

High experimental agreement of tissue radiation response applying the maximum entropy principle

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Abstract

The expression of survival fractions for radiation damaged cells has been currently based on probabilistic assumptions and experimentally fitted for each tissue, 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.

1. Introduction

The interaction of radiation with living matter, as studied by radiobiology, is an extremely difficult problem. It involves an enormous amount of interactions of many kinds, ranging from biological, chemical, electrodynamical and even quantum mechanical processes. Current models try to merge approximations coming from all these fields and regarding all these processes, aiming at more and more predictive results, despite those initial model limitations. However, it could be of some use to introduce a framework borrowed from other disciplines dealing with complex systems, giving some alternative global vision on the problem and, hopefully, extending current models beyond their limits.

The well known LQ model has been widely accepted [1 - 3] as a solution to this complex problem. It asserts that the tissue effect has a linear component due to single-track events and a quadratic component which arises from two-track events. However it is worth saying that the LQ model (with its multiple corrections) does not derive from a mechanistic theory addressing what type of targets are those considered in the underlying probabilistic model. Like other models in science it is a heuristic model justified *a posteriori* by its good fit to available data and predictive capability. Besides, it resembles a series expansion up to second order of a more complicated function.

On the other hand, the physical discipline of thermodynamics (or its microscopic counterpart, statistical mechanics) is perhaps the most general

theoretical framework dealing with complex systems. Its quantitative laws are universal since thermodynamic models are not based on the details of any particular mechanisms, but on the macroscopically observable properties. One of the thermodynamics cornerstones is the notion of entropy and the maximum entropy principle and its statistical interpretation given by Boltzmann and Gibbs [4]. This statistical link has enabled to apply the notion of entropy in diverse fields, including the theory of fluctuations, information theory and many others [5].

Maximum entropy principle is mathematically well founded and has seen an almost unlimited number of applications in physics, biology, demography, economy, etc. [6]. This principle is not even alien to medicine as it is, by example, successfully used as the base of the mutual information registration of medical images [7]. In its modern formulation it says, “Given a model of probability distributions, choose the distribution with the highest entropy.” [8]. It means that one should look for the distribution, consistent with the observed constraints, which maximizes the entropy.

There is not a unique definition of entropy. The Boltzmann-Gibbs (BG) entropy is the classical prototype of entropy function (see below). However, in 1988 Tsallis introduced a generalization of this entropy function, called *q*-entropy [9], which has shown to give surprisingly good results when applied to all kind of natural systems formed by many interacting elements (see [6] and references therein).

In this paper, the concept of entropy in both the sense of Boltzmann-Gibbs [8] and of Tsallis [10] will be used to derive a radiobiological model. We will show that this statistical physics view copes well with the experimental observations concerning the interaction of radiation with living tissues for a wide range of doses. We will also show how the LQ model becomes a particular case of the obtained expression and its characteristics and shortcomings are discussed. Finally we compare our results with some experimental data and point out some analogies between this problem and phase transition theory.

2. Radiobiology and extensivity

According to the radiobiology linear model for the cell survival fraction, the fraction of tissue surviving a radiation dose D , is

$$F_s = \exp[-\alpha D]. \quad (1)$$

F_s can be viewed as a cumulative probability of cell survival, from an initial dose of 0 to D . From this it follows that

$$p(D)dD = \alpha \exp[-\alpha D]dD, \quad (2)$$

is the killed cell probability density (per dose unit). The cumulative probability fulfils the additive property, meaning that the effects of radiation are cumulative. The additive variable here is the tissue effect, $E = \alpha D = -\ln[F_s]$.

However, the linear model (1) is not accurate enough for a higher radiation dosage and the empiric experience shows that the tissue effect must be corrected to

$$E = \alpha D + \beta D^2, \quad (3)$$

in what is called the LQ Model.

From the point of view of the probabilistic interpretation given above, one problem arises: the probability function becomes non additive. That is, the survival fraction for two doses (even if applied concurrently!) is lesser than the survival fraction for the equivalent dose, meaning that E is a superadditive variable or, as we would said in statistical physics, nonextensive.

As a result of the nonlinear nature of E in this case, the linear superposition principle is not fulfilled. The result of applying the LQ model suggests that the radiobiological problem must be approached from a non extensive formulation.

3. The classical approach

For the sake of illustration we will study now the radiobiological problem applying the maximum entropy principle to the BG extensive expression of entropy. The BG entropy function for this problem reads,

$$S = -\int_0^\infty \ln[p(E)]p(E)dE, \quad (4)$$

where E is 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 function $p(E)$ will be the one that extremizes the BG entropy subject to those conditions, that is, the solution of the optimization problem.

It is well known that among all continuous probability distributions for a positive continuous variable with a fixed mean value, the exponential distribution has the

largest entropy [5]. So the survival probability of a single cell will be

$$F_s = e^{-\frac{E}{\langle E \rangle}}. \quad (5)$$

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:

$$E = \alpha_0 D, \quad (6)$$

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

It must be noted that (5) is the experimentally proved and currently used expression for the survival fraction as a function of tissue effect and justified in the literature through empirical arguments [2]. We can take $\alpha = \alpha_0 / \langle E \rangle = 1 / \langle D \rangle$ and (5) becomes expressed in the known standard radiobiology form of the linear model.

Even though 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 (which is additive). However the empiric evidence (summarized in all radiobiological models) shows that the cell survival probability 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.

4. The generalized approach

Then we will look for the non additive solution in a similar way as before and using the definition of tissue effect (6). In order to consider a non extensive system, we will recur to Tsallis entropy [10],

$$S = \frac{1}{q-1} \left(1 - \int_\Omega p^q(E)dE \right). \quad (7)$$

It can be shown that Tsallis entropy reduces to BG entropy when the non extensivity parameter $q \rightarrow 1$. This is why Tsallis entropy can be considered as a generalization of BG entropy, which can be applied in problems where the last one is not applicable (i.e. systems with long range correlations, memory effects, etc.) [11] of which living tissues seem to be a good example.

If the probability distribution support is $\Omega = [0; \infty)$ then the solutions vanish subexponentially implying a value $q > 1$. However, if Ω is considered bounded from above, the solutions vanish superexponentially in Ω for $q < 1$ [10]. We will request this latter property for Ω , because there is clinical evidence that for some tissues a finite threshold effect exists enough to completely remove them, and also the data support this superexponential decay with the dose.

So, we will assume that the support of the $p(E)$ distribution has an upper bound $E_0 = \alpha D_0$, that is there exists some amount of absorbed radiation $D_0 < \infty$ after which no cell survives.

To apply the maximum entropy principle in the same way as before we must take into account that the mean value in this case must be replaced by the condition of the existence of the finite q -mean value [12], in addition to the appropriate normalization condition.

The problem of finding the extreme of the entropy with the above given conditions is widely studied in the literature [13]. Then, we get the expression for the survival fraction of cells under radiation in the simple following form

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

where $\gamma = \frac{2-q}{1-q}$.

The value of D_0 defines a critical point for cell survival probability. For $D < D_0$ probabilities of survival and death coexist but when D becomes equal to D_0 , a “phase transition” takes place and no cell survives any more. This behaviour resembles the phase transition in ferromagnetics near the Curie point [4].

5. Experimental agreement

In order to compare our model with the experimental data we have selected some survival curves from the literature where the survival fraction is represented as a function of the dose 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, minimizing the appropriate least squares functional using the *steepest descent* method [14]. The slope 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 $\gamma \approx 14.0$, within the error range (See [15]).

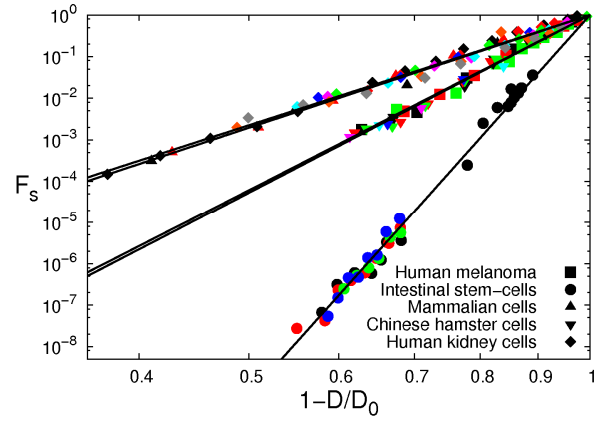


Figure 1. Survival fraction F_s as a function of the rescaled dose $1 - D/D_0$ for different tissues: intestinal stem cells, Chinese hamster cells, human melanoma, human kidney cells and cultured mammalian cells under different irradiation conditions (data extracted from [1,16-19]). Various shapes represent tissues whereas each color denotes a different radiation condition. Five solids lines represent fitting to experimental data (see details in [15]). The minimal correlation coefficient for the straight lines fit is $r^2 = 0.981$.

We must remark that this new model can be applied to radiation conditions where previous models as the LQ or its variations could not. Even in cases where previous models are useful this new interpretation does not require ruling out experimental points as outliers or other statistical tricks so usual in the area (as can be seen in [20]).

6. Conclusions

The survival fraction as a function of the absorbed energy per unit mass was derived from the maximum entropy principle. Since the linear model was obtained from the BG entropy and it does not explain the known experimental data a more general approach was introduced. Nevertheless the Boltzmann entropy treatment has shown the right expression for the tissue effect as proportional to the absorbed radiation.

A generalized expression for the survival fraction is found using the Tsallis q -entropy formulation. Despite its simplicity this new model is not subject to any constraint in the value of radiation dose or treatment conditions. The additive limit shows that this model is consistent with the known empirical laws.

The obtained law for the survival fraction exhibits a phase transition behaviour similar to second order ferromagnetic phase transitions where the imanated state corresponds to cell survival. A critical value of the absorbed energy marks the frontier between the non survivor cell region and the coexistence between survival and death probabilities. The transition between both regions occurs with a non integer critical exponent revealing a behavior similar to the ferromagnetic phase transition at the Curie point.

Rescaling every data set with the limit dose allows to find the common shape for different experimental data belonging to the same tissue. When compared with the available experimental data, the phenomenon is shown to be universal for a given tissue. Values of γ would allow to classify different tissue responses in universality classes.

We must remark that our results were found demanding only two axioms: the existence of a radiation limit under which no cell survives and the second law of thermodynamics. Using the statistical mechanics and the q-mean value of tissue effect as the generalized expectation value, the amount of cells affected by radiation is treated as a statistical ensemble.

This new approach opens a new line of work and discussion to the radiobiology community. How the involved quantities change from one tissue to another, or from one treatment to another, is not described here and lies beyond our scope. The descriptive behavior given by our results is independent of the underlying mechanisms of interaction between the living tissue and radiation. The dependency of γ on the tissue and D_0 on the treatment conditions should be worked out analyzing the properties of these new involved magnitudes.

References

- [1] Steel G. Basic Clinical Radiobiology for Radiation Oncologists. Edward Arnold Publishers; 1993.
- [2] Tubiana M. Introduction to Radiobiology. Taylor & Francis; 1990.
- [3] Mayles P, Nahum A, Rosenwald J. Handbook of radiotherapy physics. Taylor & Francis; 2007.
- [4] Landau L, Lifshitz E. Statistical physics. Pergamon Press, 1980.
- [5] Cover T, Joy A. Elements of Information Theory. John Wiley & Sons, Inc.; 2006.
- [6] Tsallis C. Nonextensive statistics: Theoretical, experimental and computational evidences and connections. *Brazilian Journal of Physics*, vol 29, 1999, pp1-35.
- [7] Maes F, Collignon A, Vandermeulen D, Marchal G, Suetens P. Multimodality image registration by maximization of mutual information. *Medical Imaging, IEEE Transactions on*, vol 16, sup 2, 1997, pp 187-198.
- [8] Harremoës P, Topsøe F. Maximum entropy fundamentals. *Entropy*, vol 3, 2001, pp 191–226.
- [9] Tsallis C. Entropic nonextensivity: a possible measure of complexity. *Chaos, Solitons & Fractals*, vol 13, sup 3, 2002, pp 371-391.
- [10] Tsallis C. Possible generalization of Boltzmann-Gibbs statistics. *Journal of Statistical Physics*, vol 52, 1988, pp 479–487.
- [11] Tsallis C. Introduction to nonextensive statistical mechanics. Springer, 2009.
- [12] Curado EMF, Tsallis C. Generalized statistical mechanics: connection with thermodynamics. *Journal of Physics A*, vol 24, sup 2, 1991, pp L69–L72.
- [13] Plastino A, Plastino A. Tsallis entropy and Jaynes' information theory formalism. *Brazilian Journal of Physics*, vol 29, 1999, pp 50-60.
- [14] Press WH, Teukolsky SA, Vetterling WT, Flannery BP. Numerical Recipes in C, The Art of Scientific Computing. Cambridge University Press, 1992.
- [15] Sotolongo-Grau O, Rodriguez-Perez D, Antoranz JC, and Sotolongo-Costa O. Non-extensive radiobiology. arXiv:q-bio.QM/1006.3410v1[q-bio.QM]. (2010)
- [16] Alper T. Relevance of experimental radiobiology to radiotherapy. *Br Med Bull*, vol 29, 1973, pp 3-6.
- [17] Hill RP, Bush RS, Yeung P. The effect of anaemia on the fraction of hypoxic cells in an experimental tumour. *British Journal of Radiobiology*, vol 44, 1971, pp 299-304.
- [18] Adams G. Hypoxic cell sensitizers for radiotherapy, in *Cancer: A comprehensive treatise*, vol 6. Plenum Press, New York; 1977. Edited by Baker F.
- [19] Barendsen G. Dose-rate effects and the repair of radiation damage. *Curr Top Radiat Res Quarterly*, vol 4, 1968, pp 293-356.
- [20] Garcia LM, Wilkins DE, Raaphorst GP. α / β ratio: A dose range dependence study. *International Journal of Radiation Oncology, Biology, Physics*, vol 67, supp 2, 2007, pp 587-593.