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SIMULATION OF DNA USING GEANT4

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Abstract: The Geant4-DNA project entails the development of open-source software for Monte Carlo simulation-based modeling using the general-purpose toolkit Geant4. The main aim of this software is to simulate biological damage caused by ionizing radiation at cellular and subcellular levels. This project was initially initiated by the European Space Agency to forecast harmful radiation effects that may affect astronauts during future long-duration space missions. In this article, the Geant4-DNA collaboration presents an overview of the entire current project, including its latest developments already available in the latest public release of Geant4 (9.3 BETA), as well as an illustrative example of modeling direct irradiation of chromatin fiber. Expected extensions, impacting multiple scientific areas such as particle physics, chemistry, and cellular and molecular biology, within the framework of the fully interdisciplinary activity of the Geant4 collaboration, are also discussed.

Keywords: *Monte Carlo, Geant4, Geant4-DNA, microdosimetry, nanodosimetry, radiobiology.*

1. INTRODUCTION

Understanding and modeling the negative effects of ionizing radiation at the cellular and subcellular levels remain a challenge for modern radiobiology research. In particular, validated modeling tools are paramount for human radiation protection in specific professional domains. Radiation protection is a real concern on a daily basis, for instance, for workers in nuclear power plants, medical personnel, staff at particle accelerators, those working in industrial facilities and research laboratories, as well as for the general public through internal exposure to radon emanating from the soil. All of them are continuously exposed to low doses of radiation (the "low dose" regime typically ranges in the microsievert level). In this regime, assessing the health hazards from ionizing radiation exposure is limited due to the absence of available experimental data. Currently, biological effects arising from such low-dose radiation exposure can only be extrapolated from data collected at much higher radiation doses, for example, from epidemiological studies conducted after the Hiroshima and Nagasaki bombings. It is widely accepted as a general consensus that biological effects from radiation are proportional to the absorbed dose and, therefore, potential radiation exposure at any dose level may lead to a biological effect without a dose threshold. Consequently, health risks to humans from low-dose radiation exposure remain largely unresolved.

1.1. General-purpose Monte Carlo Method and Open-Source Approaches

The Geant4-DNA project proposes the utilization of the Monte Carlo method. While Monte Carlo methods may require significant computational resources for modeling complex scenarios and configurations, they can achieve high precision and can be considered as an alternative solution compared to deterministic approaches. Monte Carlo methods utilize random number generators to reproduce the stochastic nature of particle interactions with matter.

Rather than developing specialized Monte Carlo simulation software with limited scope for microdosimetry and modeling biological damage solely from radiation, the Geant4-DNA project aims to enhance the general-purpose Monte Carlo simulation toolkit Geant4 with such capabilities. Geant4 is an advanced simulation tool describing particle interactions with matter, originally developed at the European Organization for Nuclear Research (CERN) in Geneva, Switzerland, for simulating experiments in high-energy physics at the Large Hadron Collider (LHC). Geant4 development follows an open-source strategy: the software is entirely transparent and absolutely free. Anyone can download the Geant4 toolkit and develop their own simulation applications. The toolkit is developed by a team of over 80 international collaborators, and users worldwide actively participate in its validation to determine its accuracy at both microscopic and macroscopic levels. Public releases are available twice a year.

Geant4 software utilizes object-oriented technology (C++), providing remarkable flexibility and extensibility, gradually leading to the development of new Geant4 applications in fields related to particle-matter interactions, not limited to high-energy physics, such as biomedical physics and space physics, ranging from submicrometer cells and ray tracing to planetary scales. All Geant4-DNA developments are included in the Geant4 toolkit and benefit from easy access to the code, ensuring wide accessibility for the radiation biology community to such computational methods.

1.2. Geant4-DNA Collaboration

The Geant4-DNA collaboration brings together developers of Geant4, who are members of the Geant4 collaboration, as well as external consultants with specific expertise, including theoretical elementary particle physics, radiolysis, and microdosimetry. The current participants of the Geant4-DNA collaboration are listed as authors of this article. The project is a full activity of the Low Energy Electromagnetic Physics Working Group of the Geant4 collaboration, and all current Geant4-DNA developments are included in the public releases of the Geant4 toolkit. They are detailed on a dedicated website.

2. Physical Processes and Models in Geant4-DNA

Physical interactions are described by specific "process classes" in C++, which compute the total cross-section of particular physical interactions (e.g., elastic scattering, ionization, etc.); a full description of the interaction outcomes is also provided (kinematics, secondary particle production, deposited energy, etc.). In Geant4-DNA, these processes are purely discrete, meaning they model all physical interactions step by step with precise tracking without using any condensation methods. Users can compute specific physical quantities according to various models (theoretical or semi-empirical) using special "model classes," which can be complementary in energy ranges or entirely alternative. One "process class" may invoke one or several "model classes".

All process and model classes in Geant4-DNA have been completely revamped for the latest public release of Geant4 (9.3 BETA - June 2009), along with all classes in the Low Energy Electromagnetic Physics package of Geant4, to adopt a coherent approach to modeling all electromagnetic interactions in Geant4. The revamped classes include new user-friendly features, such as direct access to cross-section values for a given particle energy.

2.1. Available Physical Processes and Models

The extended Geant4-DNA suite currently covers the primary interactions of light particles and ions, including electrons, protons, hydrogen particles, helium particles, and their charged states at the eV level in liquid water, the primary component of biological materials. Some of these models are purely analytical, while others use interpolation of cross-section data tables for faster computation. The list of available processes and models, as they are available in the current public release of Geant4 (9.3 BETA), is presented in Table 1, along with their applicable ranges.

2.2. Implementation of the "Physics List" in Geant4-DNA

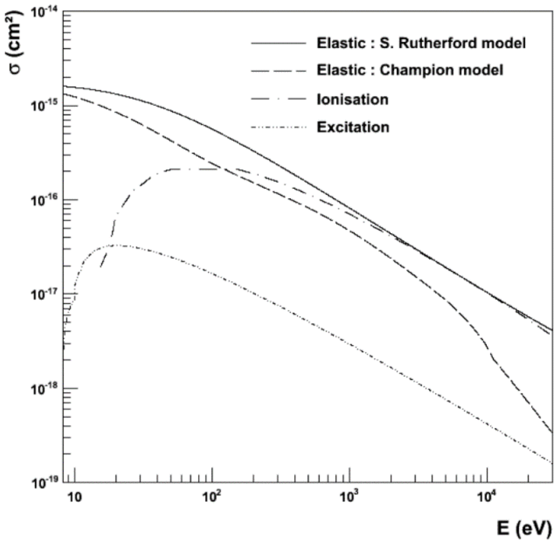
In a user application of Geant4, the user must specify in a special "physics list" class the particles and corresponding physical processes affecting these particles (e.g., electrons are sensitive to elastic scattering, excitation, and ionization). The default physics list in Geant4-DNA, containing all particles and processes listed in Table 1 and shown in Fig. 1 through Fig. 4, can be found in the "extended microdosimetry example" (for more details, see section 5), as well as on the Geant4-DNA website [2].

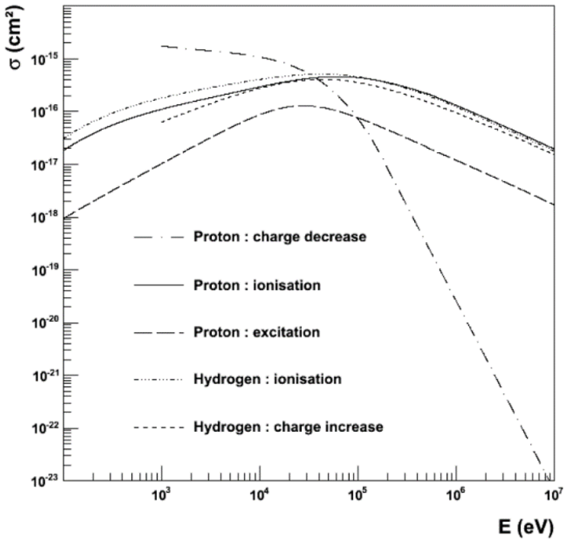
Table 1. List of Geant4-DNA physical processes available in version 9.3 BETA of the Geant4 toolkit, released in June 2009. The high- and low-energy applicability of the corresponding models is also indicated.

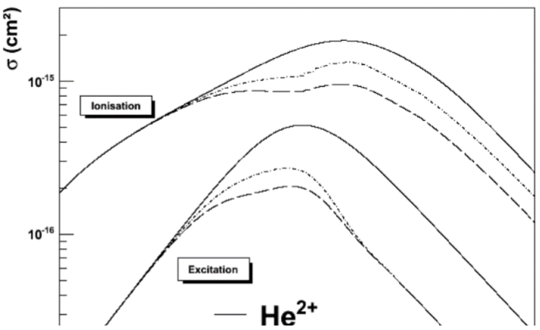
Process	**Model**	**Low energy limit**	**High energy limit**
Electrons			
Elastic scattering	Screened Rutherford Champion (alternative)	8.23 eV 8.23 eV	10 MeV 10 MeV
Excitation	Emfietzoglou	8.23 eV	10 MeV
Ionisation	Born	12.61 eV	30 keV
Proton			
Excitation	Miller and Green Born	10 eV 500 keV	500 keV 10 MeV
Ionisation	Rudd Born	100 eV 500 keV	500 keV 10 MeV
Charge decrease	Dingfelder	1 keV	10 MeV
Hydrogen			
Ionisation	Rudd	100 eV	100 MeV
Charge increase	Dingfelder	1 keV	10 MeV
He^{2+}			
Excitation	Miller and Green	1 keV	10 MeV
Ионизация	Rudd	1 keV	10 MeV
Charge decrease	Dingfelder	1 keV	10 MeV
He^{+}			
Excitation	Miller and Green	1 keV	10 MeV
Ionisation	Rudd	1 keV	10 MeV
Charge increase	Dingfelder	1 keV	10 MeV

Charge decrease	Dingfelder	1 keV	10 MeV
He (neutral helium)			
Excitation	Miller and Green	1 keV	10 MeV
Ionisation	Rudd	1 keV	10 MeV
Charge increase	Dingfelder	1 keV	10 MeV

Figures 1-4 show the total cross-section of all physical processes and corresponding models available in the Geant4-DNA extension of the Geant4 toolkit version 9.3 BETA (June 2009). Some of these models are currently undergoing improvements and are expected to be released in the next release (version 9.3) of the Geant4 toolkit in December 2009. Verification of cross-section models is the subject of another article by the Geant4-DNA collaboration.







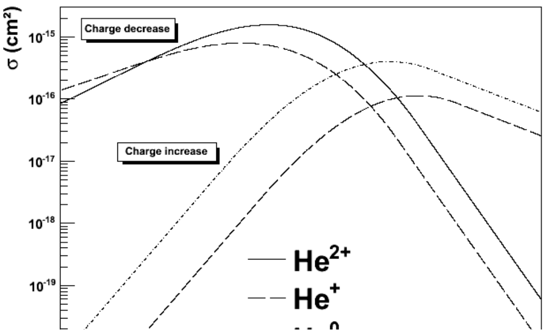


Fig. 1. Total cross-section of electron processes available in

Fig. 2. Total cross-section of processes for protons and hydrogen

Fig. 3. Total cross-section of ionization and excitation processes for neutral helium (dash-dotted line), He+ (dashed line), and He2+ (solid line) available in Geant4-DNA 9.3 BETA, depending on the energy of the incident particle (from 1 keV to 10 MeV). Ionization is the dominant process at all energies.

Fig. 4. Total cross-section of charge increase and decrease processes for neutral helium (dash-dotted line), He^+ (dashed line), and He^{2+} (solid line) available in Geant4-DNA 9.3 BETA, depending on the energy of the incident particle, in the range from 1 keV to 10 MeV. At low and high energies, the ionization process (shown in Fig. 3) remains the dominant process.

Rutherford model only) and ionization dominate at higher energies.

higher energies. For hydrogen, ionization dominates across the entire energy range.

It should be noted that the excitation and charge change (increase/decrease) processes are specific to the Geant4-DNA extension and are not available in the standard Geant4 toolkit or in the Low Energy Electromagnetic Physics package of Geant4 [3].

2.3. Structure Modeling

To illustrate the capabilities of nanoscale track modeling in the Geant4-DNA extension, Figures 5 and 6 depict the structures of tracks for several particles obtained using all processes listed in Table 1.

In Figure 5, the structure of the ionizing track of a single electron with an energy of 1 keV in liquid water is shown. The primary incident electron and the secondary electrons formed by ionization are tracked down to the lowest energy limit, which is 8.23 eV. Below this energy, electrons stop and deposit their energy in the medium. The dashed cloud represents each individual elastic scattering event. In this energy range, elastic scattering significantly dominates over excitation (purple circles) and ionization (red stars), as shown in Figure 1.

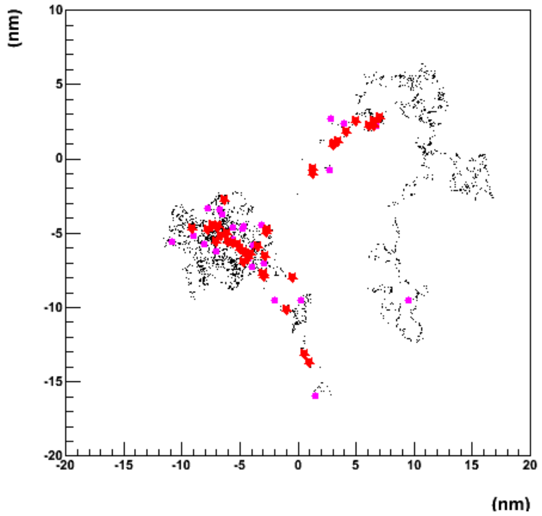


Fig. 5. 2D projection of the structure created by a single electron with an energy of 1 keV in liquid water using Geant4-DNA physical processes. The primary particle appears at position (0,0). Elementary interactions are shown: elastic scattering using the Champion theoretical model [18] (black dots), excitation using the Emfietzoglou model (purple circles), and ionization according to the Born model (red stars).

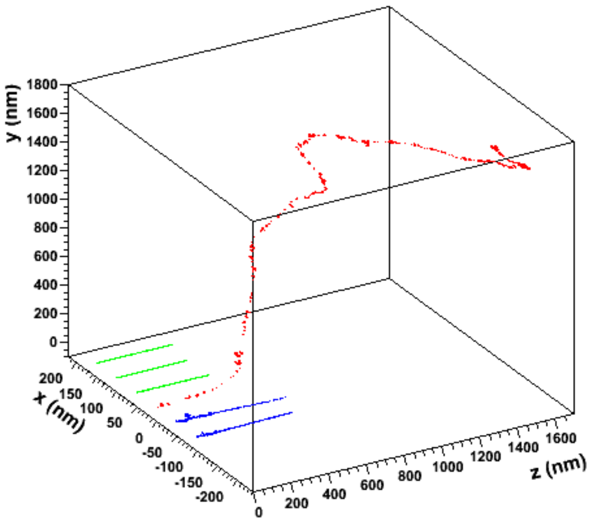


Fig. 6. Comparison of six three-dimensional track structures obtained using Geant4-DNA physical processes for single particles with an incident particle energy of 10 keV in liquid water. The particles are emitted in the direction of the positive z-axis and from different positions along the x-axis for clarity: proton (x = -50 nm), hydrogen (x = -100 nm), electron (x = 0), He^{2+} (x = 50 nm), He^{+} (x = 100 nm), helium (x = 150 nm).

In Fig. 6, a comparison of three-dimensional track structures obtained for all particles and processes available in the Geant4-DNA extension is shown. The primary particles have an initial kinetic energy of 10 keV and are emitted in the direction of the positive z-axis (see the figure legend for particle identification).

The participating particles are tracked, gradually losing their energy until they reach the energy limits specified in Table 1. Below these limits, the particles stop and deposit their energy locally. Each point in the track structure corresponds to a separate physical interaction.

3. Modeling DNA Direct Damage by Radiation

Since the physical processes and models of Geant4-DNA are fully integrated into the Geant4 toolkit, they can easily be combined with Geant4's geometric modeling capabilities. In particular, it becomes possible to implement geometries of biological objects with high resolution at the submicrometer scale and to fully track particles inside these geometries using Geant4-DNA's physical processes. These geometries represent a significant improvement over geometric models previously used for dosimetric studies using the Geant4 toolkit at the level of biological cells. Two approaches can be used to implement high-resolution geometries: voxel and atomistic.

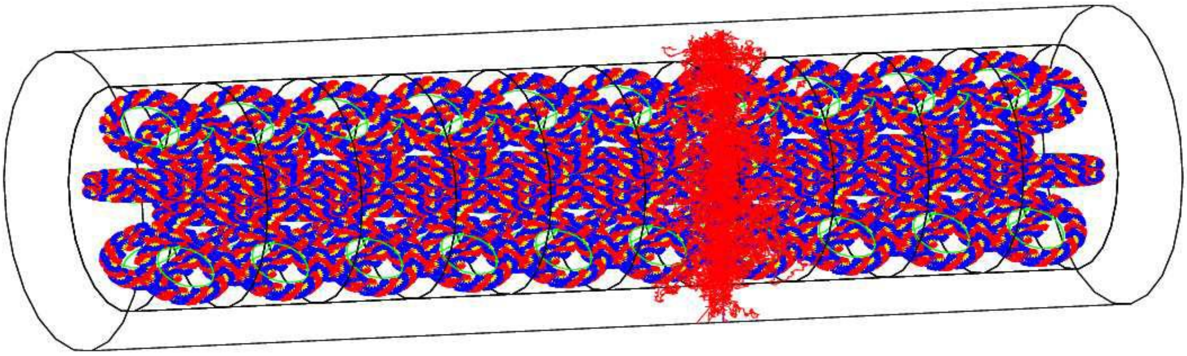
3.1. Geometries of Biological Objects Using Voxels

The voxel-based approach, based, for example, on reconstructed three-dimensional images obtained using high-resolution techniques such as confocal microscopy, was introduced in [10]. We have developed high-resolution cell geometry models for Geant4 at the submicrometer scale. These phantoms represent realistic individual human keratinocyte cells - including the cell nucleus, internal nucleoli, and cytoplasm - for more accurate dose calculations in cell irradiation experiments using microbeams of individual ions. Physical calculations were performed using Geant4's low-energy electromagnetic processes. An example "microbeam" in Geant4 demonstrates how to implement such cell phantoms and is already available to users directly in the Geant4 toolkit. It is fully documented on the Geant4 website under "advanced examples" [4].

3.2. Atomistic Geometric Model of DNA

In the atomistic approach, we propose to model biological objects with higher granularity on the nanometer scale, such as DNA molecules, using combinations of simple mathematical volumes. The geometric model of DNA presented in this article is inspired by the work of M. A. Bernal and J. A. Liendo [22] in investigating the capabilities of the Monte Carlo method PENELOPE in nanodosimetry. This model is organized at four levels of geometry: pairs of deoxyribonucleotides, DNA double helix, nucleosomes (two looped sections of DNA wrapped around a chromosomal protein called histone), and chromatin fiber (i.e., DNA assembled into chromosomes).

Figure 7. Visualization of the entire chromatin fiber in Geant4, as described in the text, irradiated by a single He+ particle with an energy of 500 keV, emitted perpendicular to the main axis of fiber rotation. Groups of phosphodiester DNA are



represented in blue and red colors. They are assembled into loops of the spiral. Each histone has two DNA loops and forms a nucleosome. Each of the 10 "slices" of this fiber contains 6 nucleosomes in the B-DNA conformation. Also shown is the complete track structure induced by the incoming particle and simulated using the Geant4-DNA physical processes. This illustration was obtained using the DAWNFILE visualizer available in the Geant4 toolkit.

The particle shower shown in Figure 9 was obtained by emitting a single He+ particle with an energy of 500 keV onto the fiber. SSB (single-strand break) is counted if one target (group of phosphodiester DNA) receives an energy deposit greater than 10.79 eV, the first level of ionization of a water molecule. DSB (double-strand break) is counted if two SSBs are located on opposite strands and are separated by no more than 10 base pairs. For illustration purposes, with such a definition, the Geant4 simulation predicts that a single He+ particle with an energy of 500 keV, for example, can generate 9 SSBs and 2 DSBs in the fiber geometry model, the result of direct interaction of ionizing particles and the geometric model.

4. Microdosimetry Example for Geant4 Users

The "microdosimetry example" in the Geant4 toolkit includes an "advanced example" called "microdosimetry example." The list of physical processes ("physics list") available in this example was adapted in Geant4 version 9.3 BETA (released in June 2009) to the new design of Geant4-DNA processes and models, which is now common for standard and low-energy electromagnetic processes and models in Geant4. It demonstrates to users how to implement the Geant4-DNA physics list (see Table 1), including the ability to identify Geant4-DNA physical processes by user-defined names, generate primary particles, and extract full three-dimensional particle track structures in liquid water using the complete set of Geant4-DNA physical processes. Additionally, a ROOT macro file is provided for convenient visualization of the track structures of tracked particles, such as those shown in Figure 5 and Figure 6.

5. CONCLUSION

This article has presented the current state and developments available in the Geant4-DNA extension for the Geant4 toolkit. The Geant4-DNA processes extend the capabilities of the Geant4 toolkit to model physical particle interactions at the submicron level in liquid water. Combined with detailed preliminary geometric models of DNA molecules, we expect to be able to simulate direct damage, such as single-strand breaks and double-strand breaks, caused by ionizing radiation.

Future developments will include the refinement and implementation of additional physical models for photons, for heavier ions such as carbon and oxygen (meeting the common requirements of new hadron therapy techniques and radiation applications in space), as well as for other biologically relevant target materials (e.g., DNA bases). These new models will cover extended energy ranges in combination with existing Geant4 physical models (standard electromagnetic processes and low-energy electromagnetic processes). In particular, the inclusion of vibration excitation models based on the work of Misko and Sanchez down to 0.025 eV is planned.

The project will benefit from the open-access availability of the Geant4 toolkit and its international visibility as it is a full component of Geant4. It will provide a freely and fully transparently integrated platform for simulating DNA damage from radiation for any interested user. The project is expected to impact several research areas beyond the initial Geant4 task for simulations in high-energy physics (HEP). Indeed, validated models will be able to cover application areas related to ionizing radiation and biological objects at the cellular level. Anticipated applications include, for example, radiation protection and microdosimetry for long-duration space programs involving humans and biological samples, as well as radiotherapeutic applications.

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