Modelling the Response of Tumour Cords to Anticancer Agents

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Abstract

Blood vessels in vascularized tumours are in general irregular and often poorly effective. However more ordered structures have been observed, where tumour cells that proliferate around blood vessels form approximately cylindrical aggregates called *tumour cords* [1]. Tumour cords generally differ from each other in size and orientation, and may or may not be surrounded by a necrotic region caused by oxygen and nutrients deprivation.

We review here some results of our studies on modelling tumour cords and their response to anticancer agents [2]-[8]. To develop these models, we have taken the idealized view of parallel, identical and regularly spaced blood vessels, as in the Krogh model of microcirculation. The basic model, in cylindrical symmetry, can be briefly described as follows.

Let r be the radial distance from the axis of the central vessel, r_0 the vessel radius, ρ_N the cord radius (let us suppose that the cord be surrounded by necrosis). Changes along the axial coordinate are disregarded. The oxygen is considered the only critical nutrient, and we assume that all cells die when its concentration falls to the threshold value σ_N. We denote by ν_P, ν_Q, ν_N the volume fractions of proliferating (P), quiescent (Q), and dead cells respectively. $u(r,t)$ denotes the (radially directed) velocity of the cellular component, and $\sigma(r,t)$ the oxygen concentration. We will assume $\nu_P + \nu_Q + \nu_N = \nu^\star$, $\nu^\star$ constant. From the mass balance, we can write

$$\frac{\partial \nu_P}{\partial t} + \nabla \cdot (\nu_P\, u) = \chi \nu_P + \gamma \nu_Q - \lambda \nu_P - m_P \nu_P\,, \tag{1}$$

$$\frac{\partial \nu_Q}{\partial t} + \nabla \cdot (\nu_Q\, u) = -\gamma \nu_Q + \lambda \nu_P - m_Q \nu_Q\,, \tag{2}$$

$$\frac{\partial \nu_N}{\partial t} + \nabla \cdot (\nu_N\, u) = m_P \nu_P + m_Q \nu_Q - \mu_N \nu_N\,. \tag{3}$$

In Eqs. (1)-(3) χ is the proliferation rate, and $\gamma(\sigma)$ and $\lambda(\sigma)$ are, respectively, the rates of the transitions $Q \to P$ and $P \to Q$. We suppose that γ and λ are nondecreasing and, respectively, nonincreasing functions of σ. $m_P(r,t)$ and $m_Q(r,t)$ are the rates representing the action of a therapeutic agent, μ_N is the degradation rate of dead cells into liquid. Since $\nu^\star$ is assumed constant, we obtain for the cell velocity the equation:

$$\nu^\star \nabla \cdot u = \chi \nu_P - \mu_N(\nu^\star - \nu_P - \nu_Q) \qquad u(r_0,t) = 0. \tag{4}$$

The equation for σ is written assuming quasi-steady diffusion

$$\Delta\sigma = f(\sigma)(\nu_P + \nu_Q)\,, \tag{5}$$

with the boundary condition $\sigma(r_0,t) = \sigma_b$. $f(\sigma)$ denotes the ratio between the consumption rate per unit volume of live cells and the diffusion coefficient, and σ_b is the oxygen blood concentration. At the interface $r = \rho_N$, we have two possible regimens:

$$u(\rho_N(t),t) > \dot\rho_N(t)\,, \qquad \sigma(\rho_N(t),t) = \sigma_N\,, \tag{6}$$

$$u(\rho_N(t),t) = \dot\rho_N(t)\,, \qquad \sigma(\rho_N(t),t) \geq \sigma_N\,. \tag{7}$$

In both cases, we impose $\sigma_r(\rho_N(t),t) = 0$ according to the quasi-steady diffusion assumption. Thus the motion of the interface takes place under two unilateral constraints. In the absence of treatment, the system admits a unique stationary state.

The model has been applied to study the response of cords to various types of treatment. In [6] the action of a cytotoxic drug has been considered. The function m_P and m_Q were simply assigned as function of t mimicking the action of a bolus administration. Numerical simulations of the model were able to predict the cellular response, and showed the occurrence of an increased oxygenation after a single dose of drug with a possible recruitment of quiescent cells into proliferation. If the drug is cycle-specific (i.e. $m_P > m_Q$), this recruitment may traslate in a (transient) increase of the overall drug sensitivity of the cell population. This suggests that if the dose is divided into two half doses administered with a suitable time interval (dose splitting), the cell killing can be more effective than in the response to the single undivided dose. To represent the effect of radiation, the model was extended [8] to take into account the repair/misrepair process of the DNA double strand breaks, according to the kinetic model proposed by Hlatky et al.(1994). In the split-dose response, it was found that the reoxygenation caused by the cell death induced by the first fraction may reduce the sparing effect of dose fractionation. The maximal reduction is achieved when the second dose is delivered at the time of maximal reoxygenation (the radiosensitivity of cells increases indeed as the oxygen concentration increases). The prediction of the reoxygenation time course might thus be useful in determining the optimal time of dose delivery.

The motion of extracellular fluids was incorporated in a more complete version of the model [4, 5]. This motion may be important in the transport of blood-born therapeutic agents of very high molecular weight. The Darcy law for the fluid flow was assumed,

and approximated equations for the longitudinal averages of the radial fluid velocity and the pressure were derived. The model also provides a description of the dynamics of the necrotic region, evidencing the different regimens implied by a solid- or liquid-like character of the necrotic mass. The mathematical description of the fluid motion was used to study the diffusive and convective transport of antibodies in tumour cords [7]. In this investigation, the bivalent binding of antibody to cell surface antigens was taken into account, whereas the possible cytotoxic effect of the binding was not considered. The model enlighted the role of parameters such as the hydraulic pressure in the vessels, the vessel permeability, the hydraulic conductivities in the cord and the surrounding tissues, the antibody binding affinity and the number of surface antigen molecules.

Keywords: tumour growth, anticancer therapies, PDE models, free boundary problems.

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