

Application of a LEM based DNA DSB kinetic rejoining model to the analysis of dose dependence after photon irradiation*

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A DNA Double-Strand Break (DSB) kinetic rejoining model has been recently presented [1], which is based on the approach currently adopted in the Local Effect Model (LEM) for the description of radiation induced biological effects [2]. Shortly, the photon dose response data and an amorphous track structure model are combined together to calculate the initial pattern of DSB induced in the target (i. e. the cell nucleus). The chromatin contained inside the nucleus is considered to be organized in so-called Giant Loops, each one involving about 2 Mbp of genome [3]. The presence of such high-order chromatin structures allows defining two different classes of DSB, namely *isolated* (iDSB) and *clustered* ones (cDSB). An iDSB is defined as a single lesion inside a loop, while a cDSB is characterized by the simultaneous presence of more than one DSB. cDSB are expected to be more difficult for the cell to repair compared to iDSB, since they may result in the loss of the structural integrity of the chromatin loop, and possibly in the migration of DNA fragments from the DSB site. In order to describe the kinetics of DSB rejoining over time, the hypothesis is made, that iDSB are rejoining by the fast component while cDSB are processed by the slow component of rejoining which are often observed in the experiments. Thus, LEM calculations of induced DSB patterns are combined with a biphasic exponential decay function having a fast (τ_{fast}) and a slow (τ_{slow}) half-life, as described by the following equation:

$$U(t) = F_{fast} \cdot e^{-\frac{\ln(2)}{\tau_{fast}} t} + F_{slow} \cdot e^{-\frac{\ln(2)}{\tau_{slow}} t} \quad (1)$$

where F_{fast} and F_{slow} correspond to the fraction of initial induced iDSB and cDSB, respectively. For a given data set involving a single cell line and different radiation qualities, Eq. 1 is used to simultaneously fit the experimental rejoining data. The initial fractions of iDSB and cDSB are fixed input parameters and characterize a specific dose and radiation quality, while the two half-life times are defined as global fit parameters. Further details can be found elsewhere [1,2].

The described model has been already applied to a large data set, where experiments performed using both low and high LET were included, obtaining an overall good agreement. The focus is now on the use of the model for the analysis of a specific biological end point. Specifically, we want to test the model ability to describe the delayed DSB rejoining observed after increasing doses of photon radiation [4]. In this case, the Poisson distribution is adopted for

the calculation of initially induced DSB patterns. An example is shown in Fig. 1, where the effects of 20 and 200 Gy are compared. Both the experiments and the model clearly show a slowed-down rejoining at 200 Gy compared to the lower dose. Importantly, in the context of our model, this is only due to an increased fraction of induced cDSB, since the two half-lives are defined as global fit parameters and therefore are identical for all the considered doses. However, in contrast to what shown by Cucinotta et al [4], other works have been published where a dose dependence was not observed [5,6]. Thus, more data are needed to further support the results presented here.

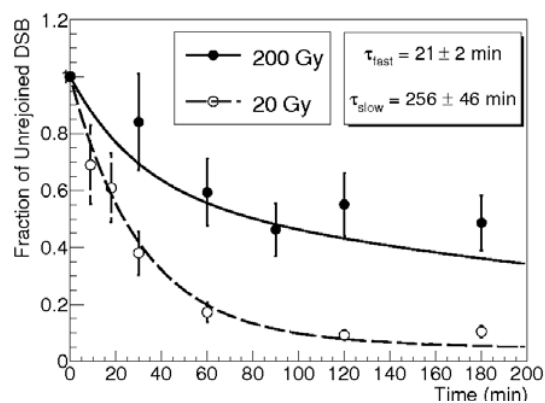


Figure 1: experimental data (symbols) and model predictions (lines) for the DSB rejoining over time after photon irradiation with 20 and 200 Gy. Experimental data were measured with filter elution techniques and are taken from Cucinotta et al [4].

A successful analysis of the end point presented here would further confirm the validity of the model. At the same time, it would be supportive for the relevance of the proposed DSB classes, and more in general of DSB clustering at the micrometer level, for the description of radiation induced biological effects not only at high but also at low LET.

References

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