TSALLIS FORMALISM IN RADIOBIOLOGY

EL FORMALISMO DE TSALLIS EN LA RADIOBIOLOGÍA

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We describe how Tsallis' formalism can be applied to the cell survival factor of cells under radiation. Some universal characteristics become revealed with this treatment. This viewpoint has potential applications in clinical radiotherapy.

Describimos cómo el formalismo de Tsallis puede ser aplicado al estudio del factor de supervivencia de células sometidas a radiación. Este tratamiento revela algunas características universales del proceso, y posee aplicaciones potenciales en radioterapia clínica.

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INTRODUCTION

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.

Their applicability limits are not clear, so multiple corrections have been developed in order to fit the experimental data. Usually expressed as $E = -\ln(F_s)$, the tissue effect gathers together several models of interaction between cells and ionizing radiation. In the linear model, tissue effect is considered linear to the radiation dose, $E = \alpha D$, and the survival fraction, $F_s = \exp(-\alpha D)$, is the cumulative survival probability of a cell under any dose D. So, the probability fulfills the additive property, so $F_s[D_1 + D_2] = F_s[D_1] + F_s[D_2]$. However, this model only fits the experimental data for some tissues under low radiation doses [1], so the tissue effect must be corrected to $E = \alpha D + \beta D^2$, called the linear quadratic (LQ) model. But then the survival fraction loses the additive property. Then, the superposition principle is not fulfilled. However, any model of interaction between radiation and living tissues must allow dividing a continuous radiation in finite intervals and the resultant tissue effect must be the same. Indeed, assuming that the dose is additive, the tissue effect is not the sum of the effects for different doses. This suggests that the radiobiological problem must be approached from a non extensive formulation [2]. Here, a general expression for survival fraction is found using the Tsallis entropy [3] definition, and assuming the existence of a critical dose that kills every single cell. This survival fraction expression fits the experimental data even where previous empirical models fail. Using the q-algebra [4, 5] a new expression to find the survival fraction of a whole treatment is shown.

TSALLIS APPROACH TO RADIOBIOLOGY

To apply the maximum entropy principle in the Tsallis version to the problem of finding the survival fraction of a living tissue [6] that receives a radiation, we postulate the existence of some amount of absorbed radiation D_0 (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 is

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

The normalization condition is $\int_0^{E_0} p(E)\, dE = 1$, and the q-mean value becomes $\int_0^{E_0} E\, p^q(E)\, dE = \langle E \rangle_q < \infty$.

With this definition, all properties of the tissue and its interaction with radiation become included in $\langle E \rangle_q$ and therefore in E_0.

To calculate the maximum of (1) under the above conditions the well known method of Lagrange multipliers [5] is applied, resulting in

$$F_s(D) = \begin{cases} \left(1 - \frac{D}{D_0}\right)^{\gamma} & D < D_0 \\ 0 & D > D_0 \end{cases} \tag{2}$$

where we introduced $E = \alpha_0 D$, $\gamma = \frac{2-q}{1-q}$, $D_0 = \frac{E_0}{\alpha_0}$. Finally, the LQ model is easily recovered from (2) in the limit $q \to 1$ up to order two in a Taylor series expansion [7, 8].

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. The exponent γ in this case, as in phase transitions, determines the universality class.

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. It is worth to find a link between the additive property of the dose and the probabilistic properties of the cell survival fraction. Let us use the function: $\exp_\gamma(x) = \left(1+\frac{x}{\gamma}\right)^\gamma$ and its inverse function: $\ln_\gamma(\exp_\gamma(x)) = x.$ Then, let us introduce the γ-product of two numbers x and y as

$$x \otimes y = \exp_\gamma\left[\ln_\gamma(x) + \ln_\gamma(y)\right] = \left[x^{\frac{1}{\gamma}} + y^{\frac{1}{\gamma}} - 1\right]^\gamma. \qquad (3)$$

Note that these definitions are not essentially different from the q-exponential and q-logarithm presented in [4]. We are just introducing these definitions to simplify the calculations. Let us now define the "generalized tissue effect" $E = -\frac{E_0}{\gamma}\ln_\gamma(F_s).$ We demand this effect to satisfy the additive property. Then the survival fraction, expressed as

$$F_s = \exp_\gamma\left(-\gamma\frac{D}{D_0}\right), \qquad (4)$$

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

$$F_s(N,D) = \left[1 - \sum_{i=1}^{N}\frac{D_i}{D_0}\right]^\gamma = \bigotimes_{i=1}^{N} F_s(D_i), \qquad (5)$$

where $\bigotimes_{i=1}^{N}$ denotes the iterated application of the γ-product. On the other hand, if the survival probabilities are independent the effect is not additive and the sum must be redefined as $x \oplus y = x + y - \frac{xy}{\gamma}$. Hence, the total survival fraction is

$$F_s(N,D) = \left[1 - \bigoplus_{i=1}^{N}\frac{D_i}{D_0}\right]^\gamma = \prod_{i=1}^{N} F_s(D_i), \qquad (6)$$

where $\bigoplus_{i=1}^{N}$ denotes the iterated application of the γ-sum.

This equation leads to new insights, as we shall point.

CONSEQUENCES

This model has shown a remarkable agreement with experimental data [7], even in those limits where previous models are less accurate, mainly at high doses. The analysis of the model 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 exposure); second, the model includes a cutoff radiation dose above which every single cell dies. Furthermore, previous models can be obtained as particular limiting cases. Besides, as for those models, its mathematical expression is simple and can be easily plotted and interpreted.

Furthermore the model was derived for radiobiological survival fraction but its applicability could be extended to other processes. Indeed, every irreversible phenomena where the individual entities can get a terminal state and that fulfils the conditions: (i) can be described with Tsallis entropy [8], (ii) keeps the maximum entropy principle, (iii) a critical cutoff exists in such a way that no alive entity remains after it, must follow (2).

In particular this could be applied to some biological interactions or clinical treatments as antibiotics or other killer drugs.

Nevertheless the expression (2), understood as survival probability, lacks the extensively property. In other words, for n events following (2) the total survival probability should be found as a composition of the survival probabilities of the successive events. However, there is no straightforward composition rule for those probabilities.

Indeed, a new view introduced by Eq. (6) is that if two doses, X_A and X_B are applied, the resulting probability from their composition has two possible values. If the dose is assumed as additive, $F_{AB} = \left(1 - D_A - D_B\right)^\gamma$ (here D is expressed in units of D_0 to simplify), the individual probabilities under the 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, $F_{AB} = \left(1 - D_A\right)^\gamma \left(1 - D_B\right)^\gamma$, doses do not fulfil the superposition principle for the equivalent physical dose, $X_{AB} \neq X_A + X_B$.

In other words, Eq. (6) has revealed, in a formal framework, *the relativity of the applied dose*. This is intuitively known in clinical practice (i.e. doses have not the same effect if continuously applied or splitted in time), but here we have provided a formal basis for this fact, that not only has conceptual importance, but also practical applications, particularly in the isoeffect problem. Results on this issue will be published later.

CONCLUSIONS

A new theoretical expression for the survival fraction of cells under radiation has been found, using the Tsallis formulation of entropy. The existence of a critical value for the absorbed radiation dose under which no entities survive is introduced in the formulation in order to get a proper expression. The new expression depends of two coefficients that characterize the tissue behavior under radiation (γ) and the specific conditions in which the radiation is applied (D_0). Here, the relation between the additivity of the dose and the survival probability has been revealed and conceptualized.

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