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Mathematical modelling of the Warburg effect in tumour cords

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ABSTRACT

The model proposed here links together two approaches to describe tumours: a continuous medium to describe the movement and the mechanical properties of the tissue, and a population dynamics approach to represent internal genetic inhomogeneity and instability of the tumour. In this way one can build models which cover several stages of tumour progression. In this paper we focus on describing transition from aerobic to purely glycolytic metabolism (the Warburg effect) in tumour cords. From the mathematical point of view this model leads to a free boundary problem where domains in contact are characterized by different sets of equations. Accurate stitching of the solution was possible with a modified ghost fluid method. Growth and death of the cells and uptake of the nutrients are related through ATP production and energy costs of the cellular processes. In the framework of the bi-population model this allowed to keep the number of model parameters relatively small.

Metabolic processes in normal tissues require oxygen. Specifically, six molecules of oxygen are consumed per oxidated molecule of glucose with the yield of approximately 32 molecules of ATP (Nelson and Cox, 2000) (36 according to Smallbone et al., 2007, 29.85 according to Rich, 2003). In many cancers intensive proliferation exceeds available oxygen supply, which leads to hypoxia. In such hypoxic conditions cells may rely only on glycolysis, the first step of glucose oxidation, to cover their energy needs. This process gives a smaller amount of ATP, two molecules of ATP per molecule of glucose, but it is possible in hypoxic conditions. In fact, most tumours are known to rely on glycolytic metabolism even in non-hypoxic conditions. This effect is known as Warburg effect or aerobic glycolysis (Warburg, 1956; Kim and Dang, 2006) and is one of the hallmarks of cancer (Hannahan and Weinberg, 2000). Glycolytic catabolism has the important side effect of tissue acidification. Lower pH is toxic to most normal cells while altered tumour cells are likely to be resistant to it and achieve another invasion advantage (Gatenby et al., 2006). In the same time, there are several therapeutic strategies which allow for targeting tumours with glycolytic metabolism (Kim and Dang, 2006; Mathupala et al., 2007).

We want to describe phenomenologically the transition of tumours from normal to glycolytic metabolism in the framework of spatio-temporal model of tumour growth. Well aware that there are several mechanisms which contribute to the Warburg effect, we assumed that this switch in metabolism happens as an all or nothing event, after which cells rely only on glycolytic metabolism even with adequate oxygen levels. The switch is assumed to happen in hypoxic conditions.

This problem received a lot of attention from the mathematical modelling community in the recent years. Such works as Gatenby et al. (2006, 2007) and Smallbone et al. (2008) have pointed to the possibility of the acid-mediated tumour invasion and studied the role of the cellular adaptivity in tumour invasion. Their discrete and continuous models and experiments demonstrate that emergence of the acid-resistant, glycolytic cell line is an important step towards cancer invasiveness. Another recent work is Gerlee and Anderson (2008), where the cellular automaton model demonstrates that an advantage of the glycolytic phenotype may also be conditioned by the density of the matrix. In Venkatasubramanian et al. (2006) ability of the cells to rely on the glycolytic metabolism was incorporated in the continuous model of tumour spheroid. In Bertuzzi et al. (2007) the rigorous analytical study of a similar model was undertaken, with a proof that the necrotic core is formed for any sufficiently large spheroid. Both in Venkatasubramanian et al. (2006) and in Bertuzzi et al. (2007) the switch to glycolytic metabolism is assumed to be reversible, and the cells return to normal aerobic metabolism when the hypoxia finishes. However, the shift towards glycolytic metabolism is often irreversible in tumours, and they may remain glycolytic even in the presence of sufficient oxygen (Kim and Dang, 2006). In this case we have to consider at least two distinct cell lines with different (probably very different) metabolic behaviour, because after the switch the cells are not the same any more.

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Having to construct a multi-population model certainly complicates the numerical method, but it also brings some advantages of the discrete models in the reign of the continuous models. In fact, possible applications of the proposed numerical approach go far beyond tumour metabolism, and it may be used to describe other genetic transformations in the course of tumour evolution.

We also tried to build the model around the idea used in Astanin and Tosin (2007), that the growth in the tissue strictly depends on the amount of the nutrients consumed (or more precisely, the quantity of ATP produced). To put it simply, growth and intensity of the metabolic processes are two sides of the same medal in this model. Insufficient ATP production, in turn, limits growth and leads to necrosis.

Another aim of the paper is to understand whether the metabolic switch gives rise to a spatial stratification in the bi-population model. In fact, near the vessels oxygen is more abundant and cells have no reason to change metabolism there. This might lead to the conclusion that tumour cords are constituted by an inner core near the vessel with cells using an aerobic metabolism, and an outer layer of cells using glycolysis.

Counter intuitively, in the simulations we observed that the cell line with glycolytic metabolism "wins", and spreads in the entire cord, though in a non-homogeneous way. The intensity of metabolism affects the cord geometry and the moment when tumour starts suffering from hypoxia. This is due to the fact that cells which rely on anaerobic glycolysis move also to the inner layer, spreading in the whole tumour. They may achieve a significant mass even if acquisition of this trait is a very rare event.

This paper has the following structure. In Section 1 we define the equations of the mathematical model, paying a particular attention to the coupling of the multiphase model with the subcellular catabolic mechanisms generating the growth, death, and switch terms in the mass balance equations. Section 2 contains some two-dimensional simulation results and their discussion. Appendices present then a non-dimensional model (Appendix A) and describe a modification to the ghost fluid method which allows to stitch solutions between two different modelling domains (Appendix B).

1. Bi-population model

In this paper we develop the approach of earlier works (Ambrosi and Preziosi, 2002; Astanin and Tosin, 2007; Preziosi and Tosin, 2008; Astanin and Preziosi, 2008) but, in addition to describing tissue growth and mechanics, we consider the transition of tumour cells from one metabolic behaviour to another, and incorporate effects of glycolytic switch in tumour cells. We carefully consider the implications of altered glucose metabolism on the energy balance in tumour cells and examine in detail the spatial effects.

In the previous works we assumed that tumour grows in a host environment. The model deals with only two cell populations, tumour cells with volume ratio ϕ_t and host cells with volume ratio ϕ_h initially occupying different domains $\Omega_t(t=0)$ and $\Omega\backslash\Omega_t(t=0)$.

Two other components of the tissue are considered in addition to cells: extracellular liquid (with volume ratio ϕ_l) and extracellular matrix (ECM, with volume ratio ϕ_m). ECM is rigid, uniform and does not remodel:

$$\phi_i + \phi_l = 1 - \phi_m = \phi_* \equiv \text{const}, \quad i := t, h. \tag{1}$$

An immediate consequence of this hypothesis is that from the macroscopic point of view the tissue would behave like a rigid porous medium, with cells and extracellular liquid moving inside a rigid scaffold. Any stress acting on the bulk tissue would be sustained by the ECM and cells in the core of the tissue would experience no stress deriving directly from the external actions. It is possible to relax this hypothesis following for instance Ambrosi and Preziosi (2009).

The interface $\partial\Omega_{th}$ between tumour and environment is a material surface moving with the common velocity of the cells

$$\vec{n}\cdot\frac{d\vec{x}_t}{dt} = \vec{n}\cdot\vec{v}_t = \vec{n}\cdot\vec{v}_h \quad \text{on } \partial\Omega_{th}(t), \tag{2}$$

which implies that if the two populations occupy initially different interfacing domains, they will always occupy different interfacing time-dependent domains. However, the two populations mechanically and chemically interact with each other. In the sense that, for instance, the growing tumour will mechanically compress the host tissue and will compete for resources. In particular, it will induce hypoxia and subsequent death of the surrounding host tissue. Then at the interface in addition to imposing continuity of velocity and stress (see (7) and (8)), continuity of oxygen and glucose concentrations and fluxes holds. Treating for the sake of simplicity the ensemble of cells as elastic fluids, neglecting liquid–cell interactions, we have the following free boundary problem, see Ambrosi and Preziosi (2002) for details:

$$\frac{\partial\phi_t}{\partial t} + \nabla\cdot(\phi_t\vec{v}_t) = \Gamma_t \quad \text{in } \Omega_t, \tag{3}$$

$$\vec{v}_t = -K\nabla(\phi_t \mathrm{S}(\phi_t)) \quad \text{in } \Omega_t, \tag{4}$$

$$\frac{\partial\phi_h}{\partial t} + \nabla\cdot(\phi_h\vec{v}_h) = \Gamma_h \quad \text{in } \Omega\backslash\Omega_t, \tag{5}$$

$$\vec{v}_h = -K\nabla(\phi_h \mathrm{S}(\phi_h)) \quad \text{in } \Omega\backslash\Omega_t, \tag{6}$$

$$\vec{v}_t\cdot\vec{n} = \vec{v}_h\cdot\vec{n} \quad \text{on } \partial\Omega_{th}, \tag{7}$$

$$\phi_t \mathrm{S}(\phi_t) = \phi_h \mathrm{S}(\phi_h) \quad \text{on } \partial\Omega_{th}, \tag{8}$$

where K is the "motility" of the cells or rate of tissue relaxation, K is inversely proportional to the drag force coefficient between cells and rigid ECM, $\mathrm{S}(\phi_i)$ is a scalar function which describes elastic forces of the compressed tissue ($\phi_i > \phi_0, \phi_0 = \text{const}$), and intercellular adhesion forces in the stretched tissue ($\phi_i < \phi_0$), Γ_t and Γ_h are growth/death rates for tumour and host cells, respectively.

In Astanin and Tosin (2007) we paid special attention to the energy balance in cells, supposing that the amount of oxygen and glucose consumed stays in direct correspondence with the intensity of tumour proliferation. We have shown that tumour growth in this model is limited by the formation of the hypoxic zone and by the availability of oxygen.

In this work we build the model upon the same idea. We assume that if ATP production is insufficient the cells stagnate and die (like in the old model), but also with a certain (small) probability may irreversibly switch their metabolic behaviour and survive. This switch corresponds to upregulation of the glycolysis, and is not present in Astanin and Tosin (2007). The growth also becomes limited by the availability of glucose as well as oxygen (glucose was assumed to be abundant in the old model).

So we introduce the second population of tumour cells which are mechanically identical to the others, but consume only glucose through glycolysis. We refer to this subpopulation as *anaerobic* or glycolytic subpopulation, while the initial oxygen-consuming subpopulation is referred to as *aerobic* one. Transition from the aerobic to the anaerobic population is supposed to be irreversible. We also assume that cells of the host always rely on aerobic glucose oxidation.

Let ϕ_1 be the volume fraction of cells with normal aerobic catabolism, and ϕ_2 be the volume fraction of cells with altered, anaerobic, catabolism. On the right-hand side of the mass balance