Non-extensive radiobiology

O. Sotolongo-Grau[*], D. Rodriguez-Perez[*], J. C. Antoranz[*,†] and O. Sotolongo-Costa[†]

[*]*UNED, Departamento de Física Matemática y de Fluidos*
[†]*UH, Cátedra de Sistemas Complejos Henri Poincaré*

Abstract. The expression of survival factors for radiation damaged cells is 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. A generalization of the exponential, the logarithm and the product to a non-extensive framework, provides a simple formula for the survival fraction corresponding to the application of several radiation doses on a living tissue. The obtained expression shows a remarkable agreement with the experimental data found in the literature, also providing a new interpretation of some of the parameters introduced anew. It is also shown how the presented formalism may have direct application in radiotherapy treatment optimization through the definition of the potential effect difference, simply calculated between the tumour and the surrounding tissue.

INTRODUCTION

One of the main concerns of a radiation oncologist is to find a treatment which, maximizing the damage over the tumor, minimizes it over the surrounding healthy tissue. In order to reach a suitable treatment the radiobiologists have developed some empirical models describing the interaction between radiation and living tissues (see [1] for a review of radiobiology models) capable of finding the survival fraction, F_s, of cells under a radiation dose, D. The applicability limits of these models are not clear so multiple corrections have been developed to fit the experimental data [2].

The concept of tissue effect, E, raised from some of these models [3] is used to compare different treatments. Usually expressed as $F_s = \exp(-E)$, E is a dimensionless magnitude that gathers several models of interaction between cells and ionizing radiation.

The simplest radiobiology model is the linear one, where the tissue effect is considered linear to the radiation dose, $E = \alpha D$, and the survival fraction, $F_s = \exp(-\alpha D)$, is viewed as the cumulative survival probability of a cell under any dose below D. This probability fullfils the additive property, meaning that the effects of radiation are cumulative following an additive model and the survival fraction for two doses could be found as $F_s[D_1 + D_2] = F_s[D_1] \cdot F_s[D_2]$.

This model, however, fits the experimental data for only some tissues and under low radiation doses [1]. The tissue effect must then be corrected to $E = \alpha D +$

βD^2, called the linear quadratic (LQ) model. The survival fraction loses the additive property, $F_s[D_1+D_2] < F_s[D_1] \cdot F_s[D_2]$, and the tissue effect becomes supperadditive, $E[D_1+D_2] > E[D_1] + E[D_2]$.

The extension to a model nonlinear in E conflicts with physical intuition which expects linear behavior. Any model of interaction between radiation and living tissues must allow to divide a continuous radiation in finite intervals and the resultant tissue effect must be the same.

Indeed, it is easy to show that, under the LQ viewpoint, if the tissue effect were additive for different radiation sessions then the additivity of the dose would not hold. Conversely, assuming that the dose is additive then the tissue effect would not be equivalent to the sum of the effects for different doses. This result suggests that the radiobiological problem must be approached from a non extensive formulation [4].

In this work we use at the first stage the Boltzmann-Gibbs (BG) entropy in order to find the expression of the tissue effect as a function of the absorbed dose. Later, along with the Tsallis entropy [5] definition, it is assumed that a critical value of the radiation dose kills every single cell and a general expression for survival fraction is found. This survival fraction expression fits the experimental data even where previous empirical models fail. Using the q-deformed functions [6, 7] a new expression to find the survival fraction of a whole treatment is found allowing to show hints to find the best treatment.

FIRST STEP: THE CLASSICAL APPROACH

First we study the extensive problem applying the BG entropy (in units of the Boltzmann constant),

$$S = -\int_0^\infty \ln[p(E)]p(E)dE, \tag{1}$$

where in this case E is, as before, the tissue effect and $p(E)$ is the cell killing probability density.

According to the maximum entropy principle, if $p(E)$ satisfies the normalization condition and a finite mean value of the tissue effect does exist, then the problem of finding the $p(E)$ that extremizes the BG entropy under the above conditions can be posed. It is well known that among all continuous probability distributions for a positive continuous variable with a fixed mean value, the maximum entropy distribution is exponential [8],

$$p(E) = \frac{1}{\langle E \rangle} e^{-\frac{E}{\langle E \rangle}}, \tag{2}$$

and the survival probability of a single cell will be

$$F_s = \int_E^\infty p(x)\,dx = e^{-\frac{E}{\langle E \rangle}}. \tag{3}$$

The survival probability here must fulfill the dose additivity property. This can be achieved if, following the discussion in the previous section, the tissue effect is proportional to the absorbed dose:

$$E = \alpha_0 D, \tag{4}$$

where α_0 is chosen as a constant that makes E dimensionaless.

It must be noted that (3) is the experimentally proven and currently used expression for the survival fraction as a function of tissue effect and justified in the literature only through empirical arguments [1]. We can take $\alpha = \alpha_0 / \langle E \rangle = 1 / \langle D \rangle$ and the expression (3) becomes expressed in the known standard radiobiology form of the linear model.

Even when the BG treatment of the problem does not cover the available data, it shows that the tissue effect must be defined as proportional to the absorbed dose of radiation. However the empiric expressions already known show, as was discussed in the introduction, that the survival probability of a cell does not fulfill the additive property. Since this is usually associated to non-extensive problems the solution must be searched using a non-extensive definition of entropy. On the other hand, the Tsallis formulation of the entropy has proved useful when applied to problems of this nature.

ONE STEP FURTHER: THE GENERALIZED APPROACH

To apply the maximum entropy principle, in the Tsallis version, to the problem of finding the survival fraction of a living tissue [9] that receives a radiation, 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 performs like the usual one but with a few modifications.

The Tsallis entropy becomes

$$S_q = \frac{1}{q-1} \left(1 - \int_0^{E_0} p^q(E) dE \right),$$ (5)

the normalization condition is in this case $\int_0^{E_0} p(E) dE = 1$ and the q-mean value becomes $\int_0^{E_0} p^q(E) E dE = \langle E \rangle_q < \infty$. 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 (5) under the above conditions the well known method of Lagrange multipliers [7] is applied, obtaining

$$E_0 = \frac{2-q}{1-q} \left(\frac{\langle E \rangle_q}{2-q} \right)^{\frac{1}{2-q}},$$ (6)

and

$$p(E) = \left(\frac{2-q}{\langle E \rangle_q} \right)^{\frac{1}{2-q}} \left(1 - \frac{1-q}{2-q} \left(\frac{2-q}{\langle E \rangle_q} \right)^{\frac{1}{2-q}} E \right)^{\frac{1}{1-q}}.$$ (7)

Then the survival factor is

$$F_s(E) = \int_E^{E_0} p(x)dx = \left(1 - \frac{E}{E_0}\right)^{\frac{2-q}{1-q}},\tag{8}$$

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 (8) can be written

$$F_s(D) = \begin{cases} \left(1 - \frac{D}{D_0}\right)^\gamma & \forall D < D_0 \\ 0 & \forall D \geqslant D_0 \end{cases},\tag{9}$$

where we introduced $E = \alpha_0 D$, $\gamma = \frac{2-q}{1-q}$ and $D_0 = E_0/\alpha_0$. Finally, the LQ model is easily recovered from (9) in the limit $q \to 1$ up to order two in a Taylor series expansion [10].

Tsallis based Survival fraction properties

The linear model for the tissue effect [1] implies that if the dose is additive the corresponding survival fraction is multiplicative. Though this property belongs only to the linear model and not to more general descriptions like the LQ model [1] and others, we think it is worth to find a link between the additivity property of the dose and the probabilistic properties of the cell survival fraction.

Let us define the $\exp_\gamma(x)$ function

$$\exp_\gamma(x) = \left[1 + \frac{x}{\gamma}\right]^\gamma,\tag{10}$$

and its inverse function

$$\ln_\gamma(\exp_\gamma(x)) = x.\tag{11}$$

Then, consider the γ-product of two numbers x and y as

$$x \otimes_\gamma y = \exp_\gamma\left[\ln_\gamma(x) + \ln_\gamma(y)\right] = \left[x^{\frac{1}{\gamma}} + y^{\frac{1}{\gamma}} - 1\right]^\gamma.\tag{12}$$

Note that definitions (10) and (11) are not essentially different from the q-exponential and q-logarithm presented in [6]. We are just introducing these definitions to simplify the calculations.

Let us now define the "generalized tissue effect" as $E = -\frac{E_0}{\gamma} \ln_\gamma(F_s)$. We demand this effect to satisfy the additive property. Then the survival fraction, F_s, expressed as $\exp_\gamma(-\gamma\frac{E}{E_0}) = \exp_\gamma(-\gamma\frac{D}{D_0})$, becomes γ-multiplicative. This implies that the statistical independence of the survival fractions is only possible when $\gamma \to \infty$ ($q \to 1$).

The survival fraction for the sum of the effects after N doses becomes

$$F_s(NE) = \left[1 - \sum_{i=1}^N \frac{E_i}{E_0}\right]^\gamma = \exp_\gamma\left[-\sum_{i=1}^N \gamma\frac{E_i}{E_0}\right] = \left[\bigotimes_{i=1}^N\right]_\gamma F_s(E_i),\tag{13}$$
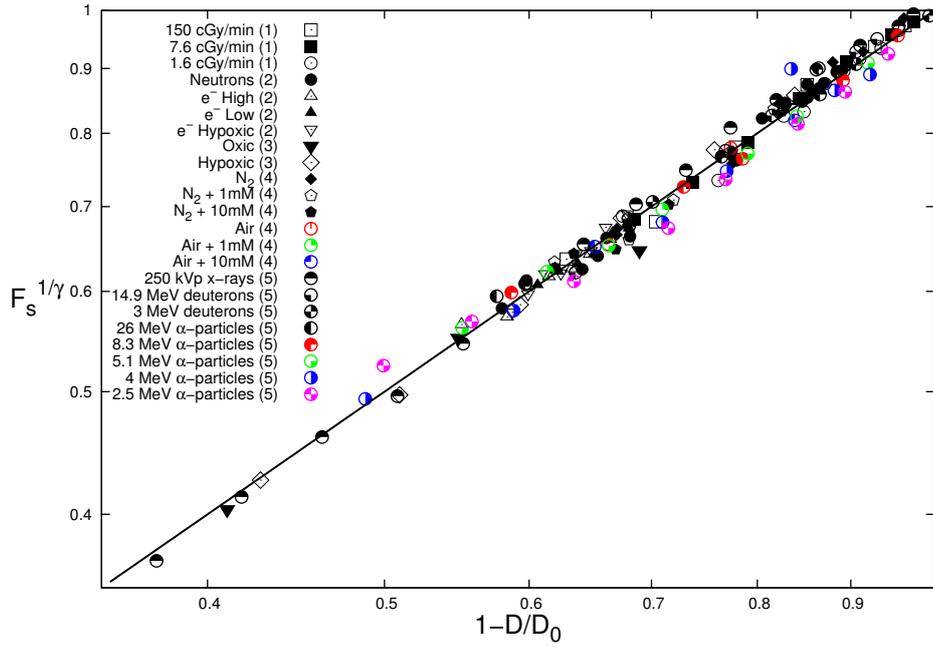
FIGURE 1. Normalized survival fractions, $(F_s)^{1/\gamma}$, as a function of the rescaled radiation dose, $1 - D/D_0$. The straight line shown is $y = x$. Values for γ and D_0 are detailed in table 1.

where $\left[\bigotimes_{i=1}^{N}\right]_\gamma$ denotes the iterated application of the γ-product.

EXPERIMENTAL AGREEMENT

Equation (9) 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 where the survival fraction F_s is represented as a function of D for different radiation conditions. However, if D is rescaled as $1 - D/D_0$, as usual in phase transition phenomena, all curves corresponding to the same tissue collapse to the same straight line in a log-log plot.

The expression of $\ln[F_s]$ has been fitted for 23 experimental data sets, corresponding to 5 different tissues, in terms of the rescaled variable $\ln[1 - D/D_0]$, minimizing the appropriate least squares functional using the *steepest descent* method [11]. The slope of these lines are the values of γ meaning that D_0 is the natural unit of D.

Figure 1 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 γ as $(F_s)^{1/\gamma}$ clearly manifesting the universality of interaction of radiation with living tissues. Fitting parameter values γ and D_0 are summarized in Table 1.

All the information about the kind of radiation, radiation rate, etc. is contained in the phenomenological term D_0, whereas tissues are characterized by γ. This makes (9) a very general expression with universal characteristics since the phase transition

described by (9) is homomorphic with the phase transition of ferromagnets near the Curie point [17]. The exponent γ in this case, as in ferromagnetic phase transitions, determines the universality class. Then γ in our case deals only with the kind of tissue that interacts with radiation [10].

IS IT POSSIBLE TO DESIGN THE BEST PROTOCOL?

The expression for the survival fraction after N doses of radiation must allow to compare the damage provoked on the tumor and surrounding tissue cells if the magnitudes γ and D_0 are known for both, tumor and tissue. Let us assume we know the recommended radiation dose D_+ per session for a treatment with N sessions at several values of N. We will define the potential effect as

$$\chi = -\ln\left[F_s\right], \tag{14}$$

and then the recommended potential effect per dose over the tumor will be,

$$\chi_+ = -\gamma^{(t)}\ln\left[1 - \frac{D_+}{D_0^{(t)}}\right], \tag{15}$$

where $\gamma^{(t)}$ and $D_0^{(t)}$ are the characteristic radiation coefficients for the tumor. If we have already characterized the healthy tissue around the tumor with $\gamma^{(h)}$ and $D_0^{(h)}$ then we can find the survival fraction of cells after the treatment for the tumor,

$$\Theta^{(t)} = \exp_{\gamma^{(t)}}\left[N\ln_{\gamma^{(t)}}\left[\exp\left(-\chi_+\right)\right]\right], \tag{16}$$

and the healthy tissue,

$$\Theta^{(h)} = \exp_{\gamma^{(h)}}\left[\frac{\gamma^{(h)}D_0^{(t)}}{\gamma^{(t)}D_0^{(h)}}N\ln_{\gamma^{(t)}}\left[\exp\left(-\chi_+\right)\right]\right]. \tag{17}$$

In order to find the best treatment all we need is to calculate the difference of potentials for the treatment,

$$\Delta\chi = \chi^{(t)} - \chi^{(h)} = \ln\left[\frac{\Theta^{(h)}}{\Theta^{(t)}}\right], \tag{18}$$

and guarantee that it will be positive. This could be achieved taking advantage of the different responses to radiation of tumor and normal tissues. Also, if this response is too close for an specific kind of radiation or a given dose rate, those conditions could be changed looking for a higher potential difference.

CONCLUSIONS

A new theoretical expression for the survival fraction of cells under radiation has been found, using the Tsallis formulation of entropy. The clinical existence of a critical value for the absorbed radiation dose under which no cells survive is introduced in the formulation and an expression is obtained. The new expression depends on two coefficients that characterize the tissue behaviour under radiation (γ) and the specific conditions in which the radiation is applied (D_0).

The Tsallis mathematical formalism allows to redefine the multiplication operation giving a way to find the survival fraction after several radiation sessions. If the characteristic coefficients are known for the tumor and the surrounding tissue then some hints can be given to choose the less harmful, albeit most efficient, treatment to apply.

ACKNOWLEDGMENTS

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TABLE 1. Values for γ and D_0 obtained from the fitting with experimental data.

(1) Human melanoma ($\gamma = 14.0 \pm 0.9$) irradiated at different dose rates. Data extracted from [12].

150 cGy/min	$D_0 = 27 \pm 2$ Gy
7.6 cGy/min	$D_0 = 38 \pm 4$ Gy
1.6 cGy/min	$D_0 = 46 \pm 5$ Gy

(2) Intestinal stem-cells ($\gamma = 30.5 \pm 0.4$) irradiated with different particles an conditions. Data extracted from [13].

Neutrons	$D_0 = 36.0 \pm 0.7$ Gy
Electrons (high dose rate)	$D_0 = 62.2 \pm 1.2$ Gy
Electrons (low dose rate)	$D_0 = 68.8 \pm 1.6$ Gy
Electrons (hypoxic conditions)	$D_0 = 162 \pm 3$ Gy

(3) Cultured mammalian cells ($\gamma = 8.9 \pm 0.6$) exposed to x-rays under oxic and hypoxic conditions. Data extracted from [14].

Oxic	$D_0 = 21.7 \pm 1.4$ Gy
Hypoxic	$D_0 = 61 \pm 4$ Gy

(4) Chinese hamster cells ($\gamma = 14.2 \pm 0.6$) irradiated in the presence or absence of misonidazole. Data extracted from [15].

Hypoxic	$D_0 = 85 \pm 7$ Gy
Hypoxic, 1mM	$D_0 = 46 \pm 3$ Gy
Hypoxic, 10mM	$D_0 = 33 \pm 2$ Gy
Aerated	$D_0 = 29 \pm 3$ Gy
Aerated, 1mM	$D_0 = 28 \pm 3$ Gy
Aerated, 10mM	$D_0 = 32 \pm 4$ Gy

(5) Human kidney cells ($\gamma = 8.8 \pm 0.3$) exposed in vitro to radiations of different energies. Data extracted from [16].

250kVp x-rays	$D_0 = 22.4 \pm 0.8$ Gy
14.9MeV deuterons	$D_0 = 22 \pm 3$ Gy
3MeV deuterons	$D_0 = 17 \pm 2$ Gy
26MeV α-particles	$D_0 = 15 \pm 2$ Gy
8.3MeV α-particles	$D_0 = 9.1 \pm 1.2$ Gy
5.1MeV α-particles	$D_0 = 7.5 \pm 0.8$ Gy
4MeV α-particles	$D_0 = 6.9 \pm 0.6$ Gy
2.5MeV α-particles	$D_0 = 9.2 \pm 0.7$ Gy