Does tissue annihilation dose change along radiotherapy protocols?

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Abstract

Purpose: The aim of this letter is to extend a previous nonextensive survival fraction model from single dose to fractionated radiotherapy treatments.

Methods: Two limit cases, doses given simultaneously and with a long time gap between them, are considered and matched to provide a general expression for the survival fraction.

Results: A new parameter emerges linking both limits, playing the role of the tissue radioresistance. A critical dose per fraction is found, providing the condition of total target annihilation, as a function of the new parameter.

Conclusions: The possibility of target tissue annihilation depends only on the critical dose per fraction, determined by the new radioresistance parameter.

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Recently a new model of survival fraction as function of the radiation dose has been developed [1] using the Tsallis entropy definition [2] and the maximum entropy principle. However, radiobiology models pursue not only survival fraction models but isoeffect relationships. Indeed, the well known linear quadratic (LQ) model [3] owes its success to providing simple isoeffect relationship for doses in the clinical range.

However LQ model, and its associated family, has raised controversy [4] and has been both extensively criticized [5–7] and defended [8, 9]. Nevertheless it has become the standard radiobiology model, replacing the nominal standard dose (NSD) model [10] for isoeffect relationships, even when the community is well aware of its limitations and statistical flaws on its validation and fitting [11].

In order to extend the maximum entropy model to fractionated therapies two facts must be taken into account. If two radiation beams affect a tissue at the same time or if two radiation exposure events occur immediately one after another, the total effective dose must be the simple sum of both applied doses. On the other hand, if the two radiation sessions (fractions, in what follows) are weakly time correlated, for example, far apart enough in time (although the actual meaning of "far apart enough" is to be determined), they could be considered as independent fractions. Hence, the survival fraction in this case will be just the product of the respective survival fractions.

Survival fraction, F_s, for a single radiation dose, d, is [1]

$$F_s(d) = \begin{cases} \left(1 - \frac{d}{D_0}\right)^\gamma & \forall d < D_0 \\ 0 & \forall d \geqslant D_0 \end{cases}, \tag{1}$$

where D_0 is the annihilation dose and γ the tissue extensivity index. This model has shown a remarkable agreement with available experimental data [1, 12], even in those limits where previous models are less accurate. Also, its mathematical expression is simple and can be easily plotted and interpreted. A new expression for the survival fraction of a fractionated treatment can be found that provides a better understanding of isoeffect relationships. This letter will focus on the consequences the new concepts, introduced by this Tsallis based model, have on fractionation.

The survival fraction after n concurrent (*i.e.* highly correlated) doses must be,

$$F_s = \left[1 - \sum_{i=1}^{n} \delta_i\right]^\gamma, \tag{2}$$

where $\delta_i = d_i/D_0$ is the dimensionless dose after the i-th fraction or radiotherapy session.

However, if the fractions are uncorrelated the survival probabilities must be independent,

$$F_s = \prod_{i=1}^{n} (1 - \delta_i)^{\gamma} \,. \tag{3}$$

This implies that, for a treatment composed by independent fractions, the effective dose becomes nonadditive.

In order to deal with intermediate situations, i.e. treatments whose radiation fractions are neither completely nor incompletely independent, sum and product operations need to be further generalized. It is possible to write (2) as a product, finding the expression that turns F_s after $n-1$ fractions into F_s after n fractions. So it takes the form,

$$F_s = \prod_{i=1}^{n} \left(1 - \frac{\delta_i}{1 - \sum_{k=1}^{i-1} \delta_k} \right)^{\gamma} , \tag{4}$$

meaning that the annihilation dose in the denominator gets reduced, in practice, by an amount δ_i after adition of the i-th fraction. On the other hand, for independent fractions this critical dose remains constant along the treatment.

Let us introduce the coefficient $\epsilon \in [0, 1]$ relating equations (3) and (4) such that $\epsilon = 1$ implies radiation fractions are completely correlated while $\epsilon = 0$ means they are fully independent. Then, new nonextensive sum, $\bigoplus$, and product, $\bigotimes$, operators can be defined consistently to hold,

$$F_s = \prod_{i=1}^{n} \left(1 - \frac{\delta_i}{1 - \epsilon \bigoplus_{k=1}^{i-1} \delta_k} \right)^{\gamma} = \bigotimes_{i=1}^{n} (1 - \delta_i)^{\gamma} = \left(1 - \bigoplus_{i=1}^{n} \delta_i \right)^{\gamma} , \tag{5}$$

subject to the condition $\bigoplus_{i=1}^{n} \delta_i = \sum_{i=1}^{n} \delta_i$, for $\epsilon = 1$. According to both limits interpretation, ϵ values will vary with the time between fractions and also with tissue repairing or recovering capabilities.

A single radiation fraction with an effective dimensionless dose Δ equal to the whole fractionated treatment could be found such that,

$$F_s = (1 - \Delta)^{\gamma} = \left(1 - \bigoplus_{i=1}^{n} \delta_i \right)^{\gamma} . \tag{6}$$

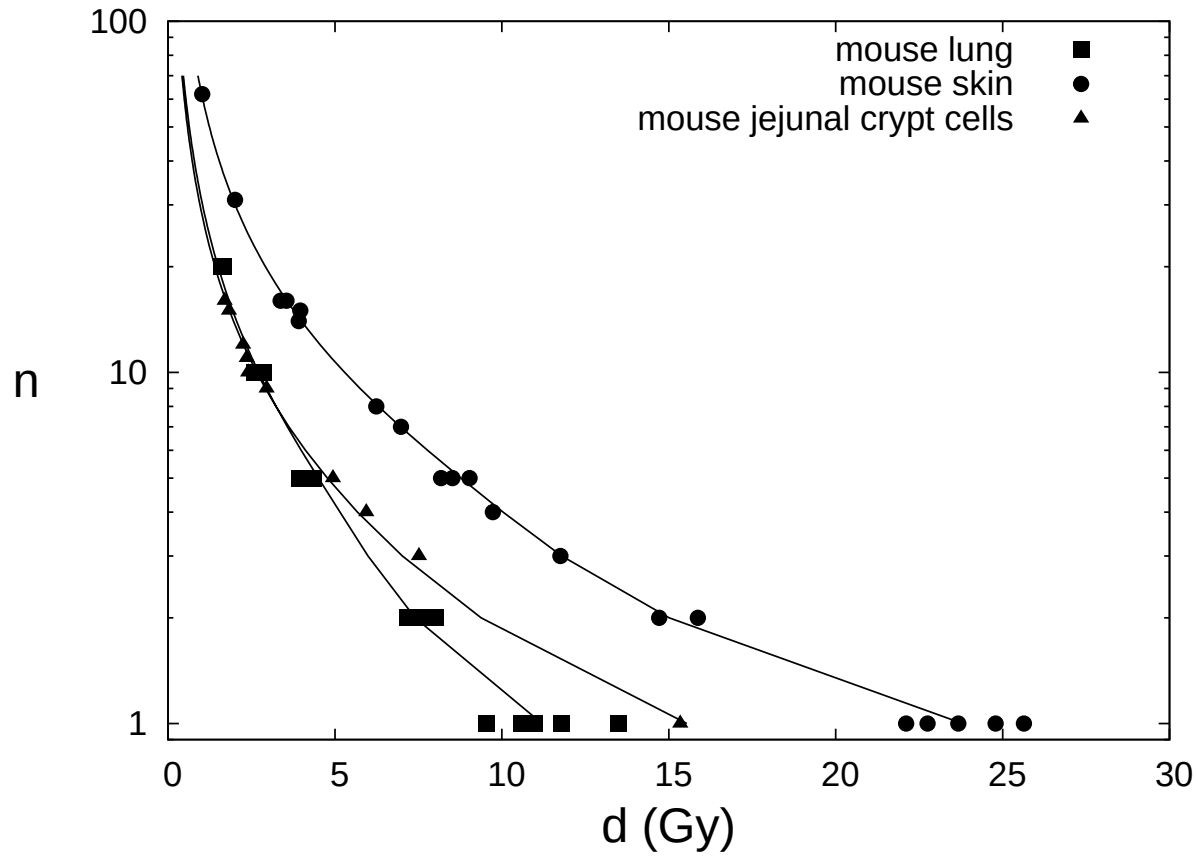

Figure 1: Isoeffect relationship data reported for mouse lung by [13] ($\epsilon = 0.50$, $D_0 = 11.3$ Gy), mouse skin by [14] ($\epsilon = 0.58$, $D_0 = 24.0$ Gy) and mouse jejunal crypt cells by [15] ($\epsilon = 0.62$, $D_0 = 16.1$ Gy), fitted to our model.

After the i-th fraction, the dimensionless effective dose becomes,

$$\Delta_i = \Delta_{i-1} + \delta_i \left[\frac{1 - \Delta_{i-1}}{1 - \epsilon \Delta_{i-1}} \right], \tag{7}$$

assuming $\Delta_1 = \delta_1$.

All fractionated treatments sharing the same value of $\Delta = \Delta_n$ will provide the same value for the survival fraction. So, the same Δ will provide the isoeffect criterion for the fractionated therapy.

In order to check the model reliability, it has been fitted to data from [13–15] using a weighted least square algorithm, as shown in Figure 1. Since ϵ values for tissue reaction are far from the limiting behaviors, it is worth to further study the biophysical interpretation of this new parameter.

Assuming the same dose per fraction, δ, (7) becomes a recursive map, describing the

behavior of the effective dose in a treatment. For a given ϵ there is a critical value of δ,

$$\delta_c = 1 - \epsilon, \tag{8}$$

dividing the plane (ϵ, δ) in two different regions (see figure 2). For a treatment with $\delta < \delta_c$, there will always be a surviving portion of the tissue since always $\Delta_n < 1$. However, if $\delta > \delta_c$, after enough fractions $\Delta_n > 1$, meaning that effective dose has reached the critical value and every single cell of tissue has been removed by the treatment. Then it is possible to find n_0, the threshold value of n, that kills every cell, for a given therapy protocol. This is shown in inset of Figure 2.

If the desired result is the elimination of the radiated tissue cells, *i.e.* surrounding tissue is not a concern for treatment planning, n_0 will represent the minimum number of sessions needed to achieve this goal; any session after that will be unnecessary. On the contrary, if the therapy goal is tissue cells conservation (for instance in order to preserve an organ), then the number of sessions must be lower than n_0.

The parameter ϵ is a cornerstone on isoeffect relationships. A fractionated therapy of fully independent fractions requires a greater radiation dose per fraction, or more fractions, in order to reach same isoeffect as would a treatment with more correlated fractions. The ϵ coefficient acts here as a relaxation term. Immediately after radiation damage occurs ($\epsilon = 1$) tissue begins to recover, as ϵ decreases, until the tissue eventually reaches its initial radiation response capacity ($\epsilon = 0$). In other words, the formerly applied radiation results in a decrease of the annihilation dose (initially equal to D_0) describing the effect of the next fraction. The more correlated a fraction is to the previous one, the larger the value of ϵ and, thus, the larger the effect on the critical dose will be. Notice that unlike γ, that characterizes the tissue primary response to radiation, ϵ characterizes the tissue trend to recover its previous radioresistance.

Correlation between fractions can be translated in terms of the late and acute tissue effects of radiobiology. Indeed, damaged tissue repairing and recovering capabilities should determine the value of ϵ. Given a dosage protocol, an early responding tissue would correspond to ϵ close to 0, whereas late responding tissue, would have ϵ closer to 1. Notice that in current working models for hyperfractionated therapies this repairing and recovering effects are introduced as empirical correction factors [16].

As it was shown in [1], nonextensivity properties of tissue response to radiation for single

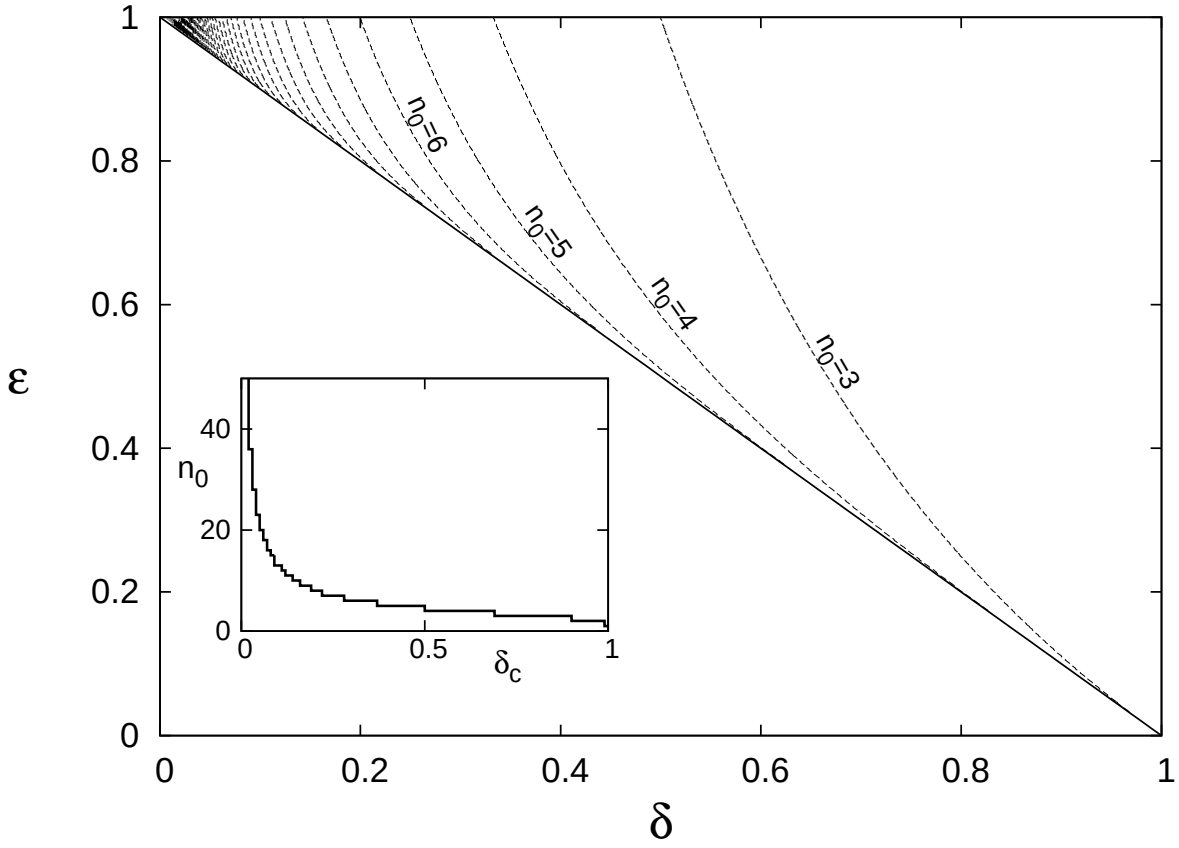

Figure 2: The larger plot represents n_0 isolines as a function of δ and ϵ (dashed lines) above $\delta_c(\epsilon)$ (solid line); below this line, killing all tissue cells is impossible. The small one represents critical values n_0 in terms of δ_c.

doses are more noticeable for higher doses than predicted by current models. On the contrary, nonextensive properties for fractionated therapies stand out at lower doses per fraction. Indeed, for high dosage a few fractions are applied in a treatment and different ϵ values would not require to change n. However, in the lower dosage case, more radiation fractions need to be applied and the ϵ parameter may become crucial. In this case n values move away from each other for isoeffect treatments with different ϵ. So, in order to achieve the desired therapy effects, fractionated radiotherapy must be planned for a tissue described by γ, varying δ according to ϵ. This ϵ coefficient should be experimentally studied as its value tunes the annihilation dose along radiotherapy protocols.

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