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Numerical insight into the Dual Radiation Action Theory

John J. Tello[a,b,c], Sébastien Incerti[d,e], Ziad Francis[f], Hoang Tran[g], M.A. Bernal[a,*]

[a] Instituto de Física "Gleb Wataghin", Universidade Estadual de Campinas, Brazil
[b] University of Pavia, Physics Department, via Bassi 6, I-27100 Pavia, Italy
[c] INFN-Sezione di Pavia, via Bassi 6, I-27100 Pavia, Italy
[d] CNRS, IN2P3, CENBG, UMR 5797, F-33170 Gradignan, France
[e] University of Bordeaux, CENBG, UMR 5797, F-33170 Gradignan, France
[f] Saint Joseph University, Faculty of Science, R.U. Mathematics and Modelling, Department of Physics, Beirut, Lebanon
[g] IRFU/DPhN, CEA, Université Paris-Saclay, F-91191 Gif-sur-Yvette, France

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ABSTRACT

This work studies the first and second order mechanisms for the induction of lethal lesions in DNA after irradiation with protons and α-particles. The purpose is to numerically study the mechanisms behind the Dual Radiation Action Theory (DRAT) for these heavy particles. A genetic material geometrical model with atomic resolution is used. It accounts for the explicit position of 5.47×10^9 base pairs, organized up to the chromatin level. The GEANT4-DNA Monte Carlo code was employed to simulate the interaction of these ions with the genetic material model. The number of lethal lesions induced by one- and two-track mechanisms was determined as a function of dose. Values of the α/β ratio were estimated as well as corresponding relative biological effectiveness (RBE). The number of lethal lesions produced by one-track and two-track mechanisms depends on the dose and squared dose, respectively, as predicted by the DRAT. RBE values consistent with experimental results were found, at least for LET below ~100 keV/μm. Double strand break spatial distributions are qualitatively analyzed. According to this work, the α parameter determined from cellular surviving curves depends on both the physical α and β parameters introduced here, and on the specific energy deposited by a single track into the region of interest. We found an increment of the β parameter with LET, yet at a slower rate than α so that the α/β ratio increases with LET. In addition, we observed and explained the saturation of the α parameter as the dose increases above ~6 Gy.

1. Introduction

The Linear-Quadratic (LQ) model has been the most successful radiobiological model developed so far to reproduce cell killing curves after irradiation with ionizing particles, at least for doses between 2 and 15 Gy [1,2]. It is able to predict the surviving fraction of cells in a colony after irradiation with ionizing particles. It has a primordial importance in radiation therapy of cancer as it may be used to determine the iso-effect dose when alternative fractionation regimes are used. This model also permits to estimate the physical absorbed dose that has to be delivered with a proton beam, for instance, in order to get the same biological effect as that obtained with a given dose imparted by photons. In addition, the LQ model can be used to predict the tumor control probability and normal tissue complication probability after a radiotherapy treatment. For instance, this model has recently been used to study the radio-sensitivity of mixed cellular colonies, comparing the LQ approach with the one based on Tumor Control Probability [3].

The cell killing mechanisms behind the LQ model are mainly based on the Dual Radiation Action Theory. That is, cell killing occurs when chromosomal aberrations are formed due to the misrejoining of two double DNA strand breaks (DSB). As early as 1942, Lea and Catcheside [4] reported based on experimental results that both the numbers of chromatid interchanges and chromosome interchanges induced in cells by X-rays increase more rapidly than the first power of the dose. In addition, the total number of interchanges increases with the dose rate. Both observations suggested the existence of a non-linear mechanism for chromosomal aberration formation. They also reported that the number of interchanges produced by neutron irradiation increases linearly with dose. In fact, these authors proposed a formula of the type $\alpha D + \beta D^2$ to fit the number of chromatid and chromosome interchanges observed, where D is the absorbed dose. Furthermore, they developed a very sophisticated multi-parameter biophysical model to reproduce the number of interchanges per unit absorbed dose. They postulated that the probability for the interchange of two DSB separated by a distance x

* Corresponding author.
E-mail address: mabernal@ifi.unicamp.br (M.A. Bernal).

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is of the form $e^{-x/h}$, where h is a characteristic distance. Their results suggest that this function is rather valid, with h∼0.83 μm for neutron irradiation.

The work of Lea and Catcheside was used by Kellerer and Rossi as the basis for the development of the Dual Radiation Action Theory (DRAT) in Radiobiology [5,6]. This has been the most popular theory for chromosomal aberration and it is widely accepted that DSB is the initial molecular damage that leads to such aberrations (see [7] and references therein). This model also states that the number of lesions per cell is of the form $k(\xi D + D^2)$, where k is a proportionality constant and ξ is the dose at which the linear and quadratic terms contribute equally to the number of induced lesions. Three models for the sub-lesion interaction probability $g(x)$ were proposed in Ref. [6],

$$g(x) = \begin{Bmatrix} 1 & x \leqslant h \\ 0 & x > h \end{Bmatrix} \tag{1}$$

$$g(x) = e^{-x/h} \tag{2}$$

$$g(x) = e^{-(x/h)^2}. \tag{3}$$

They showed that taking h as 0.4 μm, 0.2 μm, and 0.1 μm in Eqs. (1)–(3), respectively, the three models provide similar results.

In short, the DRAT states that the number of lethal lesions (LL) per cell has linear and quadratic terms as a function of the dose. The LQ model uses this result and combines it with the assumption that the probability for a cell to be inactivated by the radiation is Poisson distributed and that only one lethal damage is enough to kill the cell. Thus, the cell survival probability is $e^{-N_{LL}}$, where N_{LL} is the mean number of LL per cell. This is just the probability for a cell (or its nucleus) to have no lethal damage. The DRAT can also be described by the following differential equation system

$$\dot{N}_{RL}(t) = 2p\dot{D} - \mu N_{RL}(t) \tag{4}$$

$$\dot{N}_{LL}(t) = \alpha\dot{D} + p \in \dot{D} N_{RL}(t), \tag{5}$$

where N_{RL} and N_{LL} are the mean number of Repairable and Lethal Lesions induced in DNA respectively, $\dot{D}$ is the dose rate, p is the probability per unit absorbed dose for inducing lesions, μ is the damage repair rate, and $\in$ is the probability of interaction between an existing lesion and a new one. The parameter α is the probability for producing a LL per unit dose. A brief review on mathematical formalisms behind several radiobiological models, including the LQ model, can be found in Ref. [8]. It is commonly accepted that α is related to the interaction of two DSB produced by the same particle track so it is dose-rate independent. The solution for the number of LL is

$$N_{LL}(t) = \alpha D + \frac{2\beta D^2}{\mu^2 t^2}(\mu t - 1 + e^{-\mu t}), \tag{6}$$

where $\beta = p^2 \in$ comes from the term that accounts for the induction of lethal damage by the interaction of two DSB produced at different times (by independent primary particle tracks). Then, it is dose-rate dependent. This solution has been obtained supposing that the dose rate is constant. For acute irradiation, as that carried out in high dose-rate radiotherapy treatments, the irradiation time is much lower than the repair time scale, that is $\mu t \ll 1$. In this situation, the second order expansion of the exponential term leads to the following number of LL per cell

$$N_{LL} = \alpha D + \beta D^2. \tag{7}$$

Notice that the result shown in Eq. (7) has nothing to do with the statistical distribution used to model the surviving cell fraction, which is the Poisson distribution in the LQ model. The α/β ratio is similar to the parameter ξ introduced in the DRAT (see comments above).

All these arguments strongly suggest that there is a mechanistic basis for the LQ model, at least for the dependence of the number of LL per cell as a function of dose. In fact, Hawkins [8] introduced the microdosimetric-kinetic model for explaining the relation between cell death RBE and the incident particle LET. Like the DRAT, this model is based on the pairwise interaction of reparable sublethal lesions for inducing cell death. The author found that RBE increases linearly with incident particle LET up to about 40–90 keV/μm. He also concluded that the departure of RBE from the linearity is probably due to the non-Poissonian behavior of the distribution of lethal lesions per cell as LET increases above the mentioned interval. As can be seen below, the current work proposes an approach that does not initially assume any distribution for this process since the interaction of particles with cells (DNA) is accounted for in a natural stochastic way, based on Monte Carlo simulations.

There is an old debate on whether the LQ model has mechanistic groundings or not. On one side, Zaider [10] argued that there is no mechanistic basis for using the LQ model to reproduce cellular survival curves. The main criticism is the use of a Poisson distribution to quantify the probability for a cell to be inactivated but he agrees with Eq. (7) for modelling the number of lesions. Despite that he used theoretical arguments to reject this distribution, he acknowledged that the LQ model has proven to be successful in reproducing *in vitro* cellular surviving data and fulfilling some consistency checks about its mechanistic groundings. On the other side, Sachs and Brenner [11,1] defended the mechanistic basis of this model and alleged that even some kinetic models, like that shown in Eqs. (5), leads to the LQ formalism after a first-order expansion. This work puts this discussion aside and focuses on the DRAT.

Hadron-therapy is a radiation therapy modality in frank expansion worldwide [12]. However, the radiobiology associated with heavy charged particles is a matter of intensive study nowadays [13], as it has a primordial importance for the treatment planning process. Experiments have shown that the α/β ratio for a given cell line increases as the radiation linear energy transfer (LET) increases. In addition, there is an actual discussion on whether the β parameter increases with LET or not (see for instance Ref. [14]). Friedrich et al. [15] has recently published a very complete review on the RBE for ion beams, including the behavior of the α and β parameters as a function of LET.

To our knowledge, it is not possible to experimentally discriminate between the first (α) and second (β) order mechanisms of damage generation described before. Thus, the Monte Carlo method for radiation transport simulation emerges as a good tool to study this problem. Particles can be followed independently and each DSB can be tagged according to the primary particle that induces it. The dual action model has been chosen in this study because it can be studied using our biophysical model. That is, a model based on the combination of Monte Carlo simulations and a DNA geometrical model.

The aim of this work is to demonstrate numerically the predictions of the DRAT, at least for the early direct DNA damage induced by light ions. Namely, the mean number of LL in cells irradiated by ionizing particles can be obtained by combining linear and quadratic terms as a function of dose. In addition, an insight into the mechanisms behind the parameters α and β can be provided. There are experimental evidences that nearly 55% of the initial number of DSBs undergo faithful rejoining at high doses [16,17], thus, we decided to set this value as the initial probability of repair of the sublesions. As high LET particles are used in this study, for which the number of LL per cell does not follow the Poisson distribution, in principle, [10], the RBE_{10} values determined according to the LQ model for these qualities are just estimates. For particles with LET below 100 $keV/\mu m$, both the α/β ratio and the RBE_{10} were obtained and compared with the data available. Also, 3D DSB distributions were determined, whose clustering pattern is closely related to the RBE of charged particle beams. The rationale of this work is to develop an *ab initio* platform for estimating RBE of ionizing particles from the interaction of these particles with DNA geometrical models and coupling this physical process to biological damage through a biophysical model.