

## A LEM based DNA DSB kinetic rejoining model\*

F. Tommasino<sup>1</sup>, T. Friedrich<sup>1</sup>, U. Scholz<sup>1</sup>, G. Taucher-Scholz<sup>1</sup>, M. Durante<sup>1,2</sup> and M. Scholz<sup>1</sup>

<sup>1</sup>GSI, Darmstadt, Germany; <sup>2</sup>Institut für Festkörperphysik, Technische Universität, Darmstadt, Germany

In the context of ionising radiation induced DNA damage, the DNA double strand breaks (DSB) are actually considered the dominant effect of radiation action leading to cell killing. Several experimental methods have been developed in order to measure the DSB induction and repair in cells. By means of gel electrophoresis techniques, for example, is possible to measure the DSB induction and the following rejoining over time after irradiation [1, 2]. The resulting curve is often fitted with a combination of two exponential functions, representing the fast and the slow component of rejoining. When comparing the effect of different radiation qualities on the rejoining kinetics, a delay is in general observed in the rejoining process when high ionisation densities are involved (i.e. high LET ion irradiation) and consequently more clustered damage is induced.

The recent version of the Local Effect Model (LEM) combines the photon input data and an amorphous track structure model with a detailed consideration of the spatial distribution of the initial damage (DSB) [3, 4]. The high order chromatin structure is actually taken into account, assuming that the DNA content inside the cell nucleus is organised in “giant loops” of DNA [5], each one comprising around 2Mbp of DNA. This allows the definition of two different classes of damage, namely ‘isolated’ (iDSB) and ‘clustered’ (cDSB) double strand breaks, when only one and two or more DSB are induced in the loop structure respectively. Obviously, cDSB are expected to be more difficult for the cell to process because the integrity of the loop structure is lost. The fractions of induced iDSB and cDSB strongly depend on the ionisation density, with a higher fraction of cDSB being the result of a high LET irradiation, compared to the photon case.

The LEM predictions in terms of iDSB and cDSB can be used to develop a DSB kinetic rejoining model. The basic assumption is that a correspondence can be found between the two classes of DSB defined in the LEM and the two components of DSB rejoining which are usually observed in the experimental curves. According to this concept, an increase in the fraction of DSB rejoining with a slow kinetic would be the effect of an increase in the fraction of induced cDSB. In this context, once experimental data are available and experimental conditions are known (radiation quality, cell line), we can use the LEM to predict the fractions of iDSB and cDSB corresponding to the particular case (in the photon case, Poissonian distribution of DSB is assumed). These values are then used to derive the fraction of unrejoined DSB:

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

where  $F_{iDSB}$  and  $F_{cDSB}$  are the fractions of induced iDSB and cDSB respectively, and  $\tau_{fast}$  and  $\tau_{slow}$  are the half-lives of the two components. After the input parameters are available from simulations, we can use the function to fit experimental data, obtaining  $\tau_{fast}$  and  $\tau_{slow}$  as fitted parameters. In Fig. 1 a preliminary application of the model is shown; it demonstrates, that a consistent simultaneous description of low- and high-LET rejoining data can be achieved based on half-lives derived from the photon data ( $\tau_{fast}=16\pm 1\text{min}$ ,  $\tau_{slow}=146\pm 28\text{min}$ ) and the different contributions of iDSB and cDSB for the different radiation qualities.

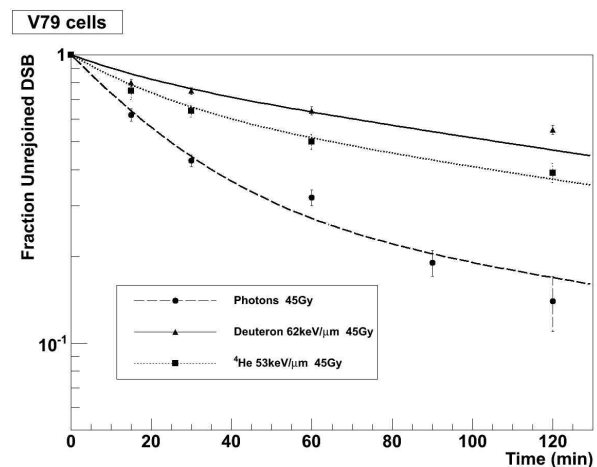


Figure 1: application of the rejoining model to experimental data shown in [1], the points refer to experimental data, while lines show the results obtained with the model.

A successful application of the model presented here to a wide spectrum of experimental data, involving different cell lines and different radiation qualities, would represent a partial validation for the mechanistic bases of DNA damage on which the LEM is built. Work is actually ongoing in this direction.

## References

- [1] Belli et al., Int. J. Rad. Bio. 76 (2000) 1095
- [2] Stenerlow et al., Int. J. Rad. Bio. 76 (2000) 549
- [3] M. Scholz et al., Radiat. Envir. Biophys. 36 (1997) 59.
- [4] Friedrich et al., Int. J. Radiat. Biol., 88 (2012) 103.
- [5] Yokota et al., J. Cell Biol., 130 (1995) 1239.

\* This work is supported by DFG-funded Graduiertenkolleg 458GRK 1657) and is part of HGS-HIRe