Original Article

Circular Mitochondrial DNA: A Geant4-DNA User Application for Evaluating Radiation-induced Damage in Circular Mitochondrial DNA

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Abstract

Background: The aim of this study was to develop a nucleotide geometrical model of the circular mitochondrial DNA (mt-DNA) structure using Geant4-DNA toolkit to predict the radiation-induced damages such as single-strand breaks (SSB), double-strand breaks (DSB), and some other physical parameters. **Methods:** Our model covers the organization of a circular human mt genetic system. The current model includes all 16,659 base pairs of human mt-DNA. This new mt-DNA model has been preliminarily tested in this work by determining SSB and DSB DNA damage yields and site-hit probabilities due to the impact of proton particles. The accuracy of the geometry was determined by three-dimensional visualization in various ring element numbers. The hit locations were determined with respect to a reference coordinate system, and the corresponding base pairs were stored in the ROOT output file. **Results:** The coordinate determination according to the algorithm was consistent with the expected results. The output results contain the information about the energy transfers in the backbone region of the DNA double helix. The output file was analyzed by root analyzing tools. Estimation of SSBs and DSBs yielded similar results with the increment of incident particle linear energy transfer. In addition, these values seem to be consistent with the corresponding experimental determinations. **Conclusions:** This model can be used in numerical simulations of mt-DNA radiation interactions to perform realistic evaluations of DNA-free radical reactions. This work will be extended to supercoiled conformation in the near future.

Keywords: *Geant4, geometrical model, mitochondrial-DNA, Monte Carlo, radiation*

Introduction

The main target of lesions induced by ionizing radiation exposure is believed to be the genomic DNA in the cell nucleus.[1] Many studies have been conducted on the effects of radiation on cell organelles other than the nucleus.[1-6] It has been suggested that these organelle effects are not caused by the nuclear reaction to radiation but are due to the direct effect of radiation.[1,7] Mitochondria may occupy approximately 30% of the total cell volume.[8] Ionizing radiation can cause various lesions in circular mitochondrial DNA (Cmt-DNA), such as strand breaks, base mismatches, and large deletions, which also occur in nuclear DNA.[1] Mitochondria may be a target of radiation, in addition to the cell nucleus.[2] However, mitochondrial DNA (mt-DNA) comprises approximately 0.25% of the total cellular DNA, and the entire mt-DNA includes active genes for protein synthesis.[2,9,10] In contrast, the portion responsible for protein coding in nuclear DNA (99.75% of the total cellular DNA) is only approximately 1%.[9] Therefore, the genetic cause of the direct biological effects seems to lie in the coding regions of mt-DNA. In addition, histone protection does not efficiently protect mt-DNA, and an efficient DNA repair system is not active;[4] hence, more unrepaired lesions are likely to accumulate.

Human mt-DNA is a circular molecule that is among the smallest known mt-DNAs, and it contains 16,659 bases. The proximity of mt-DNA to sites of reactive oxygen species production renders it particularly susceptible to damage. Recent evidence has indicated that base excitation repair and mismatch repair may be induced in the mitochondria during oxidative insult.[2] Deletion in the mt genome is also commonly induced after cellular exposure to ionizing radiation.[11]

Geant4 is a general purpose, open-source simulation toolkit that is well suited for microdosimetry purposes and radiation

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interactions in water.[12,13] Various attempts have been made to predict early damages to DNA. Geant4-DNA can be utilized to address this problem in the following three steps: (1) Using clustering algorithms to estimate the damages, (2) performing geometrical simulations of the structure, and (3) using the first and second approaches together. Energy deposition patterns in media can be analyzed and tuned to adapt to the experimental DNA strand break data using clustering algorithms.[14,15] A clustering algorithm was added to the Geant4-DNA examples in December 2015 (Geant4 version 10.2). In the geometrical approach, attempts were made to develop geometrical models of biological molecules. Using physical, chemical–physical, and chemical and biological processes in combination with Geant4-DNA, physical modeling of a DNA geometrical structure in liquid water was first conducted by Bernal *et al*.[16] The aim of their simulation was to estimate single-strand break (SSB) and double-strand break (DSB) in a simplified DNA structure formed by a series of chromatin cylindrical forms, using some radionuclides, cobalt gamma rays, or soft X-rays as the radiation sources.

The next attempt in Geant4-DNA was the geometrical description of 6 giga base pairs in nuclear DNA, followed by A-DNA, B-DNA, and Z-DNA conformation description in further researches.[17] Using the DBSCAN clustering algorithm with Geant4-DNA, physical processes in geometrical models led the authors to estimate the quantity and complexity associated with increasing DNA density.[18-20] As in experimental investigations, the authors focused on the nuclear genome. The genomic DNA Monte Carlo (MC) simulation method developed in the whole nuclear DNA project is a unique and elegant approach for theoretical investigations of nuclear DNA; however, because of its several organization levels – double helix, beads on a string, solenoid, and chromatin loop – it seems to be a heavy and time-consuming code to execute in an ordinary computer. The methodology used to develop the code, because of DNA complexity, makes it very difficult to modify it in a simple manner for mt-DNA investigations. Even though it is a tedious task, researchers are trying to achieve a complete application to simulate the interaction of radiation with cell organelles.[21,22] To the best of our knowledge, there have only been a few similar MC studies on nuclear DNA at atomic or nucleotide resolution.[16,23] The PDB4DNA package in Geant4-DNA was developed to simulate radiation effects on molecules within their Protein Data Base (PDB) files,[24] but there is no way to use it for mt-DNA because of the lack of PDB files in this case. This is why a specific purpose model is being presented through this application.

In this study, we tried to add the circular mt genome to achieve a nucleotide resolution of the whole cell genome including mt-DNA. The low-energy package prepared in Geant4-DNA can be used to simulate the energy deposition physics of ionizing radiation at the nanometric scale for radiobiological applications.[25,26] Therefore, the mt-DNA geometries created in this study are directly exportable in a form suitable for use in MC simulations using Geant4-DNA processes.

In this study, circular mt-DNA model was developed using the Geant4 MC simulation tool, considering the sugar and base pair level of granularity. The structure of the paper is as follows: first, we present the basic feature of simulation of DNA molecule model with base pair resolution, which is common to Geant4-DNA and other examples. Then, the specific characteristics of this application (those that serve to determine the structure) are discussed, including visualizations of the structure by the Geant4 tools to clarify the description. Finally, the algorithm for assigning SSBs and DSBs to the mt-DNA geometry is proposed. This is used to compute an estimation of the mt-DNA damage.

Methods

CmtDNA is a Geant4 application that simulates energy deposition to base pairs in mt-DNA molecules with circular geometries and estimates the SSB and DSB damage. Users can visualize particle tracks using the Open Graphics Library (OGL) tool in Geant4. Figure 1 depicts the Unified Modeling Language (UML) diagram of the application in the Geant4 toolkit. Green boxes correspond to CmtDNA. Our model covers the organization of a circular human mt genetic system. Pairs should be separated by a distance of 0.33 nm. An optimization process is used to determine the geometrical dimensions of the structure. Bases and sugars are assumed to be spheres with radii of 0.17 nm and 0.48 nm, respectively, according to other studies.[16] The number of base pairs per complete rotation in a double helix is taken to be 10.3, which is the experimental value. Rotation takes place through a three-dimensional (3D) rotation matrix with a rotation degree of 360°/10.3.[16]

Determination of the circular geometrical structure

The procedure for determining the structure is described in detail as follows:

1. The rotation in a circular structure is obtained by another 3D rotation matrix, which is multiplied by the first one. The final 3D coordinates of each base pair can be found using this composite rotation matrix. Figure 2 depicts the rotating structure with an expanded view of the circular DNA system. The rotation degree for each base pair is calculated as 360° divided by the total number of base pairs in a circle. Figure 3 is a simplified visualization of the geometry with 166 base pair–sugar elements, created using the OGL visualization tool in Geant4
2. Nucleotide and sugar pairs are known to be ordered into a double helix shape. They are defined within the mt-DNA as a geometrical object
3. The build process for a circular double helix is described as follows: The first nucleotide pair is placed,

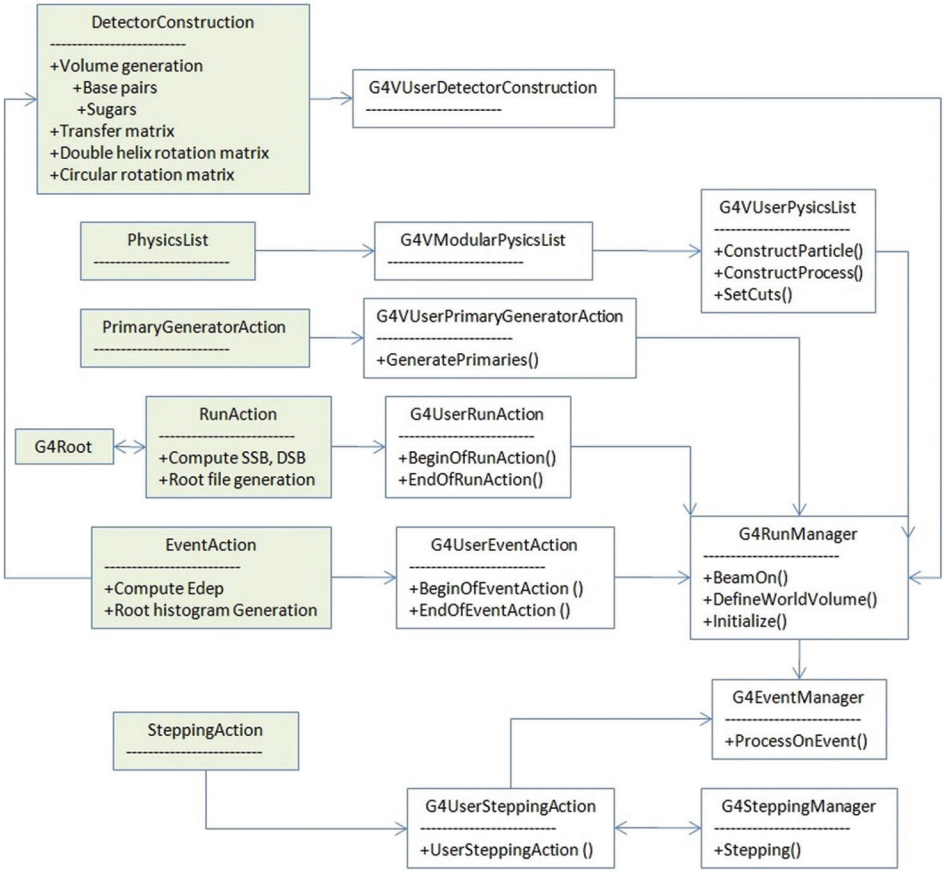

Figure 1: Unified Modeling Language diagram of the circular mitochondrial DNA Geant4 user application: Geant4 virtual classes (white), Geant4-implemented classes and interface to the ROOT analysis software (green)

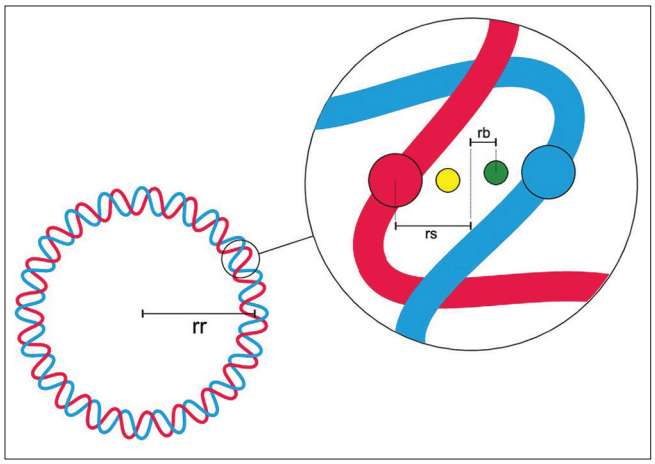

Figure 2: Rotating structure with an expanded view of the circular DNA system

and the next base pair is translated in the Z-axis. In the next step, it is rotated by 2π/10.3 to complete a double helix rotation. After that, it is rotated again in a circular path to form the complete circular shape of an mt-DNA molecule

4. The mathematical algorithm for geometry construction is described below:
   - Definition of the n^{th} sugar:

$$SP_n = \begin{bmatrix} -rs\mathrm{Cos}(n\theta_0)\ 0\ rs\mathrm{Sin}(n\theta_0) \\ rs\mathrm{Cos}(n\theta_0)\ 0\ -rs\mathrm{Sin}(n\theta_0) \end{bmatrix} \quad (1)$$

Rotation matrix for the n^{th} element:

$$\mathrm{Matrix}_n = \begin{bmatrix} \mathrm{Cos}(n\varphi_0) & -\mathrm{Sin}(n\varphi_0) & 0 \\ \mathrm{Sin}(n\varphi_0) & \mathrm{Cos}(n\varphi_0) & 0 \\ 0 & 0 & 1 \end{bmatrix}, \quad (2)$$

$$\varphi_0 = \frac{2\pi}{\mathrm{Num}},\ n = 0,1,2,\ldots,(\mathrm{num}-1),$$

$$D_n = \left[SP_n \times \mathrm{Matrix}_n\right]_{2\times 3} = \left[D_n^1\ D_n^2\right] \quad (3)$$

   - The n^{th} spin, regardless of its permutation matrix, should be transformed into geometrical coordinates. Thus, the geometrical parametric equation of spin is given as follows:

$$P_n = \begin{bmatrix} x = rr\mathrm{Cos}(n\varphi_0) \\ y = rr\mathrm{Sin}(n\varphi_0) \\ z = z_0 \end{bmatrix}, \quad (4)$$

$$\mathrm{SugarLocation}_n = \left[D_n^1 + P_n\ D_n^2 + P_n\right], \quad (5)$$

Here, D^1_n and D^2_n describe the first and second columns of D_n, respectively.

   - The geometrical positioning of the base pairs is given by:

$$b\_SP_{\mathrm{n}} = \begin{bmatrix} -rb\mathrm{Cos}(n\theta_0) & 0 & rb\mathrm{Sin}(n\theta_0) \\ rb\mathrm{Cos}(n\theta_0) & 0 & -rb\mathrm{Sin}(n\theta_0) \end{bmatrix} \quad (6)$$

- Thus, the permutation matrix for the n^{th} element is as follows:

$$D_{\mathrm{n}} = \left[b\_SP_{\mathrm{n}} \times \mathrm{Matrix}_{\mathrm{n}}\right]_{2\times 3} = \left[b\_D_{\mathrm{n}}^{1} \quad b\_D_{\mathrm{n}}^{2}\right] \quad (7)$$

- Similarly, the location of the base pairs is given by:

$$\mathrm{BasePairLocation}_{\mathrm{n}} = \left[b\_D_{\mathrm{n}}^{1} + P_{\mathrm{n}} \quad b\_D_{\mathrm{n}}^{2} + P_{\mathrm{n}}\right] \quad (8)$$

Results

Geometry consistency by visualization

First, we checked the visualization of a 0.1 MeV proton in interaction with an mt-DNA molecule and its water environment. Then, the code was run with the complete number of base pairs in the molecular structure. The hit locations were determined with respect to a reference coordinate system, and the corresponding base pairs were stored in the ROOT software output file. The coordinates determined by the algorithm were consistent with the expected results, as shown in Figure 4, which is plotted using the ROOT software and shows the hit sites in the exact structure for model. The results can be compared with those for any other arbitrary DNA shape, owing to the assumption of a standard circular structure model in this study and the probabilistic nature of MC calculations.

Algorithm for evaluating the single-strand breaks and double-strand breaks

SSBs are assumed to occur when a minimum energy deposition of 8.22 eV is delivered to the sugar-phosphate sphere. This minimum energy is the same in all Geant4-DNA models. DSBs are assumed when two SSBs occur in opposite sides of the molecule at a distance of 10 base pairs or less [Figure 5]. This parameter is obtained from the studies of Nikjoo *et al*.[27-29] and is also used in other Geant4 examples.[24,30-34]

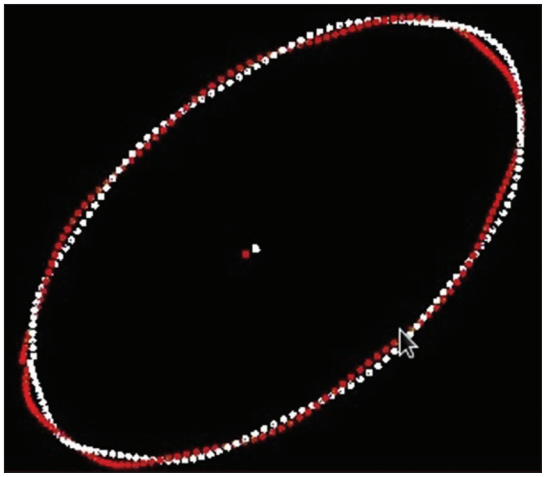

Figure 3: Simplified visualization of the circular geometry with 166 base pairs and sugars created by the Open Graphics Library visualization tool in Geant4

Output production

All the ionizations produced by the projectile and the secondary electrons were recorded in a ROOT file format. The output file was processed by analyzing the routines.

The output results are stored in an MtDNA. root file, containing only information about the energy transfers in the backbone region of the DNA double helix. The output file can be analyzed by root analyzing tools. The parameters reported in output root files are: (1) Strand breaks, which are distinguished with different flags (1 or 2), (2) types of particles for the current step, (3) type of process for the current step, (4) flag of the strand (1 or 2) in the double helix, (5) track position of the current energy transfer (in nm), (6) 3D analysis of the track position of the current energy transfer (in nm), which is shown in Figure 4, (7) energy deposit corresponding to the energy transfer (in eV), (8) total energy loss along the current step (in eV), and (9) step length of tracks (in nm). Using these options helps users to analyze their studies in advance.

The SSBs and DSBs calculated using our optimized algorithm, which is described by a UML diagram in Figure 1, are output to an MtDNA. out ASCII file.

Setup of the simulations

The simulation was tested for proton particles. Protons with sixteen different energies (100, 200, 300, 400, 500, 600, 700, 800, 900, 1×10^3, 2×10^3, 5×10^3, 1×10^4, 2×10^4, 5×10^4, and 1×10^5 keV) were emitted as primary particles. For the energy tracking, 10^5 particles were simulated independently. A track is formed by all energy transfer points originating from the projectile and the secondary particles created by interactions. The target material was water.

Discussion

The aim of this study was to develop a nucleotide resolution geometrical model of the circular mt-DNA structure using the Geant4-DNA toolkit to predict radiation-induced damage, such as SSBs, DSBs, energy deposition, and some other physical parameters.

The current model includes all 16,659 base pairs of human mt-DNA. One should note that the primary purpose of

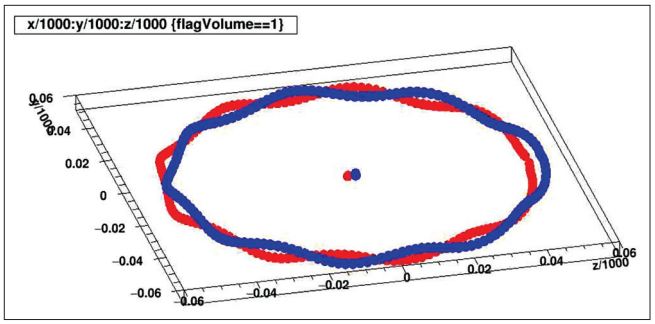

Figure 4: 3D analysis of the track position of the current energy transfer (in nm) for the circular mitochondrial DNA

this study was not to investigate all radiation-induced effects on mt-DNA, but to introduce a new geometrical model suitable for this purpose. The benchmarks of the model were compared with some other simulation and experimental studies.

Mean mitochondrial DNA hit number

To validate our model against other simulations in this scope, the mean number of mt-DNA hits for protons of different energies was compared with the study of Meylan *et al.*[23] for the DnaFabric project [Figure 6]. The results in both studies show that the number of DNA hits decreases when the energy of the incident proton increases. This trend was expected as an increase in energy that corresponds to a decrease in the linear energy transfer (LET).

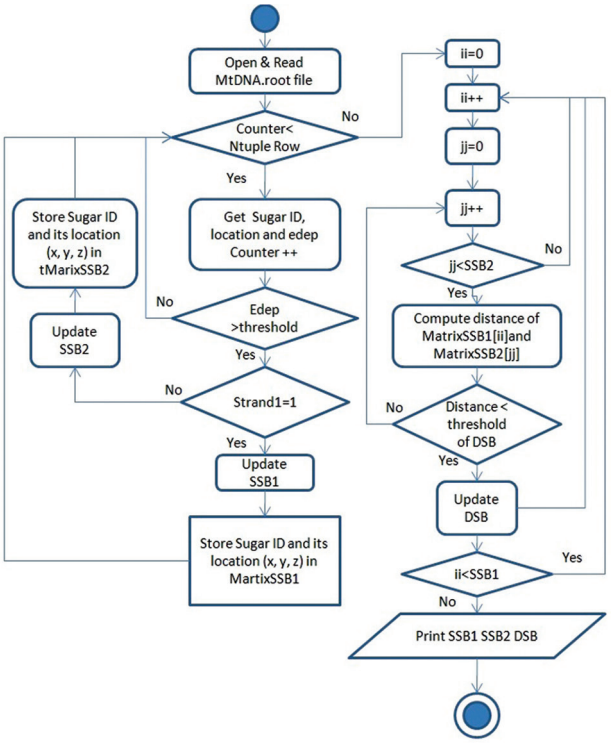

Figure 5: Activity diagram of the algorithm converting energy depositions into DNA strand breaks

Linear energy transfer and hit number

Figure 7 shows the relation between the LET and the energy deposited in the mt-DNA (equivalently, the number of SSBs). Indeed, an increase in the radiation LET increases the density of energy transfer points in the tracks and consequently, the probability to obtain an energy deposition on sensitive areas (backbone region), leading to an increase in DNA damage. We also observe that the increase in the number of SSBs is more pronounced for protons between 0.5 and 2 MeV (41.9–16.9 keV/μm). Our results are similar to those obtained by Dos Santos *et al.*,[19,20] Bernal *et al.*,[17,35] and Souici *et al.*[36]

Energy and mitochondrial DNA hit probability

Figure 8 shows the relation between deposited energy and site-hit probability. The fact that the hit probability increases with increasing deposited energy is in agreement with the results of the experimental studies conducted by Zhou *et al.*[36,37] and Souici *et al.*[36,37]

Distribution of hit-sites and energies

Figure 9 shows the distribution of hit-sites as a function of radial distance for various incident proton energies (0.1, 1, 10, and 100 MeV). It shows that the total sites-hit decreases by increasing the energy, and it has a rapid fall off at large steps in general. It has a relatively good agreement with Tran *et al.*'s study on water nanoparticles in trend.

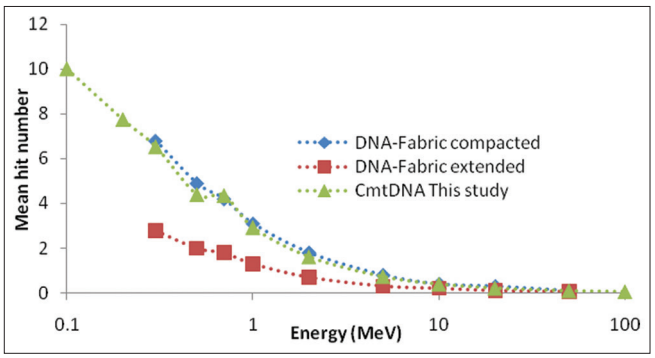

Figure 6: Mean number of hits per track

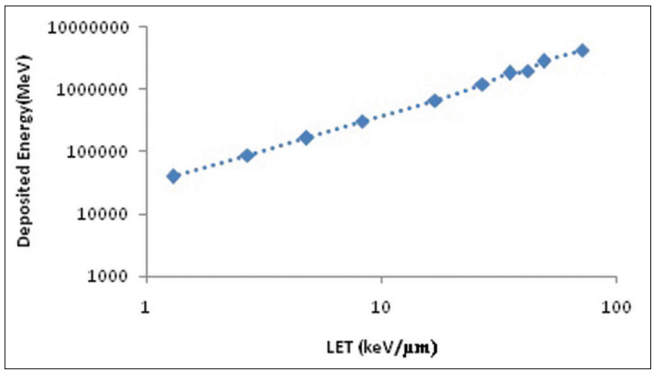

Figure 7: Relation between linear energy transfer and deposited energy

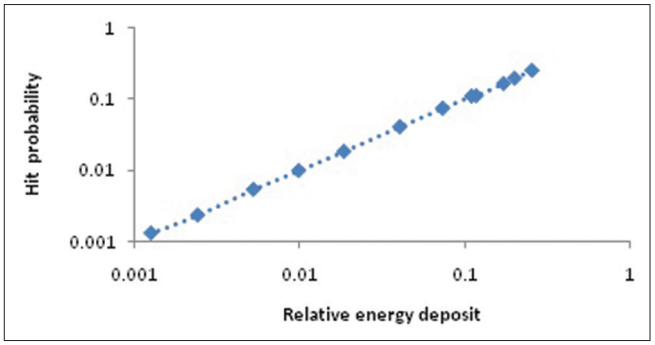

Figure 8: Relation between relative-deposited energy and mitochondrial DNA hit probability

Radial extension of proton tracks at various energies

Radial extension of proton tracks at various energies up to 500 keV is compared with experimental data reported by Souici *et al*. [Figure 10]. This fraction appears to be >90% for 500 keV protons and increases when the proton energy decreases below 500 keV, such as that reported in Souici *et al*.'s investigation.[36] In our study, the step length of the proton tracks in the Bragg peak region is in agreement with the experimental and simulation investigations.[36,38]

Now, it is possible to use our code to obtain calculation evidences of mt-DNA fragmentation due to direct and indirect effects, which mainly occurs as a consequence of proton track overlapping. In other words, fragmentation takes place in the intersection areas of neighboring proton tracks due to cumulative events. In addition, a linear behavior of the direct effects as a function of LET was also suggested by Dos Santos *et al*., who assessed the influence of chromatin density on the number of clustered damages created by protons for nuclear DNA.

The SSB and DSB calculations were performed through an optimized procedure that uses all the output data on the interactions, which are stored in an MtDNA. root file. Our approach seems to be better than that used in the PDB4DNA example,[24] which performs SSB and DSB calculations in each event and reflects the additive nature of DNA damage. The mean number of SSBs and DSBs per track for different energies and for the circular mt-DNA geometry is shown in Figure 11. The results show that the number of SSBs increases with decreasing energy (or, equivalently, increasing LET) for all simulated energies. Therefore, the results discussed in this section reinforce the validation of the present code and allow a better understanding of the method by which fragmentation occurs when direct and indirect effects are taken into account.

Conclusions

This study introduces the CmtDNA tool, a Geant4 application that includes geometrical model to facilitate the study of mt-DNA radiation-induced damage. The model for base pair resolution of human mt-DNA was developed based on real data for the circular mt-DNA structure. This new mt-DNA model has been preliminarily tested in this work by visualization and estimation of the SSBs and DSBs produced by irradiation with protons of different energies. This model can be used in numerical simulations of the interaction between radiation and mt-DNA to perform realistic evaluations of DNA-free radical reactions. Attempts to extend this simulation tool to include other cytoplasm organelles are in progress.

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Conflicts of interest

There are no conflicts of interest.

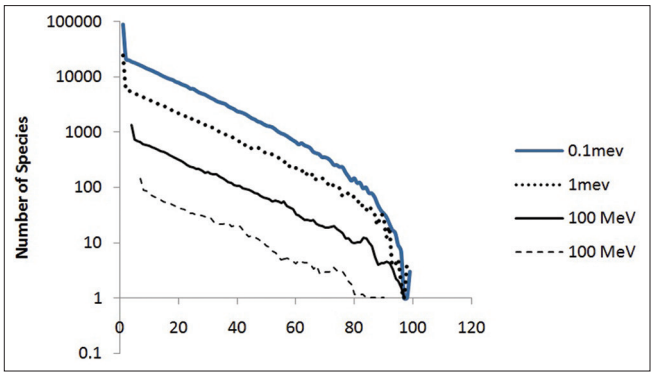

Figure 9: Distribution of radiolytic species as a function of relative radial distance for various incident proton energies (0.1, 1, 10, and 100 MeV)

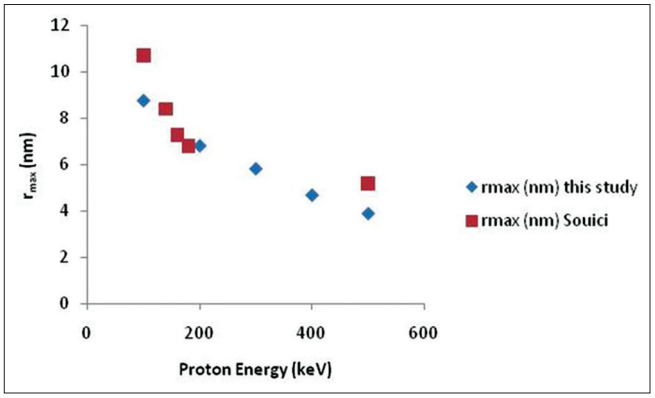

Figure 10: Radial extension of proton tracks at various energies

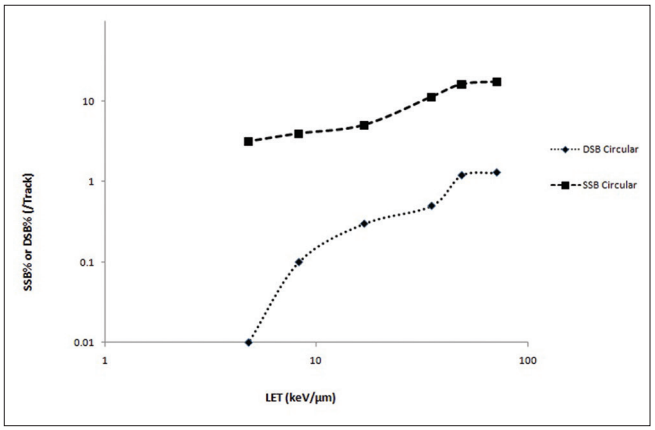

Figure 11: Single-strand breaks and double-strand breaks as a function of the linear energy transfer caused by proton irradiation in a circular structure

References

1. Kam WW, Banati RB. Effects of ionizing radiation on mitochondria. Free Radic Biol Med 2013;65:607-19.
2. Azzam EI, Jay-Gerin JP, Pain D. Ionizing radiation-induced metabolic oxidative stress and prolonged cell injury. Cancer Lett 2012;327:48-60.
3. Kam WW, Lake V, Banos C, Davies J, Banati R. Apparent polyploidization after gamma irradiation: Pitfalls in the use of quantitative polymerase chain reaction (qPCR) for the estimation of mitochondrial and nuclear DNA gene copy numbers. Int J Mol Sci 2013;14:11544-59.

4. Larsen NB, Rasmussen M, Rasmussen LJ. Nuclear and mitochondrial DNA repair: Similar pathways? Mitochondrion 2005;5:89-108.
5. Malik AN, Czajka A. Is mitochondrial DNA content a potential biomarker of mitochondrial dysfunction? Mitochondrion 2013;13:481-92.
6. Yukawa O, Miyahara M, Shiraishi N, Nakazawa T. Radiation-induced damage to mitochondrial D-beta-hydroxybutyrate dehydrogenase and lipid peroxidation. Int J Radiat Biol Relat Stud Phys Chem Med 1985;48:107-15.
7. Somosy Z. Radiation response of cell organelles. Micron 2000;31:165-81.
8. Kam WW, McNamara AL, Lake V, Banos C, Davies JB, Kuncic Z, *et al.* Predicted ionisation in mitochondria and observed acute changes in the mitochondrial transcriptome after gamma irradiation: A Monte Carlo simulation and quantitative PCR study. Mitochondrion 2013;13:736-42.
9. ENCODE Project Consortium, Birney E, Stamatoyannopoulos JA, Dutta A, Guigó R, Gingeras TR, *et al.* Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature 2007;447:799-816.
10. Clayton DA. Transcription and replication of mitochondrial DNA. Hum Reprod 2000;15 Suppl 2:11-7.
11. Prithivirajsingh S, Story MD, Bergh SA, Geara FB, Ang KK, Ismail SM, *et al*. Accumulation of the common mitochondrial DNA deletion induced by ionizing radiation. FEBS Lett 2004;571:227-32.
12. Agostinelli S, Allison J, Amako K, Apostolakis J, Araujo H, Arce P, *et al*. Geant4 – A simulation toolkit. Nucl Instrum Methods Phys Res A 2003;506:250-303.
13. Allison J, Amako K, Apostolakis J, Araujo H, Dubois PA, Asai M, *et al*. Geant4 developments and applications. IEEE Trans Nucl Sci 2006;53:270-8.
14. Francis Z, Incerti S, Ivanchenko V, Champion C, Karamitros M, Bernal MA, *et al.* Monte Carlo simulation of energy-deposit clustering for ions of the same LET in liquid water. Phys Med Biol 2012;57:209-24.
15. George NP, Ngo KV, Chitteni-Pattu S, Norais CA, Battista JR, Cox MM, *et al.* Structure and cellular dynamics of *Deinococcus radiodurans* single-stranded DNA (ssDNA)-binding protein (SSB)-DNA complexes. J Biol Chem 2012;287:22123-32.
16. Bernal MA, Sikansi D, Cavalcante F, Incerti S, Champion C, Ivanchenko V, *et al*. An atomistic geometrical model of the B-DNA configuration for DNA-radiation interaction simulations. Comput Phys Commun 2013;184:2840-7.
17. Bernal MA, deAlmeida CE, Incerti S, Champion C, Ivanchenko V, Francis Z, *et al.* The influence of DNA configuration on the direct strand break yield. Comput Math Methods Med 2015;2015:417501.
18. Francis Z, Villagrasa C, Clairand I. Simulation of DNA damage clustering after proton irradiation using an adapted DBSCAN algorithm. Comput Methods Programs Biomed 2011;101:265-70.
19. Dos Santos M, Clairand I, Gruel G, Barquinero JF, Incerti S, Villagrasa C, *et al.* Influence of chromatin condensation on the number of direct DSB damages induced by Ions studied using a Monte Carlo code. Radiat Prot Dosimetry 2014;161:469-73.
20. Dos Santos M, Villagrasa C, Clairand I, Incerti S. Influence of the DNA density on the number of clustered damages created by protons of different energies. Nucl Instrum Methods Phys Res B 2013;298:47-54.
21. Incerti S, Douglass M, Penfold S, Guatelli S, Bezak E. Review of geant4-DNA applications for micro and nanoscale simulations. Phys Med 2016;32:1187-200.
22. McNamara A, Geng C, Turner R, Mendez JR, Perl J, Held K, *et al.* Validation of the radiobiology toolkit TOPAS-nBio in simple DNA geometries. Phys Med 2017;33:207-15.
23. Meylan S, Vimont U, Incerti S, Clairand I, Villagrasa C. Geant4-DNA simulations using complex DNA geometries generated by the DnaFabric tool. Comput Phys Commun 2016;204:159-69.
24. Delage E, Pham QT, Karamitros M, Payno H, Stepan V, Incerti S, *et al*. PDB4DNA: Implementation of DNA geometry from the Protein Data Bank (PDB) description for Geant4-DNA Monte-Carlo simulations. Comput Phys Commun 2015;192:282-8.
25. Incerti S, Baldacchino G, Bernal M, Capra R, Champion C, Francis Z, *et al*. The Geant4-DNA project. Int J Model Simul Sci Comput 2010;1:157-78.
26. Karamitros M, Incerti S, Champion C. 376 the geant4-DNA project. Radiother Oncol 2012;102 Suppl 1:S191-2.
27. Nikjoo H, O'Neill P, Terrissol M, Goodhead DT. Quantitative modelling of DNA damage using Monte Carlo track structure method. Radiat Environ Biophys 1999;38:31-8.
28. Nikjoo H, O'Neill P, Goodhead DT, Terrissol M. Computational modelling of low-energy electron-induced DNA damage by early physical and chemical events. Int J Radiat Biol 1997;71:467-83.
29. Nikjoo H, Emfietzoglou D, Watanabe R, Uehara S. Can Monte Carlo track structure codes reveal reaction mechanism in DNA damage and improve radiation therapy? Radiat Phys Chem 2008;77:1270-9.
30. Tajik M, Rozatian AS, Semsarha F. Simulation of ultrasoft X-rays induced DNA damage using the Geant4 Monte Carlo toolkit. Nucl Instrum Methods Phys Res Section B 2015;342:258-65.
31. Semsarha F, Raisali G, Goliaei B, Khalafi H. Microdosimetry of DNA conformations: Relation between direct effect of (60) Co gamma rays and topology of DNA geometrical models in the calculation of A-, B- and Z-DNA radiation-induced damage yields. Radiat Environ Biophys 2016;55:243-54.
32. Semsarha F, Goliaei B, Raisali G, Khalafi H, Mirzakhanian L. An investigation on the radiation sensitivity of DNA conformations to 60 Co gamma rays by using Geant4 toolkit. Nucl Instrum Methods Phys Res B 2014;323:75-81.
33. Raisali G, Mirzakhanian L, Masoudi SF, Semsarha F. Calculation of DNA strand breaks due to direct and indirect effects of auger electrons from incorporated 123I and 125I radionuclides using the geant4 computer code. Int J Radiat Biol 2013;89:57-64.
34. Tajik M, Rozatian AS, Semsarha F. Calculation of direct effects of 60 Co gamma rays on the different DNA structural levels: A simulation study using the Geant4-DNA toolkit. Nucl Instrum Methods Phys Res B 2015;346:53-60.
35. Bernal MA, Sikansi D, Cavalcante F, Incerti S, Champion C, Ivanchenko V, *et al*. Performance of a new atomistic geometrical model of the B-DNA configuration for DNA-radiation interaction simulations. J Phys Conf Ser 2014;490:12150.
36. Souici M, Khalil TT, Muller D, Raffy Q, Barillon R, Belafrites A, *et al.* Single- and double-strand breaks of dry DNA exposed to protons at Bragg-peak energies. J Phys Chem B 2017;121:497-507.
37. Zhou X, Liu X, Zhang X, Zhou R, He Y, Li Q, *et al.* Non-randomized mtDNA damage after ionizing radiation via charge transport. Sci Rep 2012;2:780.
38. Tran HN, Karamitros M, Ivanchenko VN, Guatelli S, McKinnon S, Murakami K, *et al*. Geant4 Monte Carlo simulation of absorbed dose and radiolysis yields enhancement from a gold nanoparticle under MeV proton irradiation. Nucl Instrum Methods Phys Res B 2016;373:126-39.