A Boltzmann-Tsallis approach towards cell survival curve in Radiobiology

B.W.Q. Tan[1#], *H.Q.* Tan[2#] *and A.H.* Chan[2*]

[1]*Department of Medicine, National University Health System, Singapore*
[2]*Department of Physics, National University of Singapore, Singapore*
[#]Equal contributions

Abstract This paper outlines a phenomenological approach towards cell survival curve at low dose using tools of extensive Statistical Mechanics and nonextensive Statistical Mechanics. An Ising chain model is developed for the cell survival curve and the canonical ensemble formalism based on Boltzmann Gibbs statistic and Tsallis statistic is presented. The resulting cell survival curve shows excellent agreement with the experimental data and the physical parameters from our Tsallis model (N', q) can be shown to provide clear classification between healthy and cancerous cells. In this paper, we also provides possible biophysical interpretation to the (N', q) parameters where N' is representative of the amount of repairable DNA content in the nucleus and q represents the degree of correlation in DNA damage. Overall, this is the first time a Statistical Mechanics approach is used in Radiobiology, and could present a new perspective.

1 Introduction

The modelling of the cell survival has always attracted attention as it is widely used in radiotherapy and fractionation schemes [1,2]. It is a graph of the proportion of cell survival against the dose of the radiation. The first model being proposed is known as the Lea's Target Theory [3]. It assumes a radiation-sensitive region in a cell which gets inactivated upon radiation and eventually leads to cell death. This follows a Poisson distribution as given in equation (1). D_0 is defined as the dose that gives an average of one hit per target. There are various variants of the target theory such as Single Hit Multi-Target (SHMT), Multi-Hit Single Target (MHST) etc but they fail to agree with the experiment data at large dose.

$$P(survival) = exp(-D/D_0) \tag{1}$$

An improvement to the Lea's Target theory is known as the Linear Quadratic (LQ) Model given in equation (2). Both the parameters α and β are determined experimentally and the ratio α/β gives the overall shape of the graph. There are various justification of the LQ model using Track theory, Lethal-Potentially Lethal model (LPL) and Repair Saturation model

[2,4,5]. Despite the wide use of the LQ model in radiotherapy and fractionation, it still does not fully agrees with the experimental data in the large dose regime [2].

$$P(survival) = exp(\alpha D - \beta D^2) \tag{2}$$

The exponential function present in equations (1) and (2) resemble Boltzmann's distribution and this motivates the statistical mechanics approach towards this problem which is the highlight of this paper. In this paper, a physical model for the radiation damage process will be proposed using the Ising model. Then, the cell survival curve will be deduced from a statistical mechanics point of view using the Boltzmann's canonical ensemble formalism. Thereafter, a more general Tsallis canonical ensemble formalism will be introduced as it is more suited for complex and correlated system which better describe the radiation-DNA system. This paper is motivated by the work of Sotolongo-Grau [6]. In their paper, they make use of Tsallis entropy to deduce a phenomenological cell survival curve which gives a better fit to experimental data compared to LQ model. Despite the success, the method lacks physical justification and insights. In contrast, this paper provides a physical model and theory based on Tsallis canonical ensemble applied to Ising model and derive the prediction of the cell survival curve excellently at low dose together with a biophysical interpretation of the q parameter. Finally, this method is applied to a large dataset of normal and cancerous cells where it can be shown that q clearly differs for cancerous and normal cells and could be used as a mean for classification.

Generalization using Tsallis Entropy

The use of Tsallis entropy or non-extensive statistical mechanics in modelling various real world phenomena has shown to be a great success [7,8]. Non-extensive statistical mechanics provides a natural framework for describing correlated system.
In radiobiology, the production of a cloud of secondary electrons from Compton scattered electron in X-ray radiation [10] can be modelled as spatially correlated damage in the Ising chain model. Thus, in this section of the paper, the Tsallis formalism will be developed. The non-extensive partition function is defined as

$$Z_q = \sum_{i=1}^{2N} \binom{2N}{i} e_q^{-\beta_q'(i\lambda+\varepsilon)} = \sum_{i=1}^{2N} \binom{2N}{i} e_q^{-\beta_q'\varepsilon} \otimes \left(e_q^{-\beta_q'\lambda}\right)^{\otimes^i} \tag{3}$$

Where the q-exponential and q-product is defined as follows,

$$e_q^x = [1 + (1-q)x]^{\frac{1}{1-q}} \tag{4a}$$

$$x \otimes y = [x^{1-q} + y^{1-q} - 1]^{\frac{1}{1-q}} \tag{4b}$$

$$x^{\otimes^n} = [nx^{1-q} - (n-1)]^{\frac{1}{1-q}} \tag{4c}$$

$$\beta_q' = \frac{\beta_q}{1+(1-q)\beta_q U_q}, \qquad \beta_q = \frac{1}{kT_q} \tag{4d}$$

The partition function cannot be factorized into a product of single unit partition function due to the q-product. The partition function in equation (10) is derived from the optimization of Tsallis entropy under the two constraints below.

$$\sum_{i=1}^{W} p_i = 1 \tag{5}$$

$$\sum_{i=1}^{W} P_i E_i = U_q \tag{6}$$

Where P_i is the Escort probability distribution defined to be

$$p_{\mathrm{i}} = \frac{p_i^q}{\sum_{i=1}^{W} p_i^q} \tag{7}$$

The form of the partition function in equation (3) allows the "internal energy" U_q to be additive such that for two independent systems, $U_q(A+B) = U_q(A) + U_q(B)$. As mentioned in previous section, the internal energy in the canonical ensemble is interpreted as the dose deposited by radiation in a cell nucleus. Proceeding as in the Boltzmann Gibbs formalism,

$$D - 2N\varepsilon = 2N\lambda \frac{p_\lambda^q}{p_0^q + p_\lambda^q} \tag{8}$$

Where,

$$p_0 = \frac{e_q^{-\beta_q{}'\varepsilon}}{e_q^{-\beta_q{}'\varepsilon} + e_q^{-\beta_q{}'(\varepsilon+\lambda)}}, \qquad p_\lambda = \frac{e_q^{-\beta_q{}'(\varepsilon+\lambda)}}{e_q^{-\beta_q{}'\varepsilon} + e_q^{-\beta_q{}'(\varepsilon+\lambda)}} \tag{9}$$

Solving equation (8) above, one obtains

$$\beta_q{}' = \frac{1-\Lambda}{(q-1)[\Lambda(\varepsilon+\lambda)-\varepsilon]} \tag{10}$$

Where,

$$\Lambda = \left[\frac{2N\lambda}{D-2N\varepsilon} - 1\right]^{\frac{1-q}{q}} \tag{11}$$

In this scenario of possible correlated damage, we need to modify the survival probability expression by including two terms. First, is the probability of SSB with no NSB in direct neighboring unit, and second, NSB in just one unit. Thus,

$$P(survival) = \frac{e_q^{-\beta_q{}'\varepsilon}}{Z_q} + \frac{2e_q^{-\beta_q{}'(\epsilon+\lambda)} e_q^{-2\beta_q{}'\epsilon}}{Z_q^3} \tag{12}$$

Substituting the expression for β_q' into the equation above, the cell survival curve under Tsallis formalism is obtained. In the limit of $q \to 1$, the cell survival curve for Boltzmann Gibbs distribution is obtained.

To further facilitate the comparison between the cell survival curve obtained above and the experimental result, a modification needs to be made involving the dose definition. In the model above, the "dose" D is the *microscopic* energy deposited in the proximity of the DNA whereas in the context of cell survival curve, the dose is the energy deposited in each cell per unit mass. Assuming a linear relation between them, $D = D(Gy)S$, where $D(Gy)$ is the definition of dose in the context of cell survival curve and S is the constant of proportionality. Plugging this expression into equation (10) above,

$$\Lambda = \left[\frac{2\lambda}{\frac{D(Gy)}{\frac{N}{S}} - 2\varepsilon} - 1\right]^{\frac{1-q}{q}} \tag{13}$$

We can then redefine a new constant N' such that $N' = N/S$. Thus, the N variable is replaced by N'.

2 Results and Discussions

In the previous section, the Cell Survival Curve (CSC) is derived in equation (11) using Tsallis statistics. In the model, the only free parameters are (N', q). The dependence of CSC on different N' and q values are shown in FIG 1 (Top) below. In general, the cell survival decreases more under a lower value of N' and a higher value of q. The biophysical interpretations will be discussed further in this section.

Next, we applied the model to a set of 19 data sets of CSC where different types of cells (healthy and cancerous) are exposed to X-ray. For each CSC, we extract the N' and q values from the model and the "survival fraction at 1 Gy" (SF1) from the data set. An example of the fitting is shown in **Figure 1** (Bottom), where a Least Mean Square fit routine [9] is used to find the optimal (N', q) values. We propose that N' represents the amount of DNA content in the cell amenable to DNA repair while q represents the extent of correlated unrepaired damage to the DNA. This factor can depend on a host of factor such as the quality of radiation (Compton electrons and photoelectrons from X-ray tends to have different energy and different degree of clustered damage, chromosome geometry and DNA repair mechanism.

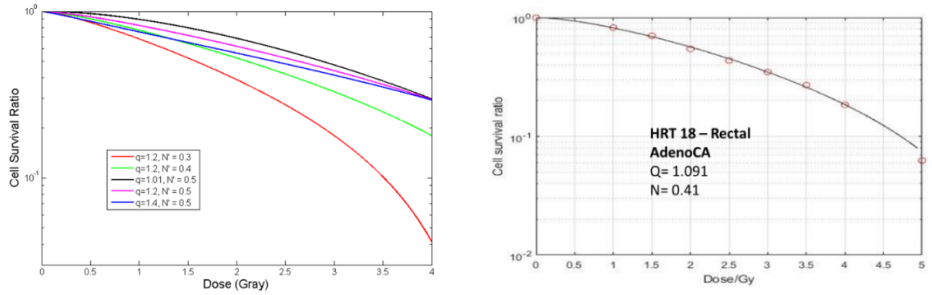

Figure 1. (Left) A comparison of the CSC obtained from equation (19) with different values of N' and q. (Right) An example of the fit applied to a particular data set.

3 Conclusion

This paper outlines a new model to integrate statistical mechanics (extensive and nonextensive) with cell survival curve by making modification to the Ising model. It makes use of Boltzmann and Tsallis canonical partition function to derive the curve. The curve requires 2 input parameters (N', q) which has its own biophysical meaning as mentioned in the paper. As far as we know, this perspective of looking at cell survival curve has not been reported. This new Tsallis approach agrees well with the CSC experimental data sets and the determination of the parameters lead to a clear clustering of radio-sensitive and radio-resistant survival fraction in the (N', q) parameter space. This suggests that these parameters of biophysical origin can be used for classification of cell's response towards radiation. The finalized results and developments of this model will be published in a subsequent manuscript.

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