# Modeling of time-dose-LET effects in the cellular response to radiation

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## Abstract – Dissertation

This work is dedicated to the elucidation of time-dose- and if applicable linear energy transfer (LET) effects in the cellular response to ion or photon radiation. In particular, the common concept of the Local Effect Model (LEM) and the Giant Loop Binary Lesion (GLOBLE) model, which explains cell survival probabilities on the hand of clustering of double-strand breaks (DSB) in micrometer-sized sub-structural units of the DNA, was investigated with regard to temporal aspects. In previous studies with the LEM and GLOBLE model, it has been demonstrated that the definition of two lesion classes, characterized by single or multiple DSB in a DNA giant loop, with two repair fidelities is adequate to comprehensively describe the dose dependence of the cellular response to instantaneous photon irradiation or ion irradiation with varying LET. Furthermore, with the GLOBLE model for photon radiation, it has been shown that the assignment of two repair time scales to the two lesion classes allows to adequately reproduce time-dose effects after photon irradiation with an arbitrary constant dose-rate. In this work, the results of four projects that strengthen the mechanistic consistency and the practical applicability of the LEM and GLOBLE model will be presented. First, it was found that the GLOBLE model is applicable to describe time-dose effects in the cellular response to two split photon doses and in the occurrence of deterministic radiation effects. Second, in a comparison of ten models for the temporal course of DSB rejoining, it was revealed that a bi-exponential approach, as suggested by the LEM and GLOBLE model, finds a relatively large support by 61 experimental data sets. Third, in a comparison of four kinetic photon cell survival models that was based on fits to 13 dose-rate experiments, it was shown that the GLOBLE model performs well with respect to e.g. accuracy, parsimony, reliability and other factors that characterize a good approach. Last but not least, the dynamic concept of two time scales of cellular repair was introduced in the LEM. The consistency of predictions with this new kinetic model for ion radiation effects was verified and an agreement with experimental data was detected. In summary, the theoretical evidence that the time-dose-LET-dependence of the cellular response to radiation is explicable with radiation-characteristic damage distribution patterns on micrometer-scale was affirmed.