STSM Scientific Report

The semi-analytical scheme of the probabilistic two-stage model (Kundrát et al, Phys. Med. Biol. 2005; Kundrát, Phys. Med. Biol. 2006) enables to describe the cell killing effects of ionizing particles while taking into account the stochastics of particle traversals over cell nuclei, the induction of damage to DNA, and its repair by the cell. In conjunction with a simple physical model of proton and light ions' Bragg peaks, this radiobiological model has been used to predict the biological effectiveness along the penetration depth of ion beams (Kundrát, Radiat. Prot. Dosim. 2006; Kundrát, Phys. Med. Biol. 2007 subm.). Model predictions are in excellent agreement with measured data, indicating potential applications of the model in treatment planning calculations in hadron radiotherapy. However, at present, individual model parameters, such as the per-track probabilities to induce severe damage to DNA, are derived directly from cell survival data measured under track-segment irradiation. To increase the predictive power of the present scheme, a detailed microscopic radiobiological model is clearly desirable. Looking for correlations between the patterns of energy deposition, radical distribution, and specific DNA damage on the one hand and the resulting biological endpoints on the other hand is a key step in addressing these issues.

Prof. Paretzke and Dr. Friedland's group at GSF Neuherberg, Germany is among the world leaders in the field of Monte Carlo track structure simulations (Friedland et al, Radiat. Prot. Dosim. 2002; Radiat. Res. 2003; Radiat. Phys. Chem. 2005). The PARTRAC Monte Carlo code developed by their group includes modules simulating initial physical processes of energy deposition and radical formation in water by radiations of different qualities, subsequent radical reactions, and the attacks of OH radicals on cellular DNA. A multi-scale model of chromatin structure is implemented, representing atomic coordinates within nucleotides, DNA helices, nucleosomes, chromatine fibre structures and fibre loops, following the backbone predicted by the SCD model (Kreth et al, Biophys. J. 2004).

The aim of the STSM was to foster the collaboration between Dr. Friedland's and Dr. Kundrát's groups, which started by Dr. Kundrát's one-week visit at GSF in October 2006. Within the STSM, Dr. Kundrát was introduced to the PARTRAC code developed for track structure simulations at GSF. Motivated by the efforts to look for correlations between track-structure characteristics and the biological effectiveness of radiations of different qualities, Dr. Kundrát performed detailed track-structure simulations for selected ions and energies. The energies (0.5, 1, 5, 10, 50, and 250 MeV for protons, 1, 5, 10, and 100 MeV/u alpha particles, 2.4, 4.2, 5.4, 11, 18, 25, 77, 191, and 266 MeV/u carbon, and 1.9, 11, 89, 194, and 395 MeV/u oxygen ions) were selected to cover the range of interest in light ion radiotherapy and also to correspond to energies at which biological experiments were performed. A spherical cell nucleus of 10 μm diameter with the chromatin structure corresponding to human lymphocytes, irradiated by a mono-directional ion beam, was considered. A random rotation of the source with respect to the cell nucleus was performed prior to the simulation to avoid any artefacts arising from a potential alignment of the chromatin structure axes with the beam direction.

The performed simulations include the estimated direct radiation-induced DNA damage as well as indirect effects mediated by OH radical attacks. The simulated

DNA damage was classified into clusters using several different classification schemes. In particular, in agreement with the results in (Kundrát and Stewart, Radiat. Prot. Dosim. 2006), a good correlation with a typical RBE – LET behaviour was found for damage clusters containing at least 2 strand breaks and at least 3 or 4 elementary DNA lesions in total; damage clusters were scored as different ones if separated by at least 20 undamaged bp.

While the per-track yields of specific clusters of DNA damage were found to significantly increase with increasing linear energy transfer (LET), at a given LET value they vary only slightly with ion's charge. This observation might be important for future developments of the probabilistic two-stage model of cell killing by different radiations, since so far the per-track damage probabilities have been within the model framework derived independently for different ions, and the results e.g. for proton and carbon tracks in V79 cells have been significantly different (cf. Kundrát, Phys. Med. Biol. 2006).

In addition, possible ways of incorporating cellular repair processes into the PARTRAC code and their detailed biophysical modelling have been discussed.

The results of the studies performed under this STSM are very promising indeed. In particular, they will be used in ongoing efforts to increase the predictive power of the cell killing model under development by Dr. Kundrát's group by proposing a microscopic radiobiological submodule to predict the per-track probabilities to induce lethal DNA damage by radiations of different qualities in different cells.