Simulation of DNA damage using the "molecularDNA" example application of Geant4-DNA

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Abstract: The scientific community has a large interest in the studies of DNA damage and response after exposure to ionizing radiation. Several in-silico methods have been proposed so far to model and study the mechanisms of DNA damage using Monte Carlo simulations. The "molecularDNA" example is one of the most recent applications to simulate the irradiation of human cancer cells and bacteria using Geant4-DNA. This example enables the simulation of the physical, physico-chemical and chemical stages of liquid water irradiation, including radiolytic processes following the particle irradiation of the pre-defined human cell geometries and it can be used to calculate the early direct and non-direct DNA damage such as single (SSB) and double strand breaks (DSB) as well as DNA fragment distribution. The application is user friendly and can be used following simple macro commands. The results of the Monte Carlo simulation are compared to experimental data of DSB yields, as well as with previously published simulation data.

Keywords: Geant4-DNA, Monte Carlo simulation, cancer, protons, helium ions

1. Introduction

There are large efforts worldwide to perform accurate modelling and validation of radiobiological measurements of radio-induced DNA damage. The main goal is to understand cancer formation. The first software toolkit that was made available to the user community in full open access and able to model DNA damage and repair is the Geant4-DNA (http://geant4-dna.org/). The Geant4-DNA toolkit can simulate the physical interaction of radiation at the DNA scale, as well as the physico-chemical and chemical stages of water radiolysis. A new "molecularDNA" example of Geant4-DNA, publicly released in December 2022 in the Geant4 toolkit version 11.1, is presented in this manuscript [1 - 8].

2. Materials and Methods

The "molecularDNA" example incorporates a geometrical model of a human cell, consisting of a continuous Hilbert curve that produces a fractal-based DNA chain, made of straight and turned chromatin sections including nucleosomes, and placed inside an ellipsoid imitating the human cell nucleus. It enables the simulation of the direct and non-direct early DNA damage induction and a quantitative measure of this damage through counting the number of single strand breaks, SSB, DSB and DNA fragments distribution. The “human cell” geometrical configuration was irradiated with protons of energies in the range of 0.15 to 66.5 MeV, corresponding to the LET range from 73.5 to 1 keV/μm and both SSB and DSB yields, as well as their ratio, were calculated [1]. The SSB/DSB ratio, the DNA fragment length frequency distribution for 1 MeV incident protons, the damage kinetics as a function of DNA repair time and also the surviving fraction curves of NB1RGB cells as a function of delivered dose are also reported in [1]. The lung carcinoma, HTB-177, and breast adenocarcinoma MCF-7, cancer cell lines were modelled and incorporated into the "molecularDNA" example, starting from the default "human cell" geometry. The simulation of the irradiation with alpha particle beams was performed in the LET range up to 80.3 keV/μm and compared to experimental data [2].

3. Results

The "molecularDNA" example application of the Geant4-DNA was used to quantify early DNA damage in human cancer cells upon irradiation with alpha particle beams, as a function of linear energy transfer (LET), as described in [2]. Considering the difference in size for the different types of nuclei for HTB-177 and MCF-7 cell lines used, with respect to the "molecularDNA" default human cell geometry, subtle modifications to the voxel size and the number of nucleosomes were used to maintain the number of 6.4 Gbp in each DNA molecule. In Figure 1, the number of DSBs is normalised to the dose and the number of base pairs and is plotted as a function of LET. For both cell lines studied, the simulation results are within the experimental uncertainties, except for the

highest LET of 39.1 ± 1.1 keV/μm, due to the limitation of the experimental method of DSB evaluation as described in [2].

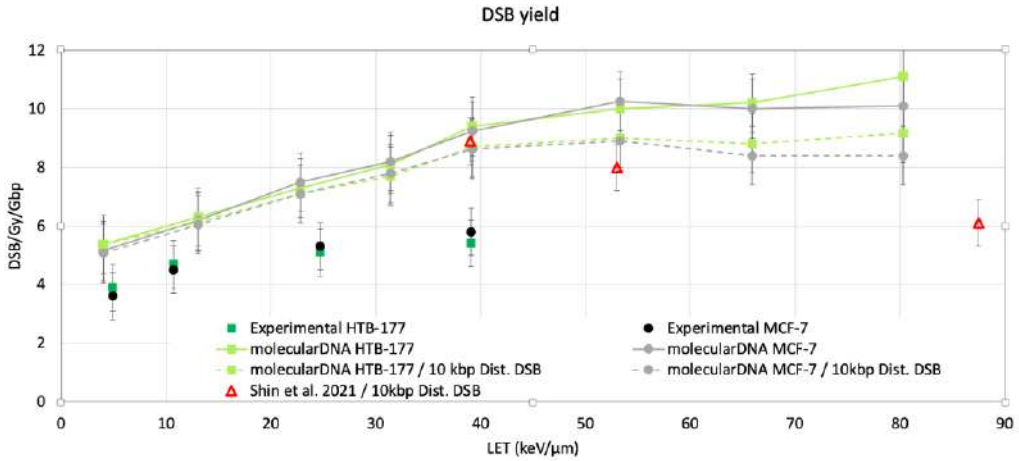

Figure 1. DSB yield as a function of LET, shown in light green and grey lines, for the HTB-177 and MCF-7 cells, respectively. The previous results [7] are shown as red triangles. Experimental data are shown in green squares and black dots, for HTB-177 and MCF-7 cell lines, respectively. This figure was reprinted from Physica Medica, 112, K. Chatzipapas, M. Dordevic, S. Zivkovic, N.H. Tran, N. Lampe, D. Sakata, I. Petrovic,A. Ristic-Fira,W.-G. Shin, S. Zein, J. M.C. Brown, I. Kyriakou, D. Emfietzoglou, S. Guatelli, S. Incerti, Geant4-DNA simulation of human cancer cells irradiation with helium ion beams, 102613, Copyright (2023), with permission from Elsevier.

4. Conclusions

The "molecularDNA" example application of Geant4-DNA has extensive possibilities for the modeling of DNA damage following irradiation with particles of different types, such as protons and alpha particles, as summarized in this manuscript. The simulation incorporates physical, physicochemical and chemical stages of liquid water irradiation, including radiolytic processes and is used to calculate direct and non-direct DNA damage. The "molecularDNA" application was benchmarked with respect to previous studies of the Geant4-DNA collaboration, as well as to experimental data available, for both proton and alpha particle irradiation. To achieve a more conclusive understanding of radiation induced damage in cells, more experimental data will be collected in a higher LET range. The simulation parameters will be adjusted as well.

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