Stochastic effects in a discrete RT model with critical behaviour

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Abstract. The effects of radiation on a tissue (being it healthy or cancerous) are well described by current linear-quadratic (LQ) radiobiological model for low absorbed doses around the 2 Gy often used in clinical fractionation. However, experimental data show a disagreement between the predicted and the observed effect of large doses. The Sotolongo et al. (2011) radiobiological (SRB) model, derived from Tsallis nonextensive entropy, has shown a good agreement with experiments for high absorbed doses, where LQ overestimates the dose required for a required effect. Other studies have reported a crossover in LQ model where its effects are underestimated for large doses. In this paper we develop a mechanistic version of the SRB model and show that it can reproduce both behaviors with a minimum set of assumptions. We compare the results of our simulations with some data reported in the literature. We also trivially adapt this model to fractionated radiotherapy and, in particular, to hypofractionation for which we draw some conclusions.

1. Introduction
In [1] the Sotolongo radiobiological model (SRB) was introduced to explain the observed deviations of the linear-quadratic model (LQ) observed at high doses, mainly in in vitro experiments. The LQ model was introduced by Kellereir & Rossi as a good approximation to more involved theoretical mechanistic models which included responses of cells to radiation [2]; despite being an approximation to these models it has been used as a sort of constitutive relation in which to include new correcting factors that fit better the observations [3]. That is, what was once introduced as an ab initio model, has become just a practical one.

SRB model was introduced as the result of Tsallis entropy, \( S_q \), maximization [4, 5]. The problem of the probability distribution of the dose \( D \) required to kill a cell then becomes

\[
S_q = \frac{1 - \int_D p^q(x)dx}{q-1} = \max, \quad \int_D p(x)dx = 1
\]

requiring a finite \( q \)-mean [5]

\[
\int_D p^q(x)dx = \langle D \rangle_q < \infty
\]

The success of the prediction required a working hypothesis to fix the support of the \( D \) distribution (its valid interval): the existence of a critical dose \( D_0 \) which could obliterate the
radiated tissue. For \( D \) ranging from 0 to \( D_0 \) the resulting survival fraction \( F_s \) (the probability of killing a cell with a dose lower or equal to \( D \) ) becomes

\[
F_s(D) = \left( 1 - \frac{D}{D_0} \right)^{-\gamma}
\]

\( \gamma = (2 - q)/(1 - q) \)

According to [1], \( \gamma \) only depends on tissue and type of radiation used in the therapy, whereas \( D_0 \) may include these and other irradiation conditions (e.g. dose rate). At first glance, the LQ model can be obtained as a second order approximation of the SRB for the logarithm of the survival fraction around \( D = 0 \), such that

\[
\alpha = \gamma/D_0, \quad \beta = \gamma/2D_0^2
\]

For doses close to that critical value, however, both models are expected to disagree. In the case of multifractionation based on the SRB, it was shown in [6] that mathematical consistency of the nonextensive operations requires that the survival fraction of two successive dose fractions \( d_1 \) and \( d_2 \) takes the form

\[
F_s(d_1 \oplus d_2) = \left( 1 - \frac{d_1}{D_0} \right)^{-\gamma} \left[ 1 - \frac{d_2}{D_0 - \epsilon d_1} \right]^{-\gamma}
\]

the session-coupling coefficient \( \epsilon \) takes values from 0 (independent doses) to 1 (continuous irradiation) and thus describes the tissue radiosensitivity recovery between successive fractions.

The objective of this paper is to study the consequences of the finite size effects on the results predicted by SRB radiobiological model [1]. These effects become important close and above the critical dose \( D_0 \) and will become important to assess the results of large doses for radioresistive (low \( \gamma \) ) tissues.

2. Methods

Let the radiation may affect randomly a number of \( N \) finite discrete units in each cell. Let these units represent \( N \) alternative pathways in the function of a cell that chooses one randomly at a given moment among those available, such that just one of them is enough to keep the cell alive, but if the chosen pathway is suddenly not available the cell will die. Then if at a given moment the cell has \( n \) of its units damaged, the probability of being killed by a damage of \( \delta n \) of the remaining \( N - n \) units will be \( \delta n/(N - n) \). We will, however, consider a probability proportional to this, with a proportionality factor \( s \). If we write this killing probability as

\[
p = -\delta F_s/F_s
\]

and identify it with a decrease in the survival fraction \( p = -\delta F_s/F_s \), we arrive at

\[
\frac{\delta F_s}{F_s} = -s \frac{\delta n}{N - n}
\]

It is simple to relate the absorbed dose with the (expected) number of units damaged, \( D \sim n \), and the critical dose with the total number of units, \( D_0 \sim N \), to get to

\[
\frac{\delta F_s}{F_s} = -s \frac{\delta D}{D_0 - D}
\]

The SRB model can be seen as a mean field approach to this discrete model of cell damage and survival, just identifying the \( s \) parameter with the \( \gamma \) exponent by taking the first derivative in eq. 1.

Let us start after a radiation dose that has damaged \( n_1 \) units. A fraction \( r \) of the damaged units will not recover, thus in the next session we will start from only \( N - rn_1 \) intact units. That is, if no recovery happens between fractions, the number of units available at the start of the second fraction will be \( N - n_1 \); \( r = 1 \), no time to recover, corresponding to continuous
irradiation. If all the \( n_1 \) damaged units get recovered between fractions, the second fraction will affect the \( N \) original functional units: \( r = 0 \), complete recovery, thus independent doses. This means that the survival fraction after the next radiation dose would be

\[
\frac{\delta F_s}{F_s} = -s \frac{\delta n}{(N - r n_1) - n}
\]

As before, this recovery fraction can be identified with the \( \epsilon \) parameter of the SRB model, eq. 2.

3. Results and discussion

Figure 1 compares experimental data from reference [8] with different models: LQ, SRB and discrete model. As can be seen in this figure for low doses (and high survival fraction) all models work. The SRB model, that was fitted for doses lower than 6 Gy (before the onset of the linear exponential behavior) overestimates the effect of radiation dose. LQ model follows the experimental data up to 8 Gy, but detaches from it from this point. Only the discrete model follows the experimental data up to 13 Gy (around a 60% further in the dose). Other models exist [9, 10] that fit the experimental data more or less up to the same extreme value, but all of them either need more hypotheses or are ad hoc mathematical constructions, which provide no hints as to the radiobiological behavior.

The results of different simulations covering a wide range of parameter values (\( \gamma \) and \( N \)) can be seen in figures 2. Each simulation includes the statistics of an initial number of \( 10^8 \) cells. Figure 2a shows how, for a fixed \( \gamma \) the survival curves extend to higher doses when the number of units decreases, i.e., the SRB corresponds to a very large number of units, whereas the exponential behavior (shown as linear in the semilog plot) appears for small values of \( N \). On the other hand, figure 2b shows how, for a fixed number of units, as \( \gamma \) decreases a crossover separating two well defined behaviors appears; for a given difference between the theoretical SRB model and the simulation, it is reached at lower doses (relative to the critical one, \( D_0 \)) as \( \gamma \) increases.

What does \( N \) mean, radiobiologically? As the \( \gamma \) parameter, introduced in [SRb], describes the radiosensitivity of a tissue for low doses, the \( N \) describes the change of radiosensitivity at high doses. That is, as shown in figure 2a, \( N \) determines (for a given cell line) the effectivity of radiation. Counterintuitively, a larger number of units does not imply less radiosensitivity: that is because the cost in dose of removing one unit is also lower, as \( D_0 \) (the critical dose) remains the same. In other words, as \( N \) decreases, we need a larger amount of radiation to destroy the same number of cells.
Figure 2. (a) Dimensionless results of simulations for a fixed $\gamma = 3.75$ and different number of units: $N = 10, 30, 100, 1000$. (b) Dimensionless results of simulations for different $\gamma = 1.875 \times 2^k$ ($k = 1, \ldots, 5$) and fixed number of units, $N = 30$.

4. Conclusions
The discrete model provides a natural continuation to describe the linear exponential behavior observed at high doses in radiotherapy. As the SRB model accounted for observed changes in the usual $\alpha$ and $\beta$ parameters of the LQ model (dependent on the range of doses used to fit the model to the data), the new model describes the change of regime at high doses for low radiosensitivity tissues. As we mentioned before, other models either need more radiobiological hypotheses or are ad hoc mathematical constructions; ours provides a new simple parameter that rules this behavior.

Acknowledgements
Authors acknowledge the financial support from the Spanish Ministerio de Economia y Competitividad under project FIS2012-37408.

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