A sensitivity analysis of the Giant LOop Binary LEsion model

L. Herr[*1,2]*, T. Friedrich*[1]*, M. Durante*[1,2]*, and M. Scholz*[1]
[1]GSI, Darmstadt, Germany; [2]TU Darmstadt, Germany

The Giant LOop Binary LEsion model (GLOBLE) describes cell survival probabilities after photon irradiation in dependence of dose and dose rate. Its input parameters are closely linked to features of cellular repair of induced DNA double strand breaks (DSBs). Their values - derived e.g. from fits to experimental data - are considered to be cell line characteristic. Therefore, an investigation of the impact of the GLOBLE parameters on predicted cell survival probabilities helps to understand the extent in which certain repair features affect cell line specific radiosensitivities. In the following, it will be shown in how far a 10% increase in GLOBLE input parameters changes the model output.

Methods

In the GLOBLE, the effectiveness of radiation in cell killing depends on the spatio-temporal distribution of induced DSBs. The organization of the DNA in giant loops (≈ 2 mega base pairs) whose ends are attached to the nuclear matrix suggests that a single DSB (isolated DSB, iDSB) in such a subunit is less harmful and faster to repair than multiple coexistent DSBs (clustered DSB, cDSB) since the latter allow for a loss of DNA fragments. In the model, iDSB or cDSB lead to lethal events with cell line specific probabilities ϵ_i or ϵ_c and the corresponding half-life times of repair are HLT_i and HLT_c. Depending e.g. on the dose, the dose rate, the linear energy transfer etc. the expected numbers of radiation induced iDSB and cDSB can be scored and with ϵ_i and ϵ_c the cell survival probability can be calculated. The model setup and examples for possible applications are presented in detail in [1,2].

In order to test the impact on cell survival the parameters of an hypothetical cell line $\epsilon_i = 0.0086$, $\epsilon_c = 0.32$, $HLT_i = 0.49h$ and $HLT_c = 5h$ were in turns increased by 10%. The relative change in the effect - the negative logarithm of the survival - was plotted over a range of doses and dose rates occurring in photon cell survival experiments.

Results and discussion

In figure 1 the relative change in the effect after a 10% increase of ϵ_i (A), ϵ_c (B) and HLT_i (C) is plotted over the dose and dose rate. Expectedly, higher probabilities for lethal events after DNA damage (A, B) increase the effectiveness of radiation in a dose and dose rate dependent manner. Panels A and B show that at low doses or dose

rates, the lethality of iDSB (ϵ_i) has much more impact on cell survival probabilities than the one of cDSB (ϵ_c). In the transition to high doses and dose rates this overweight switches over-proportionally. This is due to the fact that the fraction of radiation induced iDSB is dominant at low doses and dose rates and that the fraction of cDSB grows over-proportionally when the dose and dose rate are increased.
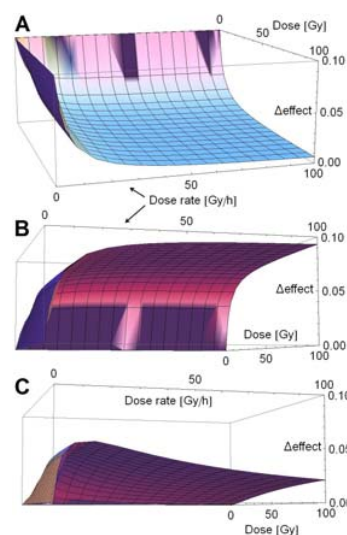
An increase of HLT_i generally raises the effectiveness of radiation since the probability to induce at least a second DSB in a giant loop - implying a more harmful cDSB - increases the longer an iDSB remains unrepaired. However, at low doses or dose rates the impact of HLT_i on cell survival is small due to the lack of cDSBs in this range. If the dose is increased, the parameter gains continuously in importance because of the growing fraction of cDSB. Due to the impossibility for a cell to repair some damage if high dose rates are applied, the impact of HLT_i initially grows with the fraction of cDSB if low dose rates are increased but decreases again after a maximal impact has been reached at dose rates around 10 Gy/h.

The impact of HLT_c on cell survival probabilities is negligible in comparison to the importance of the other three parameters and therefore not shown explicitly.

References

[1] Friedrich T, Durante M, Scholz M; Radiat Res 2012; 178: 385-394.

[2] Herr L, Friedrich T, Durante M, Scholz M; PLoS ONE 2014; 1(9).