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Performance of a new atomistic geometrical model of the B-DNA configuration for DNA-radiation interaction simulations

M A Bernal1, D Sikansi1, F Cavalcante1, S Incerti2, C Champion2, V Ivanchenko3, Z Francis4,5 and M Karamitros2,6

1 Instituto de Física Gleb Wataghin. Universidade Estadual de Campinas, SP. Brazil
2 Université Bordeaux 1, CNRS/IN2P3, Centre d’Etudes Nucléaires de Bordeaux-Gradignan, CENBG, Chemin du Solarium, BP 120, 33175 Gradignan, France.
3 Ecoanalytica, 119899 Moscow, Russia
4 Geant4 Associates International Ltd, United Kingdom
5 The Open University, Faculty of Science, Department of Physical Sciences, Walton Hall MK7 6AA, Milton Keynes, United Kingdom.
6 CNRS, INCIA, UMR 5287, 33400 Talence, France

E-mail: mbernalrod@gmail.com

Abstract. We have recently developed an atomistic model of the B-DNA configuration, up to the 30-nm chromatin fiber. This model is intended to be used in Monte Carlo simulations of the DNA-radiation interaction, specifically in conjunction with the Geant4-DNA extension of the Geant4 Monte Carlo toolkit. In this work, 11449 parallel chromatin fibers have been arranged within a cube mimicking a cell nucleus containing about 6.5*10^9 base pairs. Each atom in the model is represented by a sphere with the corresponding van der Waals radius. Direct single, double and total DNA strand break yields due to the impact of protons and alpha particles with LET ranging from 4.57 to 207.1 keV/µm have been determined. Also, the corresponding site-hit probabilities have been calculated.

1. Introduction

The knowledge on the biological effects induced by ionizing radiations on living beings is of paramount importance for areas such as medical radiation therapy and diagnostic, among others. Monte Carlo simulations of the radiation-DNA interaction process have been successfully coupled to biophysical models to study this matter [1, 2]. The use of ion beams in radiation therapy is particularly complex from the radiobiological point of view due to the stronger dependency of their relative biological effectiveness as a function of the particle energy when compared to that of photon and electron beams. In a recent work [3], the development of an atomic-resolution B-DNA geometrical model has been addressed and an accompanying open source subroutine to determine the closest atom containing an arbitrary point in space has been released. This model accounts for various organization levels of the DNA, from the nucleotide pair up to the 30-nm chromatin fiber, and it should be integrated in the GEANT4-DNA extension of the Geant4 Monte Carlo simulation toolkit to determine direct and indirect strand break yields in the near future.
In this work, a cell nucleus model has been built by arranging segments of the chromatin fiber described in our previous work [3]. This development is a long step forward with respect to a recently published work [4] in which a cell nucleus model was constructed by using the non-atomistic DNA model described in Ref. [5]. The performance of this model was tested by determining the direct total, single and double strand break yields due to the impact of protons and alpha particles within a wide linear energy transfer (LET) range. Site-hit probabilities have been also determined.

2. Material and methods

The details of the B-DNA atomistic model used in this work can be found elsewhere [3]. A simple geometrical model of a cell nucleus was developed by aligning 11449 3.36-µm long chromatin segments within a cube. This nucleus contains about 6.52 Gbp, which is approximately the number of bp in a human cell, and it defines the region of interest (ROI) in our simulations. The ROI was placed at 2.6 µm depth in a semi-infinite water phantom, with the fibers axis normal to the surface. This system was uniformly irradiated with 0.5, 1, 5, 7, and 10 MeV protons, and 2, 5, 7 and 10 MeV alpha particles. The corresponding Monte Carlo simulations were carried out with the GEANT4-DNA sub-package [8]. The LET of the incident particles at the middle of the ROI ranges from 4.57 to 207.1 keV/µm. Direct total (TSB), single (SSB) and double (DSB) strand break yields were determined by the use of two approaches. In the first one, a SSB is recorded if an inelastic collision with an energy deposition greater than 8 eV occurs within one van der Waals radius around any of the atoms conforming the phosphodiester group. The union volume of these atoms defines the target volume. In the second one, a SSB is accounted for in the same situation but using two van der Waals radii and with an additional probability going from 0 to 1 when the deposited energy ranges from 5 to 35 eV. The latter method was implemented in order to compare our results with those reported by Friedland et al. [7]. In any case, a DSB is counted if two SSB occur on opposite strands and within 10 bp. A fixed number of histories were assigned to each simulation batch, according to the incident particle type and energy.

3. Results

The radiation doses absorbed into the ROI for all particle-energy combinations were in the 12-15 Gy range. Figure 1 shows the direct TSB, SSB and DSB yields determined by following the two approaches described in the former section. The first one leads to TSB yields significantly...
higher than those reported for protons by the Friedland’s group [7], mainly because practically all deposited energies are high enough to provoke a strand break, despite that only one van der Waals radius around each atom was used to define the target volume. However, our results are close to those reported in the mentioned reference when the second approach is used, which is similar to the one used by these authors. Differences should be attributed to slight differences in the van der Waals radii used and in the geometrical model per se. It is good to remark that our results also describe the quasi-constant direct TSB yield (see the discussion on this behavior in Ref. [9]) and the slight decrement shown for LET greater than about 40 keV/µm.

It can be observed in the mid graph of Fig. 1 that the SSB yield decreases as the primary particle LET increases. This fact has been previously reported by experimental works (e.g. see Ref. [10]). In addition, SSB yields due to alpha particle impact, determined by Milligan et al. [6] in solutions with high free radical scavenger concentrations, are also shown. It should be pointed out that these experimental results were obtained with up to three-fold uncertainties, so they should only serve as a coarse reference.

From the analysis of the bottom graph of Fig. 1, it can be seen that, unlike the TSB results, DSB yields obtained with the second approach are higher than those determined with the first one. This means that the increase of the atom size has a greater influence on the DSB yields than the reduction of the probability to produce a SSB according to the deposited energy. Unfortunately, only the total DSB yields determined by Friedland and colleagues are shown since they did not report the corresponding direct damage probabilities. According to the consistency of the TSB yields and the DSB yield results, it could be induced that direct and indirect damages have similar contribution to the total DSB yield, at least for protons in this LET range. It should be kept in mind that by using two van der Waals radii non-scavengable damage is accounted as part of the direct damage. Also, it can be seen that protons are more effective to induce DSB than alpha particles at the same LET. This was attributed to a higher capacity of protons to form clustered depositions when compared to alpha particles with the same LET (see discussions on this matter in Refs. [10] and [11]). DSB yields determined by Milligan et al. in the conditions described above are also shown. The experimental method used to determine these yields strongly underestimates the counti

Figure 2 displays the probabilities for any primary or secondary particle to hit a phosphodiester group (known as site-hit probability) as a function of the primary particle LET at the half depth of the ROI. The horizontal line represents the site-hit probability (SHP) determined through the division of the total volume occupied by the targets by that of ROI. This SHP should be retrieved if the energy deposition events were uniformly distributed within the ROI [3]. The SHPs obtained during simulations agree with that predicted by the volumes ratio for LET values up to about 100 keV/µm. Above this LET value, this SHP tends to increase appreciably over the geometrically predicted value. Thus, it seems that ionizing particles with very high LET produce SHPs greater than that induced by uniformly distributed ionization events.

![Figure 2](image-url) **Figure 2.** Site-hit probabilities due to the impact of protons (○) and alpha particles (●). Uncertainty of the order of the symbol size or smaller are not shown. The line (——) represents the geometrically determined SHP.
4. Conclusions
A new B-DNA atomistic model has been preliminarily tested in this work by determining direct DNA damage yields and site-hit probabilities due to the impact of protons and alpha particles for a wide LET range. The direct TSB yields found with this model for protons are consistent with those reported by Friedland et al., who used a similar atomistic geometrical model. Our SSB yields decrease with the increment of the incident particle LET, as described in other published works. In addition, these values seem to be consistent with the corresponding experimental determinations reported by Milligan et al. However, the results for direct DSB yields overestimate those reported by these authors, probably due to the difficulties they had to count very short DNA fragments. In the near future, this geometrical model will be tested by also having into account the indirect damage induced by chemical species.

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References