The Dynamics of Tumour Cords Following the Delivery of a Cell Killing Agent

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Abstract: The tumour cord response to a cell killing agent is described by a mathematical model that represents the cord as a continuum with cylindrical symmetry, and accounts for cell motion by a purely kinematic approach. The model includes oxygen diffusion from the central vessel, the dependence of cell proliferation on oxygen concentration, the drug diffusion and the degradation of dead cells. An example of model simulation is presented.

Key-Words: Tumour growth; Cancer treatment; PDE models; Free boundary problems

1 Introduction

Although the microarchitecture of the tissue in solid tumours is quite irregular, tumour cells arranged in cylindrical structures around central blood vessels are observed in some human and experimental tumours. These structures are named tumour cords [1]. Oxygen and nutrient deprivation in cells remote from vessels lead to cell death, so that tumour cords are generally surrounded by necrosis. The response of tumour cords to a single dose of radiation or drug has been experimentally investigated in [2,3]. Mathematical models describing the cell population in the cord at the stationary state and the cord growth within a normal tissue have been recently proposed [4,5,6]. In Bertuzzi et al. [7,8], a model that describes the cord response to radiation or drugs was proposed: here we summarize this model, showing a simulation of a typical response.

2 Model assumptions

Let us consider a tumour cord inside a regular array of parallel and identical cords. The main assumptions of the model are summarized as follows: (i) Cylindrical symmetry is assumed. We denote by r_0 the radius of the central vessel, and by r the radial distance from the axis. Let B be the radius of the cylindrical boundary where there is no exchange of matter. (ii) All variables that describe the cell population state, the cell velocity field and the concentrations of chemicals are independent of the axial coordinate. (iii) Cell velocity is radially directed. (iv) Oxygen is the only species of "nutrient" considered, $\sigma(r,t)$ denoting its local concentration. (v) Cells die if σ falls to a threshold σ_N. In addition, random cell death, either spontaneous and induced by treatments, may occur within the cord. The rate of spontaneous cell death, $\mu(\sigma)$, is a nonincreasing function of σ. (vi) The rate of cell proliferation, $\chi(\sigma)$, is a nondecreasing function of σ. We take $\chi=\chi_0$ for $\sigma\geq\sigma_P$, and $\chi=0$ for $\sigma\leq\sigma_Q$, $\sigma_Q\in(\sigma_N,\sigma_P)$. Below σ_P, the progression rate through cell cycle slows down and/or the fraction of quiescent cells increases. Below σ_Q, all cells become quiescent and, if σ increases over σ_Q, resume instantaneously the proliferative status. (vii) Dead cells are degraded to a fluid waste at a rate μ_N within the cord, and at a rate $\tilde{\mu}_N$ in the necrotic region.

Within the cord we have thus viable cells, dead cells and extracellular fluids, for which we assume equal mass densities. Under the continuum hypothesis, we consider the volume fractions occupied locally by these components, denoted by ν_V, ν_N and, respectively, ν_E ($\nu_V+\nu_N+\nu_E=1$). Two regions can be defined: the cord, where $\nu_V>0$, and the surrounding necrotic zone

(N) where $\nu_V = 0$. In N, only dead cells and extracellular fluids are present. We denote by $\rho_N(t)$ the cord radius.

To represent cell motion in a purely kinematic framework, we make the further simplifying assumptions: (viii) The velocity of the cellular component is the same for both living and dead cells, and is given by the scalar field $u(r,t)$. (ix) The volume fraction ν_E of extracellular fluids is constant.

3 Model equations

Let us define:

$$\nu(r,t) = \nu_V(r,t)/(1-\nu_E)\,. \tag{1}$$

From the mass balance for the viable cells, we can write for ν the following equation for $r_0 < r < \rho_N(t)$:

$$\frac{\partial \nu}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(ru\nu) = \left[\chi(\sigma) - \mu(\sigma) - \mu_R(t,\sigma) - \mu_C(c,\sigma)\right]\nu \tag{2}$$

where μ is the rate of spontaneous cell death, μ_R is the death rate due to radiation, and μ_C is the death rate due to the cytotoxic drug, $c(r,t)$ denoting the drug concentration. By writing the mass balance of the sum of the viable and dead cells, and taking into account assumption (ix), it is easy to obtain

$$\operatorname{div} u = \frac{1}{r}\frac{\partial}{\partial r}(ru)$$

$$= \begin{cases} \chi(\sigma)\nu - \mu_N(1-\nu) & r_0 < r < \rho_N(t) \\ -\tilde{\mu}_N \quad \text{in N.} \end{cases} \tag{3}$$

From Eq. (3) with $u(r_0,t) = 0$, the velocity field is obtained as

$$ru = \begin{cases} \int_{r_0}^{r} z\left[(\chi(\sigma)+\mu_N)\nu - \mu_N\right] dz & r_0 < r \le \rho_N(t) \\ \rho_N u(\rho_N,t) - (\tilde{\mu}_N/2)(r^2 - \rho_N^2) & r > \rho_N(t). \end{cases} \tag{4}$$

Diffusion is the dominant transport mechanism for oxygen and it can be considered quasi-stationary. Thus we have:

$$\Delta\sigma = f(\sigma)\nu\,, \tag{5}$$

with the boundary conditions

$$\sigma(r_0,t) = \sigma^\star\,, \qquad \left.\frac{\partial\sigma}{\partial r}\right|_{r=\rho_N(t)} = 0\,, \tag{6}$$

where $f(\sigma)$ is the ratio between the consumption rate (times $1-\nu_E$) and the oxygen diffusion coefficient. If $u(\rho_N,t) - \dot{\rho}_N > 0$, that is, if the cells enter the necrotic zone, the cord boundary $r = \rho_N$ is defined by the condition

$$\sigma(\rho_N(t),t) = \sigma_N\,, \tag{7}$$

and the interface is a *non-material* free boundary. Otherwise, the cord boundary becomes a *material* interface defined by

$$\dot{\rho}_N = u(\rho_N(t),t)\,, \tag{8}$$

and the following inequality has to be satisfied

$$\sigma(\rho_N(t),t) \ge \sigma_N\,. \tag{9}$$

The existence and uniqueness of a stationary solution of the above model in the absence of treatment has been proved [7], under the condition $\chi_0 > \min\mu$. In this state, the radius ρ_N of the cord is constant, and a radius B_0 exists where $u = 0$, representing the outermost boundary of the system formed by the cord and the surrounding necrosis. During the treatment, the equation

$$\dot{B} = u(B(t),t)\,, \quad B(0) = B_0\,, \tag{10}$$

that describes the motion of the external boundary of the system, has to be considered.

Also for the drug transport, diffusion is assumed to be the dominant transport mechanism. Moreover, we do not distinguish the extracellular from the intracellular drug concentration. Thus we can write for the drug concentration c the following equation:

$$\frac{\partial c}{\partial t} - D_C\Delta c = -\varphi_C(c,\sigma)\nu\,, \tag{11}$$

with

$$c(r_0,t) = c^\star(t)\,, \tag{12}$$

$$\left.\frac{\partial c}{\partial r}\right|_{r=B(t)} = 0\,, \tag{13}$$

$$c(r,0) = 0\,, \tag{14}$$

where: D_C is the diffusion coefficient of the drug, $\varphi_C(c,\sigma)$ represents the net rate of drug consumption by the tumour cells, and the function $c^\star(t)$ in (12) represents the pharmacokinetics of the drug in the tumour vasculature. We note that the dependence of φ_C on σ may indirectly account for the different drug consumption by cycling and quiescent cells.

The existence and uniqueness of the solution of Eqs. (2), (3), (5), (10) and (11) with the

corresponding boundary conditions and the stationary state as initial condition, that gives the evolution of the cord after the treatment, was also established in [7].

4 Response to treatment: numerical results

The numerical simulation of the response to treatment has been obtained assuming the stationary state as initial condition. The simplest case, that however represents a prototype of cord response and that will be illustrated here, is that of the response to radiation when μ_R is a function $\beta(t)$ of time only. $\beta(t)$ describes the delayed effects that follow the delivery of a single dose of radiation at $t=0$. We assumed for $\beta(t)$ a trapezoidal pattern with duration T and maximal value μ_{Rmax}. The function $f(\sigma)$ was assumed Michaelis-Menten as described in [4].

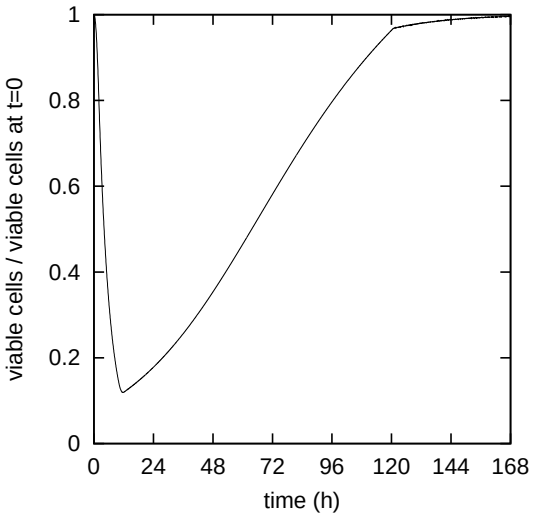

Fig. 1. Evolution of viable cell population. Parameters values: $r_0 = 20$, $\sigma^\star = 35$, $\sigma_P = 20$, $\sigma_Q = 1.125$, $\sigma_N = 1$; $\chi(\sigma)$ increasing as a Michaelis-Menten curve in (σ_Q, σ_P) from zero to $\chi_0 = \ln 2/24$; $\mu(\sigma) = 0$, $\mu_N = 0.02$, $\tilde{\mu}_N = 0.01$; $\mu_{Rmax} = 0.24$, $T = 12$. O_2-concentration in mmHg, length in μm and time in h.

Figure 1 represents the ratio between the total volume (per unit cord length) of viable cells and its value at $t = 0$. As Fig. 2 shows, the cord boundary ρ_N, which is non-material at the stationary state, quickly turns into a material interface and it remains so during all the regression phase, confirming the crucial role of the constraints in the model. Then, it switches

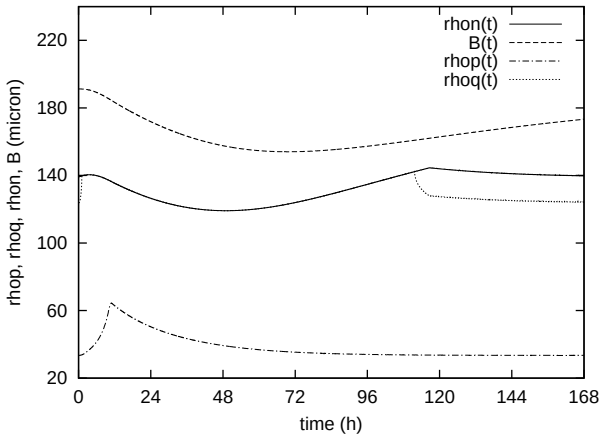

Fig. 2. Cord size response. Parameters values as in Fig. 1.

again to be non-material during the regrowth phase with a slope discontinuity. Figure 2 also shows $B(t)$, and the radii $\rho_P(t)$ and $\rho_Q(t)$ where oxygen tension has the values σ_P and σ_Q respectively. The time course of these latter radii reveals a substantial reoxygenation of the cord after the treatment. This phenomenon is better illustrated by Fig. 3, that shows the oxygen concentration at $r = \rho_N(t)$. Whereas the minimum of viable cell number occurs at $t = T$, the minima of ρ_N and B occur later, this fact being related to the non-instantaneous degradation of dead cells.

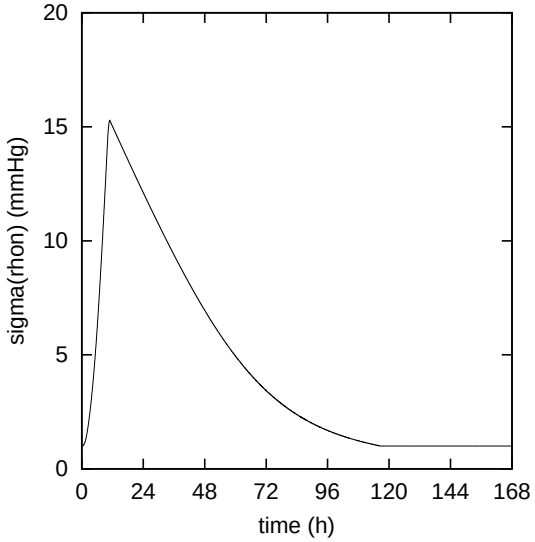

Fig. 3. Oxygen concentration at cord boundary. Parameters values as in Fig. 1.

Simulations of the response with μ_R being also a function of σ, to account for the reduced

radiosensitivity of hypoxic cells, showed a general pattern of the response similar to that of Figs. 1 and 2. In this case, because of the reoxygenation of the cord, the model predicts that the response to a two-fractions treatment is more effective than the response to a single unsplitted dose (provided that the effects of sublethal damages and repair are neglected).

The response shown in Figs. 1–3 is also representative of the general features of the response to drug administered as a single bolus when drug pharmacokinetics is rather fast. Extensive simulations of model response have been reported in [8].

5 Conclusions

The model, despite the numerous simplifying assumptions and idealizations, appears able to capture both the response of the cell population and the evolution of cord size after treatment, *i.e.*, the regression of the cord radius followed by its regrowth. Moreover, the model emphasizes the role of the degradation rate of dead cells on the macroscopic response of the tumour mass. The model is a first step towards a deeper insight of the events that follow treatment administration, and of their relevance in the assessment of the efficacy of treatment schedules.

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