references in Table 2.

4 | ADDITIONAL ASPECTS OF THE TM

This review will now consider selected modelling efforts of the mathematical and computational oncology community with regards to modelling tumour–TM interactions. In

Section 4.1, cell–ECM interactions are discussed while in Section 4.3 cell–vessel interactions are considered.

4.1 | Tumour interactions with the ECM

The ECM, on a basic level, is composed of a structured mesh (matrix) of fibres (e.g. collagen and fibronectin) within a gel of glycoproteins. We have previously discussed cell–cell adhesion but another important adhesive process in cell biology is cell–matrix adhesion. Focal adhesions are protein complexes which connect the cell's cytoskeleton to the ECM [11, 110]. Focal adhesions not only directly and mechanically link the cell to the ECM but they also act as points of signalling (mechanotransduction); transmitting information about the mechanics of the extracellular environment to cells through biochemical signalling molecules. Focal adhesion mechanotransduction plays an important role in regulating both the shape and migration of cells [11]. Specific focal adhesion proteins which act as mechanotransducers are the ECM protein, fibronectin and cell-membrane receptor integrins. Fibronectin also binds to collagen fibres in the ECM. Collagen fibres give structure to tissue but also, naturally, by extension, to the TM. Furthermore, cell–ECM interactions may have a lasting impact on the structure of the ECM. Modelling of the ECM (and cells) typically considers it (them) to be primarily viscoelastic, however, upon interaction they may exhibit a degree of plasticity—changing shape and structure permanently (or at least until the next interaction). Such plastic deformation of the fibrous ECM structure is often characteristic of the TM; fibres, for example, align around solid tumours [111–113].

The fibrous connective tissue of the ECM performs a wide variety of functions within the healthy body. In terms of cancer, and within the TM, the structure of the ECM and the interaction of cancer cells with individual fibres of the matrix drive almost all aspects of cell behaviour from its proliferation to migration. ECM binding is implicated, for example, in proliferative signalling; experimental data, backed up by in silico models, have shown that border cells (those connected to the ECM) of an MCTS are less proliferative than cells in the interior [49]. Moreover, malignant cells activate the 'integrin migration pathway' and crawl towards and along the protein network of the ECM; migration through the protein network results in the rearrangement of the ECM structure as cancer cells use the integrin pathway to cut-off the fibres and re-orient the ECM [114, 115]. Cell migration can happen as a collective process that presents in different ways depending on the tumour type and the nearby environment leading to different migration structures [18, 20].

The physical properties of the environment itself affect tumour development and progression. It is widely known that cells prefer stiff matrices to softer ones (*durotaxis*, [10]). Tumours themselves are known to be stiffer than normal tissue [116, 117]. The stiffness of the ECM not only affects cell–ECM adhesion (and as such modulates cell-spreading and migration, [118]) but it also affects the epigenome altering the cancer cell pheno- and genotypic behaviour [8, 9, 119]. It has been shown that stiff ECM promotes tumour progression [120, 121]. On the other hand, it has been shown that TRCs are more proliferative in soft rather than stiff environments [12]. To fully understand cancer development and local tissue invasion, it is important to model the ECM alongside the cancer cells. To model the ECM, it is natural to incorporate fibres as additional agents within an agent-based model.

4.2 | Cell–fibre interactions

It is worthwhile to begin this section by referring to the movement mechanisms of cells. The spatial behaviour of cells (including their movement) is governed by their polarity. Epithelial cells, for example, have apical-basal polarity, while migratory cells are polarised with front-rear polarity [122]. Changes in a cell's polarity phenotype is characteristic of both tumourigenesis [123] and metastases [124]. Within the TM when cells encounter ECM fibres they adhere to them and 'crawl' along them [125] potentially re-modelling the ECM in their wake [126].

In [98], the ECM fibres are modelled using a force-based, individual-based model in which cells adhere to fibres causing changes to the directional movement of cells but also accounts for restructuring of the fibres. Single-cell experiments are carried out to determine the effect that the cell's environment (in this case a 2D substrate) has on its migration. By placing a single cell in a domain segregated by substrates with different matrix stiffnesses [98] were able to reproduce the experimental results of [10] showing that cells are drawn preferentially to stiffer matrices, hypothesising that it was the lack of matrix reorientation by the cell that drives *durotaxis*. In a second experiment, they showed the observable 'follow-the-leader' behaviour of collective cell migration [127]. Figure 6 reproduces, with permission, their fig. 10, in which a single non-polarised cell becomes polarised and 'follows' the path of polarised 'leader' cell. It can also be seen from these experiments how the ECM is re-modelled in the wake of the cell's path, fibres having been realigned as the cells have passed through.

In [94], the 2D model of [98] is extended to 3D and matrix fibres are incorporated into a CBM for tumour

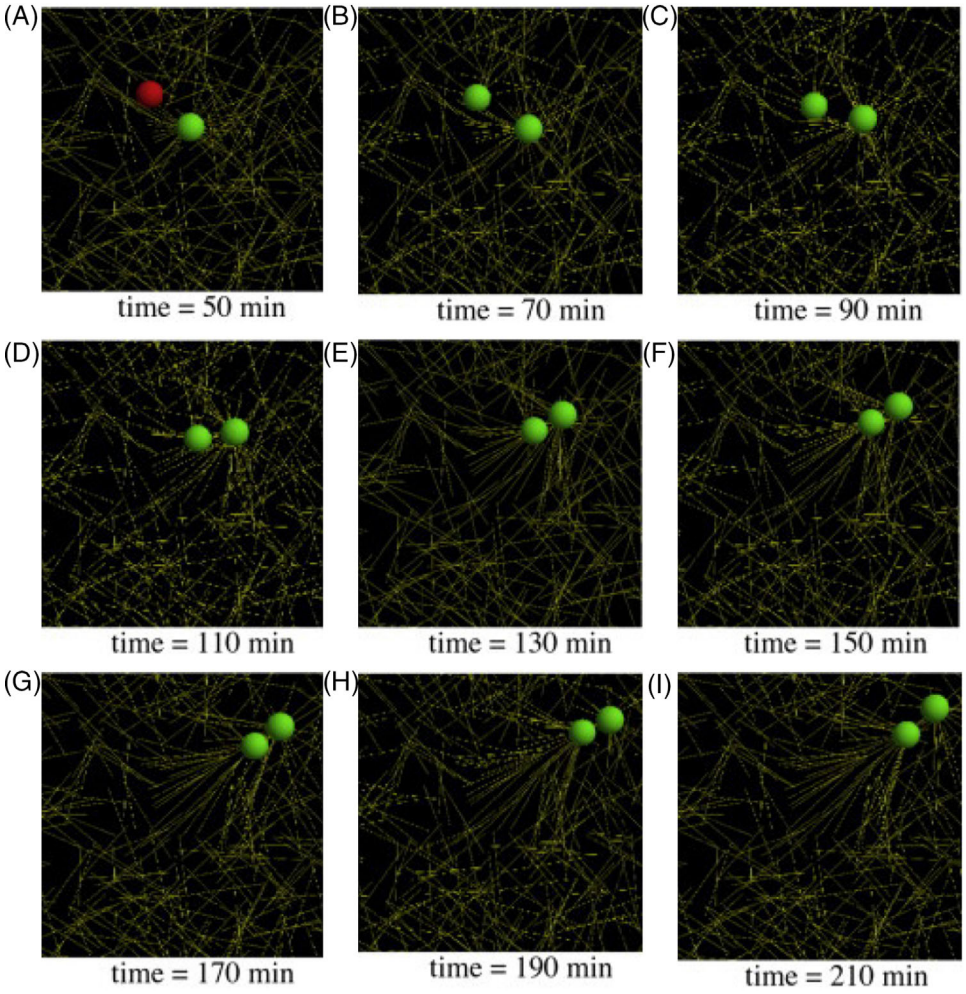


FIGURE 6 Snapshots in time indicating how two cells collectively migrate through the matrix. A non-polarised cell (red in plot A) becomes polarised (turning green) and then follows the path of the existing polarised cell (green in plot A). Reprinted from [98], Copyright (2012), with permission from Elsevier

growth. Each individual fibre is modelled explicitly by a thin cylinder (described by its extrema and radius), and the three-dimensional computational domain is filled with fibres of a given distribution of positions and orientations. In this work, the movement of cells along fibres is modelled by extending the force-based approach to cell–fibre interactions by incorporating attractive and repulsive forces between cells and fibres which cause cells to move along fibres; a cell in contact with a fibre will feel an adhesive force, parallel to fibre orientation and a repulsive force orthogonal to the fibre [128]. A cell–fibre interaction force is computed as the sum of these orthogonal/repulsive and parallel/adhesive terms, and added to the right-hand side of the equation of motion of each cell (Equation 1); the form of these forces can be found in [94].

Figure 7, reproduced, with permission, from [94] (their fig. 4) shows how a tumour develops oriented along fibres which are uniformly distributed aligned with the y-axis. Initially a single cancer cell is placed within a fibrous domain, the resulting tumour which has developed (after 9000 timesteps, approximately 6 days) is shown in Figure 7. Whereas, in the absence of fibres, one would typically see a spherical tumour mass form (as in Figure 4), here the growth has been stretched out along the fibrous tissue.

The model in [94], however, overly simplifies the biology underpinning cell–fibre interactions. It does not account for the reverse mechanical processes in which cells affect the fibres; in order to gain tractability as a 3D model the simplification of fixed fibres was made unlike the 2D model in [98]. In reality, individual fibres and the matrix as a whole are plastic as described above and so also move and re-model around an invading tumour or single invading cell. Furthermore, it may well be the case that rather than preserving polarity and moving along fibres unidirectionally migrating cancer cells may repeatedly reverse their polarity and move periodically up and down matrix tracks as in the single-cell experiments of [129].

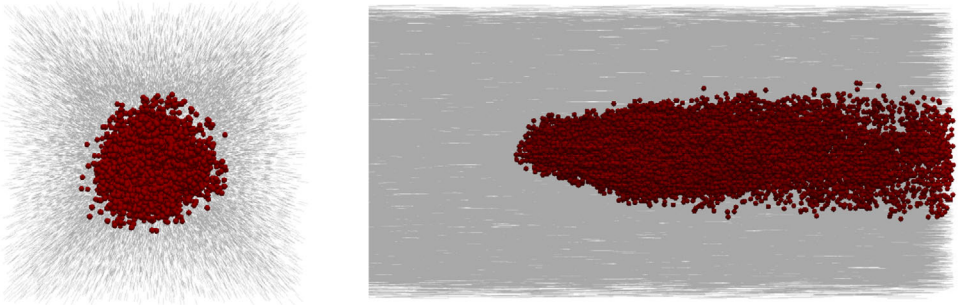


FIGURE 7 Figures showing the results of a simulation of tumour growth within a domain of uniformly distributed fibres (aligned with the y-axis) after 9000 timesteps. Cells are represented by red spheres, fibres in grey. Left: View orthogonal to the fibre orientation (xz-plane). Right: View in the yz-plane, cropped on the left side. Reprinted from [94], Copyright (2020), with permission from Elsevier

A further biologically relevant aspect that links cancer cells to the ECM is matrix re-modelling by degradation. MMPs are enzymes which degrade ECM proteins (e.g. collagen fibres) through proteolysis. Proteolytic re-modelling of the ECM by MMPs is a key step towards cancer invasion [6]. Fibre degradation is taken into account in current state-of-the-art continuum models, see, for example, [130].

The use of forces to model tumour–TM interactions is only one way to account for the inherent biomechanics, alternative models of cell–ECM interactions include [131], for example, who use Hookean springs which act via the basement membrane which links cells to the connective tissue. Biomechanics though are vitally important to the functioning of the ECM; a comprehensive review of ECM mechanics and how this interplays with cellular behaviour can be found in [132] while discussion of ECM re-modelling and its role in tumour progression and metastasis can be found in [126].

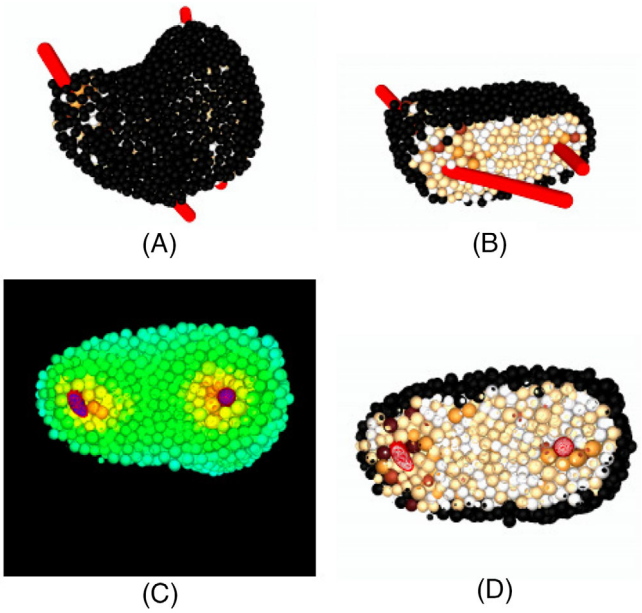


FIGURE 8 Simulation results of a tumour cord interacting with two blood vessels (black cells are necrotic). (A-B) Tumour cord growing around two vessels, (C) oxygen profile levels in the tumour cord, (D) cross-section showing corresponding development of tumour cells. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, *Bulletin of Mathematical Biology*, [99], Copyright (2018)

4.3 | Tumour interactions with the Vasculature

Another important aspect of the TM is the vasculature. Blood vessels weave through the tissue supplying it with oxygen and other vital nutrients. Cell–vessel interactions are both mechanical and biochemical.

4.3.1 | Mechanical cell–vessel interactions

Cells interact mechanically with segments of the vessel network. In [94], they assume that repulsive and adhesive forces act between a cell and a vessel segment and that these forces are analogous to those between cells (Section 3), for further details, see [94]. Their simulations show tumours developing and embedding within pre-existing vasculature. The proliferation of cancer cells around blood vessels—modelling so-called 'tumour cords' is simulated in [99]. In the case of a tumour chord rather than a spherical tumour growing with the classical radial profile (necrotic core, quiescent and proliferative outer ring), the opposite profile is derived with necrotic regions on the outside furthest away from the central blood vessel(s). Figure 8 is reproduced, with permission, from [99] (their fig. 15).

In order for cancer to metastasise and spread to secondary sites around the body, cancer cells must be able to access the vessel network. Intravasation (and its analogous reverse, extravasation) is the process by which a cell enters (or leaves) the vascular network. In [102], they model the key metastatic process of intravasation using a CBM

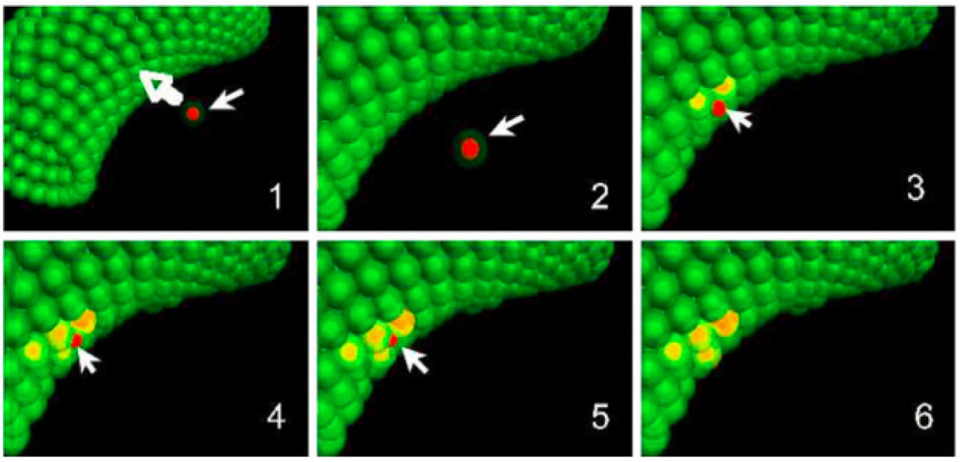


FIGURE 9 Spatiotemporal evolution dynamics of a malignant cell (red nucleus coloured cell, marked with a full arrow) approaching a blood vessel to undergo TEM. When the malignant cell attaches to the vessel, the VE-cadherin bonds are disrupted and new N-cadherin bonds are formed (shown in yellow). After some time, the malignant cell manages to disrupt the endothelial bonds enough to open a gap in the vessel and undergo TEM. Copyright IOP Publishing. Reproduced with permission from [102]. All rights reserved

coupled to a deterministic model of the intracellular protein pathways which allow cells to migrate through the vessel endothelial wall (transendothelial migration, TEM) [133, 134]. In this case, adhesion of the cancer cell with the vessel endothelia is key, and as before adhesion is driven by cadherins. Vascular endothelial cadherins (VE-cadherin) bind the cells of the vessel wall together. A cancer cell disrupts endothelial bonds binding itself to the wall using N-cadherin. Figure 9 is reproduced, with permission, from [102] and shows a single cell approach and then intravasate a vessel wall.

4.3.2 | Biochemical interactions: The hypoxic phenotype

Cancer cells, like normal cells, respond to the availability of oxygen, although the malignant response is anything but normal. We can characterise cancer cells into phenotypes based on their access to oxygen (e.g. normoxic, hypoxic and necrotic). Hypoxic cells are chronically lacking in sufficient oxygen, this deficiency of the main cell nutrient rather than being tumour suppressing actually drives tumour progression in numerous ways [5]. Jain lists the following responses of tumour cells to hypoxia: switch to anaerobic metabolism; resist apoptosis; undergo the epithelial–mesenchymal transition (EMT); induce a cancer stem-cell 'repopulating' phenotype, resist anti-cancer therapies; cause inflammation and immunosuppression; genomic instability and angiogenic. Notice that these classical behaviours are closely aligned with the *Hallmarks of Cancer* [2, 3]; the hypoxic phenotype is what drives cancer progression and makes it so deadly.

Hypoxia is a main driver of the EMT) [135]. The EMT occurs when epithelial cells detach (losing their cell–cell adhesion and polarity) and gain mesenchymal cell attributes (migration, invasion and differentiation). The EMT is the first step towards cancer metastasis. In [136], they model the EMT and metastasis using a hybrid on-lattice individual-based approach. Hypoxia also drives angiogenesis, with hypoxic tumour cells releasing VEGF which signals for tumour angiogenesis. McDougall and co-workers are leading experts in modelling angiogenesis [137–141]. In [93], they incorporate normoxic, hypoxic and necrotic phenotypes into a CBM to show how the hypoxia phenotype is implicated in the formation of pseudopalisades (hypercellular 'walls' surrounding necrotic zones) in glioblastoma.

5 | CONCLUSIONS

This paper provides a selected review of in silico models for tumour growth and development, with specific emphasis on centre-based force-based agent-based models. For a critical evaluation of the available agent-based modelling techniques, their advantages and disadvantages including discussion of computational costs, see, for example, [76]. A great many authors are contributing to this vibrant area of research as shown throughout the paper and the references herein. Specifically, key authors in the field include Drasdo and coworkers [95, 107, 108, 142–146]. However, no review of such models would be complete without mentioning the work of Macklin and co-authors [147–149] who have recently launched *PhysiCell* a comprehensive open source C++ code designed to simulate the growth 3D cell

colonies with natural applications to growing tumours. Cell mechanics are modelled in much the same way as described here with adhesion and repulsion forces acting both between cells and their environment. The environment itself is modelled though reaction-diffusion partial differential equation (PDEs) making it what is commonly described of as a hybrid model. For details of this powerful tool, we direct the reader to the code guide [150]. In particular, one aspect of the TM which has not been discussed here, although which is a vital part, are tumour-associated immune cells; *PhysiCell* has been used to model how immune cells attack an MCTS [150], other agent-based models of tumour immune interactions—include [151–154]. Szymańska and co-workers are also developing hybrid models in which individual cells are treated as agents while the environment is described as a continuum [155–157], in such a case while computational efficiency is enhanced the nuances of specific environmental biomechanics, such as movement along fibres, are lost.

Beyond highlighting state-of-the-art research in the field, the main take home message is that biomechanics need to be taken into account. One might contrast individual-based models with reaction-diffusion models of cancer. While reaction-diffusion models (for example, [158–160]) do offer insight they do not include biomechanics nor can they account for phenotypic variations that are well captured through an agent-based force-based approach. Even for the subset of reaction-diffusion-taxis models (161], for example) where biomechanics may be implied they are not taken into account explicitly. Individual-based modelling, then, has significant advantages over reaction-diffusion models in determining the key mechanisms which drive metastatic spread. Perhaps in the future greater effort should be put into integrating reaction-diffusion models with biomechanics in order to gain the advantages of both approaches.

Agent-based modelling of tumour growth, however, is just a single strategy in the global effort of the scientific community in the fight against cancer. Indeed, mathematical (and computational) oncology is a growing field in which research is being done on a broad range of topics spanning from modelling intracellular genetic pathways (see, for example, [162–164]) to modelling cancer therapies (see, for example, [165–167]). Looking to the future, a multi-scale model of a growing tumour within the TM should seek to bring together not only the biomechanical aspects laid out above but equally other aspects from the diverse field of study. By incorporating intracellular pathways (such as in [101, 103]) which results in phenotypic differences between cells it is possible to derive a realistic heterogeneous cancer cell population. By using imaging combined with the modelling techniques above to render in vivo tumours in silico it is possible to simulate in real time and space the development of tumours predicting how they will invade and metastasise. By trialing cancer therapies on in silico tumours (as in [50, 141, 168]) clinicians can devise optimal therapy protocols that can at once become both the standard of care and patient-specific. In combination, these techniques will truly push the frontier of our understanding of cancer and lead towards personalised medicine where each patient can be treated truly individually.

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