Modeling Direct and Indirect Action DSBs from Intracellular Gold Nanoparticles Using a Single Cell Model with Complete Human Genome in Geant4

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Purpose

To investigate the enhancement of double strand breaks (DSBs) from intracellular gold nanoparticles (GNPs) using a single cell Geant4 model.

Introduction

Gold nanoparticle aided radiotherapy has been of great interest in Radiation Oncology research over the last few years. Hundreds of articles have been published on GNP-mediated radio-sensitization and in-vitro and in-vivo experiments have consistently shown some degree of radio-sensitization for brachytherapy sources, kV and MV photon sources, electron sources, and proton sources. However, most observed radio-sensitization is significantly greater than what is predicted via most models. This project aims to investigate the GNP-induced radio-sensitization using single cell model with more complex mechanism and more realistic geometry. The yield of DSBs after irradiation is an important indicator to evaluate and predict the DNA damage. Both direct and indirect strand breaks (SBs) were considered to quantify the number of DSBs in this work.

Methods

A detailed Geant4 single cell model was built using complex DNA geometry and Geant4-DNA extension to record the direct SBs from energy deposition during the physical stage and indirect SBs from the reactions between hydroxyl radical (OH·) and 2-deoxyribose during the chemical stage. In physic stage, Geant4-DNA physics was used within the cell, and Livermore physics to model the interactions in GNPs. After that, the water radiolysis was implemented in physicochemical and chemical stages to simulate the indirect damage. Moreover, a detailed ellipsoid single cell model with complete human genome and a clustering algorithm was implemented in the calculation chain to quantify single strand breaks (SSBs) and double strand breaks (DSBs) directly from direct and indirect SBs. The size and number of GNPs modeled was a realistic intracellular concentration obtained from published literature and consisted of 12,000 individual GNPs 90 nm in diameter. Two intracellular localizations of the GNPs were implemented in this work: uniformly distributing within 1 µm from the nuclear wall, and uniformly distributing within cytoplasm. Mono-energetic photons (100 keV) and two clinical sources (250-kVp, 6-MV) were chosen to investigate GNP radio-sensitization in this model.

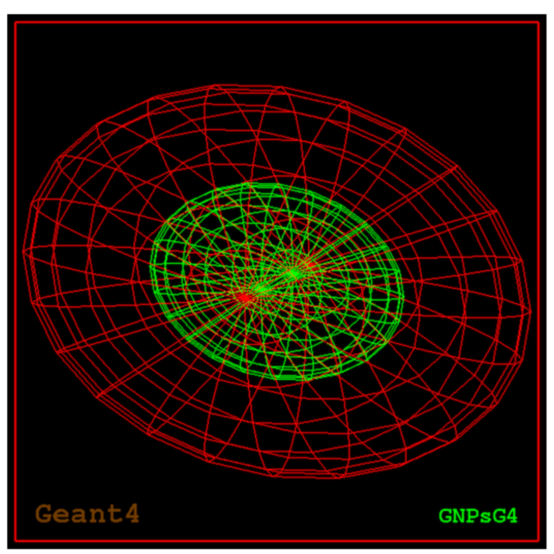

Figure 1: Single cell model was built using the dimensions of a human fibroblast cell nucleus.

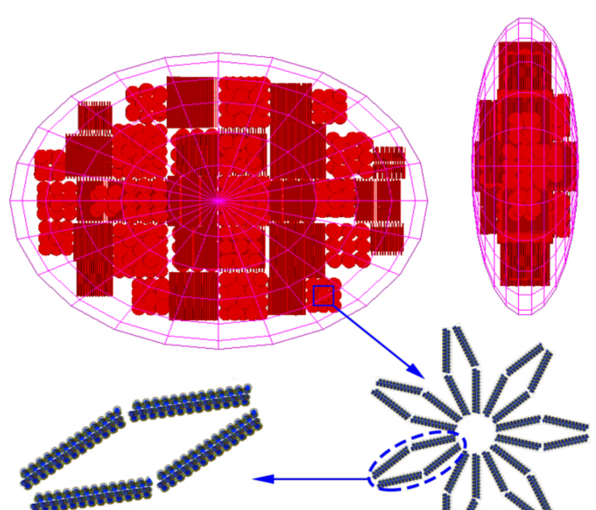

Figure 2: Physical volume of DNA in the cell nucleus with multi organization levels.

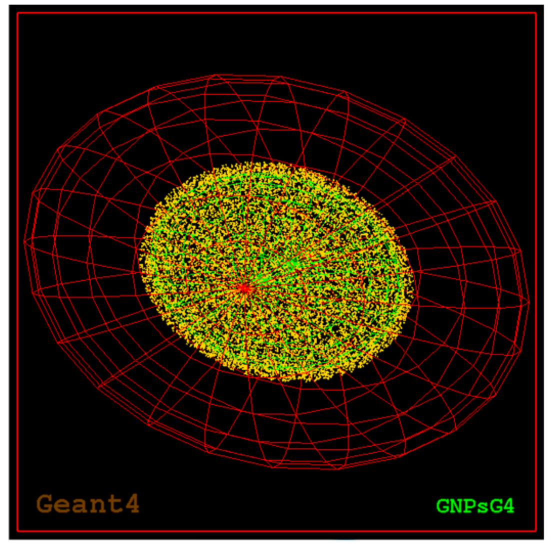

Figure 3: GNPs were modeled within 1 µm from the cell nucleus.

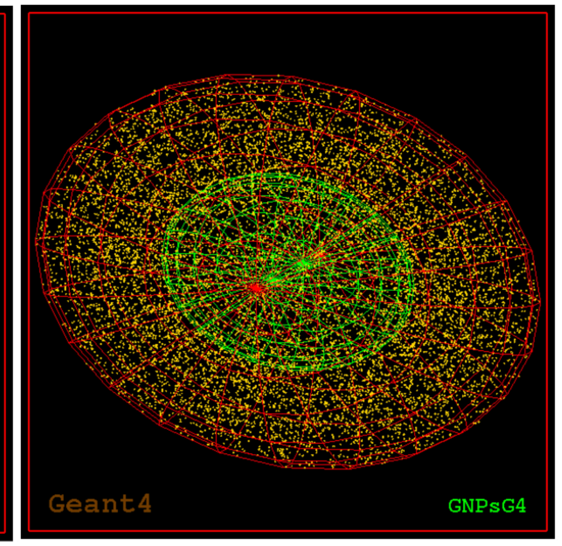

Figure 4: GNPs were uniformly distributed in cytoplasm.

Results

As shown in Figure 5a and Figure 5b, when GNPs are abutting to the nucleus, significant enhancement of energy deposition was found in nucleus after radiation of 100 keV photon beam. Figure 6 shows more generation of photoelectrons when GNPs are present in cell. Figure 7 shows, the 100 keV photon simulation have a large increase of more than 22% for cell dose when GNPs are in cytoplasm and abutting to the nucleus. The increase in DSB number was much higher at 64% when GNPs are in close proximity to the nucleus. Other two gamma sources shown similar trend. The GNP-induced enhancement of single strand breaks (SSBs), direct and indirect SBs are also shown in these plots. Figure 10 shows the changes of DSB yield with normalized proportions of direct and indirect SBs in 6MV source, to indicate their contributions to DNA damages.

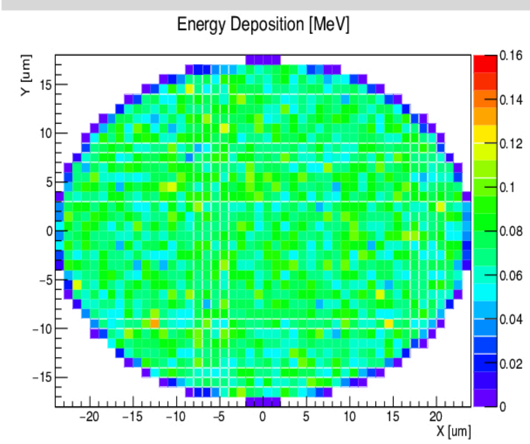

Figure 5a: 2D energy deposition distribution without GNPs in cytoplasm and with 100 keV photon beam.

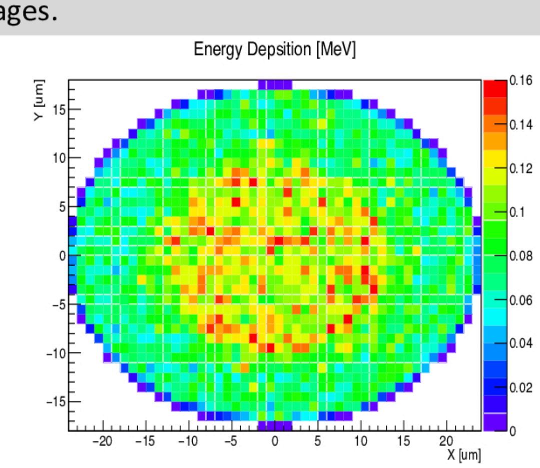

Figure 5b: 2D energy deposition distribution for 90 nm GNPs within 1 µm from the nucleus and with 100 keV photon beam.

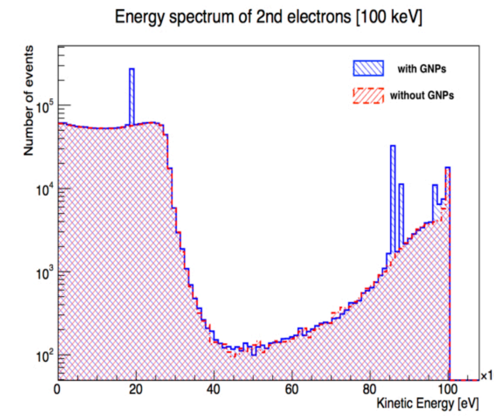

Figure 6: Energy spectrum of secondary electrons from 100 keV photon source. GNPs made lots of photoelectrons.

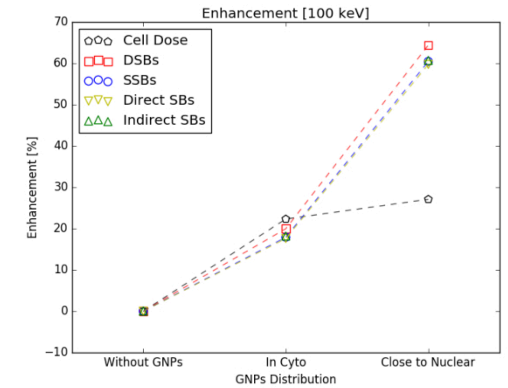

Figure 7: GNP-induced enhancement in 100 keV photon beam.

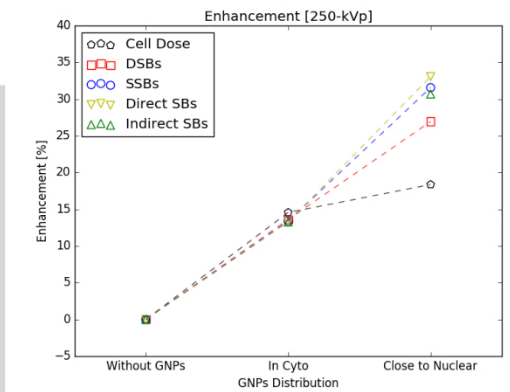

Figure 8: GNP-induced enhancement in 250-kVp photon beam.

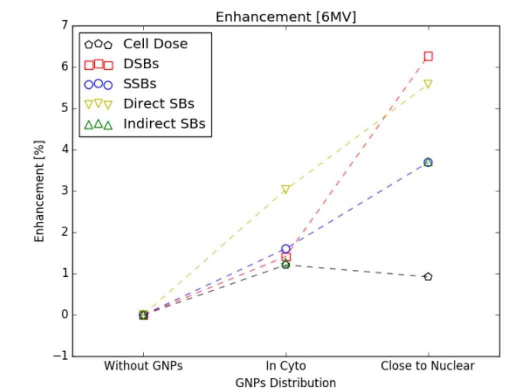

Figure 9: GNP-induced enhancement in 6MV photon beam.

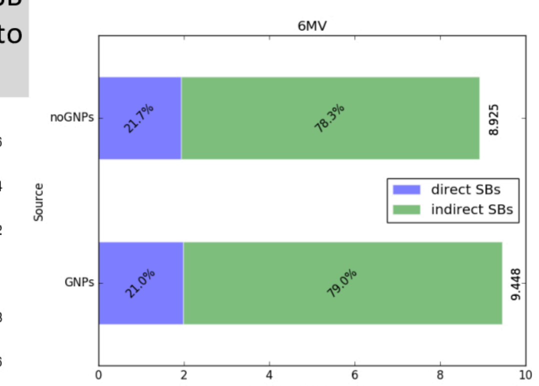

Figure 10: The yield of DSB for 6MV photon beam with contributions of direct and indirect SBs.

Conclusion

The results show the importance of investigating indirect action SBs using a realistic cell model. It is difficult to study the radio-sensitization mechanism from physical dose enhancement alone, especially for clinically relevant high energy sources. In order to further understand the role of GNPs and the possible mechanisms involved in the GNPs induced radio-sensitization effect, more sophisticated models that consider chemical interactions should be implemented.