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ORIGINAL ARTICLE

Investigation of Auger Electron Emitting Radionuclides Effects in Therapy Using the Geant4-DNA Toolkit: A Simulation Study

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Abstract

Purpose: The biological effects of ionizing radiation at the cellular and subcellular scales are studied by the number of breaks in the DNA molecule that provides a quantitative description of the stochastic aspects of energy deposition at cellular scales. The Geant4 code represents a suitable theoretical toolkit in microdosimetry and nanodosimetry. In this study, radiation effects due to Auger electrons emitting radionuclides such as ^{195m}Pt ^{113m}In, ^{125}I, and ^{201}Tl are investigated using the Geant4-DNA.

Materials and Methods: The Geant4-DNA is the first Open-access software for the simulation of ionizing radiation and biological damage at the DNA scale. Low-energy electrons, especially Auger electron from Auger electron emitting radionuclides during the slowing-down process, deposit their energy within a nanometer volume.

Results: The average number of Single-Strand Breaks (SSB) and Double-Strand Breaks (DSB) of DNA as a function of energy and distance from the center of the DNA axis are shown.

Conclusion: The highest DSBs yield has occurred at energies less than 1 keV, and ^{195m}Pt induces a higher DSBs yield.

Keywords: Geant 4-DNA; Auger Electron; Double-Strand Break; Single-Strand Break; Radionuclide; Targeted Therapy.

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1. Introduction

The research of radiation-induced damage is performed for a wide range of radiation sources and geometries. This damage may lead to biological effects like affecting the genome and cancer. When ionizing radiation interacts with DNA, the biophysical effects are introduced. Ionization events during the slowing-down process in low energy electrons occur in nanometer distances that are comparable to DNA and chromatin scales [1]. The Auger decay, characterized by short-ranged electrons, leads to an intense local deposition of energy around radionuclide. In therapeutic applications, this can be used to cause damage to the DNA of malignant cells. Auger emitters also find applications in biology and radiobiology where their effects can be used to probe fundamental mechanisms. Low-energy electrons are recognized as having an important effect on cellular radiation damage [2]. Eventually, damage to DNA may give rise to genetic effects or cancer [3]. Understanding radiation damage requires knowledge of biological lesions. For finding out the mechanisms of ionizing radiation interaction with DNA, it is necessary to determine the parameters related to DNA. DNA is sensitive to the effects of radiation. DNA damage includes SSB and DSB. DSB leads to a non-repair damage state and causes cell death [1, 4, 5]. One of the ionizing radiations is Auger electron emitting radionuclides. Auger electron emitting radionuclides with energies ranging from eV to keV are suitable for targeted therapy. The Auger electrons' range is from cell to subcellular scale [6-9]. Auger electrons can lose their energy deposit near the DNA. Knowledge of radiation-induced parameters can guide us in choosing a suitable radionuclide. For this reason, Auger electrons have good potential for use in targeted therapy. Auger electron emitters are suitable to treat small tumors [10, 11]. Understanding Auger electrons' effects in cellular and subcellular scale experimental and simulation methods have been done [12-14]. Few studies have been done on the effects of radiation therapy at the nanoscale [15]. For example, the effects of the Auger electron emitting radionuclide ^{125}I on DNA have been investigated, but other radionuclides have received less attention [9, 13]. Also, since the Auger electrons interactions are random processes, Monte Carlo codes are the most suitable tools to simulate radiation-induced damage and investigation biological effects. The most Monte Carlo codes for simulations of radiation transport in the matter are GEANT4 [16], PITS99 [17], PARTRAC [18], and KURBUC [19]. Ionizing radiation induces DNA damage in the mammalian cell nucleus. DNA damages are categorized in SSB and DSB [3, 4]. Most SSBs are repaired, while DSB repairs are almost impossible [20, 21]. Simulating low-energy electrons in biology has attracted attention in recent decades.

Several Monte Carlo codes have been developed to evaluate biological damage induced by ionizing radiation at nanoscales. Monte Carlo models describing the biophysical procedures related to radiation-related cell death have been used since the 1960s [22]. Monte Carlo codes play an important role in investigating radiation effects at the micro and nanoscales [2, 23]. Radiobiological models can be applied to the simulation of biological effects for the clinical treatment systems. These codes can be used as an investigation toolkit for studying radionuclide targeted techniques, such as targeted therapy with Auger electron, where they allow studying the effect of radiation at the cellular and sub-cellular scales [24, 25]. The Geant4-DNA, which is an extension of Geant4, is suitable for the simulation of ionizing radiation biological damage at the DNA scale. It has been extended for particle interactions with liquid water down to the eV in Geant4-DNA [26-31]. The geometry of DNA is classified into three main types: linear, volume, and atomic models [18, 32, 33]. Pomplun and Bernal proposed the first atomic DNA model developed an atomistic B-DNA model [34, 35]. This code can be used to investigate the effects of Auger electron emitting radionuclides. The Geant4-DNA is used to evaluate the damage due to radiation in DNA.

2. Materials and Methods

Geant4 is software-based on the Monte Carlo method. This code is a general-purpose code and is widely used in various fields, including high energy physics, space studies, medicine, and radiobiology. This code has a large number of libraries, and the user has Open-access to its data source. This code contains an initial set of physical processes in water in various energy ranges. The Geant4-DNA is an extension of Geant4. The Geant4-DNA allows describing low energy particle interactions at the nanometer scale. This code is suitable for dosimetry and nanodosimetry and software based on the C++ programming language. It can simulate particle interactions with matter in a wide range of energy, geometries, and dimensions [14, 22, 28-30, 36].

The energy cutoff for electrons is 7.4 and 100 eV for protons and 1 keV for α particles. The Geant4-DNA can describe low energy particle interactions at the cellular and subcellular scales. In this code, liquid water is used for Particle interactions, which is a reasonable estimation of the biological processes. An atomic model of B-DNA is used in this study. B-DNA is the most probable structure of DNA in living cells [37]. Many studies have shown the capability of the Geant4-DNA with its Low Energy Electromagnetic package to simulate the radiation at the cellular and subcellular scales, and it has physical models for electron interactions in liquid water [22, 26, 28, 38]. In this study, the ^{113m}In, ^{201}Tl, ^{195m}Pt, and ^{125}I spectrums presented in the report American Association of Physicists in Medicine (AAPM) are used (Table 1) [24]. In the simulation study, 1 million electrons are used as the source of primary charged particles.

The electrons are randomly generated around the DNA molecule [39]. In this study, we are using the B-DNA model extracted from the protein data bank. (Figure1). Pdb4dna, which uses DNA geometry extraction from the Protein Data Bank (PDB), is used for the simulation process [28, 39]. The DNA molecule for a normal human cell has about 6×10^9 base pairs or 3.6×10^{12} daltons with a complex structure. So, 1bna, a B-DNA structure extracted from PDB with 12 base pairs, is used. DNA damage

Table 1. Auger electrons spectrum for ^{201}Tl, ^{113m}In, ^{125}I and ^{195m}Pt [24]

^{113m}In			^{125}I		
Process	**Energy(MeV)**	**Yield/Decay**	**Process**	**Energy(MeV)**	**Yield/Decay**
CK NNX	3.58E-05	7.38E-01	CK NNX	0.0299	3.51
CK MMX	1.24E-04	2.73-01	Auger NXY	0.0324	10.9
CK LLX	1.97E-04	4.48E-02	CK MMX	0.127	1.44
Auger MXY	3.76E-04	6.22E-01	CK LLX	0.219	0.264
Auger LMM	2.71E-03	2.44E-01	Auger MXY	0.461	3.28
Auger LMX	3.2E-03	5.99E-02	Auger LMM	3.05	1.25
Auger LXY	3.7E-03	3.4E-03	Auger LMX	3.67	0.340
Auger KLL	1.98E-02	2.59E-02	Auger LXY	4.34	0.211
Auger KLX	2.32E-02	1.28E-02	Auger KLL	22.4	0.138
Auger KXY	2.68E-02	2.68E-02	Auger KLX	26.4	0.059
Auger NXY	1.63E-05	2.3E+00	Auger KXY	30.2	0.0065
^{195m}Pt			^{201}Tl		
Process	**Energy(MeV)**	**Yield/Decay**	**Process**	**Energy(MeV)**	**Yield/Decay**
CK NNX	1.71E-04	6.05E+00	CK NNX	1.72E-04	4.41E+00
Auger NXY	5.67E-05	1.29E+01	CK LLX	7.73E-04	3.22E-01
CK MMX	4.07E-04	1.8E+00	CK MMX	4.06E-04	9.23E-01
CK LLX	1.41E-03	5.51E-01	Auger MXY	1.83E-03	2.03E+00
Auger MXY	1.73E-03	3.4E+00	Auger LMM	7.58E-03	5.41E-01
Auger LMM	7.36E-03	9.89E-01	Auger LMX	9.89E-03	2.35E-01
Auger LMX	9.50E-03	4.15E-01	Auger LXY	1.20E-02	1.91E-02
Auger LXY	1.15E-02	3.58E-02	Auger KLL	5.50E-02	2.68E-02
Auger KLL	5.21E-02	1.57E-02	Auger KLX	6.63E-02	1.53E-02
Auger KLX	6.28E-02	7.80E-03	Auger KXY	7.75E-02	1.5E-03
Auger KXY	7.33E-02	1.20E-03	Auger NXY	6.44E-05	7.93E+00
			CK OOX	4.53E-05	2.84E+00
			Auger OXY	1.61E-05	1.76E+01

induced by ionizing radiation is direct or indirect. For direct damage, threshold energy is the least amount of energy required to cause a break in each strand of DNA. For DNA damage simulations, in direct damage, the threshold energy is chosen as 10.79 eV (10.79 eV lowest ionization energy of water in Geant4-DNA code) [40]. In calculating DNA strand breaks, we have considered both direct and indirect mechanisms. The methodology adopted to estimate DNA indirect effect can be found in Pomplun and Raisali work, for which the radicals are not traced.

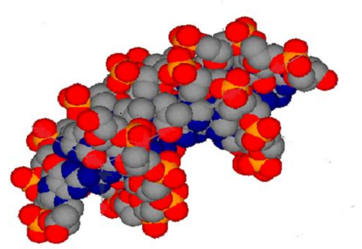

Figure 1. The molecular structure of DNA macromolecule (1bna.pdb)

Still, they are only taken into account. In these works, the direct and indirect effect is found in the same way; the only difference is their energy threshold. For the indirect effect, the energy threshold is 17 eV as the minimum required energy deposition for producing a radical pair [9, 34, 41]. If the energy deposition in the sugar-phosphate groups is equal to or more than the energy threshold, an SSB occurs. The direct or indirect damage induced to the opposite strands of the DNA within less than 10 bp is considered as DSB (Figure 2) [5]. Since the critical part of the cells consists of about 70% water, when the cell is exposed to ionizing radiation, more radiation energies are absorbed by the water molecules, resulting in free radicals' production. These effects are known as indirect effects of ionizing radiation.

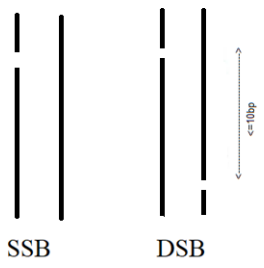

Figure 2. Representation of SSB and DSB

In the chemical stage, chemical species are OH, e_{aq}, H_2O_2, H. Among these chemical radicals, OH has the most significant ability to interact with DNA. Hydroxyl radicals will interact with sugar and base groups in DNA much more than other species (e_{aq}, H) [42]. The probability of interacting OH radical with sugar-phosphate and base is 20% and 80%, respectively. The sugar-phosphate radical leads to SSB with a probability of 65%. Thus probability damage or strand breaks production due to the interaction of OH radical with DNA is 13% (P_{OH} = 13%) [4, 43]. Therefore, hydroxyl radical is responsible for DNA damage [44]. So, strand breaks are obtained by using these probabilities.

3. Results

The average yield of SSB per decay as a function of distance from DNA central axis and the average yield of DSB per decay as a function of distance from the DNA central axis is shown for ^{195m}Pt, ^{113m}In, ^{125}I and ^{201}Tl in Figures 3 and 4.

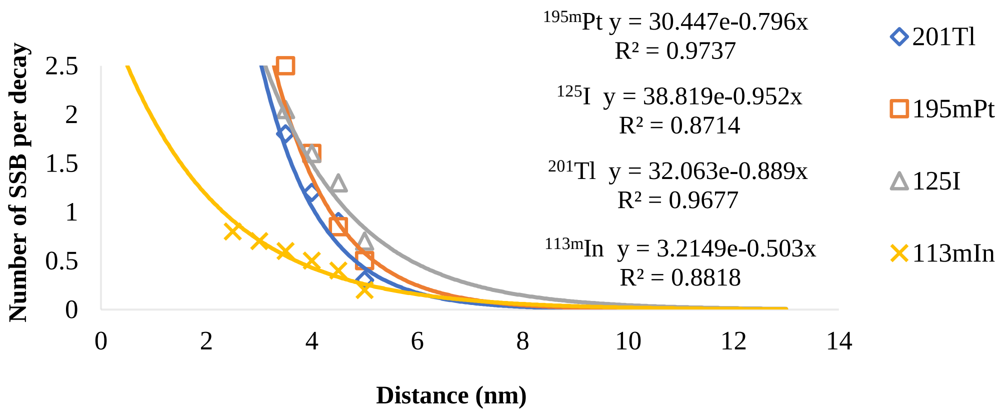

Figure 3. Number of SSBs per decay versus the distance to the center of DNA in ^{195m}Pt, ^{201}Tl, ^{125}I ,and ^{113m}In

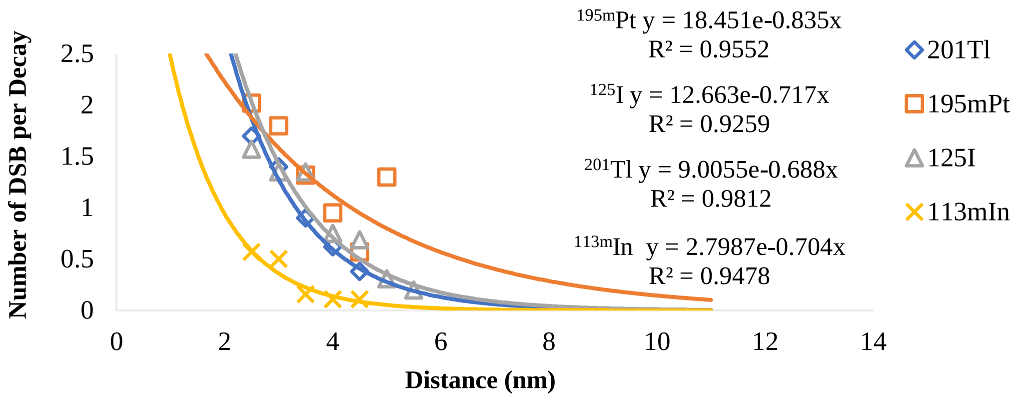

Figure 4. Number of DSBs per decay versus the distance to the center of DNA in ^{195m}Pt, ^{201}Tl, ^{125}I ,and ^{113m}In

The DSB yield values at different monoenergies were obtained and compared with other work (Figure 5 and Table 2). Also, yield values obtained for selected radionuclides are reported in Table 3.

4. Discussion

The average yield of SSB and DSB per decay as a function of distance from DNA central axis were obtained. Also the calculated yields of DSB per gray per dalton of DNA were shown. The differences in the yield values perceive in due to differences in the physical and DNA geometry. For example, in Geant4, the total ionization cross-section for 1 keV electron is about 20% higher for MOCA8B compared with Geant4-DNA, while the total excitation cross-section is about 5 times higher [36]. In the experimental results, when intracellular oxygen decreases, damage decreases [51]. Threshold energy for a direct damage can be the different in other works. The damage to DNA by SSB is less severe than DSB due to possible self repairers of the DNA molecule. The DSB per decay decreases with increasing the distance between the decay site and the DNA's central axis. That is due to smaller

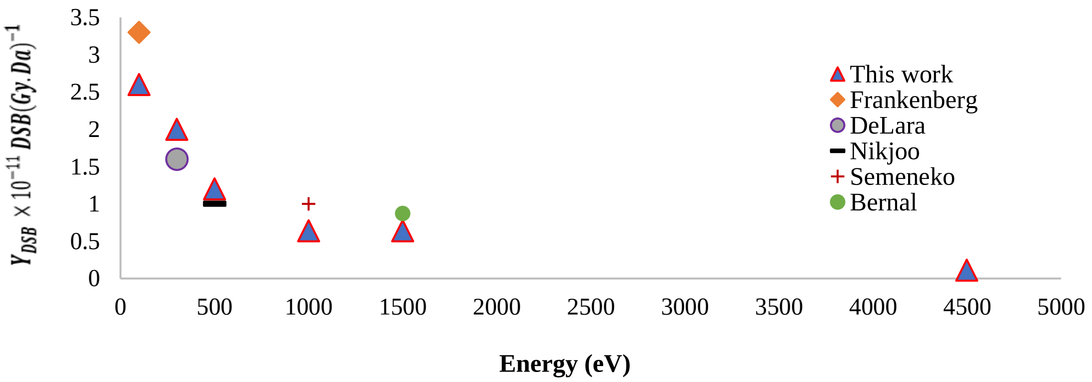

Figure 5. DSB yield values in various energy

Table 2. Yield comparison using monoenergy electrons with other works

Initial Energy (eV)	Y_{DSB} $DSB(Gy.Da)^{-1}$ In Experimental and Simulation	Y_{DSB} $DSB(Gy.Da)^{-1}$ in this Work
100	1.6×10^{-11} [45] & 3.3×10^{-11} [46]	2.6×10^{-11}
300	1.6×10^{-11}	2×10^{-11}
500	1×10^{-11} [4, 47]	1.2×10^{-11}
1000	1×10^{-11} [47]	0.87×10^{-11}
1500	0.66×10^{-11} [32]	0.64×10^{-11}
4500	-	0.11×10^{-11}

Table 3. Yield comparison of radionuclides with other work

Radionuclide	Yield of SSB per Decay in This Study	Yield of DSB per Decay in This Study	DSB per Decay in Other Work	Y_{DSB} $DSB(Gy.Da)^{-1}$ in This Study	Y_{DSB} $DSB(Gy.Da)^{-1}$ in Other Work
^{195m}Pt	3.9	2.02	-	1.4×10^{-11}	-
^{201}Tl	3.4	1.7	-	1.2×10^{-11}	-
^{113m}In	0.8	0.46	-	1.3×10^{-11}	-
^{125}I	2.86	1.57	1.1[48]	0.85×10^{-11}	0.6-0.9$\times 10^{-11}$ [49]& 1.17×10^{-11} [50]

energy transfer of moving charged particle (Auger electron) to DNA molecule. High-density irradiation is in the vicinity of DNA. Damage is when the distance between an Auger electron emitting atom and DNA is about 2.5 nm, and 90% decreases occur when the distance is about 6 nm. The obtained equations show that DSB and SSB decrease exponentially. Regressions analysis performed using the least-squares methods with R^2 values higher than 0.87. The highest value of DSB yield occurs at energies less than 1 keV, as shown in Figure 5 and Table 2. ^{195m}Pt registers more DSB yield in this study.

5. Conclusion

The present work reports a first attempt to extend our detailed calculations of direct and indirect radiation effects of Auger electrons emitting radionuclides such as ^{195m}Pt ^{113m}In, ^{125}I, and ^{201}Tl using the Geant4-DNA model (pdb4dna). In this study, the production of DSBs and SSBs of these radionuclides' atoms from the DNA central axis at different distances and different Auger electron energy were investigated. The number of DSBs and SSBs decreases exponentially by increasing the distance from the center of DNA. The highest damage occurs when the distance between an Auger electron emitting atom and DNA is about 2.5 nm. The highest damage also has been occurred at energies < 1 keV in the proximity of DNA. Auger electron and costar-kroning with an energy of less than 1 keV (belonging to the M and N transition and some of the L layer transition) are the most effective electrons in the production of strand breaks in DNA. The DSBs are 1.57, 0.46, 1.7, and 2.02 per decay for ^{125}I, ^{113m}In, ^{201}Tl, and ^{195m}Pt ,respectively. Among these radionuclides ^{201}Tl and ^{195m}Pt induce more DSB per decay. The platinum isotope shows a higher yield and could be of valuable interest. ^{195m}Pt is not only due to its suitable decay property; it is an antitumor agent in chemotherapy. Its short half-life and low energy gamma emission capable of producing an image for reflecting the damage's progress can be a suitable choice in targeted therapy. In general, the Geant4-DNA toolkit is a suitable tool for simulating the biological effect caused by ionizing radiation at nanoscales. This code provides the user with more details of the number of possible strand break damages in terms of range, energy, half-life, radiation intensity, and position of decay of different types of Auger electron emitting radionuclides. This code allows us to choose suitable radionuclides in targeted therapy. The results of this study and other work can help researchers for the synthesis design of suitable radiopharmaceuticals. These radionuclides have physical characteristics useful for targeted radiotherapy, while it does not damage healthy cells.

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