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Geant4.10 simulation of geometric model for metaphase chromosome

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ABSTRACT

In this paper, a geometric model of metaphase chromosome is explained. The model is constructed according to the packing ratio and dimension of the structure from nucleosome up to chromosome. A B-DNA base pair is used to construct 200 base pairs of nucleosomes. Each chromatin fiber loop, which is the unit of repeat, has 49,200 bp. This geometry is entered in Geant4.10 Monte Carlo simulation toolkit and can be extended to the whole metaphase chromosomes and any application in which a DNA geometrical model is needed. The chromosome base pairs, chromosome length, and relative length of chromosomes are calculated. The calculated relative length is compared to the relative length of human chromosomes.

1. Introduction

Cells are the smallest unit of life, which have many parts with different functions. One of the major parts of a cell is the nucleus. Inside the nucleus of each cell, the DNA molecule is packed and the packing of these molecules creates structures called chromosomes. In fact, chromosomes are constructed from DNAs tightly twisting around protein cores. Each cell has certain numbers of chromosomes. For example, there are 23 chromosome pairs in human cells. An important specification of DNA is that it can replicate or make copy of itself.

Ionizing radiation affects cells and causes DNA damage [1]. Single strand breaks (SSB),double strand breaks (DSB), base damage, DNA–DNA and DNA protein cross-links have been considered as various types of radiation-induced DNA damage [2]. These damages can lead to cell dysfunction, apoptosis or even cancer [3]. Cells are most sensitive to radiation during mitosis (M phase) and interphase (G2 phase) [4,5].

Theoretical studies to investigate the effects of radiation at the cellular and molecular levels are based on the Monte Carlo (MC) method. Because of the stochastic nature of radiation emissions, transportation and detection processes, Monte Carlo track structure codes have become an important tool in the modeling and calculation of radiation-induced damage in biological molecules in the last three decades [6–9]. For example one of the most used software programs, PARTRAC (PARticle TRACks) code, has many achievements in modeling of DNA damage by simulating higher-order chromatin structure [10]. Another Monte Carlo code, PENELOPE (Penetration and ENErgy LOss of Positrons and Electrons), has validated microdosimetric [11] and nanodosimetric [9] 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 [12] and proved previously [13,14]. The Geant4 Monte Carlo simulation toolkit is open-source simulation software, which enables to simulate biological damages induced by ionizing radiation at the cellular and sub-cellular scales [15].

Modeling the three dimensional structure of DNA molecules is a way to describe cell nucleus. Indeed, the precise implementation of DNA geometry is of key importance in order to take into account the spatial structure of energy depositions along the particle track generated by Monte Carlo Track Structure (MCTS) codes. Several geometrical models have been developed to simulate the interaction of ionizing particles with DNA. One of the pioneer works in this field is the one published by Charlton et al. [16], in which only two organization levels (nucleotides pairs and DNA strands) were accounted for and the targets were modeled. According to these authors, the first atomistic DNA model was developed by Pomplun [17] to study the damage yield due to ^{125}I Auger electrons. This model included 82 nucleotide pairs along a straight segment of B-DNA. Later, Moiseenko et al. [18] built an atomistic representation of the B-DNA, having into account only two organization levels

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(up to the double helix). So far, the most sophisticated genetic material geometrical model was introduced by Friedland et al. in PARTRAC code [10]. However; its full description is not available publicly, which limits its use by other research groups.

The aim of this paper is to describe a geometrical model with atomic structure (up to metaphase chromosome which is the most sensitive to ionizing radiation [4]). Metaphase chromosome was not mainly simulating in the literature. In this geometrical model, all levels are constructed according to mathematical equations. According to this geometrical model, chromosome base pairs and Chromosomal parameters (chromosome length, relative length [19]) are calculated. It has to be noticed that these sophisticated geometrical models are implemented in the Monte Carlo toolkit Geant4 which is publicly available for the scientific community.

2. Method

2.1. The Geant4-DNA package

Geant4 (GEometry ANd Tracking 4) is the only general-purpose and open source simulation toolkit. Because of its general-purpose nature and because of its object-oriented architecture, Geant4 is well suited for use in many areas such as high energy physics, space physics studies, and medical applications [20]. Geant4 offers a broad selection of physics processes and particle types, making it a very powerful and flexible computational tool for analyzing the interactions of particles with matter for energies between a few eV and 10 PeV [21].

Geant4-DNA physics processes are a new set of low-energy processes recently attached to the Geant4 toolkit to handle microdosimetry and nanodosimetry simulations [22–24]. These processes can generate detailed track structures of ionizing particles based on water interaction cross sections for the modeling of radiobiological effects at cellular and sub-cellular scale, such as DNA molecules [12].

2.2. Simulation method

This study presents a geometric model for metaphase chromosome from base pair, nucleosome, chromatin fiber, and chromatin fiber loop to the arm of chromosome. In this model, two DNA loops wrapped around histon protein to form the nucleosome. Six Solenoid [25] arrangements of nucleosome produce a 30 nm chromatin fiber. The 30 nm chromatin fibers are taken together and bent to form chromatin fiber loop. The chromatin loops make chromosome arms to twist like a solenoid.

The Geant4 software is used to implement the geometry. Each step of chromosome formation is entered in Geant4.10 toolkit and all the pictures are from Qt-viewer. In addition, the Maple11 software is used for the calculation of curve lengths, step lengths and some other computations as will be noted.

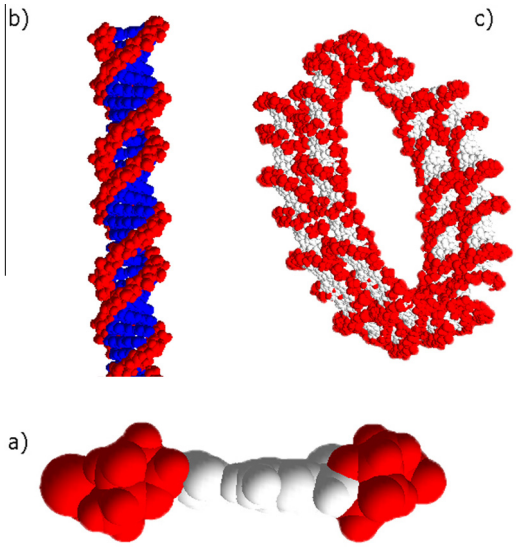

Fig. 1. 3D drawing of nucleosome in Qt-viewer: (a) a B-DNA base pair with 63 atoms [26], (b) double helix and (c) nucleosome with 175 base pairs.

3. Theory and simulation

3.1. Nucleosome

Nucleosome is the base unit of DNA-folding, which is formed by twisting DNA double helix around histon protein. We use B-DNA [26] as the base pair (bp) which has 63 atoms (Fig. 1a). The double helix is formed by twisting and displacing each bp in 36° and 0.33 nm, respectively (Fig. 1b). Each nucleosome should contain 200 base pairs and is 11 nm in diameter [26]. In this work, the solenoid model [26] is used to construct nucleosome (Fig. 1c). So nucleosome is constructed by folding two helical loops around histone according to Eq. (1), the Center of each bp is copied in (x, y, z) of the Eq. (1) by the step length of $\xi = 0.0359$; therefore, 175 base pairs are placed around histone. Note that the two helical DNA turns in the nucleosome contain 175 bp and the binding fragment, 25 bp, therefore, the total number amounts to 200 bp per nucleosome.

$$\begin{aligned} x &= 4.9375 - 2.75cos(1.75\xi) + 0.3893\xi \\ y &= 0.2228\xi - 8.9272 + 4.763cos(1.75\xi) \\ z &= 5.5sin(1.75\xi) \end{aligned} \tag{1}$$

3.2. The 30 nm chromatin fiber

Nucleosomes are wrapped in two forms of zig-zag [27] or solenoid [26]. As mentioned, the solenoid model is used. The 30 nm chromatin fiber is formed by a helix with six nucleosomes/turns. So six nucleosomes are taken together and form 30 nm chromatin fibers. To construct a solenoid chromatin fiber, Eq. (2) is used [28]. where X_i, $i = 0 \ldots 5$ is the number of nucleosome per one solenoid

$$X_i(\xi) = \begin{cases} x = \dfrac{\pi(P - 2rsin(\frac{1}{6}(2\pi i + \pi))cos(\theta(\xi - 4\pi i))) + P(-4\pi i + \xi - \pi)cos(\frac{1}{6}(2\pi i + \pi)) + 2\pi Rcos(\frac{1}{3}\pi(i-1))}{2\pi} \\ y = \dfrac{P(-4\pi i + \xi - \pi)sin(\frac{1}{6}(2\pi i + \pi)) + 2\pi rcos(\frac{1}{6}(2\pi i + \pi))cos(\theta(\xi - 4\pi i)) + 2\pi Rsin(\frac{1}{3}\pi(i-1))}{2\pi} \\ z = rsin(\theta(\xi - 4\pi i)) \end{cases} \tag{2}$$