Single Cell Model with Complete Human Genome using Geant4-DNA to Quantify Direct and Indirect Action Double-Strand Breaks

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Purpose

To quantify DNA double strand breaks (DSBs) using a single cell Geant4 model with complete human genome, and a mechanistic model of radiation chemistry in Geant4-DNA extension.

Introduction

In order to understand and predict the biological effects caused by ionizing radiation, many studies based on Monte Carlo (MC) simulation have been dedicated to simulate radiation-induced DNA damage. The stochastic nature of radiation makes MC calculations a well-suited method for simulating energy deposition and biological effects induced by ionizing radiation. The Geant4-DNA Project provides an open-source platform that allows users to simulate biological damage at the DNA scale. In our work, a detailed geometric target model was used to represent the human cell nucleus with whole DNA content, and Geant4-DNA chemistry model was applied to calculate the indirect damages by simulating the chemical reactions between the subsequent free radicals and DNA molecules.

Methods

A detailed ellipsoidal single cell model was implemented using a compacted DNA structure representing the fibroblast cell in the G0/G1 phase of the cycle using a total of 6 Gbp within the nucleus to represent the complete human genome. As shown in Figure 1 and Figure 2, several organization levels were implemented by the Geant4 Monte Carlo code, which is developed from the Geant4 extended example *wholeNuclearDNA*. This geometry was modeled in parallel for both the physical and chemical stage to record direct DNA damage caused by physical energy deposition as well as early indirect DNA damage caused by hydroxyl radicals (OH·) in the chemical and physicochemical stage with 2.5 ns duration. Thereby, the cell model was able to record the energy deposition and chemical reactions as direct strand breaks (SBs) and indirect strand breaks respectively. In this work, only the reactions between OH· and 2-deoxyribose can generate the candidates of indirect damage on DNA strand. As shown in Figure 3, to drastically reduce memory requirements and simulation times, only the immediately adjacent fraction of nucleosomes was simulated in the physicochemical and chemical stages instead of the whole DNA model in cell nucleus. The clustering algorithm DBSCAN (density-based spatial clustering of applications with noise) was implemented in the analysis process in order to quantify DSBs, which are the most critical damage generated by ionizing radiation to DNA. The detailed process of cell DNA damage tally of each event is shown in Figure 4. The model was validated against published experimental and computational results for DSB $Gy^{-1}Gbp^{-1}$ and the relative biological effectiveness (RBE) values for 250-kVp and Co-60 photons, as well as 2-100 MeV mono-energetic protons.

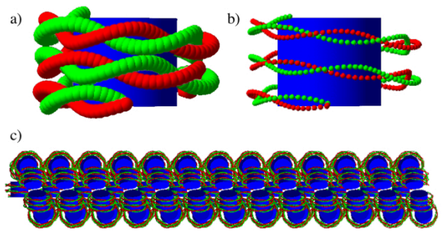

Figure 1: Smallest physical volume of DNA in the cell nucleus. a) nucleosome with DNA double helix and histone protein. b) double helix geometry with 2-deoxyribose only. c) a chromatin fiber.

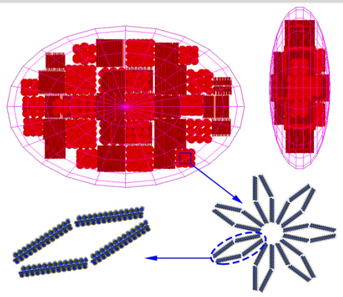

Figure 2: Highest organization levels in the model of DNA geometry.

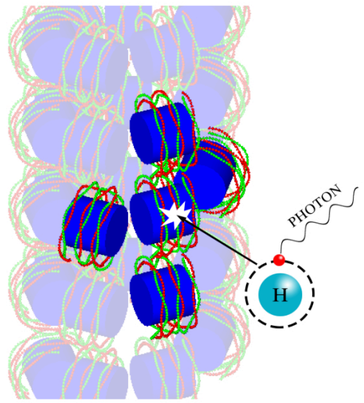

Figure 3: In order to minimize memory use and simulation time, only the four neighboring nucleosomes are activated to consider radicals diffusion.

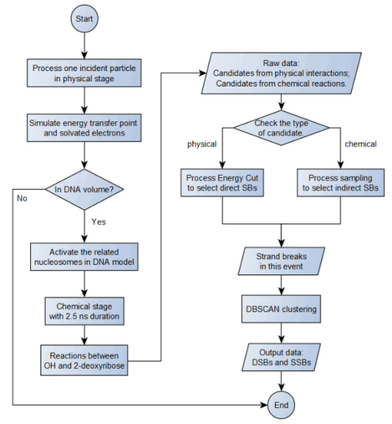

Figure 4: Flow diagram detailing the DNA damage tally process for one single event.

Results

A general agreement was observed over the whole simulated proton energy range, Co-60 beam, and 250-kVp in terms of the yield of DSB $Gy^{-1}Gbp^{-1}$ and RBE. Figure 5 shows the radicals and strand breaks simulated in our Geant4 MC code for a single proton with 50 MeV. The DSB yield was between 11.1 ± 0.9 and 8.1 ± 0.5 DSB $Gy^{-1}Gbp^{-1}$ for 2-100 MeV protons. Figure 7 shows the yield of direct and indirect SBs as a function of the energy of protons. Figure 8 shows mixed DSBs composed of direct and indirect SSBs make up more than half of the total DSBs. Moreover, the DSB yield was 8.0 ± 0.3 DSB $Gy^{-1}Gbp^{-1}$ for Co-60, and 9.2 ± 0.2 DSB $Gy^{-1}Gbp^{-1}$ for 250-kVp in this work.

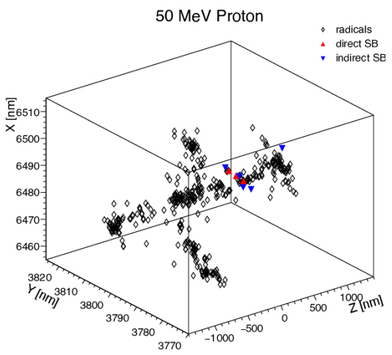

Figure 5: Radicals and strand breaks generated by a single 50 MeV proton.

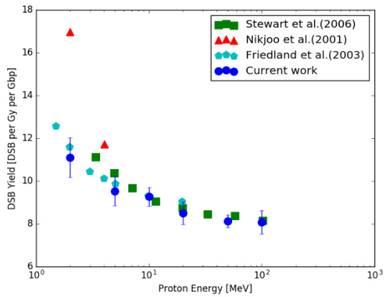

Figure 6: Yield of DSB/Gy/Gbp simulated in this work, and simulation results from the previous literatures are also presented.

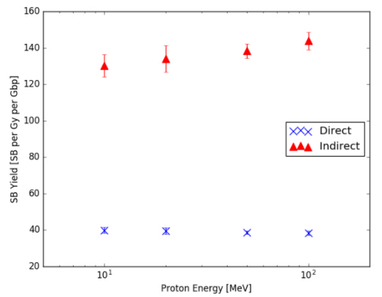

Figure 7: The simulated yields of two kinds of DNA strand breaks by mono-energetic protons with increasing kinetic energy

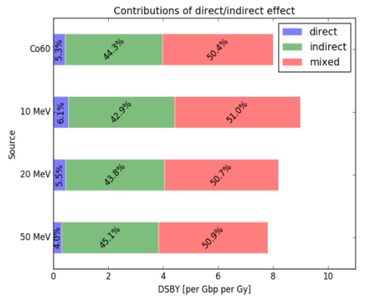

Figure 8: Yield of DSB with normalized proportions for different sources, to indicate the contributions from direct and indirect strand break.

Conclusion

The results presented indicated that the single cell model accurately simulates the radiation-induced DNA damage and shows that indirect SBs play an important role in the construction of DNA damage. The simulation of indirect SBs' contribution in DNA damage can improve the understanding of the mechanisms involved in the generation of DNA damage.

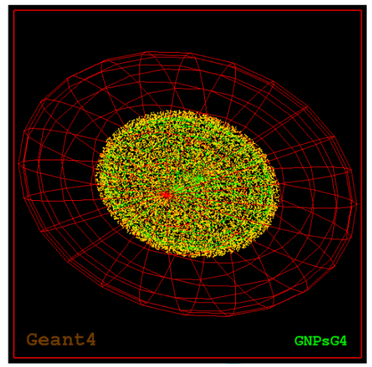

Figure 9: GNPs were modeled within 1 um from the cell nucleus.

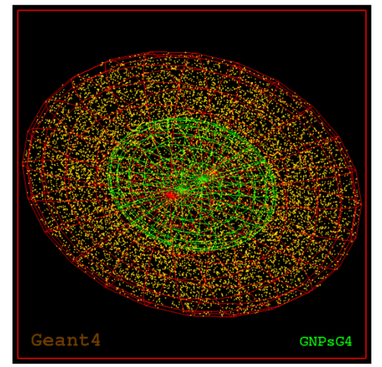

Figure 10: GNPs were modeled within the cytoplasm.

Additional Work

We used this single cell model to investigate the enhancement of DSBs from intracellular gold nanoparticles (GNPs). As shown in Figure 9 and Figure 10, two different distributions of GNPs were implemented. It is difficult to study the radio-sensitization mechanism from physical dose enhancement alone. In order to further understand the role of GNPs, more sophisticated models that consider chemical interactions should be implemented.