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An investigation on the radiation sensitivity of DNA conformations to ^{60}Co gamma rays by using Geant4 toolkit

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ABSTRACT

To investigate the impact of conformational properties of genetic material of living cells on radiation-induced DNA damage, single strand breaks (SSB), double strand breaks (DSB) and some microdosimetric quantities of A, B and Z-DNA conformations caused by ^{60}Co gamma rays, have been calculated. Based on a previous B-DNA geometrical model, models of A and Z forms have been developed. Simple 34 base pairs segments of each model repeated in high number and secondary electron spectrum of ^{60}Co gamma rays have been simulated in a volume of a typical animal cell nucleus. All simulations in this study have been performed by using the Geant4 (GEometry ANd Tracking 4)-DNA extension of the Geant4 toolkit. The results showed that, B-DNA has the lowest yield of simple strand breaks with 2.23×10^{-10} Gy^{-1} Da^{-1} and 1.0×10^{-11} Gy^{-1} Da^{-1} for the SSB and DSB damage yield, respectively. The A-DNA has the highest SSB yield with 3.59×10^{-10} Gy^{-1} Da^{-1} and the Z-DNA has the highest DSB yields with 1.8×10^{-11} Gy^{-1} Da^{-1}. It has been concluded that there is a direct correlation between the hit probability, mean specific imparted energy and SSB yield in each model of DNA. Moreover, there is a direct correlation between the DSB yield and both the mean lineal energy and topological characteristics of each model.

1. Introduction

The most probable conformation of DNA in living cells, discovered in 1953, is a right-handed double helix known as B-DNA. Moreover, other structures of DNA including the right-handed A-DNA (shorter and thicker than B form), the left-handed Z-DNA (longer and thinner than B form) and some other varieties, were characterized later [1,2].

It is known that photons and energetic charged particles alter DNA molecule (the main target for radiation-induced biological damage) by direct ionization of DNA (direct effects) and by attack of reactive radical species produced by radiolysis of its surrounding water (indirect effects) [3]. The alterations in DNA result in single strand break (SSB), double strand break (DSB), and base damage (BD) which finally lead to chromosome aberrations, mutations or cell inactivation [4]. Therefore, the calculation of DNA damage yields produced by radiation is of crucial importance.

On the basis of the energy deposition pattern of the used radiation, strand breaks may be in the simple or complex form. When the proximity of strand breaks rises, distant simple strand breaks convert to various complex strand breaks that have more dangerous defects in living cells [5].

The simple DNA damage caused by gamma rays has been studied in many experimental [6–8] and theoretical [9–11] works. Moreover, DNA strand breaks in different water contents of the cell culture media has been investigated in a previous experimental study [12].

The passage of gamma rays through a living cell produces a cascade of secondary electrons mainly through photoelectric and Compton effects [13]. These secondary electrons are responsible for damage induction in the genetic material of living cells, irrespective of the primary particle [11,14–16]. Consequently, by tracing this cascade of secondary electrons, the position and the energy of each damage-inducing interaction can be investigated [14,17]. This category of radiation studies belongs to a field known as microdosimetry and one of the most attractive methods is based on track structure analysis [18]. Nowadays, track structure studies make it possible to investigate the radiation effects on biological systems that can be used for radiation therapy procedures, analyzing the mechanism of DNA damage, and providing parameters which cannot be measured directly such as lineal energy and specific imparted energy [18].

Track-structure Monte Carlo codes are well known tools for simulation of particle and photon tracks in the fields of radiation

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research and have many applications such as study of frequency distributions of energy deposition in small sub-cellular macromolecules and it's relation to the absorbed dose of high and low linear energy transfer (LET) radiations [19–21], investigation of differences in effectiveness of different types of radiation [22], calculation of DNA damage yields from electrons and positive ions in nanometric volumes [23–25] and so on.

During two recent decades, these codes have been developed progressively and provide various quantities on the micrometric and nanometric scales of biological cells [26–28]. For example one of the most used software, PARTRAC (PARticle TRACks) code, has many achievements in modeling of DNA damage by simulating higher-order chromatin structure [9], DNA repair processes [29], chromosome aberration modeling [30] and bystander effects investigation [31]. Another Monte Carlo code, PENELOPE (Penetration and ENErgy LOss of Positrons and Electrons), has validated microdosimetric [32] and nanodosimetric [33] capabilities, in biological media. Besides, one of the powerful general purpose track structure computer codes is the Geant4 (GEometry ANd Tracking 4) toolkit, whose application to biological media and dimensions was introduced [34] and proved previously [26,35–38].

In track structure calculations, importance of geometrical properties of DNA constituents in radiation effectiveness has been considered in some studies, such as the radiation sensitivity of linear B-DNA [23], nucleosome core particle and chromatin fiber in different thicknesses [4,30]. In spite of the wide range of mentioned theoretical studies that investigate the DNA damage yields and related quantities, comparative investigation of radiosensitivity of DNA in A, B and Z forms has been concerned with rare studies [3]. In this paper, for three conformations of DNA (A, B and Z), the yields of simple strand breaks (SSB and DSB), mean lineal energy, mean specific imparted energy and the hit probability, caused by secondary electrons of ^{60}Co gamma rays, have been calculated in order to investigate the radiosensitivity of different DNA conformations.

2. Methods

2.1. The Geant4-DNA package

Geant4 is the only open-source, general-purpose Monte Carlo code for the simulation of the passage of particles through matter. This code has capabilities of microdosimetry and nanodosimetry applications, in the most recent release known as Geant4-DNA. This extension and its validated data libraries for low energy cross sections, allow the investigator to simulate the interaction of electrons in liquid water until complete thermalisation (down to 0.025 eV) [39]. The capabilities of the Geant4-DNA extension for microdosimetry and nanodosimetry have been assessed in some previous studies [36,40–42]. In this work, calculations have been made using Geant4 version 9.4.p03 (released 13 December 2011) and its Low Energy Electromagnetic (LEE) package, with new physical processes required for microdosimetry simulation including elastic scattering, excitation and ionization.

2.2. Irradiation setup

In this study, the secondary electron spectrum (6×10^6 electrons for each simulation in this study) originated from 1.173 MeV and 1.332 MeV photons emitted by ^{60}Co on a single cell scale given in the work of Hsiao and Stewart [11] has been used. These secondary electrons can be considered as the source of "primary charged particles" to irradiate the cell nucleus in the simulation, instead of transporting the primary photons. This spectrum of electrons is sampled randomly, in the volume of a spherical cell nucleus, 6 μm in diameter typical for an animal cell nucleus [43] and used for the simulation of electron transport in the situation that generally the electronic equilibrium is not established and microscale dose distribution is important such as for cell cultures irradiated with photons [11,44,45]. Total absorbed dose from the secondary electron spectrum with the mentioned number of primary electrons in radiation targets of the typical cell in each simulation was at least 4.7 kGy that is usual in many experimental studies that investigate the radioresistance of cells [46] or dependence of DNA damage yields to the absorbed dose of radiation [47].

2.3. DNA geometrical models and simulation strategy

For the calculation of DNA damage two sets of reactions should be considered: (a) the reaction of secondary electrons with the DNA (direct effects) and (b) the reaction of radical species produced due to water radiolysis by energetic electrons, with the DNA (indirect effects). Theoretical and experimental investigation of direct and indirect effects of some radiations has been reviewed by Nikjoo et al. [5]. Moreover, detailed tracing of water radiolysis products of water has been primarily developed in the recent release of the Geant4 toolkit [48].

Regardless precision of tracking of water radiolysis products in the simulation of interactions with DNA constituents, complexity of this procedure resulted to develop some alternative criteria that facilitate and accelerate the related simulations. For example, Pomplun [49,50] considered a virtual cylinder around the DNA. When the energy deposition of an event is greater than considered energy threshold of SSB production and it is inside the cylinder, but outside the atomic volumes of the DNA model, distances between this energy deposition site and the atomic volumes of DNA model and as a result the nearest volume in the DNA model will be determined. If this nearest atomic volume of DNA model belongs to its sugar–phosphate group, it is assumed a SSB as a result of indirect effect. This criterion has been used in a study that simulates indirect effects with Geant4 toolkit, recently [36].

But other criterion that has been used in the present study is based on the some evidence suggests that the hydration shell of DNA constituent can be treated as an integral part of the DNA structure; thereby, each energy deposition in these water molecules has been accounted for the atom to which water molecules are attached [51]. Hence, by considering this hydration shell in the DNA geometrical model, both direct and indirect effects can be calculated by estimation [52]. This criterion assumed that all radicals produced in the volume of the hydrated DNA geometrical model, interact with the DNA (an overestimation) and contribution of radical produced outside of the volume of the DNA geometrical model can be disregarded (an underestimation). According to the opinion of Charlton and Humm, investigation of application of these assumptions needs to further studies [52]. For this purpose and avoidance from the complexity of tracking of radical species in the simulations, energy deposition in both the structural elements of each model and their related hydration shells of the three DNA geometrical models has been calculated based on extended DNA geometrical models including the hydration shell of each base pair.

Reported structural data [53] of the three DNA conformations are given in Table 1. The data for the number of water molecules that surround the DNA geometrical models, volume of each water

Table 1
Structural parameters of B, Z and A-DNA. Data are taken from Ref. [53].

Parameter/DNA conformation	B-DNA	Z-DNA	A-DNA
Helix sense	Right handed	Left handed	Right handed
Rotation/bp (°)	36	−30	33.6
Rise/bp along axis (nm)	0.34	0.38	0.23