Simulation of double strand break yield after high LET irradiation*

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Introduction

Double strand breaks (DSB) of the DNA are considered as key lesions of radiation damage. For radiation induced DSB, two coincident single strand breaks (SSB) on opposite DNA strands are needed. These SSB pairs are typically induced by single electrons, as the yield is constant over a large dose range. For very high doses $\gg$ 100 Gy the relative contribution of DSB formed by two-electron processes gets more important, and thus the DSB yield increases. Evidence for such SSB clustering interaction was gained in plasmid experiments, where it was found that the SSB need to be closer than some 10 bp. In the inner part of ion tracks, also very high local doses occur, where consequently also an enhanced DSB yield is expected. We developed a Monte Carlo (MC) algorithm and an analytic formulation for the dose dependent DSB yield for photon radiation. The enhancement mechanism of DSB by means of SSB clustering is part of the Local Effect Model (LEM), which considers the spatial distribution of DSB to predict the RBE for charged particle irradiation [1].

Materials and Methods

We used as numerical constants for the yield computation $\alpha_{\mathrm{DSB}} = 30/\mathrm{Gy}$ and $\alpha_{\mathrm{SSB}} = 1250/\mathrm{Gy}$ per cell as DSB and SSB yield after photon irradiation at low doses, respectively. A genomic length $L_{\mathrm{Gen}} = 5.4 \times 10^9\,\mathrm{bp}$ was used. The MC algorithm assumes that SSB are randomly distributed along the genome according to Possonian statistics. SSB pairs leading to DSB are counted. The key idea of the analytic expression is that the probability to find a gap of size s between successive SSB is given by $\rho e^{-\rho s}$, where ρ^{-1} is the average distance between two SSB in bp.

Results

The MC algorithm predicts the expected DSB yield enhancement after photon radiation at very high doses. The analytic computation is a very good approximation of the MC results and can thus be used for quick evaluation within RBE models. In analogy to the linear-quadratic parameters, an $\alpha_{\mathrm{DSB}}/\beta_{\mathrm{DSB}}$ of about 8300 Gy was found, indicating the dose scale where the yield enhancement becomes important. Weighting the local yields over the radial dose distributions in track structures allows to determine the ion-energy specific DSB yield enhancements as shown in Fig. 1 for two values of the maximum distance between two interacting SSB, t, in bp.

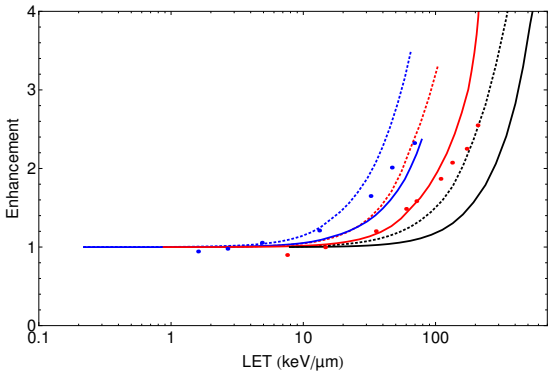

Figure 1: DSB enhancement factor η vs LET for protons (blue), helium (red) and carbon (black) as dotted and solid lines for t = 25 bp and t = 10 bp, respectively, in comparison with model data of the PARTRAC code (data points).

Discussion and Outlook

The DSB enhancement mechanism is expected to be of importance for ion beam tumor therapy. In the regions of high LET a DSB amplification of 1-4 is expected. For low energetic carbon ions as found in therapeutic extended Bragg peaks the local doses in the center of the ion tracks is about 10^5 Gy according to the track structure model of LEM. Consequently most DSB are formed by independent electrons and the DSB density is enhanced, leading to more complex damage. As both the number of DSB and their spatial correlation are important factors for RBE, the SSB clustered DSB formation is an relevant process for the effectiveness of high LET radiation. Concerning its quantification other models such as PARTRAC [2] predict different DSB yields, mostly due to assumed values of t as demonstrated in Fig 1. Here further model comparison as well as experimental investigation of DSB yields for mammalian cells is be needed, and details of the algorithms used [3] within the LEM are subject of current discussion.

References

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