Mathematical Modelling and Avascular Tumour Growth*

Interdisciplinary Research

Jennifer A Flegg and Neela Nataraj

Cancer is a global health burden; 1 in 2 people will be diagnosed with some form of cancer during their lifetime. In the Western world, 50% of cancer patients survive for 10 or more years after diagnosis, compared to 24% forty years earlier. Cancer can come in many different forms, but tissues affected by cancer tend to have common features such as abnormal cell growth rates. Cancer biology is incredibly complicated, as illustrated by the difficulties surrounding the diagnosis and treatment of cancer. However, mathematics has the potential to mediate this complexity by abstracting the system using simplifying assumptions into a mathematical framework that can be analysed and/or solved numerically to gain biological insight. This article is an introduction to the mathematical modelling of one of the important early stages of tumour growth – the avascular stage – where there is no blood supply to the tumour.

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1. Introduction

Mathematical modelling can provide deep scientific insight into a biological process and has the potential to generate theoretical predictions which could not have been anticipated in advance, thereby, stimulating further biomedical research. It can also decrease the need for time-consuming, technically difficult and often expensive experiments. As such, mathematical models should form a crucial part of biological research, including cancer re-

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search. In the context of cancer, mathematical models can provide insight into how changes in physical parameters affect the growth of many types of tumours and, therefore, propose the best possible treatment. That is, mathematical models can be used to gain insight into, for example, how anti-cancer drugs can be used to control and/or eradicate a tumour.

A tumour is a group of cells that exhibit an abnormally large net growth rate. The study of tumours is important since tumours are an immediate precursor to many cancers. In the initial stages, a tumour growing *in vivo* (in the body) is avascular (devoid of blood vessels, which provide oxygen to sustain tumour growth). During this phase, cells absorb essential nutrients for their proliferation only from the surrounding medium. As the tumour grows, eventually the nutrients from the outside medium will be consumed by the outer regions of the tumour before reaching the centre of the tumour, causing cells in the centre to die. This means that the supply and demand for nutrients in the tumour are important to include in a mathematical model for tumour growth. In this article, we limit our focus to avascular tumour growth, but it should be noted that there are many other phases of tumour growth that are important. It should also be noted that the avascular stage of tumour growth is a period prior to its clinical detection, and is, therefore, largely irrelevant for cancer diagnosis and treatment. However, an understanding of the early stages of tumour growth is critical for subsequent phases. *Figure* 1 shows an artistic schematic of a growing avascular tumour over time. Starting from a very small number of cells, the tumour grows in an approximately spherical shape. Here, green cancer cells are able to divide, yellow cancer cells called 'quiescent' are alive but unable to divide due to lack of nutrients, and the grey cells in the centre of the tumour are dead. This central dead region is called the 'necrotic core'. Red cells are the ones which have undergone recent division.

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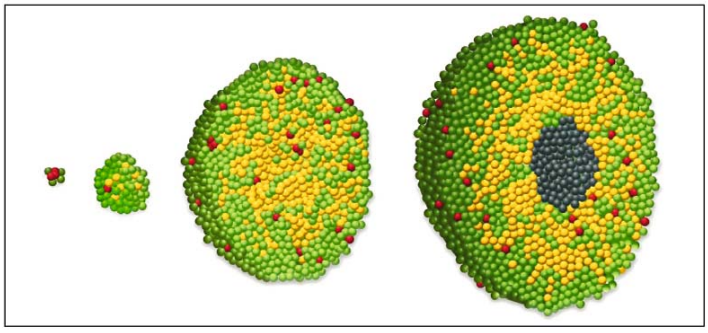

Figure 1. Artistic impression of avascular tumour growth showing dividing cells (red), cells able to divide (green), quiescent cells (yellow), and cells in the necrotic core (grey), where time is increasing from left to right.

Modelling Cycle in Interdisciplinary Mathematical Research

In interdisciplinary research, mathematics can be used to gain a scientific understanding through analysis and computer simulations of mathematical models representing a real-world problem. Mathematical modelling can be applied to solve scientific problems across disciplines including biology, economics, and manufacturing. Here, we are concerned with the modelling of avascular tumour growth.

Mathematical modelling involves identifying a real-world problem (see *Figure* 2) and simplifying it into a 'working model' of the situation. The working model is then represented by mathematical equations as part of the mathematical model by making suitable assumptions. The model is further translated into a 'computational model' that is simulated to obtain numerical results from which conclusions are drawn. The results are interpreted and compared with the known behaviour of the real-world problem. If the results do not agree well with experimental data and/or physical reality, the working model is re-examined, and the steps of the modelling cycle are revised. In practice, often several iterations of the entire mathematical modelling cycle are required for the model to capture the desired real-world behaviour. It is also possible that the mathematical model will make predictions that help in the design of more informed and appropriate experiments. In other words, both experimental work and mathematical modelling should be considered dynamic rather than static processes. Once we have a model that we are satisfied can capture

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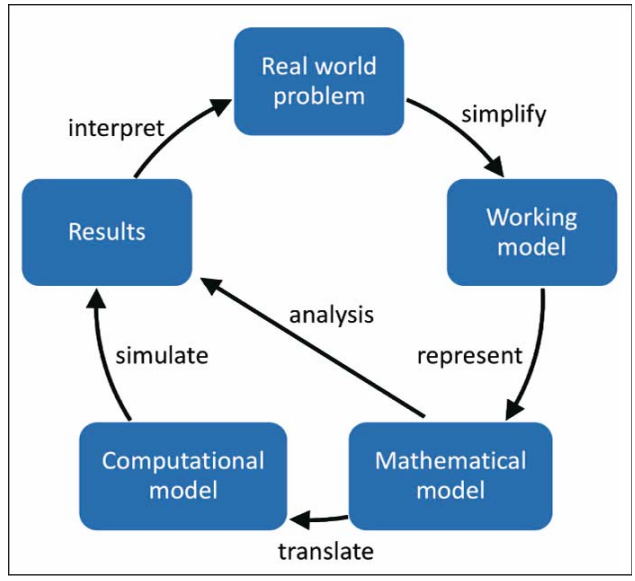

Figure 2. Schematic diagram summarising the modelling cycle in interdisciplinary mathematical research.

the essential processes of the system, we can use this model to make predictions and to perform *in silico* experiments (e.g. by computer simulation). In the case of tumour modelling, we can, for example, see how anti-cancer drugs can reduce the size of the tumour.

2. Mathematical Models of Avascular Tumour Growth

H P Greenspan was the first (in 1972) to model the spatiotemporal growth of multicellular tumour spheroids, where growth is limited by the diffusion of a chemical source of the nutrient.

Figure 3 provides an overview of some seminal contributions in the area of mathematical modelling of avascular tumours over a period of 30 years (1972–2002). After 2002, there has been a vast increase in the number and style of mathematical models developed for tumour growth. So we limit the scope here to a 30-year timeframe. Interested readers are directed to more recent reviews on mathematical tumour modelling [1–3].

H P Greenspan was the first (in 1972) to model the spatiotemporal growth of multicellular tumour spheroids [4], where growth is limited by the diffusion of a chemical source of the nutrient. Greenspan later extended the model to include mechanical effects by modelling the internal pressure differentials caused by

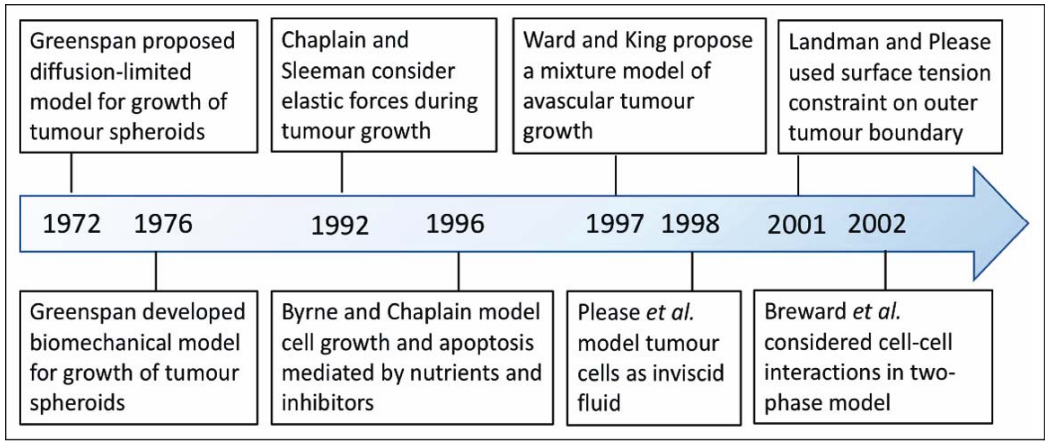

Figure 3. History of seminal papers in mathematical modelling of avascular tumour growth, 1972–2002.

cell birth/death that leads to cell motion [5]. There have been numerous extensions to the early work of Greenspan, too many to review exhaustively here, for example, to include the use of nonlinear elasticity to model large deformations [6], and the role of cell-cell interactions in cell proliferation and death [7]. In 1997, Ward and King used mixture theory to model tumour growth, whereby a tumour is treated as an agglomeration of matter consisting of a continuum of cells in two states, living and dead [8]. Authors have extended the cancer mixture model theory introduced by Ward and King to, for example, incorporate mechanical assumptions relating to the cancer cells [9], and to impose surface tension on the growing tumour spheroid to reflect the surrounding media [10]. In 2002, Breward *et al*. published a two-phase mathematical model of tumour growth comprising cancer cells and extracellular water that incorporated cell-cell interactions [11]. The model by Breward *et al*. serves as a good prototype for more recent multiphase models of tumour growth.

In this article, we will provide a detailed review of the derivation of two mathematical models only – the early contribution by Greenspan [4] and the two-phase modelling of Breward *et. al.* [11]. These are the first and last contributions, respectively, in the history provided in *Figure* 3, and comparing these two models allows us to highlight how the field was moved forward over a 30 year time period from 1972–2002.

Greenspan Model (1972)

In the 1972 work of Greenspan, the 'real-world' problem being modelled was the growth of avascular tumours. The tumour spheroid is assumed to be radially symmetric and growth is regulated by one or more diffusible chemical factors, which can either be supplied externally or produced internally.

In the 1972 work of Greenspan, the 'real-world' problem (see *Figure* 2 for modelling cycle) being modelled was the growth of avascular tumours. The tumour spheroid is assumed to be radially symmetric and growth is regulated by one or more diffusible chemical factors, which can either be supplied externally (e.g. oxygen) or produced internally (e.g. chemical inhibitors such as tumour necrosis factor). These factors regulate the local growth dynamics inside the spheroid such that when cell proliferation exceeds cell death, the tumour expands and vice-versa.

For a chemical factor, c, the governing equation is derived using the principles of conservation of mass. Considering a small arbitrary volume, V_1, of the tumour, the number of chemical molecules can change due to: (i) the net flow of material into this volume and (ii) production/destruction of material inside the volume. This concept of mass conservation can be expressed as a 'working model' (*Figure* 2) in words below:

$$\left\{\begin{array}{c}\text{Rate of change}\\ \text{in } V_1\end{array}\right\} = \left\{\begin{array}{c}\text{Net flux through}\\ \text{boundaries of } V_1\end{array}\right\} + \left\{\begin{array}{c}\text{Source/sink}\\ \text{within } V_1\end{array}\right\}. \tag{1}$$

In the case of radial symmetry in a spherical tumour, we can write the working model as a 'mathematical model' (in its differentiated form) for the chemical factor:

$$\frac{\partial c}{\partial t} = \frac{D}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) + f(c, r, t), \tag{2}$$

where $c(r, t)$ is the concentration of chemical at radius r at time t, D is the diffusion coefficient of the chemical, and $f(c, r, t)$ is the source/sink of the chemical per unit volume per unit time. To complete the mathematical model, the conservation of cell mass over the entire spheroid gives us that the volume of the spheroid changes according to:

$$\frac{dV}{dt} = \int_V S(c)\, dV, \tag{3}$$

where $V(t)$ is the volume at time t and $S(c)$ is the net growth (proliferation and death) of cells, regulated by the chemical factor. Using the assumption of spherical symmetry and $V = \frac{4}{3}\pi R^3$ where $R(t)$ is the outer radius at time t:

In 2002, Breward *et. al.* proposed a two-phase mathematical model of avascular tumour growth to study cell-cell interactions.

$$\frac{dR}{dt} = \frac{1}{R^2} \int_0^{R(t)} S(c) r^2 dr. \tag{4}$$

The model shown here ((2) and (4)) can be solved, subject to boundary and initial conditions, either analytically for certain forms of $S(c)$ and $f(c, r, t)$, or numerically otherwise (thus establishing the 'computational model'). Results from models of this form have shown good agreement to experimental data on multicellular spheroids grown *in vitro* (in a laboratory setting) [4] despite assuming that the tumour is homogeneous. In the next section, a model that relaxes the assumption of a single phase is investigated.

Breward et al. Model (2002)

In 2002, Breward *et. al.* proposed a two-phase mathematical model of avascular tumour growth to study cell-cell interactions [11]. The tumour consists of two phases – a tumour phase and an extracellular fluid phase (see schematic (*a*)on the left-hand side of *Figure* 4).

The fluid phase supplies nutrients for the mitotic division of cells and when cells die they release their contents into the fluid phase ((*b*) on the right-hand side of *Figure* 4). This internal conservation of mass along with momentum conservation forms the basis for the model formulation. Here, we present the model as a spherically growing tumour with radial symmetry where the tumour boundary moves outward because of the expanding tumour mass.

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Conservation of mass of the two phases, assuming that both are

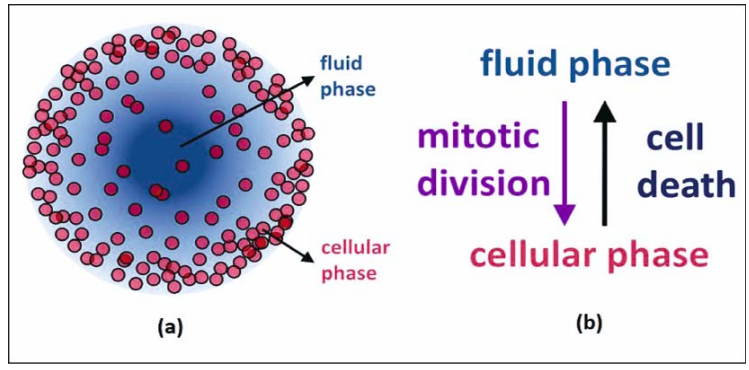

Figure 4. **(a)** Schematic of Breward *et al.* two phase model with fluid and cellular phases. **(b)** Schematic summarising mass transfer between the two phases.

incompressible (mass per unit volume does not change) leads to the following two equations:

$$\frac{\partial \alpha}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 u_c \alpha\right) = q, \tag{5}$$

$$\frac{\partial \beta}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 u_w \beta\right) = -q, \tag{6}$$

where α and β are the volume fractions of the cellular and water phases, respectively. Here, q is the rate of change of the cellular volume fraction, due to cell birth and cell death, and u_c and u_w are the velocities within the cellular and fluid phases, respectively. If there are no voids in the tumour, a reasonable assumption, then it follows that $\alpha + \beta = 1$. Assuming inertial effects are negligible, a balance of momentum gives:

$$0 = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \alpha \sigma_c\right) + F_c, \tag{7}$$

$$0 = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \beta \sigma_w\right) + F_w, \tag{8}$$

where σ_c and σ_w are the stress tensors in the cellular and fluid phases, respectively, and F_c and F_w are the source terms of momentum in each phase. It is common to take $F_w = -F_c$. The cellular phase is assumed to be a viscous fluid and the extracellular fluid an inviscid fluid (e.g. no viscous effects) so that:

$$\sigma_c = -p_c + 2\mu_c \frac{\partial u_c}{\partial r}, \tag{9}$$

$$\sigma_w = -p_w, \tag{10}$$

where p_c and p_w are the pressures in the cellular and fluid phases, respectively. Pressure in the cellular phase is taken to be the pressure in the water phase plus a term due to cell-cell interactions: $p_c = p_w + \Sigma_c$, where Σ_c depends on the volume fraction α. The momentum source term in the cellular phase is taken to be:

$$F_c = p_w \frac{\partial \alpha}{\partial r} + k_1 \alpha \beta (u_w - u_c), \tag{11}$$

with contributing terms due to interfacial pressures and a Darcy-like drag.

The oxygen concentration is governed by the conservation equation:

$$0 = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial C}{\partial r} \right) - Q_c, \tag{12}$$

where C is the oxygen concentration, and Q_c is the oxygen consumption rate. Note that a quasi-steady state has been assumed for the oxygen concentration (left-hand side of (12) is 0). The radius of the tumour, $R(t)$, moves according to the velocity of the cellular species on the outer boundary of the tumour:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = u_c|_{r=R}.$$

It is possible with some algebraic manipulation that the above equations can be simplified down to the following set of three coupled non-linear partial differential equations for α (cellular volume fraction), u_c (cellular velocity) and C (oxygen concentration) and an ordinary differential equation for R (tumour radius):

$$\frac{\partial \alpha}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 u_c \alpha) = q, \tag{13}$$

$$\frac{\partial}{\partial r}(\alpha\Sigma_c) + \frac{k_1\alpha u_c}{1-\alpha} = \frac{2\mu_c}{r^2}\frac{\partial}{\partial r}\left(r^2\alpha\frac{\partial u_c}{\partial r}\right) - \frac{4\mu_c}{r^2}\alpha u_c, \tag{14}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial C}{\partial r}\right) = Q_c, \tag{15}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = u_c|_{r=R}, \tag{16}$$

subject to the boundary and initial conditions

$$\frac{\partial C}{\partial r} = 0, \quad u_c = 0, \quad \text{at } r = 0; \tag{17}$$

$$\mu\frac{\partial u_c}{\partial r} = \Sigma_c, \quad C = C_0, \quad \text{at } r = R(t); \tag{18}$$

$$\alpha = \alpha_0, \quad R = R_0, \quad \text{at } t = 0. \tag{19}$$

Note that r is the radial distance to a point in the tumour from the centre of the tumour, where $r \in (0, R(t))$ for each $t > 0$. The above system assumes radially symmetric growth of the tumour.

3. Numerical Results

For ease of implementation, (13)–(16) are transformed onto a fixed spatial domain, $0 \leq \xi \leq 1$, by the change of variables $\xi = r/R(t)$ and $\tau = t$. The cell volume fraction equation (Equation (13)) is hyperbolic and its solution is approximated using a finite difference method with a backward difference approximation for time discretization to move from time τ_n to τ_{n+1} (see (*a*) on the left-hand side of *Figure* 5). The solution to the velocity and oxygen equations (Equations (14) and (15)) are approximated using the finite element method. The time domain, $0 \leq \tau \leq T$, is divided into K mesh points which are uniformly spaced by $\Delta\tau$. The spatial domain, $0 \leq \xi \leq 1$, is uniformly divided into N mesh points. Continuous piecewise linear polynomials (see (*b*) on the right-hand side of *Figure* 5) are used to approximate the space variables in the weak formulation for the velocity and oxygen equations.

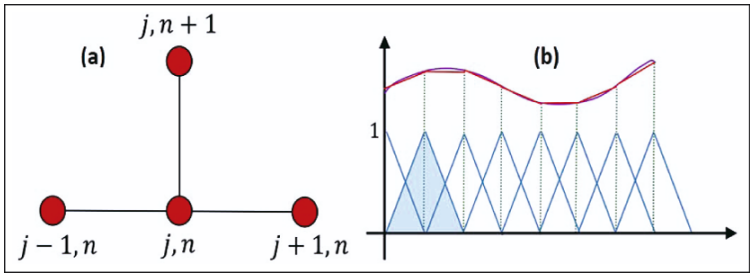

Figure 5. **(a)** Schematic of numerical method discretisation in space (index j) and time (index n). **(b)** Schematic of piecewise polynomials for spatial approximation.

The numerical results in *Figure* 6 show the variation in cell volume fraction (α), cell phase velocity (u_c), and oxygen tension (C) with respect to the radial distance from the centre of the tumour. From *Figure* 6a it is clear that as time evolves (shown in different coloured lines), the volume fraction of cells in the inner region of the tumour becomes close to zero. This region is the central necrotic core. A region of high volume fraction is present in an annular zone near the outer edge of the spheroid. This annulus of living cells is growing outward with respect to time at a velocity given by *Figure* 6b, which shows the cell velocity profiles. The corresponding oxygen tension profiles (*Figure* 6c) indicate that in the necrotic core, the oxygen tension is near to zero and increases to its maximum value at the boundary of the tumour. *Figure* 6d shows the growth of the tumour over time; over the time-scale shown here, the tumour radius grows approximately linearly.

4. Conclusion

In this article, we have reviewed some of the contributions to the literature in the field of mathematical modelling of avascular tumour growth. We discussed in detail two models, the first was an early work where many simplifications were made [4], and the second was a more complicated multiphase model by Breward *et al.* [11]. We have presented example numerical solutions of the Breward *et al.* model whereby finite difference and finite element schemes were used to give approximate solutions of the coupled nonlinear system, for which it is not possible to construct an analytic solution in general. The dynamics of the

Numerically solving the equations in higher dimensions demands a re-discretization of the spatial domain at each time-step, making the procedure computationally expensive.

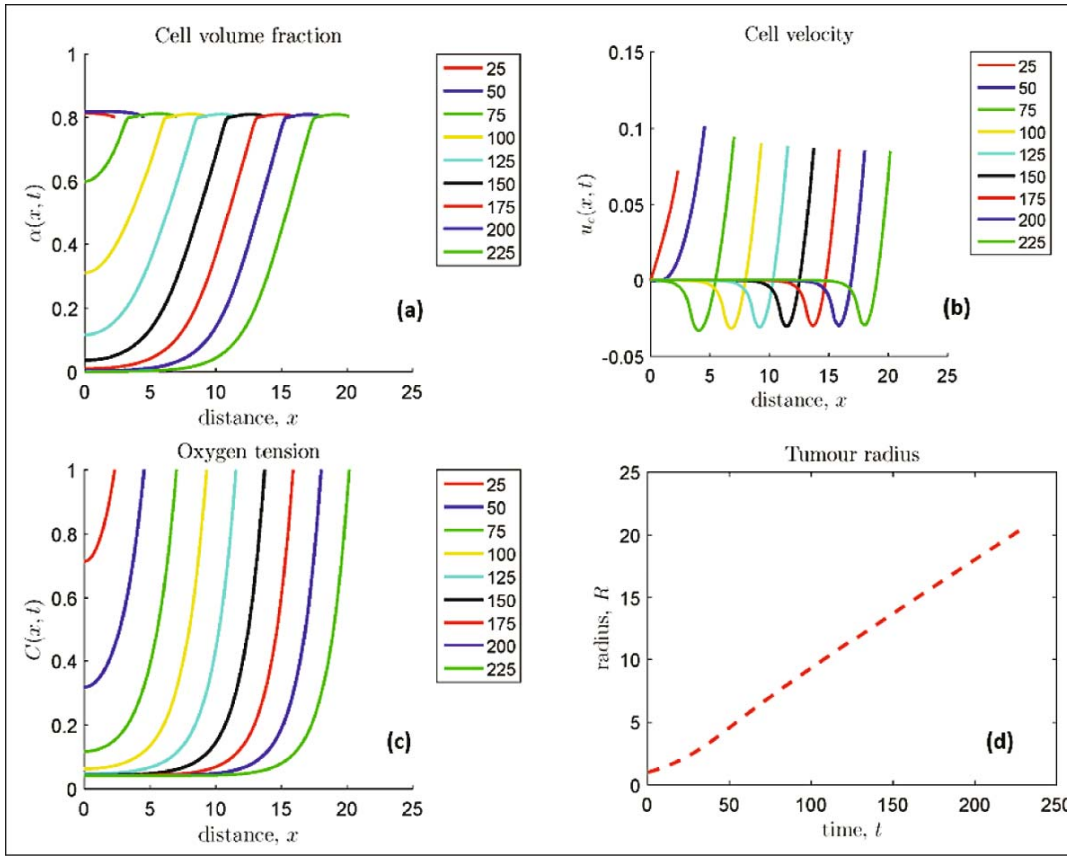

Figure 6. Finite difference-finite element simulation of the Breward *et al.* model (in spherical coordinates) and the variation of tumour radius $R(t)$ with respect to time.

moving boundary were governed by a time-dependent ordinary differential equation, which enhances the difficulty to solve such problems numerically. In one dimension it is possible to rescale the domain onto $[0, 1]$. But this is not possible in higher dimensions for non-standard geometries. Numerically solving the equations in higher dimensions demands a re-discretization of the spatial domain at each time-step, making the procedure computationally expensive. In this situation, we need to devise methods that will serve the purpose of carrying the essential information of the moving boundary without the need to consider the dynamics of the boundary explicitly. This is one of the current research directions in which work is being pursued by the authors.

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Suggested Reading

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