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Abstract

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Molecular mechanisms of DNA-repair

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The induction of DNA breaks within human cells is unavoidable, but not necessarily dangerous. Most DNA breaks are repaired by the cellular DNA damage response. However, a high concentration of breaks locally in the DNA can be fatal and result in cell death. This fatal amount of strand breaks can be induced by various methods, and in this thesis the focus will be on ionizing radiation. Low energy ions are used in ion beam cancer therapy and high LET ions are found in cosmic radiation, and here it is investigated what effect these ions have on the human DNA.

Several mechanisms on nanoscale contributes to inducing DNA damage when a cell is transversed by an ion. Here the focus is on the ion-induced shock wave, which will result in a force on the covalent bonds in the DNA backbone. This force has a large enough value to break the chemical backbone bonds, and for high energy ions, such as iron, create unrepairable damage, resulting in cell death for the irradiated cell.

However, for the low energy ions used in ion beam cancer therapy, the shock wave will only induce a few DNA breaks. To predict the correct survival rate of irradiated cell, the DNA repair mechanism needs to be investigated.

The recruitment time of the DNA repair activator proteins, MRE11 and NBS1, needs to be known in order to gain insigt in the time scale of DNA repair. Here it is discovered that they are recruited to the DNA break within tens of seconds and are transported by simple diffusion.

The software tools optimized to modeling DNA damage and repair is presented. MBN Explorer is the only tool that implements the reactive CHARMM forcefield needed to model bond breaks and thus ideal for performing shock wave simulations. The united collection of computational tools found in the browser based VIKING is useful when conducting the multiscale simulations needed to cover the mechanisms involved in DNA damage induction and repair.