Tissue Radiation Response with Maximum Tsallis Entropy

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The expression of survival factors for radiation damaged cells is currently based on probabilistic assumptions and experimentally fitted for each tumor, radiation, and conditions. Here, we show how the simplest of these radiobiological models can be derived from the maximum entropy principle of the classical Boltzmann-Gibbs expression. We extend this derivation using the Tsallis entropy and a cutoff hypothesis, motivated by clinical observations. The obtained expression shows a remarkable agreement with the experimental data found in the literature.

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One of the radiobiology main goals is to find the fraction of cells surviving under a given dose of radiation [1]. This fraction will depend on the radiation deposited on the tissue, which is on its own a very difficult transport [2] and timing [3] optimization problem, not to mention the multiple scales involved in this problem, as pointed out in [4].

Assuming the dose D of absorbed radiation is known, a mean-field model of the survival fraction F_s can be developed [1]. Current models are mainly based in what is called ''target theory,'' proposing some targets inside the cell that can be damaged by the radiation in a lethal event, provoking cell death.

The simplest radiobiology model is the linear one [1] where the survival fraction is expressed as $F_s = \exp(-\alpha D)$ arguing that the cell death under radiation follows a Poisson process. Here the survival fraction is viewed as the cumulative probability of cell survival (or complementary cumulative probability of cell death) under any dose below D. This probability fulfills the additive property meaning that the effects of radiation are cumulative following an additive model. So, the survival fraction for two doses can be found as $F_s[D_1 + D_2] = F_s[D_1]F_s[D_2]$.

This probabilistic framework calls to mind statistical mechanics and one of its cornerstones, the notion of entropy and the maximum entropy principle [5]. Statistical mechanics is perhaps the most general theoretical framework of physics. The general statistical approach provided by Boltzmann and Gibbs [6] allows us to apply the notion of entropy in diverse fields, including the theory of fluctuations [6], information theory [7], and many others.

If F_s is viewed as a probability function, then the problem could be posed in terms of the maximum entropy principle [8]. Let us denote by $p(E)$ the probability density of cell death and by $E(D)$ a dimensionless form of the radiation dose. This magnitude, usually expressed as $E = -\ln(F_s)$, is known as the tissue effect [9]. Then, under the assumption that the entropy is the Boltzmann-Gibbs (BG) entropy,

$$S = \int_\Omega p(E)\ln[p(E)]dE, \tag{1}$$

where Ω represents all the states of E, when the maximum entropy principle is demanded, the normalization condition, $\int_\Omega p(E)dE = 1$, and the mean value existence $\int_\Omega p(E)EdE = \langle E\rangle$ must be also fulfilled since $p(E)$ is a probability density.

It is known that the exponential distribution maximizes the entropy under these conditions. Then $p(E) = \frac{1}{\langle E\rangle}e^{-(E/\langle E\rangle)}$ and $F_s = \int_E^\infty p(x)dx = e^{-(E/\langle E\rangle)}$.

Until here the problem has been discussed as an extensive problem. So, the survival probability, or survival fraction, must fulfill the additive property and E must be proportional to D as $E = \alpha D$, where α is a constant that makes E adimensional. The survival fraction takes then the form

$$F_s = e^{-(D/\langle D\rangle)}, \tag{2}$$

i.e., the linear model of radiobiology.

However, this model fits the experimental data only for some tissues, under low radiation doses [1], so more complex empirical models have been built. Under the assumption that the cell death could be provoked by one or two lethal events, the linear quadratic (LQ) model [10] is expressed as $F_s = \exp[-\alpha D - \beta D^2]$. This model fits better with the experimental data for moderate radiation doses.

Some conclusions can be obtained from those models and the relation between them. First, in the transition from the linear to the LQ model, the survival fraction loses the additive property, since $F_s[D_1 + D_2] < F_s[D_1]F_s[D_2]$. A main threat here is that the superposition principle is not fulfilled. Indeed, it is easy to show that if the survival fraction were multiplicative for different radiation sessions, then the additivity of the dose would not hold. Conversely, assuming that the dose is additive then the survival fraction would not equal the product of survival fractions for different doses. It suggests that the radiobiological problem must be approached from a nonextensive formulation [11]. Second, in order to fit the experimental data a second order term had to be added to the linear model, and since the effect for high doses cannot be explained by any of those models, the conclusion is that the LQ model resembles a series approximation up to second order of a more complicated function.

In 1988 Tsallis introduced a generalization of the BG entropy function, called q entropy [12], which has been shown to give surprisingly good results when applied to all kinds of natural systems formed by many interacting elements (see [11] and references therein). In particular, it has successfully described the course of damage caused by large energy inputs leading to fractures [13] or earthquakes [14]. Hence, to cope with nonextensivity, and motivated by the analogy with those damage models, we will apply to the radiobiological problem the Tsallis entropy [11],

$$S_q = \frac{1}{q-1}[1 - \int_\Omega p^q(E)dE], \tag{3}$$

where q is the index of nonextensivity. This condition is completed by the constraints that the probability density satisfies the normalization condition and the finiteness of the q-mean value $\int_\Omega p^q(E)EdE = \langle E\rangle_q < \infty$ [15].

If the probability distribution support is $\Omega = [0;\infty)$, then the solutions vanish subexponentially implying a value $q \geq 1$. However, if Ω is considered bounded from above, the solutions vanish superexponentially in Ω for $q < 1$ [16]. We will request this latter property for Ω, because there is clinical evidence that for some tumors a finite threshold effect exists enough to completely remove them, and also the data support this superexponential decay with the dose.

To apply the maximum entropy principle in its Tsallis version to the problem of finding the survival fraction of an irradiated living tissue [17], we postulate the existence of some amount of absorbed radiation $D_0 < \infty$ (or its equivalent "minimal annihilation effect," $E_0 = \alpha_0 D_0$) after which no cell survives. The application of the maximum entropy principle is performed in the usual way but for a few modifications.

The Tsallis entropy becomes

$$S_q = \frac{1}{q-1}\left[1 - \int_0^{E_0} p^q(E)dE\right], \tag{4}$$

the normalization condition is in this case $\int_0^{E_0} p(E)dE = 1$ and the q-mean value becomes $\int_0^{E_0} p^q(E)EdE = \langle E\rangle_q < \infty$. With this definition, all properties of the tissue and its characteristics of the interaction with radiation become included in $\langle E\rangle_q$ and therefore in E_0. This is the only parameter (besides q) entering in our description. It is clear that the determination of $\langle E\rangle_q$ for the different tissues under different conditions of radiation would give the necessary information for the characterization of the survival factor.

To calculate the maximum of S_q under the above conditions the well-known method of Lagrange multipliers is applied, obtaining

$$E_0 = \frac{2-q}{1-q}\left(\frac{\langle E\rangle_q}{2-q}\right)^{1/2-q}, \tag{5}$$

and

$$p(E) = \left(\frac{2-q}{\langle E\rangle_q}\right)^{1/2-q}\left[1 - \frac{1-q}{2-q}\left(\frac{2-q}{\langle E\rangle_q}\right)^{1/2-q}E\right]^{1/1-q}. \tag{6}$$

Then the survival factor is

$$F_s(E) = \int_E^{E_0} p(x)dx = \left(1 - \frac{E}{E_0}\right)^{2-q/1-q}, \tag{7}$$

with $q < 1$ for $E < E_0$ and zero otherwise. It is not hard to see that when $q \to 1$ then $E_0 \to \infty$ and $\langle E\rangle_q \to \langle E\rangle$.

Equation (7) can be written

$$F_s(D) = \begin{cases} (1 - \frac{D}{D_0})^\gamma & \forall\ D < D_0, \\ 0 & \forall\ D \geq D_0, \end{cases} \tag{8}$$

where we introduced $E = \alpha D$, $\gamma = \frac{2-q}{1-q}$, and $D_0 = E_0/\alpha$. Finally, the LQ model is easily recovered in the limit $q \to 1$ up to order two in a Taylor series expansion. This is a restatement of our conjecture that the LQ model comes from an approximation of a more general model.

Equation (8) represents the survival fraction in terms of the measurable quantities D (radiation dose) and D_0 (minimal annihilation dose).

In order to compare our model with the experimental data we have selected some survival curves from the literature [17–21] where the survival fraction F_s is represented as a function of D for different radiation conditions. Following the usual method of phase transition theory, rescaling D as $1 - D/D_0$, all curves corresponding to the same tissue collapse to the same straight line in a log-log plot as in Fig. 1. The expression of $\ln(F_s)$ has been fitted for 23 experimental data sets, corresponding to 5 different tissues under different radiation conditions. For each tissue the steepest descent method [22] is used to minimize the least squares functional,

$$\chi^2 = \sum_i \sum_{j=1}^{n_i}\left[\gamma \ln\left(1 - \frac{D_j}{D_{0,i}}\right) - \ln(F_{s,j})\right]^2 \tag{9}$$

where i denotes the tissue experimental set (different irradiation conditions), j runs along the n_i experimental points

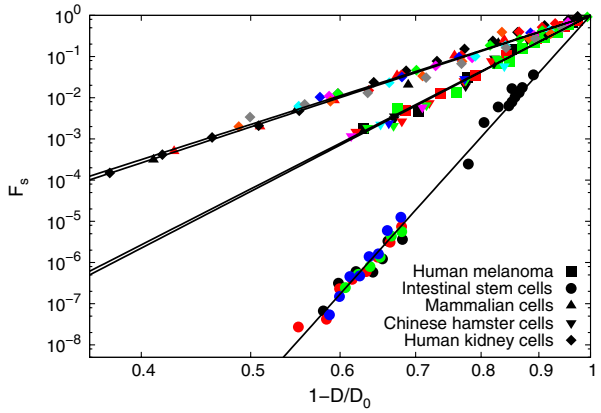

FIG. 1 (color online). Survival fraction F_s as a function of the rescaled dose $1 - D/D_0$ for different tissues: intestinal stem cells, Chinese hamster cells, human melanoma, human kidney cells, and cultured mammalian cells under different irradiation conditions detailed in [17–21]. Various shapes represent tissues whereas each color points out different radiation conditions. Five solids lines represent fitting to experimental data, detailed in [23].

(each of them reporting survival fraction $F_{s,j}$ when a dose D_j is applied), and $D_{0,i}$ is the minimal annihilation dose for the ith experimental set. The slopes of these lines are the values of γ.

This figure shows a clear grouping of tissues in universality classes corresponding to different values of γ. Intestinal stem cells are clearly grouped in a class with $\gamma = 30.5 \pm 0.4$, whereas cultured mammalian cells and human kidney cells have very close values of γ, close to 8.9. Chinese hamster and human melanoma cells are also close with values of $\gamma \approx 14.0$, inside the error range (see [23]).

On the other hand, Fig. 2 shows, in a log-log plot, the comparison of our model with all these data sets. In order to represent all data sets in the same plot the survival fraction is shown normalized by gamma as $(F_s)^{1/\gamma}$. As expected, all data sets are fully grouped in the same line with a clear manifestation of the universality of the phenomenon of the interaction of radiation with living tissues.

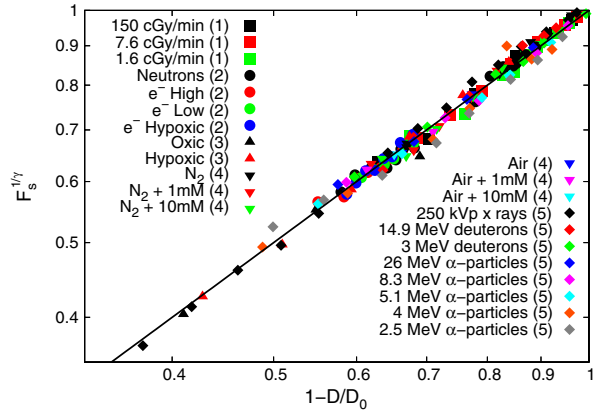

FIG. 2 (color online). Normalized survival fractions $(F_s)^{1/\gamma}$ as a function of the rescaled radiation dose, $1 - D/D_0$ for different tissues: intestinal stem cells (■), chinese hamster cells (●), human melanoma (▲), human kidney cells (▼), and cultured mammalian cells (◆) under different irradiation conditions detailed in [17–21] and grouped in [23]. The straight line shown is $y = x$.

In order to compare our model with the LQ model we will take the CHO AA8 cell line data from [24]. These data have two advantages over those shown in previous figures, a higher amount of experimental points, evenly spaced in a wide range of D values, and reported values for LQ coefficients. The usual representation for F_s plot is used in Fig. 3 illustrating one of the major advantages of our model: even though the LQ model fits experimental data well in the low and intermediate dose ranges (see [24] for their special fitting details), our model reproduces survival fraction behaviors for all the data range even at high doses where the LQ model fails. This allows the use of this model in hypofractionation radiotherapy treatments where current models cannot be applied.

The nice agreement with the data, and results as the introduction of concepts like ''minimal annihilation dose'' and universality of the tissue-radiation interaction, expresses an advantage of our approach based in Tsallis entropy. No assumption based on the radiation-tissue interaction mechanism was needed. Furthermore, the Tsallis formalism naturally introduces a nonadditive q algebra [16] that keeps the additivity of E (proportional to the absorbed energy) and generalizes other additive properties whose lack motivated this work. This is done defining the γ exponential, γ logarithm, and γ product and providing simple expressions for survival fraction in multifractionated treatments. This, and a few practical applications of these results concerning radiotherapy protocols, have been reported elsewhere [23].

Beyond any consideration about the application of entropic formulations or the validity of a given entropic

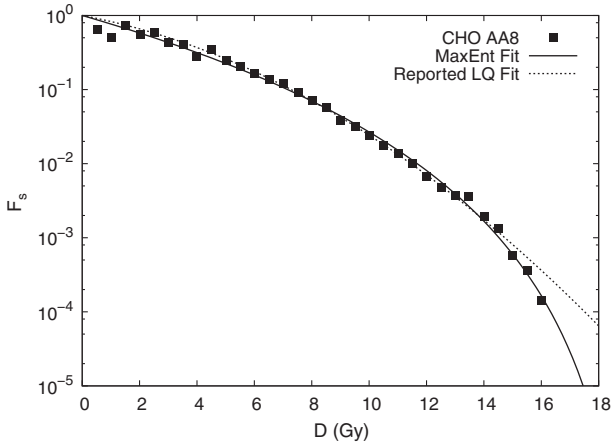

FIG. 3. Comparison between the LQ model best fit ($\alpha = 0.167 \pm 0.015$ Gy^{-1} and $\beta = 0.0205 \pm 0.0015$ Gy^{-2}) reported in [24] and our model fitted to $\gamma = 5.0 \pm 0.4$ and $D_0 = 19.4 \pm 0.4$ Gy for the cell line CHO AA8 under 250 k-Vp x rays.

form, we presented a derivation of a law describing the cell survival fraction of living cells as a function of the dose, based in the extremization of a functional under given conditions. This only fact leads to significant results grounded on a formal basis, which is an advance with respect to the empirical approaches that we have found in this field.

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