

Radiotherapy treatments using Tsallis entropy statistical approach

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Abstract. Several radiobiological models mimic the biologic effect of one single radiation dose on a living tissue. However, the actual fractionated radiotherapy requires accounting for a new magnitude, i.e., time. Here, we explore the biological consequences posed by the mathematical prolongation of a previous single radiation model to fractionated treatment. The survival fraction is obtained, together with the equivalent physical dose, in terms of a time dependent factor (similar to a repair coefficient) describing the tissue trend to recovering its radioresistance. The model describes how dose fractions add up to obtain the equivalent dose and how the repair coefficient poses a limit to reach an equivalent dose equal to the critical one that would completely annihilate the tumor. On the other hand, the surrounding healthy tissue is a limiting factor to treatment planning. This tissue has its own repair coefficient and thus should limit the equivalent dose of a treatment. Depending on the repair coefficient and the critical dose of each tissue, unexpected results (failure to fully remove the tumor) can be obtained. To illustrate these results and predictions, some realistic example calculations will be performed using parameter values within actual clinical ranges. In conclusion, the model warns about treatment limitations and proposes ways to overcome them.

1. Introduction

A recently developed model [1, 2] of radiobiology shows that Tsallis entropy definition [3] could be applied to describe radiotherapy treatments. As shown in [4] nonextensive Tsallis entropy



has been successful in describing a vast class of natural systems, some of them as complex as the development of living systems [5, 6].

This new radiobiological model, or *maxent* model, describe the survival fraction as a functional of the radiation absorbed dose, taking advantage of Tsallis entropy expression, and a minimum number of statistical and biologically motivated hypotheses.

Maxent model takes into account that a critical dose, D_0 , exists that annihilates every single cell in a tissue. Thus, the radiation dose, d , can be written as a dimensionless dose, $x = d/D_0$. This means that the support of the cell death probability density function, $p(x)$, must be $\Omega = [0; 1]$. Under these conditions Tsallis entropy functional becomes,

$$S_q = \frac{1}{q-1} \left[1 - \int_0^1 p^q(x) dx \right], \quad (1)$$

with q the nonextensivity index. The survival fraction of cells will be given by $f(x) = \int_x^1 p(x) dx$, that is the complement of the fraction of cells killed by radiation. The probability normalization condition implied by this interpretation of $p(x)$ must be complemented by the existence of a finite q -mean value as was shown in [1]. Both conditions allow the calculation of the probability density maximizing (1), using Lagrange multipliers, resulting in

$$p(x) = \gamma (1-x)^{\gamma-1}, \quad (2)$$

where $\gamma = \frac{q-2}{q-1}$. Hence, the survival fraction predicted by the model is

$$f(x) = (1-x)^\gamma, \quad (3)$$

valid for $x \in \Omega$ and requiring $\gamma > 1$.

This model shows remarkable agreement with experimental data [1, 7], even at high doses where previous models are less accurate. Furthermore, analysis of the model shows that interaction is universal for a given tissue, and is characterized by a single exponent, independent on the radiation type, energy or dose rate; on the other hand, the cutoff dose, above which every single cell dies, does depend on the characteristics of the radiation. Previous models can be derived as particular limiting cases of the mathematical expression, which can also be easily plotted and interpreted [1].

Expression (3), understood as survival probability, lacks the extensivity property, i.e., for n events following (3) the total survival probability should be found as a composition of the survival probabilities of the successive events. However, there is not a straightforward composition rule for those probabilities. For instance, let two doses, x_A and x_B be applied; the resulting composition probability can take two possible limit values:

- If the total dose is assumed additive: $f_{AB} = (1 - x_A - x_B)^\gamma$, that is, the individual probabilities under A and B events could not be treated as independent probabilities, $f_{AB} \neq f_A f_B$.
- If probabilities are multiplicative, $f = (1 - x_A)^\gamma (1 - x_B)^\gamma$, doses would not fulfill the superposition principle for the equivalent physical dose, $x_{AB} \neq x_A + x_B$.

A mathematically consistent way to crossover between both limits, is explained and analysed in what follows.

2. Composition rules

If the survival probabilities are deemed independent, the total probability for two events A and B is $f_{AB} = f_A f_B$. This condition and equation 3 lead to the composition rule

$$\begin{aligned} f_{AB} &= f_A f_B \\ x_{AB} &= x_A \oplus x_B = x_A + x_B - x_A x_B \end{aligned} \quad (4)$$

Analogously, if the dose should be additive, $x_{AB} = x_A + x_B$, the same equation leads to the composition rule

$$\begin{aligned} x_{AB} &= x_A + x_B \\ f_{AB} &= f_A \otimes f_B = \left(f_A^{1/\gamma} + f_B^{1/\gamma} - 1 \right)^\gamma \end{aligned} \quad (5)$$

In clinical treatments, that both limits are not clearly distinct. Tissue recovering capabilities make two treatments separate enough in time independent from each other as the system “loses” memory of its previous state. In radiobiological terms, the next radiotherapy session is applied after late effects of the previous one occur. However, if both doses were applied simultaneously they must be summed up, i.e., they will be composed additively. Thus, (4) and (5) are limit cases corresponding to $t = 0$ and $t \gg T$, where t is the time between successive doses and T some biological characteristic time (tissue repair time, for instance).

The description of a real fractionated process, requires to generalize sum $\oplus$ and product $\otimes$ operators, in a form that allows a smooth transition between these two limits. This was done in [2] through the introduction of a coefficient $\epsilon \in [0, 1]$ such that for $\epsilon = 1$ the expression describes completely correlated events, while $\epsilon = 0$ means they are fully independent. Thus ϵ plays the role of a “repair coefficient” between doses. The final expression encompassing both limits reads:

$$x_{AB} = x_A \oplus x_B = x_A + x_B \left(\frac{1-x_A}{1-\epsilon x_A} \right) \quad (6)$$

$$f_{AB} = f_A \otimes f_B = f_A \left[\frac{f_B^{1/\gamma} - \epsilon(1-f_A^{1/\gamma})}{1-\epsilon(1-f_A^{1/\gamma})} \right]^\gamma \quad (7)$$

from which is readily checked that both limit definitions (4) and (5) are recovered for $\epsilon = 0$ and $\epsilon = 1$ respectively.

3. Biological and physical implications

3.1. Isoeffect relationship

One of the central concepts in radiotherapy is isoeffect relationships. An oncologist usually seeks treatments that produce the same outcome on the target tissue, while causing the least damage on the surrounding healthy tissues.

Equations (7) can be generalized for the case of a multifractionated treatment to render a survival fraction F_n :

$$F_n = (1 - X)^\gamma = \left(1 - \bigoplus_{i=1}^n x_i \right)^\gamma \quad (8)$$

where n is the number of fractions x_i and X is the effective dose.

All fractionated treatments with the same value of X , will provide the same value for the survival fraction: this is the isoeffect criterion for the fractionated therapy.

The oncologist will seek among the different pairs of values (n, x_i) in equation (8) providing the same value of F for a given tissue while keeping small collateral damages to healthy tissues.

In order to check the model reliability, it has been fitted to data from [8, 9, 10] using the same weighted least squares algorithm as in [1] (see Figure 1). Those data sets are considered as a reliable source of clinical parameters (as the α/β relation of LQ model [11]). The obtained ϵ values are far from the limit cases ($\epsilon = 0$ and $\epsilon = 1$) showing a survival fraction behavior far from the pure q -algebraic limits.

Once the involved coefficients for a treatment (ϵ and D_0) are known the dosage can be tuned to obtain the desired effective dose by changing n and d . Notice that γ does not play any role in this composition.

To illustrate the practical use of the theory exposed above, let us consider the following example. A normal tissue H , characterized by typical coefficients $\gamma = 10.0$ and $D_0 = 40.0$ Gy,

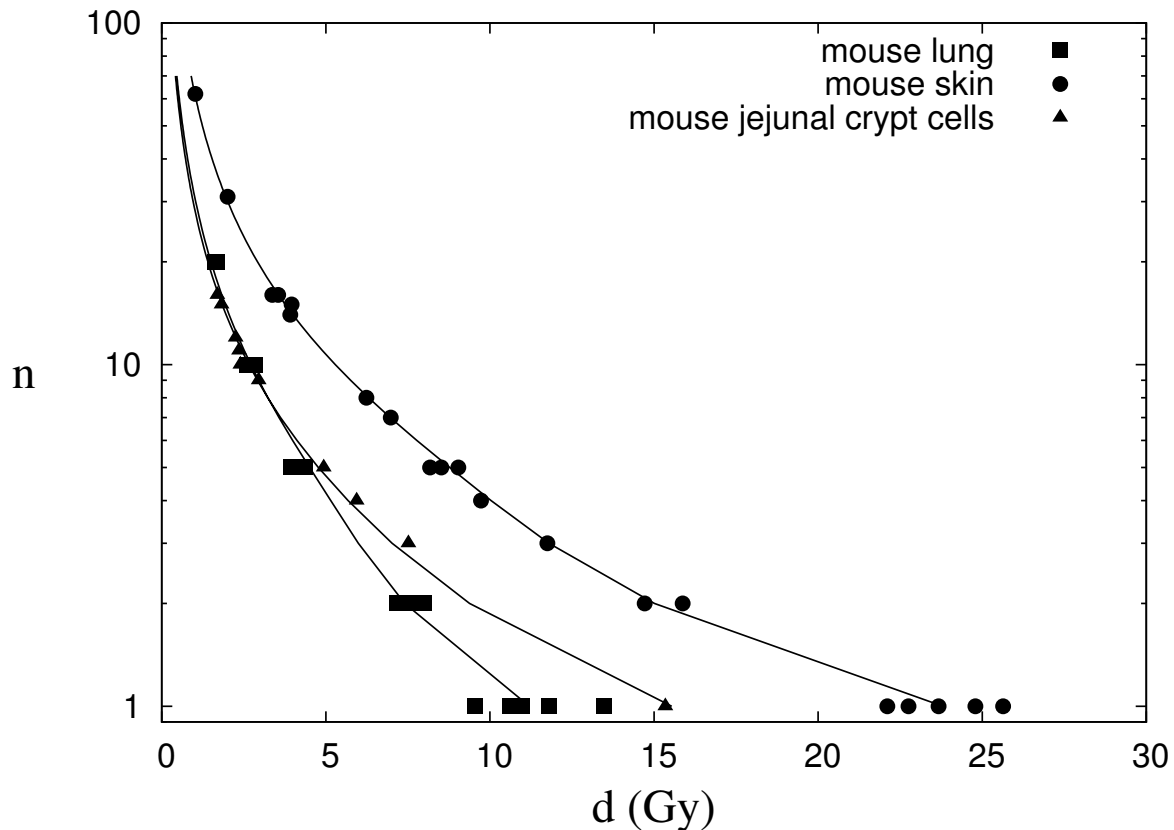


Figure 1. Isoeffect relationship data reported for mouse lung by [8] ($\epsilon = 0.50$, $D_0 = 11.3$ Gy), mouse skin by [9] ($\epsilon = 0.58$, $D_0 = 24.0$ Gy) and mouse jejunal crypt cells by [10] ($\epsilon = 0.62$, $D_0 = 16.1$ Gy), fitted to (9).

surrounded by a more resilient tumoral tissue T with $\gamma = 15.0$ and $D_0 = 80.0$ Gy. H cannot receive more than 36.0 Gy, or equivalently, $X = 0.9$. Following [11] the isoeffect curves for incomplete repair can be computed using the LQ model approximation; we will assume a typical repair half time of 3 hours for both tissues in this example. Different treatment schedules, characterized by a time (Δt) between sessions, render different survival curves. From them the ϵ values can be found in terms of Δt . This is shown in Figure 2.

3.2. Critical dosage

Assuming the same physical dose per fraction, $x_i = x$, as is the case in many radiotherapy protocols, we obtain from (6) the equivalent dose for n fractions:

$$X_i = X_{i-1} + x \left(\frac{1 - X_{i-1}}{1 - \epsilon X_{i-1}} \right) \quad (9)$$

This is the expression of a recursive map describing the evolution of the effective dose in a treatment. The stability analysis of this map shows that, for every ϵ there is a critical value of x ,

$$x_c = 1 - \epsilon, \quad (10)$$

that divides the plane (ϵ, x) in two different regions.

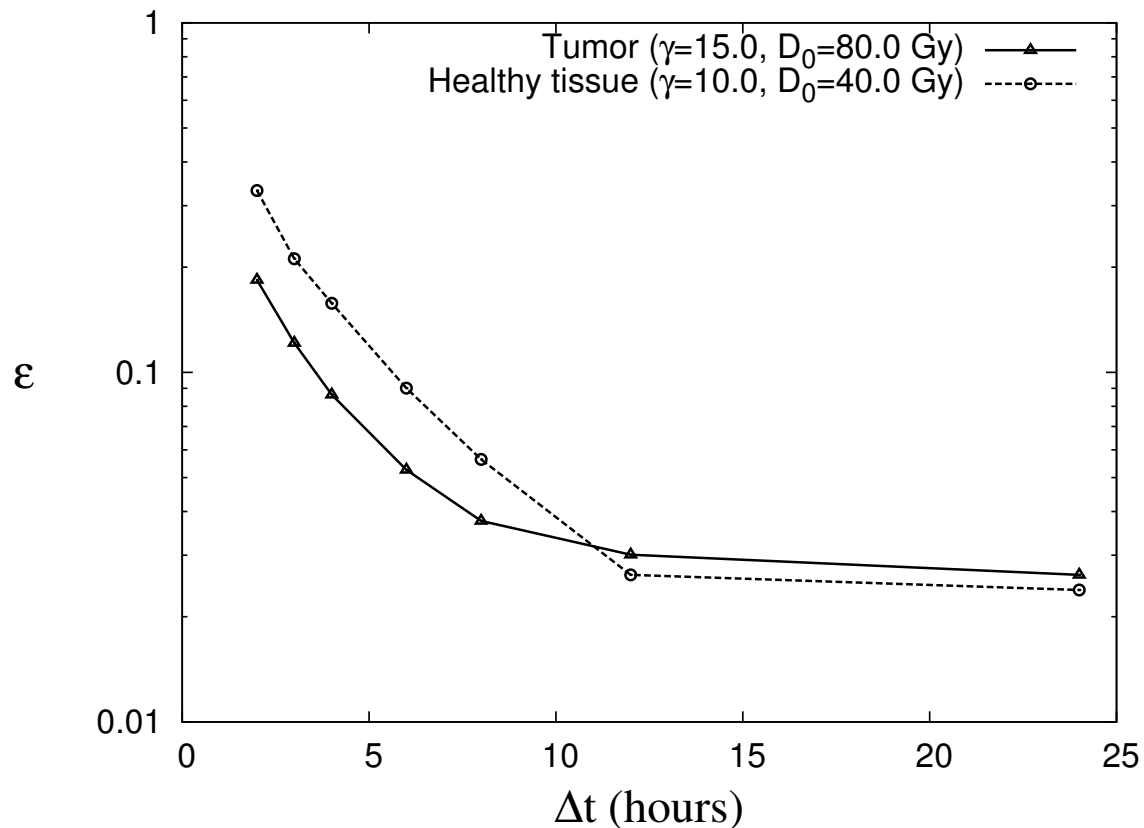


Figure 2. Session-coupling values found following the LQ model of incomplete repairment for an hypothetical tumor and healthy tissue as function of treatment time schedule.

- For $x < x_c$, there will always be a surviving portion of the tissue since always $X_n < 1$, for every n .
- For $x > x_c$, after enough fractions X_n will reach the critical value 1, thus every single cell of tissue has been removed by the treatment.

Then, for some values of ϵ it is possible to find a threshold value of n , that kills every cell, for a given therapy protocol. However, for some ϵ values, this n does not exist. This is shown in the inset of Figure 3.

4. Discussion

The session-coupling parameter ϵ is a cornerstone on isoeffect relationships. Notice that unlike γ , that characterizes the tissue primary response to radiation, ϵ characterizes the tissue trend to recover its previous radioresistance.

ϵ acts as a relaxation term: after radiation damage occurs ($\epsilon = 1$) tissue begins to recover; then ϵ gradually decreases, until the tissue recovers its initial recovery capacity ($\epsilon = 0$). This can be also interpreted as if formerly applied radiation decrease the total annihilation dose (equal, initially, to D_0). The more coupled a session is to the previous one, the larger this change (scaled by ϵ) in the the critical dose of the next session.

As it was shown in [1], all these nonextensive properties of tissue response to radiation are more noticeable the closer to the critical values, i.e., for higher doses. This has as a consequence that, for a given effect, doses predicted by traditional modes, are larger than those predicted

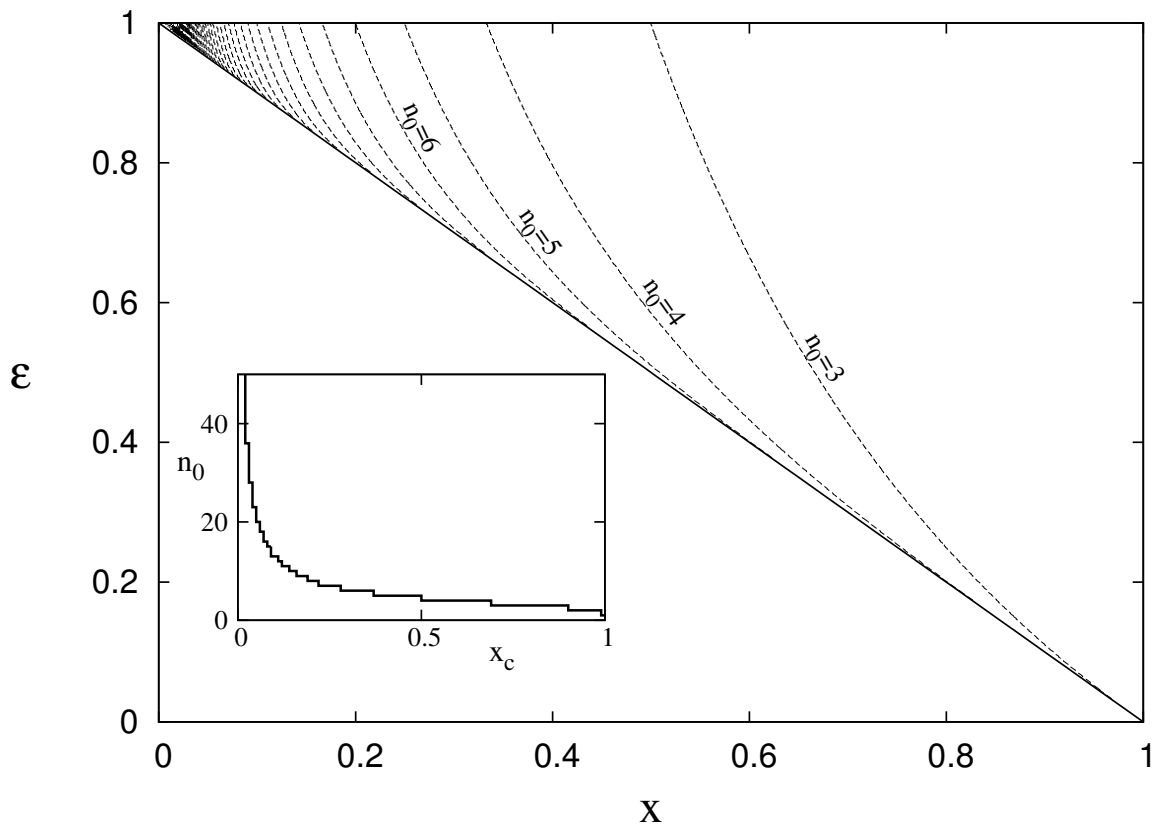


Figure 3. The larger plot represents n_0 isolines as a function of x and ϵ (dashed lines) above $x_c(\epsilon)$ (solid line); below this line, killing all tissue cells is impossible. The small one represents critical values n_0 in terms of x_c .

by our model, because traditional models do not take into account effect enhancement close to the critical point. For the same total dose, a lower dose per fraction will enhance nonextensive properties in fractionated therapies. For high doses per fraction, few fractions will be required, and then n will not depend on ϵ . However, for small doses per fraction, more sessions will be required to cause the desired effect ($F_n = 0$); furthermore, ϵ will determine whether this achievement will be possible at all at a given dose per fraction x (equation (10)).

With the model introduced above, a fractionated radiotherapy can be planned for a tissue described by γ , varying x according to ϵ , in order to achieve the desired therapy effects with minimal dose.

5. Conclusions

The *ansatz* of maximum Tsallis entropy led us to a simple nonextensive expression for the single dose survival fraction. The mathematical constraints, required to consistently define treatment compositions, naturally introduce a new parameter relating radiation sessions. The new *session-coupling* parameter takes values between 0 and 1 that describe the cross effects of independent to simultaneous doses, respectively. This has been checked estimating its value from experimental data available from multisession treatments, showing that it is relevant to describe them within the non-extensive framework.

An interesting interpretation of this new parameter is that it modulates the critical dosage (the total annihilation dose that kills every tumor cell) for the following session in terms of

the previous treatment history. As the session-coupling parameter plays the role of a “repair coefficient” between doses its dependence on time and type of tissue will require experimental characterization, as do the critical dose (radiation and tissue dependent) and the γ exponent (tissue dependent).

The session-coupling parameter completes the non-extensive radiotherapy model allowing the design of isoeffective treatments, i.e., that have the same effect on tumoral tissue, while minimizing the damage caused to healthy tissues more effectively.

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