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Monte Carlo Simulation of DNA Break Prediction Following Electron Irradiation Using Geant4-DNA Toolkit

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ABSTRACT

Introduction: The interaction of ionizing radiation with cells involves complex physical and chemical processes that can cause single-strand breaks (SSB) and double-strand breaks (DSB). DSB is one of the most deleterious forms of DNA damage caused by radiation exposure and is also poorly repaired. Misrepaired or unrepaired damage can finally lead to genomic mutations, which may initiate cancer or cell death.

Material and Methods: The Monte Carlo simulation toolkit Geant4-DNA is used in this study to simulate the physical and chemical processes that can damage the DNA of human fibroblast cells resulting from an incident electron on the DNA.

Results: Electrons are classified as low-Linear Energy Transfer (LET) radiation, typically depositing energy at a rate of approximately 0.2 to 15 keV μm^{-1} in water or soft tissue; therefore, we examined the occurrence of SSB and DSB vs. electron energy of 0.5, 0.8, 1, 10, and 100 keV. Since there are no published data for human fibroblast cells, our simulation results were compared with available experimental data and findings from other simulation models of other cell types. Our results demonstrated consistent agreement with previously published studies.

Conclusion: The outcomes of our simulation, using the Monte Carlo simulation Geant4-DNA code with the "molecular DNA" based on G4EmDNAPhysics_option6 and G4EmDNAChemistry_option3, are in line with experimental data and simulation results of other cells that have already been published. The maximum DSB value was about 1 keV, with an LET value of about 10 keV μm^{-1}.

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Introduction

Both low and high doses of ionizing radiation (IR) can have an impact on humans; the consequences vary depending on age, gender, and exposure duration [1]. IR can cause tissue integrity impairment and potentially lead to organ dysfunction. The effects of radiation on organs are influenced by the irradiation site, patient age, and total radiation dose [2,3]. Additionally, it can significantly alter certain hematological parameters and the morphology of red blood cells in human blood [4,5]. The subject of the effect of charged particles on DNA damage induction and complexity in the cell is still of interest to scientists [6]. Understanding and modeling the mechanisms of such radiation-induced DNA damage is still challenging due to its complexity.

The natural background radiation (cosmic and terrestrial), medical uses (diagnostic imaging and treatment), and space exploration activities (astronaut missions and projected space tourism) are some of the sources of IR exposure. Understanding how IR interacts with biological systems is, therefore, still a major objective in radiation biology research [7].

DNA-composing biomolecules can sustain direct damage from radiation, but they can also sustain damage via radiolysis byproducts such as hydroxyl radicals. With a better understanding of the mechanisms of radiation damage, it will be possible to estimate radiation risk more precisely, especially for radiation therapy, radiation protection, and space missions [8].

Monte Carlo simulations have shown promise in quantifying and evaluating radiation-induced damage, especially to the DNA molecule, at the subcellular level. There are various tools available right now, such as KURBUC [9], PARTRAC [10], Geant4-DNA [11] , gMicroMC [12], and MPEXS-DNA [13].

Folkard et al. 1993, determined the threshold energy for breakage of plasmid DNA (pBR322) (not cells themselves) as a function of monoenergetic electron exposure. They found that the threshold for double-strand break ranged from 25 to 50 eV, while it was 25 eV for single-strand break in DNA [14].

De Lara et al., 2001, evaluated the efficacy of ultrasoft X-rays as a function of photon energy in inducing damage, double-strand breaks, and cell death in monolayers of cultured Chinese hamster cells. The results showed that as photon energy decreased, the radiation became more effective in breaking DNA

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strands (i.e., greater biological effectiveness occurred at lower energies) [15].

Fulford et al., 2001, employed Monte Carlo simulation to quantify single- and double-strand breaks in plasmid DNA in an aqueous medium (in a water-based model system, not a cell) after exposure to alpha particles and ultrasoft X-rays. The modeling and experimental data correlated well for both types of strand breaks [16].

Semenenko et al., 2004, studied the effects of electrons, protons, and α-particles on a model human cell. The damage was introduced and modified in a cell model using A Fast Monte Carlo Algorithm after irradiation with 4.5 keV electrons, 0.3 MeV protons, and 2.0 MeV α particles. The authors observed that the mean number of elementary damages per lesion increases as the particle Transfer of Linear Energy (LET) increases (4.5 keV electrons, LET ~ 0.2 keV μm^{-1}), 0.3 MeV protons; LET = ~58.5 keV μm^{-1}, 2.0 MeV α particles; LET = ~168 keV μm^{-1}) [17].

Lampe, Karamitros, Breton, Brown, Kyriakou, et al., 2018, employed a basic test geometry in a new study implemented in Geant4-DNA. An initial attempt was made to understand how various configurations of physics models and parameters for the calculation of damage would influence the estimation of DNA damage. Using low-energy electrons as primary particles, a range of parameters was explored to try to derive a configuration that aligned with the results of previous studies in this area [18].

Mokari et al., 2018, worked on damage to a B-DNA model and a 3 μm water sphere using the Geant4-DNA code to model 'Simulating DNA damage from Electrons of energy 100 eV to 4.5 keV'. The study examined direct damage and damage from the indirect source of hydroxyl radical (•OH), focusing on the simple and complicated single and double-strand breaks (SSB and DSB). Findings revealed that most of the interactions resulted in no damage, and complex damage considerably contributed to DSBs, particularly distinguishing low-energy electrons (less than 500 eV) for which substantial differences were noticed due to smaller ionization and excitation cross-sections presented in the code. The strand break threshold energy's effect on damage yields was analyzed [19].

Matsuya et al., 2019, measured and calculated single- and double-strand breaks (SSB and DSB) in DNA for Chinese hamster cells and human cells based on a Monte Carlo simulation. The cells were irradiated with gamma rays and electrons as the main particles. The electron energy ranged from 0.01 keV to 100 keV. As part of experimental observations, they also examined foci formation after X-ray irradiation. The simulated and experimental results compared favorably [20].

Mokari et al., 2020, employed a realistic computational B-DNA model to calculate and contrast direct and indirect damage in DNA by low-energy electrons with energies ranging from 0.001 keV to 100 keV. The authors evaluated the differences between two cross-section models, Default and CPA100, by means of Monte Carlo simulations with the Geant4-DNA toolkit. The three phases of the simulation were physical, chemical, and the damage-formation phase that relates to the induction of single-strand breaks and double-strand breaks with both physical and chemical interactions. This study showed that the CPA100 model (a.k.a. G4-DNA-option6) appears to have better agreement with experimental evidence in hand at present. [21].

Margis et al., 2020 employed track-structure simulations integrated with the low-energy Geant4-DNA extension to obtain lineal energy spectra within spherical volumes of the computation of lineal energy densities around DNA double-strand breaks (DSB). The study assessed the impact of varying DSB yields from different physics models, target sizes, and the particle tracking cutoff energies. It was determined that the production of DSBs varies considerably with the energy of the incident electrons, that the tracking cutoff energy exerted a large influence (>100%), and that the physics model and target diameter choices exerted a moderate influence (~10 to 30%), along with the diameter of the target [22].

Matsuya et al., 2020, suggested a basic clustered analysis focusing on ionization and electronic excitation events within a scope of 10 base pairs, estimating yields of multifaceted DNA damage induced by electron and X-ray irradiation. The authors addressed damage complexity by reflecting on tracks of the incident electron beams, finding a high correlation between the computational results and the experimental results. Matsuya also emphasized that 43.5% of the DSBs during 70 kVp X-ray exposure were complex DSBs with BD, portraying the phenomenon of damage accumulation. It enables the quantification of intricate forms of DNA damage that in vitro techniques cannot measure [23].

This study aims to examine the occurrence of SSB and DSB in the DNA of human fibroblast cells generated by an electron with an energy of 0.5, 0.8, 1, 10, and 100 keV, using the Monte Carlo simulation Geant4-DNA code "molecular DNA" with G4EmDNAPhysics_option6 and G4EmDNAChemistry_option3. The "molecular DNA" was initially developed by Lampe [24].

Materials and Methods

DNA Strand Breaks

A double-helical two-stranded structure of DNA (Deoxyribonucleic acid) was postulated in 1953 by Watson and Crick. Approximately 3 billion base pairs of the DNA are packaged into 23 chromosomes, making a total of 6 billion base pairs, as shown in Figure 1. The DNA nucleotides are made up of a nitrogenous base (adenine, guanine, cytosine, or thymine), a phosphate group, and a deoxyribose sugar molecule. Therefore, the genetic functions of DNA can be understood as the combination of two characteristics: a polymer that exists

as a double-helical string that facilitates the packaging, accessibility, and replication of the information store, and a tape that contains the information store that encodes the sequences of proteins and RNA molecules. Importantly, the base sequence determines the physical characteristics of the polymer as well as the coding of proteins and RNA molecules [25,26].

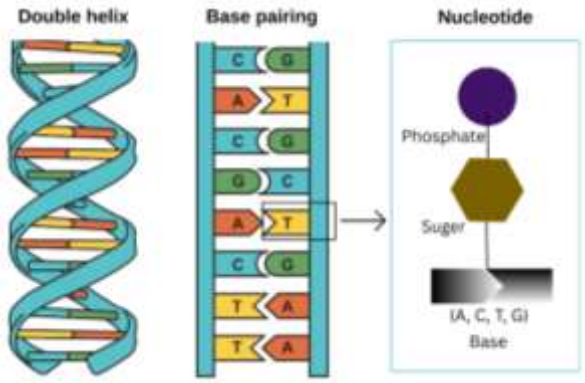

Figure 1. Schematic illustration of the DNA double helix. A, T, G, C, S, and P represent Adenine ($C_5H_5N_5$, Orange), Thymine ($C_5H_6N_2O_2$, Yellow), Guanine ($C_5H_5N_5O$, Green), Cytosine ($C_4H_5N_3O$, Blue), Sugar ($C_5H_{10}O_4$, deoxyribose, Gold), and Phosphate (H_3PO_4, Purple), respectively.

As illustrated in Figure 2, radiation can lead to DNA strand breaks both directly and indirectly. As illustrated in Fig. 2, Single-strand breaks (SSB) in DNA happen in one of the strands of the DNA double helix, whereas Double-strand breaks (DSB) occur when both strands of the DNA duplex are cut. Complex single-strand breaks (cSSB) occur in one strand of the DNA double helix while having multiple strand breaks, and each strand break distance is smaller than 10 base pairs among these damages. DSB is considered to be the most critical type of damage [27,28].

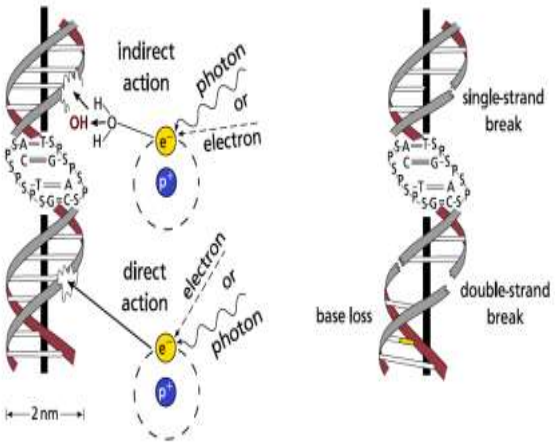

Figure 2. DNA damage induced by ionizing radiation [30]

Direct damage refers to the damage of DNA molecules through their direct ionization or excitation by charged particles. Indirect damage involves damage to the DNA molecule's structural integrity due to the interaction of particles with nearby chemicals. This process generates a significant number of free radicals (e.g., OH•). OH• is widely regarded as the primary factor behind indirect damage [29].

Simulation Configuration

The physical and chemical characteristics, along with the definitions of damage, are used in this study as predetermined values. Histones were also taken into consideration for completeness of the DNA nucleus geometry, as in Ref. [8]. Because they are scavenging materials, histones tend to absorb reactive radicals. Consequently, it was crucial to consider their influence.

Our simulation was designed to use a geometrical representation of a human cell, which is thoroughly detailed by Sakata et al. [31]. A continuous Hilbert curve fractal-based DNA chain made up of straight and turned chromatin segments, including histones, makes up the implemented geometry in more detail [32]. A 7.1 μm × 2.5 μm × 7.1 μm semi-axes ellipsoid that mimics the human cell nucleus contains the continuous DNA chain structure, which is roughly 6.4 Gbp long. The effective nucleus density with this configuration is around 0.015 bp/nm^3 [33].

The G4EmDNAPhysics_option6 physics list was selected for calculating electron energy transport. The diffusion distance was set at 9 nm, and the maximum diffusion time was set at 5 ns. Free radical species that enter the histone region are killed by histones, which are thought to be ideal scavengers.

To create direct DNA damage, the charge transfer effect in the hydration shell (R_{dir}) must be within 3.5 Å, which is correlated with the radius of nucleotide molecules [31] throughout an energy range of $E_{min}^{break} =$ 5 eV to $E_{max}^{break} = 37.5$ eV.

Within 1 ps following irradiation, the excited H_2O^* and ionized H_2O^+ water molecules created during the physical stage dissolve into radical species via dissociation channels during the pre-chemical stage. After the pre-chemical phase is over, chemical species spread out and interact with the DNA targets or one another to cause indirect damage. To generate indirect chemical DNA damage, we selected *G4EmDNAChemistry_option3*, where the probability of indirect damage by OH radicals is P_{OH}^{break} is chosen to be 0.405 eV. While the end time of the chemistry stage T_{chem}, and the killing distance within which a reactive species like •OH must be from DNA to be considered able to cause a break d_{kill}^{chem} are 5 ns, and 9 nm, respectively.

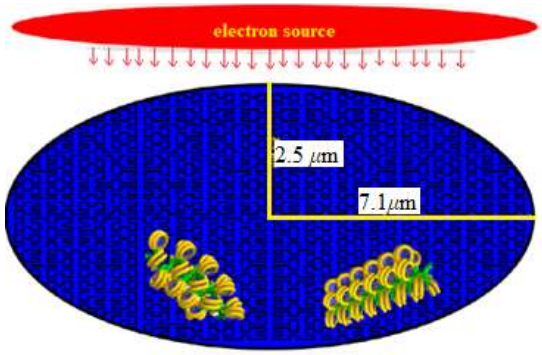

Figure 3 a) Two-dimensional representation of the human fibroblast ellipsoidal cell nucleus and its sub-structure. The Hilbert curve, or fractal path of DNA, is represented by the black lines inside the ellipsoidal water cell. Two chromatin fiber segments, including histones, are depicted: a straight segment and a twisted segment that is out of proportion to the rest of the figure's geometry. Radiation is emitted by the red disk.

Results

Genetic material is the most sensitive to radiation because it carries inherited genetic effects. Loss or alteration of this information can be caused by mutations that have formed or through changes in the cell's chromosomal characteristics. This paper aims to predict the DNA break that may be induced in human fibroblast cells irradiated by electrons with E (keV): 0.5, 0.8, 1, 10, and 100. Table 1 presents the energy and Transfer of Linear Energy (LET; is the amount of energy transferred per unit track length) of electrons used in this study, and the number of SSB and DSB yields on human fibroblast cell DNA per Gy Gbp and associated errors (%). Figure 4 outlines the yield breaks, such as (SSB and DSB), in a human fibroblast cell after electron irradiation. Figure 5 depicts the DSB per Gy Gbp as a function of LET for incident electrons on human fibroblast cell DNA.

Table 1. Shows the SSB and DSB yield on human fibroblast cell DNA per Gy Gbp and associated errors (%) for the investigated energies and their corresponding LET, where the unit of LET stands for keV μm^{-1}

Energy (keV)	LET (keV μm^{-1})	SSB (Gy^{-1} Gbp^{-1})	Error %	DSB (Gy^{-1} Gbp^{-1})	Error %
0.5	18.6	16.070	3.01×10^{-4}	1.460	1.0×10^{-3}
0.8	14.9	108.957	7.71×10^{-5}	10.983	2.07×10^{-4}
1	12.5	147.509	5.18×10^{-5}	16.251	1.2×10^{-4}
10	2.2	175.169	3.07×10^{-6}	7.460	1.07×10^{-5}
100	0.4	216.436	5.11×10^{-6}	5.687	2.61×10^{-5}

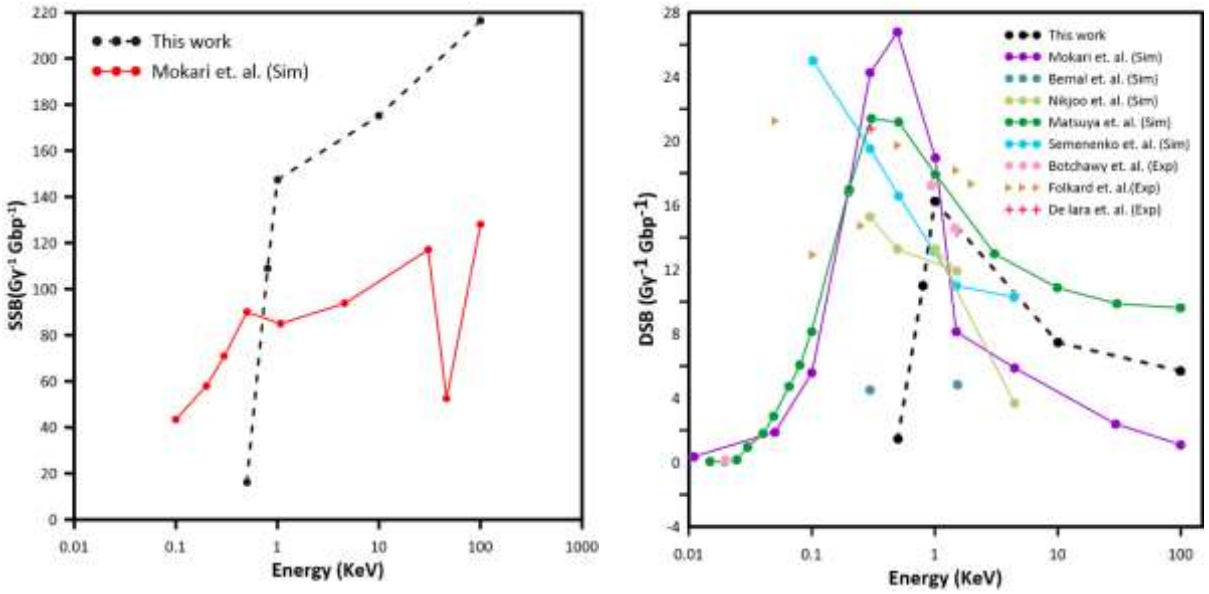

Figure 4. SSB and DSB yields for incident electrons on human fibroblast cell DNA as a function of energy for human cell geometry in comparison with the published results of simulations (Sim) [17,20,34–36] and experimental (Exp) data [15,37,38].

Discussion

Figure 4 (Left) illustrates the impact of electrons on DNA single-strand breaks (SSB) in a human cell. Higher radiation energy leads to more physical encounters between DNA and the impacting particles. It is logical that as electron energy increases, the number of breaks increases. Because the other strand is intact, the cell can fix this kind of damage to its DNA fairly easily; repair systems just have to piece together the two ends. Fig. 4 (Right) demonstrates, meanwhile, the effects of electrons on double-strand breaks DSB. Electron stopping power in liquid water often shows a maximum (Bragg peak) in the range of 100 eV to 1 keV. Very low-energy electrons (<1 keV) often produce dense, localized ionizations, causing significant damage directly to the DNA molecule. About 1 keV, the stopping power is almost entirely collisional; radiative losses (bremsstrahlung) are negligible; therefore, our simulation study predicted the maximum yield for these breaks is at an electron energy of 1 keV, with an LET value of about 10 keV μm^{-1} as depicted in Fig. 5, possibly related to the Geant4 cross sections and chemical reaction rates as well as to the radiation ranges [39]. Our results are in line with most published simulations (Sim) [17,20,34–36] and experimental (Exp) data [15,37,38]. Mokari M., et al., 2020 [21] calculated direct and indirect DNA damage induced by low-energy electrons (0.011-100 keV) using default and CPA100 cross-section models within Geant4-DNA. They concluded that the DSB was lower than experimental values for energy above 1 keV, and higher than experimental values for energy less than 1 keV. While Nikjoo H., et al. 2001 [34], used a Monte Carlo simulation of electron tracks of low-energy (0.3, 1.5,4.5 keV) in liquid water and a B-DNA model to determine the spectrum of DNA damage; based on his study, he showed that an elevated LET leads to a higher induction of DNA double-strand breaks (DSBs). It is complicated for the cell to repair such double-strand breaks once both DNA strands are damaged simultaneously.

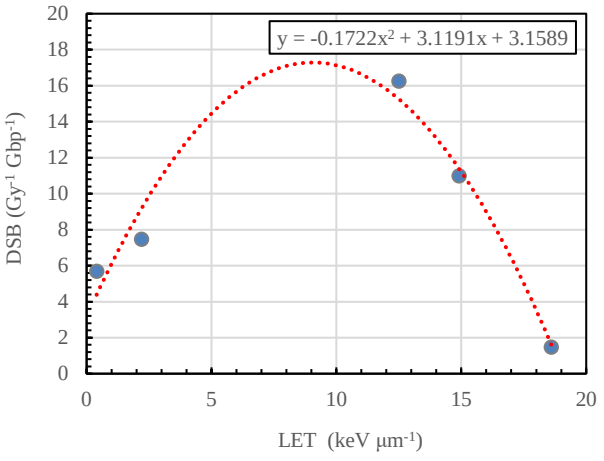

Figure 5. Number of DSB per Gy Gbp as a function of LET for incident electrons on human fibroblast cell DNA.

Conclusion

With the help of a Monte Carlo simulation, "molecular DNA" (developed on top of the Geant4-DNA toolkit, which calculates SSBs and DSBs induced by electrons in a fractal chromatin-based human cell nucleus model), we have been trying to improve our understanding of how strands are broken using ionizing particles like electrons. Our simulation results are compared with the simulation results available in the literature and experimental data. This work leads us to the conclusion that electrons are hazardous to human cells, and DNA in particular, because they can induce double-strand breaks. The maximum DSB yields were at 1 keV, with an LET value of about 10 keV μm^{-1}, possibly related to the Geant4 cross sections and chemical reaction rates, as well as to the radiation ranges. This study may benefit clinical radiation therapy by increasing the rate of killing cancer cells, as well as understanding DNA strand break repair processes. Our simulation faced limitations in computational cost, tracking efficiency, and memory consumption, which may affect the accuracy. We hope we can use computer clusters in the future.

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