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A model for cell migration in tumour growth

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ABSTRACT

Tumour growth results, in particular, from cell–cell interaction and tumour and healthy cell proliferation. The complexity of the cellular microenvironment may then be framed within the theory of mixtures by looking at cell populations as the constituents of a mixture. In this paper the balance equations are reviewed to account for directionality onto a collective migration of the tumour cell population, via an attractive force of the chemotactic type, in addition to the customary pressure term. The density of tumour cells turns out to be governed by a hyperbolic differential equation. By neglecting, as usual, the inertia term it follows that the density satisfies a backward, or forward, diffusion equation according as the attraction, or pressure effect, prevails. Uniqueness of the solution to the backward equation is investigated and a family of solutions is described. An estimate is given for the growth rate of a tumour profile.

1. Introduction

A tumour consists of the abnormal growth of a group of cells whose behaviour is markedly different from that of the other cells of the tissue. Solid tumors tend to destroy the surrounding extracellular matrix (ECM), to invade it while replacing healthy cells, and to spread to other tissues by the process of metastasis. Hence the dynamics of tumour growth depends on cell–cell and cell–ECM interactions, tumour and healthy cell proliferation, availability of oxygen and nutrients, and so on [11].

A wide literature has been devoted to the formulation of deterministic mathematical models of tumour growth (see, e.g., [8,18]). Some simplified approaches consist of reaction-diffusion partial differential equations (PDE) describing the evolution of tumour cell density, enzyme concentration and/or nutrient density [21]. Further simplifications are obtained by considering spatially homogeneous cancer tissues, leading to systems of ordinary differential equations for the unknown time-dependent concentrations of the main constituents of a tumour [12]. More realistic approaches to tumour growth involve the space properties of the cell populations and, in this sense, continuum mechanics offers the natural framework for appropriate models. To capture the complexity of the cellular microenvironment, often models have been framed within the theory of mixtures [5] by looking at cell populations as the constituents of a mixture, the cell proliferation and death being modelled by the mass growth associated with chemically-reacting constituents. The papers [1,6,2,3,13] and refs therein provide a wide view of the literature on the subject.

The main advantage of framing models of cell populations within the theory of mixtures is that the theory embodies the basic laws of physics, specifically, the balance equations for mass and linear momentum. This general framework is supplemented with specific assumptions regarding, e.g., the structure of the force fields acting on cells [15], which should mainly come from experimental observations. Furthermore, the mass growths, rather then the increase of cell numbers, account for proliferation and death of the corresponding populations.

One major aim of the present contribution is to introduce model forces accounting for a class of directional collective migration of tumour cells during tissue invasion and metastasis [10,19,17] and to discuss the inherent qualitative effects.

Indeed, it is known that cancer cells of some tumour types can migrate individually or collectively during tumor growth. In collective movement the cells involved can affect each other through adhesion, force-dependent and signalling interactions. In particular directed cell migration is highly influenced by cellular sensing of local gradients in the concentration of chemical factors. This mode of cellular guidance is named chemotaxis and various external factors, both chemorepellents and chemoattractants, are considered to model directionality onto migratory cell populations [17,22]. Of course, chemical gradients do not act directly as external forces on cells; rather, cells move within the tissue under the action of internal forces which may arise, e.g., as a reaction to chemical gradients,

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interactions with the ECM, adhesion to other cells. From the macroscopic point of view we model this behavior of the cells in collective migration as determined by a force term proportional to the gradient of the density (equivalently, volume fraction) of cells. A natural interpretation is that the directions of growing tumour cell density correspond to greater numbers of cell contacts and communication signals, which are ultimately responsible for the aggregative behaviors.

The purpose of this paper is to set up a general scheme for collective motion of migrating cancer cells, within the framework of the mixture theory, under the assumption that the driving force is proportional to the gradient of the density (or volume fraction) of tumour cells. Additional force terms are also considered, such as a friction-type force describing interactions with the ECM matrix. The mixture is formed by a solid ECM, an extracellular liquid phase, and the two cell populations of tumour and healthy cells. Attention is then addressed to the determination of a PDE for the tumour cell density.

Various assumptions are examined, which lead to qualitatively different model equations for the tumour cell density: an hyperbolic equation, a parabolic equation and a parabolic equation for backward diffusion. The parabolic equation for backward diffusion occurs when the intensity of the attractive force is larger than the pressure term. The occurrence of a parabolic backward equation is the main novelty from the viewpoint of mathematics. Uniqueness of the solution is shown to hold in one space dimension and an integral expression for a class of solutions is established. By an elementary argument, an estimate is given for the growth rate of a tumour profile.

2. Balance equations

We consider a solid phase, the extracellular matrix (ECM), and a liquid phase, the extracellular fluid. Two cell populations are regarded to live in the fluid, the tumour and the healthy cells. We denote by the subscripts T, H, F, and E the quantities pertaining to tumour cells, healthy cells, fluid, and ECM. The fluid contains also chemical nutrients which are involved in the proliferation process and the chemotaxis effects. Dead cells are taken to disintegrate into waste products and re-usable materials within the extracellular fluid.

We regard ECM as a fixed substratum and let the healthy cells adhere to the substratum. Hence we say that the velocities $\mathbf{v}_T$, $\mathbf{v}_F$ are unknowns whereas $\mathbf{v}_H$ and $\mathbf{v}_E$ are assumed to be zero [15]. The constituents are regarded as incompressible with the same true mass density ρ. Hence it is convenient to use the volume fractions ϕ_T, ϕ_H, ϕ_F, ϕ_E so that the effective mass densities are

$$\rho_T = \rho\phi_T, \quad \rho_H = \rho\phi_H, \quad \rho_F = \rho\phi_F, \quad \rho_E = \rho\phi_E.$$

It is understood that

$$\phi_T + \phi_H + \phi_F = f < 1$$

f being the porosity of the ECM.

The balances of mass for the T, H, and F populations are given by the continuity equations

$$\partial_t\phi_T + \nabla\cdot(\phi_T\mathbf{v}_T) = h, \tag{1}$$

$$\partial_t\phi_H = -g, \tag{2}$$

$$\partial_t\phi_F + \nabla\cdot(\phi_F\mathbf{v}_F) = -h + g, \tag{3}$$

where h and g are functions of ϕ_T, ϕ_H, and the volume fraction ϕ_N of the nutrients. For the sake of simplicity we regard the nutrients as a part of the fluid and do not consider them as a constituent with proper balance equations. The mass density of the ECM is assumed to be constant because $\mathbf{v}_E = 0$ and the ECM does not participate into proliferation or death processes. In so doing we neglect that the ECM is degraded by the action of tumour cells. Possible expressions for the growths h and $-g$ of the cells populations are given in detail e.g. in [12,20]. The growth h models the production of tumour cells as a consequence of the interaction with the fluid (water, nutrient, and other growth factors) and the decrease because, e.g., of the natural killers. The minus in front of g is a reminder that ϕ_H is expected to decrease in favour of ϕ_F. The growth in the fluid merely accounts for the overall balance of mass in the mixture.

To account for directionality onto the migratory tumour cell population we allow for two terms in the balance equation of momentum, namely a pressure (gradient) which provides repulsion and a density gradient which provides attraction. We then write the equations of motion for the constituents as

$$\begin{aligned}\rho\partial_t(\phi_T\mathbf{v}_T) + \rho\nabla\cdot(\phi_T\mathbf{v}_T\otimes\mathbf{v}_T) = -\nabla p_T + \alpha\nabla\phi_T \\ -\beta\phi_T\mathbf{v}_T + \gamma(\mathbf{v}_F - \mathbf{v}_T),\end{aligned} \tag{4}$$

$$\rho\partial_t(\phi_F\mathbf{v}_F) + \rho\nabla\cdot(\phi_F\mathbf{v}_F\otimes\mathbf{v}_F) = -\nabla p_F + \gamma(\mathbf{v}_T - \mathbf{v}_F), \tag{5}$$

$$\mathbf{v}_H = \mathbf{v}_E = 0,$$

where α, β, and γ are positive constants. The structure of Eqs. (4) and (5) is consistent with the theory of mixture. Specifically, we assume that the stress tensor for the tumour cells and the fluid is merely a pressure tensor while $\alpha\nabla\phi_T$, where $\alpha > 0$, is the (attractive) body force on the tumour cells. The pressures p_T and p_F are functions of ϕ_T and ϕ_F, respectively. Moreover,

$$-\beta\phi_T\mathbf{v}_T = -\beta\phi_T(\mathbf{v}_T - \mathbf{v}_E)$$

is the friction force between tumour cells and ECM. Likewise, $\gamma(\mathbf{v}_F - \mathbf{v}_T)$ and $\gamma(\mathbf{v}_T - \mathbf{v}_F)$ are the interaction forces between tumour cells and fluid.

The term $\alpha\nabla\phi_T$ in the equation of motion for tumour cells is unusual in the literature though it is not fully new. In [14,7] the pressure, on the tumour cells, is taken to be proportional to ϕ_T,

$$p_T = \phi_T P,$$

P being viewed, to our mind, as the pressure of the mixture. Next the interaction force is taken as

$$\mathbf{m}_T = P\nabla\phi_T + \ldots.$$

the dots indicating contributions arising from the relative velocities. Hence the contribution to the equation of motion is

$$-\nabla p_T + \mathbf{m}_T = -\phi_T\nabla P + \ldots$$

It is apparent that the term $P\nabla\phi_T$ in $\mathbf{m}_T$ has been so chosen that the resulting force in the equation of motion is $-\phi_T$ times the gradient of the pressure P and thus provides diffusion. To our mind, diffusion is just naturally related to the pressure p_T of the tumour phase; moreover, an attractive term $\nabla\phi_T$ in $\mathbf{m}_T$ need not have just P as a factor and so a generic term $\alpha\nabla\phi_T$ seems more appropriate in that it models the attraction between tumour cells driving the collective migrative motion.

Mathematically, the contribution $\alpha\nabla\phi_T$ has the same structure as chemotactic effects, but ϕ_T refers to cells, not to chemical factors; moreover, ϕ_T is constrained by the mass balance equation (1) rather then a reaction-diffusion equation.

Quite often the interaction force $\mathbf{m}_T$ is relatively small and then the effective, driving force is the resultant of the pressure term $-\nabla p_T$ and the attractive force $\alpha\nabla\phi_T$. This aspect becomes apparent in the next developments.