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Technical note

Modelling the radiotherapy effect in the reaction-diffusion equation

Giovanni Borasi [a,*], Alan Nahum [b]

[a] University of Milano Bicocca, Milano, Italy
[b] Physics Dept., Liverpool University, Liverpool, UK

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ABSTRACT

Purpose: In recent years, the reaction-diffusion (Fisher-Kolmogorov) equation has received much attention from the oncology research community due to its ability to describe the infiltrating nature of glioblastoma multiforme and its extraordinary resistance to any type of therapy. However, in a number of previous papers in the literature on applications of this equation, the term (R) expressing the 'External Radiotherapy effect' was incorrectly derived. In this note we derive an analytical expression for this term in the correct form to be included in the reaction-diffusion equation.
Methods: The R term has been derived starting from the Linear-Quadratic theory of cell killing by ionizing radiation. The correct definition of R was adopted and the basic principles of differential calculus applied.
Results: The compatibility of the R term derived here with the reaction-diffusion equation was demonstrated. Referring to a typical glioblastoma tumour, we have compared the results obtained using our expression for the R term with the 'incorrect' expression proposed by other authors.

1. Introduction

In recent years the reaction-diffusion equation [1,2] has received much attention from the scientific community; in particular, this equation has been used to describe the infiltrating nature of glioblastoma multiforme and its extraordinary resistance to any type of treatment [3–6]. Radiotherapy, however, is known to confer some benefit to patients in term of an increased survival time [7]. To describe the effect of external-beam fractionated radiotherapy (EBRT), recent papers [8–13] include a dimensionally incorrect mathematical expression [14,15], obtained from the linear-quadratic (LQ) model for cell killing. Subsequently some of the authors [16] of the above-cited papers have ***re-interpreted*** this term in an attempt to circumvent the incorrect dimension problem.

In this paper we develop from first principles an expression for the radiotherapy term (R) and we explicitly demonstrate its compatibility with the LQ model. This contrasts with a recently proposed 're-formulation' [16], that even when dimensionally 'reinterpreted', is ***in***compatible with LQ theory. Furthermore, we present the difference in numerical results between using our expression and that in the last quoted paper.

2. Materials and methods

The reaction-diffusion equation [1,2], including the effect of the external beam Radiotherapy (EBRT), can be written as a partial differential equation (PDE)

$$\frac{\partial c(\mathbf{x},t)}{\partial t} = \nabla \cdot [\mathbf{D}(\mathbf{x}) \nabla c(\mathbf{x},t)] + \rho c(\mathbf{x},t) \cdot \left(1 - \frac{c(\mathbf{x},t)}{c_{max}}\right) + Rc(\mathbf{x},t) \quad (1)$$

where $c(\mathbf{x},t)$ denotes the tumour cell density $[l^{-3}]$ at position $\mathbf{x}$ and time t. If B is the domain in which Eq. (1) is solved, in our case the whole brain volume, zero flux at the anatomical boundaries means that no tumour cells can leave the brain or enter it from the outside. In mathematical terms:

$$\mathbf{n} \cdot \nabla \cdot [\mathbf{D}(\mathbf{x}) \cdot \nabla c(\mathbf{x},t)] = 0 \qquad \text{for } \mathbf{x} \text{ on } \partial B \quad (2)$$

where $\mathbf{n}$ is the unit vector perpendicular to the elementary surface. The term $\rho[t^{-1}]$ gives the tumour proliferation per unit time, so that the term $\rho c(x,t)$ represents the total number of new tumour cells generated per unit volume and unit time (i.e. proliferation). The term in the curved parentheses:

$$\left(1 - \frac{c(\mathbf{x},t)}{c_{max}}\right) \quad (3)$$

is dimensionless and dampens the proliferation when $c(x)$ approaches c_{max}, giving a sigmoidal shape (logit) to the growth curve of a Glioblastoma tumour. In addition, this term makes this

* Corresponding author.
E-mail address: giovanni.borasi@gmail.com (G. Borasi).

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PDE nonlinear and, until now, impossible to solve analytically in three dimensions (see below). If $c(x,t) \ll c_{max}$, as in the initial stages of the tumour growth, the term tends to unity and the equation becomes linear. $\mathbf{D}(\mathbf{x})$ is the diffusion coefficient [l^2t^{-1}], a vector indicating, at each position $\mathbf{x}$, the intensity of the diffusion in the three spatial directions. c_{max} [l^{-3}] is the maximum carrying capacity of the tumour tissue. In this context $\mathbf{D}(\mathbf{x})$ is assumed to be constant with respect to time. c_{max} and ρ are assumed constant respect to time and position.

Mathematically, Eq. (1) can be considered a conservation law: the variation in the time of the cell concentration at a point (on the left side of the equals sign) should be equal to the sum of the terms on the right side. This side includes the diffusion from external regions toward the considered point (first term), then the total number of new tumour cells generated per unit volume and unit time (i.e. proliferation) and, finally, the effect of EBRT, R [t^{-1}]. This term should be a negative, scalar quantity, so that Rc(x,t) represents the decrease of cell concentration due to EBRT. The above considerations are translated into a mathematical formalism in Chapter 11, Vol. II of [17]. The separate effect of diffusion and proliferation on tumour growth is well represented in Fig. 1 of [18].

If $\mathbf{D}(\mathbf{x})$ is known in a volume (from using diffusion MR), Eqs. (1) and (2) can be solved numerically at each point of the domain. To solve Eq. (1), an initial condition must be assumed, i.e. $c(0,\mathbf{x}) = c_0(\mathbf{x})$.

The main issue here is the analytical form of the 'R' term.

The correct form of the R term, in the framework of linear-quadratic model [19–22] can be derived by considering its definition ("the relative change of cell concentration/density per unit time, at time t"). In mathematical terms, consider delivering a dose $q(\tau)$, at a constant dose rate I for time τ, starting at $\boldsymbol{\tau_0} = 0$, and ending after a time period $\Delta\tau$, where $0 \leqslant \tau \leqslant \Delta\tau$. To avoid any confusion we first consider a single treatment. τ indicates the time during this (single) irradiation and is set to zero at the start, while $q(\tau)$ indicates the cumulative dose delivered at time τ. At the end of this single fraction the dose accumulated will be: $q = I{\cdot}\Delta\tau$. The variable t, used, as an example, in Eq. (1), represents the *total time since the start of the radiation treatment* i.e. including the sum of the n irradiation fractions (assumed to deliver equal doses), the time between the fractions and the 'observational time', after the end of the whole treatment.

As before, considering a single irradiation and following the LQ model, the cell concentration at time τ, is then:

$$c(\tau) = c(0) \cdot e^{-(\alpha \cdot q(\tau) + \beta \cdot q(\tau)^2)} = c(0) \cdot e^{-(\alpha \cdot I \cdot \tau + \beta \cdot I^2 \cdot \tau^2)} \tag{4}$$

For simplicity we will not consider here the "overall treatment time" effect; if necessary, this can be inserted into the LQ model [23].

The time (partial) derivative of (4) is then:

$$\frac{\partial c(\tau)}{\partial \tau} = -c(0) \cdot e^{-(\alpha \cdot I \cdot \tau + \beta \cdot I^2 \cdot \tau^2)} \cdot (\alpha \cdot I + 2 \cdot \beta \cdot I^2 \cdot \tau) = -c(\tau) \cdot (\alpha \cdot I + 2 \cdot \beta \cdot I^2 \cdot \tau) \tag{5}$$

so that R becomes:

$$R(\tau) = \frac{\partial c(\tau)}{\partial \tau} \cdot \frac{1}{c(\tau)} = -(\alpha \cdot I + 2 \cdot \beta \cdot I^2 \cdot \tau) \tag{6}$$

We can see from the above equation that $R(\tau)$ is the relative variation in cell density per unit irradiation time due to ionizing radiation after a time τ; naturally it is negative as irradiation *reduces* cell number. Expression (6) depends explicitly on the duration of the fractional irradiation. This expression can be useful to study the cell concentration trend during this short period of irradiation (of the order of minutes). In general, however, the sampling of the total time variable t is much longer than $\Delta\tau$, for example of the order of one day. In this case we have to consider the mean value of (6) over the irradiation time $\Delta\tau$. This value for R can be easily obtained as:

$$R = -\frac{\int_0^{\Delta\tau} (\alpha \cdot I + 2 \cdot \beta \cdot I^2 \cdot \tau') d\tau'}{\int_0^{\Delta t} d\tau'} = -\frac{\alpha \cdot I \cdot \Delta\tau + \cdot \beta \cdot I^2 \cdot \Delta\tau^2}{\Delta\tau} = -(\alpha \cdot I + \beta \cdot I \cdot q) \tag{7}$$

This is the correct expression to be introduced into Eq. (1) for a single irradiation, when the total sampling time from the starting of irradiation is longer than the irradiation time. The reason for calculating a mean value over the irradiation time $\Delta\tau$ is that, after the irradiation there is no cell-killing effect (R = 0). When n fractions are given, the R term is the sum of all the terms (7), considering n, the total number of fractions given in the total time t. The generalization for unequal fractions is immediate.

For the sake of simplicity, in the previous expressions we considered only the time dependence of the various quantities. Naturally the variables c, I, and R depend also on the spatial coordinate r. The correctness of expression (6) and (7) can be easily verified by taking the limit of the Eq. (1), when the first two terms after the equals sign are negligible (in other words when we consider only the variation in cell number due to Radiotherapy). By integrating the simple first-order equation so obtained, we recover expression (4), which is the basic LQ equation.

The expression for R proposed in [16] is:

$$R = -k \cdot [1 - e^{-(\alpha \cdot q + \beta \cdot q^2)}] \tag{8}$$

where k is a unit constant, $k = 1$ [day^{-1}], inserted to comply dimensionally with Eq. (1). In this case, by integrating the above first-order equation, we obtain

$$c(\tau) = c(0) \cdot e^{-k \cdot \int_0^{\tau} [1 - e^{-(\alpha \cdot q(\tau') + \beta \cdot q(\tau')^2)}]} \tag{9}$$

This expression is profoundly different from the basic LQ expression (4).

Recalling that $I = q/\Delta\tau$, and considering that $k = 1/\Delta\tau$, it is evident that Eq. (7) is the limiting value of Eq. (8) when the exponent tends to zero.

3. Results

In Fig. 1, we compare, for different α, the R values obtained from Eqs. (7) and (8) with two different assumptions: a) $q = 2$ Gy and $\alpha/\beta = 10$ Gy^{-1} (low value of the exponent in Eq. (8)) and b) $q = 8$ Gy and $\alpha/\beta = 3$ Gy^{-1} (high value of the exponent of Eq. (8)). In both cases $\Delta t = 1$ day.

As expected, for condition a) the percentage error in the cell concentration obtained with Eq. (8) compared to Eq. (7) is small (for $\alpha = 0.07$ Gy it is about 8%), while for condition b) the error is much greater (for $\alpha = 0.12$ Gy it is 73%).

The importance of using the correct R value can be most clearly appreciated by considering the effect on the cell concentration corresponding to different irradiation protocols. As an example, following [16], we consider here the response of a hypothetical tumour to EBFRT when the total dose is constant (61.2 Gy) but is administered in either 1 or 35 sessions. The corresponding single i.e. fractional doses are then 61.2 and 1.75 Gy respectively. First we assume that the radiobiological parameters are: $\alpha = 0.0305$ Gy^{-1}, $\alpha/\beta = 10$ Gy. The tumour is assumed to receive a spatially uniform dose. The other parameters required in Eq. (1) are assumed constant respect to space and time, with values of diffusion, D, of 1.43 cm^2/year and growth rate $\rho = 16.25$/year. These latter values are averages of the published ranges [24]. The treatment fractions are given once per day (starting on Monday and ending on Friday of each week). The simulations are a subset of

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