Tsallis entropy approach to radiotherapy treatments

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ABSTRACT

The biological effect of one single radiation dose on a living tissue has been described by several radiobiological models. However, the fractionated radiotherapy requires to account for a new magnitude: time. In this paper we explore the biological consequences posed by the mathematical prolongation of a previous model to fractionated treatment. Nonextensive composition rules are introduced to obtain the survival fraction and equivalent physical dose in terms of a time dependent factor describing the tissue trend towards recovering its radioresistance (a kind of repair coefficient). Interesting (known and new) behaviors are described regarding the effectiveness of the treatment which is shown to be fundamentally bound to this factor. The continuous limit, applicable to brachytherapy, is also analyzed in the framework of nonextensive calculus. Here a coefficient that rules the time behavior also arises. All the results are discussed in terms of the clinical evidence and their major implications are highlighted.

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1. Introduction

As can be seen in Ref. [1] (and other works in the same issue) nonextensive Tsallis entropy [2] has become a successful tool to describe a vast class of natural systems. A recently developed model [3] of radiobiology shows this entropy definition could also be applied, not only to the development of living systems [4,5], but also to radiotherapy treatments.

The new radiobiological model (maxent model in what follows) takes advantage of the Tsallis entropy expression to describe the survival fraction as a functional of the radiation absorbed dose. This model is also based on a minimum number of statistical and biologically motivated hypotheses.

The maxent model assumes the existence of a critical dose, D_0, that annihilates every single cell in the tissue. The radiation dose can be written as a dimensionless quantity in terms of that critical dose as $x = d/D_0$, where d is the radiation dose. Then the support of the cell death probability density function, $p(x)$, in terms of the absorbed dose x, becomes $\Omega = [0; 1]$. The Tsallis entropy functional can be written,

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

where q is 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. In order to maximize functional (1) we must consider the normalization condition,

$$\int_0^1 p(x)\, dx = 1.\tag{2}$$

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Also, following Ref. [6], we must assume the existence of a finite q-mean value,

$$\int_0^1 p^q (x) x\mathrm{d}x = \langle x \rangle_q . \tag{3}$$

Then the Lagrange multipliers method leads to,

$$p (x) = \gamma (1 - x)^{\gamma - 1} , \tag{4}$$

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

$$f (x) = (1 - x)^\gamma , \tag{5}$$

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

   This model has shown a remarkable agreement with experimental data [3,7], even in those limits where previous models are less accurate, mainly at high doses. The analysis of the model fit to experimental data also provides new hints about the tissue response to radiation: first, the interaction of a tissue with the radiation is universal and characterized by a single exponent (not dependent on the radiation type, energy or dose rate); second, the model includes a cutoff dose (this one, dependent on the characteristics of the radiation) above which every single cell dies. Furthermore, previous models can be derived as particular limiting cases. Finally, as for those models, its mathematical expression is simple and can be easily plotted and interpreted.

   The maxent model was derived for radiobiological survival fraction but its applicability could be extended to other processes. Indeed, every phenomena describable in terms of Tsallis entropy [8], fulfilling the maximum entropy principle and exhibiting a critical cutoff (represented here by $x = 1$), must follow (5).

   Nevertheless the expression (5), understood as survival probability, lacks the extensivity property. In other words, for n events following (5) 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.

   Indeed, if two doses, x_A and x_B are applied, the resulting probability from their composition has two possible 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, $f_{AB} \neq f_A f_B$. On the other hand, 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, $x_{AB} \neq x_A + x_B$.

   The subject of this manuscript is to develop the composition rules that would lead to the survival fraction and the equivalent physical dose of a fractionated processes, and to derive the biological implications of such rules. This will be approached within the frameworks of q-algebra and q-calculus [9–11], as far as they are the natural ones for the maxent model.

2. Composition rules

   Each event described by (5) represents a measured energy impact, or dose, x causing an irreversible effect or hazard over a group of individual entities leading to a survival probability of those entities. As (5) represents a nonextensive process, an appropriate set of composition rules must be developed in order to find the effect of several combined events on the group of entities.

   As it has just been exposed, if those composition rules are defined keeping the superposition principle for the dose, the probabilities are not independent of each other and *vice versa*, if the probabilities are multiplicative, the dose becomes nonadditive [12]. Luckily, the nonextensive thermostatistics provides tools to find the right expressions in each case [9–12].

   If the survival probabilities are independent, the total probability for two events A and B is $f_{AB} = f_A f_B$. So the nonextensive sum must be constructed as $x \oplus y = x + y - xy$ and we can write,

$$\begin{aligned} x_{AB} &= x_A \oplus x_B = x_A + x_B - x_A x_B \\ f_{AB} &= f_A f_B. \end{aligned} \tag{6}$$

On the other hand, if the dose is additive, $x_{AB} = x_A + x_B$, the nonextensive product must be $x \otimes y = \left(x^{1/\gamma} + y^{1/\gamma} - 1\right)^\gamma$ so we can write,

$$\begin{aligned} x_{AB} &= x_A + x_B \\ f_{AB} &= f_A \otimes f_B = \left(f_A^{1/\gamma} + f_B^{1/\gamma} - 1\right)^\gamma . \end{aligned} \tag{7}$$

   The main issue here is that in clinical treatments both limits are not clearly distinct. Indeed, when events occur separate enough in time, tissue recovering capabilities make physical consequences of one of them independent from the others'. From a radiobiologist's point of view this is similar to applying the next radiotherapy session after late effects of the former occur. However, if the events occur simultaneously the dose must be considered additive. In other words, (6) and (7) represent limit cases of the interaction process corresponding to $t = \infty$ and $t = 0$ respectively, where t is the time between successive events.

In order to describe a real fractionated process, new generalized sum and product operators need to be introduced, taking into account that (6) and (7) must hold in the multiplicative and additive limits, respectively.

The resulting probability in (6) is the product of partial probabilities, and for the whole process,

$$F_n = \prod_{i=1}^{n} (1 - x_i)^{\gamma}, \tag{8}$$

where i runs along the events.

However, if the dose is additive, the total survival fraction follows,

$$F_n = \left(1 - \sum_{i=1}^{n} x_i\right)^{\gamma}. \tag{9}$$

Notice that it is possible to write (9) as a product, finding the expression that turns F after $n - 1$ events into F after n events. So, (9) can be recast in the form,

$$F_n = \left(1 - \frac{x_n}{1 - \sum_{k=1}^{n-1} x_k}\right)^{\gamma} \qquad F_{n-1} = \prod_{i=1}^{n} \left(1 - \frac{x_i}{1 - \sum_{k=1}^{i-1} x_k}\right)^{\gamma}. \tag{10}$$

This expression can be interpreted as a modified (8) in which the denominator, which plays the role of the annihilation cutoff, gets reduced, in practice, by an amount x_i after addition of the i-th event. On the other hand, for independent events this critical cutoff would remain constant along the whole process.

The new operators for nonextensive sum, $\oplus$, and product, $\otimes$, must be defined to hold,

$$F_n = \bigotimes_{i=1}^{n} (1 - x_i)^{\gamma} = \left(1 - \bigoplus_{i=1}^{n} x_i\right)^{\gamma} = \prod_{i=1}^{n} \left(1 - \frac{x_i}{1 - \epsilon \bigoplus_{k=1}^{i-1} x_k}\right)^{\gamma}, \tag{11}$$

subject to the condition $\bigoplus_{i=1}^{n} x_i \to \sum_{i=1}^{n} x_i$, for $\epsilon \to 1$. In this way, (8) and (10) will be the limits of the new operators. Indeed, the coefficient $\epsilon \in [0, 1]$ acts as a session-coupling coefficient for Eqs. (8) and (10) such that $\epsilon = 1$ implies events are completely correlated while $\epsilon = 0$ means they are fully independent, i.e. not coupled.

Even though (11) gives a closed and univocal definition of $\oplus$ and $\otimes$ operators, this is an implicit definition. In order to use these operators an explicit definition is desired.

The analytical expression for the new operators $\oplus$ and $\otimes$ can be found assuming there is a single event with an effective dimensionless dose X corresponding to the whole process such that,

$$F_n = (1 - X)^{\gamma} = \left(1 - \bigoplus_{i=1}^{n} x_i\right)^{\gamma}. \tag{12}$$

After the i-th event, the dimensionless effective dose would become,

$$X_i = X_{i-1} + x_i \left(\frac{1 - X_{i-1}}{1 - \epsilon X_{i-1}}\right), \tag{13}$$

assuming $X_1 = x_1$. When the n-th event is given, then $X_n = X$.

From this follows that,

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

$$f_{AB} = f_A \otimes f_B = f_A \left[\frac{f_B^{1/\gamma} - \epsilon \left(1 - f_A^{1/\gamma}\right)}{1 - \epsilon \left(1 - f_A^{1/\gamma}\right)}\right]^{\gamma} \tag{14}$$

and limit definitions (6) and (7) are recovered for $\epsilon = 0$ and $\epsilon = 1$ respectively. According to both limit interpretations, session-coupling ϵ values will depend on the time between events and also on tissue repair or recovery capabilities.
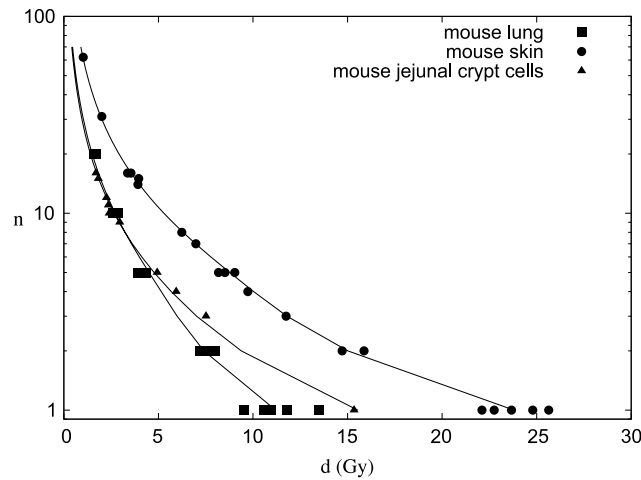
Fig. 1. Isoeffect relationship data reported for mouse lung by Ref. [13] ($\epsilon = 0.50$, $D_0 = 11.3$ Gy), mouse skin by Ref. [14] ($\epsilon = 0.58$, $D_0 = 24.0$ Gy) and mouse jejunal crypt cells by Ref. [15] ($\epsilon = 0.62$, $D_0 = 16.1$ Gy), fitted to (13).
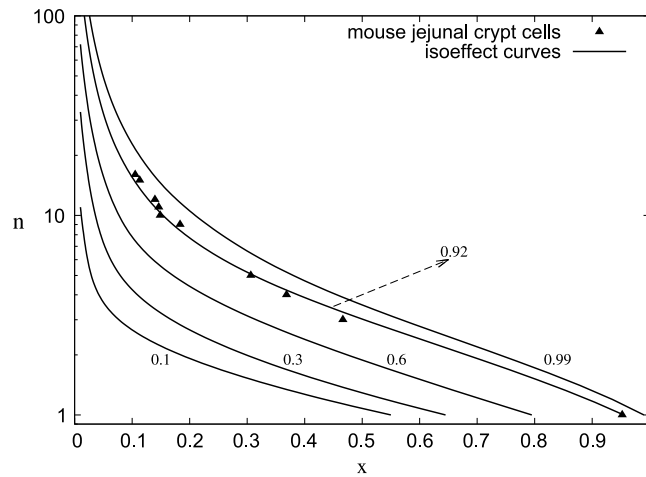

Fig. 2. Isoeffect curves for mouse jejunal crypt cells by Ref. [15]. Curves are calculated based on fitted parameters $\epsilon = 0.62$ and $D_0 = 16.1$Gy for different values of X in (13), shown for every plot.

3. Biological and physical implications

3.1. Isoeffect relationship

One of the central concepts of radiotherapy is isoeffect relationships. An oncologist usually seeks treatments that produce the best outcome on the target tumor (F_{tumor}), while causing at most the maximum allowed damage on the surrounding healthy tissues (F_{tissue}). In other words, he seeks among the pairs of values (n, x) that give the same value of F_{tissue} for the healthy tissue that one attaining the maximum value of F_{tumor}. Given the expression (12) this can be reduced to find the pairs (n, x) that render the same value of X.

Indeed, all fractionated treatments sharing the same value of effective dose, X, will provide the same value for the survival fraction. So, the same X will provide the isoeffect criterion for the fractionated therapy.

In order to check the model reliability, it has been fitted to data from Refs. [13–15] using a weighted least squares algorithm [3]. Those data sets are considered as a reliable source of clinical parameters (as the α/β relation of LQ model [16]). The results of the fit are shown in Fig. 1.

The obtained session-coupling coefficients show a survival fraction behavior far from the pure q-algebraic limits ($\epsilon = 0$ and $\epsilon = 1$). Since ϵ values for usual tissue reaction differ from limiting values, it is worth further studying the biophysical interpretation of this new parameter.

Every X value provides a different isoeffect relationship, as shown in Fig. 2. Once a treatment's coefficient values (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, thus reducing the number of model parameters to take into account here.

As there is not enough experimental data available, in order to find session-coupling ϵ values for known tissues or tumors we will use the LQ model of incomplete repairment to show how our model could be used to assess the desired therapy schedule.
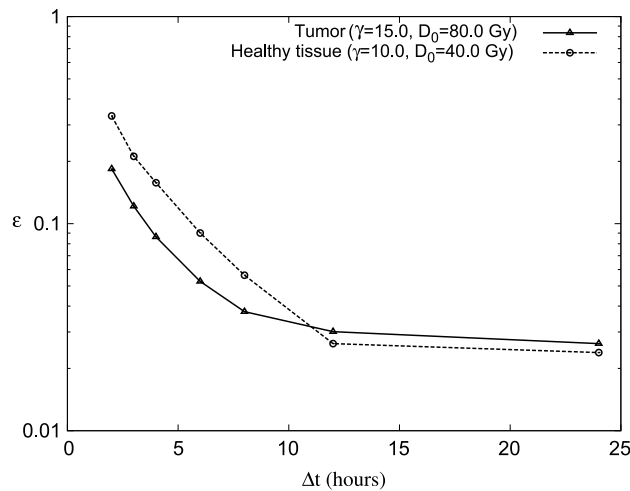
Fig. 3. Session-coupling values found following the LQ model of incomplete repairment for an hypothetic tumor and healthy tissue as function of treatment time schedule.
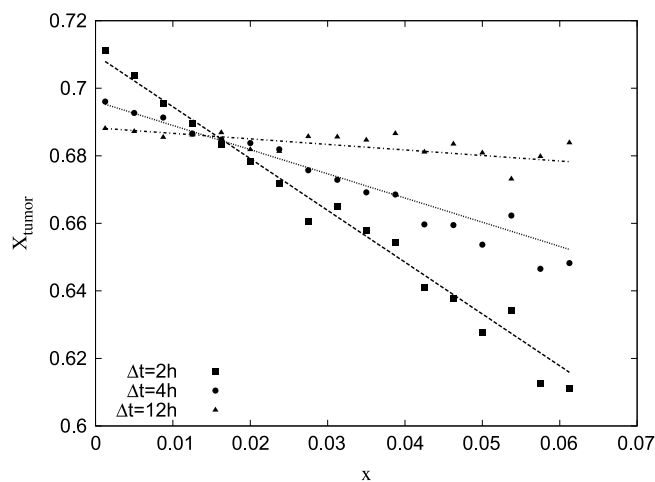

Fig. 4. X values as function of session dimensionless dose x found for the hypothetic tumor T following the treatment schedules of incomplete repairment as function of treatment time schedule. Lines represents the approximate behavior of X values.

Let us suppose a healthy tissue H with $\gamma = 10.0$ and $D_0 = 40.0$ Gy surrounding a more resilient tumor T with $\gamma = 15.0$ and $D_0 = 80.0$ Gy. Now we will assume that H cannot receive more than 36.0 Gy or $X = 0.9$. After finding the corresponding LQ model α and β values is easy to reproduce the isoeffect curves for incomplete repairment following Ref. [16] if the cell repair half time is known. We had chosen a repair half time of 3 h for H and T but the same procedure could be applied for different repair half time values. Each of these curves represents a different treatment schedule characterized by the time (Δt) between sessions. From these curves the ϵ values as a function of Δt could be found as shown in Fig. 3.

After the values of ϵ have been determined for the tumor then the effective dose X received for each schedule could be found as shown in Fig. 4. This shows us that for small x values the best outcome is reached at more consecutive sessions, whereas for more separated sessions the appropriate dosage is attained at higher x values. In particular, for the case of sample tissues H and T, described above, best results are found with a more fractionated treatment with its fractions scheduled as close as possible.

Note that for a real example this procedure must be followed after finding the experimental values of ϵ for each schedule. Even though illustrative, this example must be taken with caution as it is based on another model whose validity limits are not clear.

3.2. Critical dosage

Assuming the same physical dose per fraction, $x_i = x$, as is the case in many radiotherapy protocols, expression (13) becomes that of a recursive map, describing the evolution of the effective dose in a treatment. The analysis of this map shows that, for every ϵ there is a critical value of x,
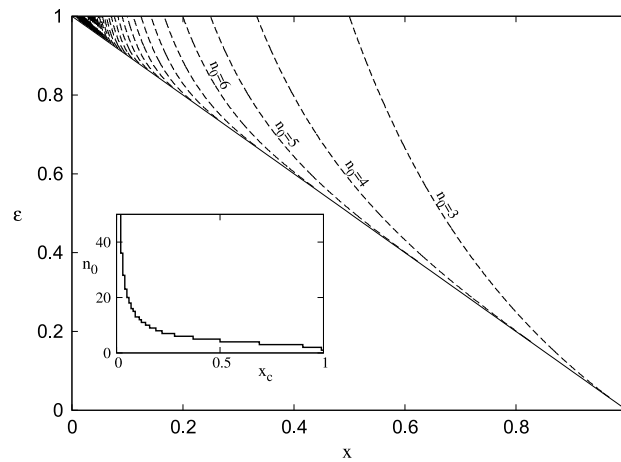
$$x_c = 1 - \epsilon, \tag{15}$$

Fig. 5. 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.

dividing the plane (ϵ, x) in two different regions (see Fig. 5). For a treatment with $x < x_c$, there will always be a surviving portion of the tissue since always $X_n < 1$, for every n. However, if $x > x_c$, after enough fractions $X_n > 1$, 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 the inset of Fig. 5.

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 represents the minimum number of sessions needed to achieve this goal; any session after that will be unnecessary. On the contrary, if the therapy goal requires the conservation of tissue cells (for instance in order to preserve an organ), then the number of sessions must be lower than n_0.

The session-coupling 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 the same isoeffect as a treatment with more correlated fractions. The session-coupling coefficient acts here as a relaxation term. Immediately after radiation damage occurs ($\epsilon = 1$) the 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 coupled a session 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 recovering capabilities should determine the value of ϵ. Given a dosage protocol, to an early responding tissue would correspond ϵ close to 0, whereas for a late responding tissue, would be ϵ closer to 1. Notice that in current working models for hyperfractionated therapies these repair and recovery effects are introduced as empirical correction factors [17], as will be required for the session-coupling coefficient.

As it was shown in Ref. [3], nonextensivity properties of tissue response to radiation for single doses are more noticeable for higher doses than predicted by current models. On the contrary, for the same total dose, a lower dose per fraction will enhance nonextensive properties in fractionated therapies. Indeed, for high dosage a few fractions are applied in a treatment and a change in n is not required for different ϵ values. 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 x according to ϵ. The session-coupling coefficient should be experimentally studied as its value tunes the annihilation dose along a radiotherapy protocol.

4. Continuous formulation

4.1. Continuous limit

For some radiation treatments as brachytherapy the irradiation is applied in a single session but for a prolonged period of time. If the discrete irradiation sessions were close enough (13) could be written as,

$$\dot{X} = r\frac{1 - X}{1 - \epsilon X} \tag{16}$$

where r stands for the average absorbed radiation per unit time. At the early stages of continuous irradiation the effective dose is in general small, and is possible to assume $\epsilon X \ll 1$ and $\frac{1}{1 - \epsilon X} \simeq 1 + \epsilon X$. Then,
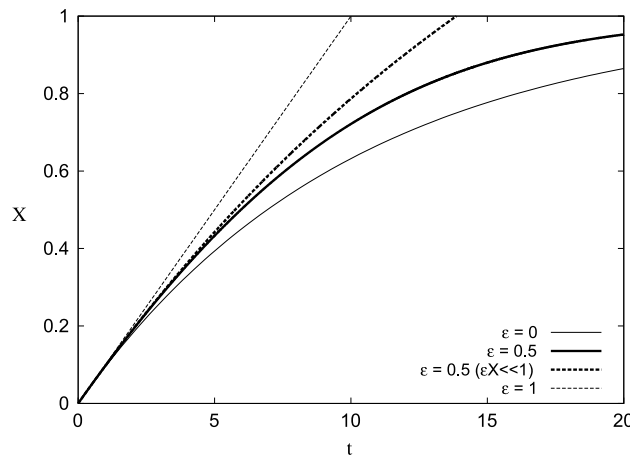
Fig. 6. Continuous limit approximation behavior for $r = 0.1$. As expected the solution of (16) (thick continuous line) goes between a linear effect for $\epsilon = 1$ (thin continuous line) and the exponential approach to cutoff dose corresponding to $\epsilon = 0$ (thin dashed line). Solution of (17) is represented by the thick dashed line.

$$\dot{X} \simeq r\left[1 - (1 - \epsilon)X\right], \tag{17}$$

where the terms of second order in ϵX and above have been neglected. However, as can be seen in Fig. 6 this approximation moves away from (16) as time increases.

4.2. Continuous irradiation

It is obvious from dose additivity properties that in the continuous irradiation case and for two time instants t_0 and t_1 close enough,

$$X = \int_{t_0}^{t_1} r\,\mathrm{d}t, \tag{18}$$

where r is the dose rate per unit time. However if both instants of time are far enough to make relevant the tissue recovering capabilities this expression becomes invalid. So, whereas a usual integration process could become valid in a short time period this is not true for longer intervals. So, in a similar way as was already done for the sum operation, a new definition for integration must be introduced.

This can be done following Ref. [10] and introducing the q-algebraic sum and difference,

$$\begin{aligned} x \boxplus y &= x + y - \theta xy \\ x \boxminus y &= \frac{x - y}{1 - \theta y} \end{aligned} \tag{19}$$

where $\theta \in [0, 1]$. In those terms, a nonextensive derivative operation follows such that,

$$\frac{\mathcal{D}}{\mathrm{d}t}f = \lim_{t \to t_0} \frac{f(t) \boxminus f(t_0)}{t - t_0} = \frac{\dot{f}}{1 - \theta f}. \tag{20}$$

Then we can define the physical absorbed dose rate, r, as the nonextensive time derivative of the equivalent dose,

$$r = \frac{\mathcal{D}}{\mathrm{d}t}X = \frac{\dot{X}}{1 - \theta X}. \tag{21}$$

Expression (21) can be rewritten as a standard ODE,

$$\dot{X} + \theta rX = r, \tag{22}$$

which can be solved in the usual way taking into account that θ and r are in general functions of time. In the absence of recovering effects, the applied effective dose would increase linearly, due to the applied radiation r. However a resistance force (θrX), that depends not only on tissue recovering characteristics but also on the dose rate and the effective dose itself, will slow down this increase.

In order to illustrate the behavior described by (22), let us suppose r is constant (a common case in clinical practice) and θ slowly varying in time, so that it can be also taken as a constant. Then it is straightforwardly obtained,

$$X = \frac{1}{\theta}\left\{1 - \exp\left(-\theta rt\right)\right\}, \tag{23}$$

allowing to find the needed irradiation time to kill every cell in the tissue ($X = 1$),

$$t_k = -\frac{\ln(1-\theta)}{\theta r}, \tag{24}$$

and showing that effective dose increases at a decreasing speed,

$$\dot{X} = r \exp(-\theta r t), \tag{25}$$

until tissue cells get annihilated at time $t_k(X = 1)$. Under continuous irradiation, the survival fraction decreases faster at the beginning of the irradiation process. However, depending on dose rate and the θ coefficient, the killing process speed slows down until eventually every cell is killed. If the recovery capacity is very high ($\theta = 1$) the radiation effects stack slowly and there will always be surviving tissue cells ($t_k = \infty$). Those radiation damages stack faster as long as tissue cells are less capable to recover and if there is no recovery at all ($\theta = 0$) the effective radiation dose grows linearly in time and cells get killed faster ($t_k = 1/r$). This time shortening behavior with decreasing recovering rate is also shown by other radiobiological models [18,19].

Comparing (17) and (22) we see that, in the limit of continuous dosage, they become the same expression with $\theta \simeq 1 - \epsilon$. However this relation may become invalid at high exposures as effective dose becomes larger and ϵX becomes of order 1, as shown in Fig. 6. At this point, the fractionated and continuous treatments differ.

This shows θ could be considered constant only for a limited time of the continuous irradiation. It must be studied, in general, as a function of time, describing the growing resistance of tissue to be annihilated. This function should make (22) mimic the behavior of (16), shown in Fig. 6.

5. Conclusions

The use of Tsallis entropy and the maximum entropy *ansatz* (second law of thermodynamics) have allowed us to write a simple nonextensive expression for the single dose survival fraction. The mathematical constraints, required to define the probabilities composition such that the two limiting behaviors are described, introduce a new parameter, relating the radiation sessions. The fits to available experimental data show that usual treatment have nontrivial values of this parameter, *i.e.*, are not close to the limiting behaviors. This makes the study of this coefficient relevant for clinical treatments and experimental setups.

The existence of a varying critical dosage arises from these composition rules, providing a criterion to adjust the critical treatment that kills every tumor cell or minimize the damage caused to healthy tissue. This could be accomplished changing the number of sessions or the radiation dose by session, allowing to switch between isoeffective treatments.

Also an expression for the effective dose in continuous irradiation treatments has been found, showing it is phenomenologically linked to the previous one. This has the potential to provide isoeffect relationships in continuous dose treatments such as brachytherapy. Besides, a relation between fractionated and continuous therapies could be established from the obtained coefficients.

Acknowledgments

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