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Validation of the radiobiology toolkit TOPAS-nBio in simple DNA geometries

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Abstract

Computational simulations offer a powerful tool for quantitatively investigating radiation interactions with biological tissue and can help bridge the gap between physics, chemistry and biology. The TOPAS collaboration is tackling this challenge by extending the current Monte Carlo tool to allow for sub-cellular in silico simulations in a new extension, TOPAS-nBio. TOPAS wraps and extends the Geant4 Monte Carlo simulation toolkit and the new extension allows the modeling of particles down to vibrational energies (~ 2 eV) within realistic biological geometries. Here we present a validation of biological geometries available in TOPAS-nBio, by comparing our results to two previously published studies. We compare the prediction of strand breaks in a simple linear DNA strand from TOPAS-nBio to a published Monte Carlo track structure simulation study. While TOPAS-nBio confirms the trend in strand break generation, it predicts a higher frequency of events below an energy of 17.5 eV compared to the alternative Monte Carlo track structure study. This is due to differences in the physics models used by each code. We also compare the experimental measurement of strand breaks from incident protons in DNA plasmids to TOPAS-nBio simulations. Our results show good agreement of single and double strand breaks predicting a similar increase in the strand break yield with increasing LET.

Keywords

Monte Carlo simulation; Track structure; DNA strand break; Validation

1. Introduction

The TOol for PArticle Simulation (TOPAS) wraps and extends the general purpose Monte Carlo code Geant4, to create a user-friendly toolkit more readily available for both research and clinical physicists [1]. TOPAS was originally designed specifically for applications in proton therapy but is now available for use in many different areas of radiation therapy research. Users interact with TOPAS via a custom-designed parameter control system that allows ease of use, reliability, and repeatability without sacrificing exibility. Although dose calculations have become increasingly accurate, dosimetric indices alone may not provide a full picture of the quality of a treatment plan with respect to the biological outcome. New advances in this area are most likely to come from the complex interface of physics, biology and chemistry. To help achieve this goal a new TOPAS extension, TOPAS-nBio, has been developed to give users the capability of developing Monte Carlo simulations on a micro- or nano-meter scale, with the aim of understanding how radiation interacts with cells.

Monte Carlo simulations most commonly used for dosimetric studies in radiotherapy use condensed history simulation techniques, providing information on a macroscopic level. Monte Carlo codes that use methods for simulating ionizing particle tracks, interaction by interaction at the nanometer level, are referred to as track structure codes. Since low energy secondary electrons (< 1 keV) play a significant role in generating biological damage through the formation of ionization and excitation events, the physical models used in track structure algorithms extend to very low energies. These codes are thus powerful tools for understanding the mechanisms of radiation-induced damage by predicting the distribution of energy depositions within biological structures, such as DNA. Currently there are numerous Monte Carlo track structure algorithms that model the physical stage i.e. modeling particles and their low energy secondary electrons within a medium. Some of these codes additionally take into account the physicochemical interactions that occur after the physical stage, simulating oxidative radical species formation [2]. The majority of track structure codes are however the propriety of the author and are only distributed within research collaborations or to authorized users (e.g., PARTRAC [3], RITRACKS [4], MC4 [5], KURBEC [6]). Codes that have been sufficiently developed for public distribution require users to have advanced programming skills to develop their own applications (e.g., Geant4 [7], Penelope [8]), and thus have not found widespread use with radiobiologists.

TOPAS-nBio aims to provide users without advanced programming skills with an easy-to-use tool in which to model biology experiments. The user interacts with TOPAS-nBio via the same advanced parameter control system already implemented in TOPAS. A graphical-user-interface (GUI) specifically for the TOPAS-nBio extension will make the toolkit even more convenient. Users have the ability to design their own biological geometries by accessing a comprehensive catalog of geometries that are controlled via the parameter file system or GUI. The available geometries range from the micro-scale (cells, organelles) to the nano-scale (DNA molecule). Users also have the choice of performing condensed history simulations within micrometer geometries using the Geant4 physical models (e.g., dose to a cell) or advanced track structure simulations using the physical models in Geant4-DNA (e.g., strand break damage to a DNA segment) [9].

TOPAS has been well validated for proton therapy applications [10]. We aim to extend this careful testing and validation strategy to the TOPAS-nBio extension. Benchmarking can be done by comparing to other track structure simulation codes or to experimental data of measured DNA damage. Validation is a challenging task since the available data may be dependent on the experimental preparation and unknown biological mechanisms. Here we present the first validation study of TOPAS-nBio using simple DNA strand models. In this study we compare our simulation results to two previously published studies; an early track structure simulation of strand damage in simple linear DNA segments [11] and experimental measurements of strand damage to proton irradiated DNA plasmids [12].

2. Methods

2.1. TOPAS-nBio

Users of the TOPAS-nBio extension require the full TOPAS toolkit to run radiobiology simulations. The TOPAS parameter text file system has been adopted by TOPAS-nBio and is designed to allow for a large number of inter-related simulation parameters to be controlled with exibility and ease. A graphical user interface (GUI) is also under development that will allow users to interact with the extension more conveniently. The TOPAS-nBio extension will be open-source and freely available, giving advanced users the ability to edit or generate biological geometry class files.

TOPAS-nBio provides the user with an extensive library of ready-to-use biological geometries both on a micro and nanometer scale. The extension provides users with several cell geometry types and the exibility of specifying parameters such as the cell dimension and chemical composition. The user also has the capability of including organelles (e.g., nucleus, mitochondria) to any cell model and can control the placement and size of each organelle (see Figure 1a). On the nanometer scale, users have the option of modeling the various stages of DNA hierarchal folding within the nucleus (chromatin territories, chromatin fibers and double helix DNA strands wrapped around histones (see Figure 1b)). The full nucleus geometry has been adapted from Geant4-DNA. Users can however also model single chromatin fibers or single double helix strands. TOPAS-nBio can read in geometries from the Protein Data Bank (PDB) [13] as well as DNAFabric [14] (see Figure 1c). Although nuclear DNA is a primary radiation target, TOPAS-nBio allows other non-nuclear target sites to be modeled (e.g., mitochondria [15, 16]).

Since TOPAS is built on top of Geant4, TOPAS-nBio utilizes the Geant4 physics models. For microdosimetric applications (dosimetric quantities within micrometer sized volumes), TOPAS-nBio simulations can be performed with Geant4 condensed history techniques; e.g., using the low energy electromagnetic physics models based on the Livermore libraries or the Penelope physics processes. In this case, users can specify their own material compositions for cellular structures (e.g., cytosol, nucleus) [17]. For track structure modeling, TOPAS-nBio uses the Geant4-DNA physics processes [18, 19] in liquid water (*G4_WATER*). Monte Carlo track structure codes are generally limited to media consisting of either liquid water or vapor. Since there are no direct experimental data for excitation and ionization cross-sections in liquid water, these algorithms are based on data for a mixture of both states. Additionally, TOPAS-nBio allows use of both condensed history and track structure simulations in a

single simulation. For example, track structure techniques can be used within the nucleus of the cell, while faster condensed history techniques can be used elsewhere in the simulation volume. Although this feature is also available in Geant4, TOPAS-nBio allows the user to specify these regions within parameter text files and does not require any advanced programming skills. TOPAS-nBio also allows for chemical interaction modeling through access to the Geant4-DNA chemistry models; this is important for accurately predicting indirect damage from the production of free radical species [20, 21].

Damage from ionizing radiation in the form of DNA lesions is not randomly distributed along the DNA molecule. When energy from radiation is deposited in matter, multiple damage sites that typically span less than ~ 20 base-pairs (bp) of DNA are created [22, 23]. When these damaged sites consist of two single-strand breaks (SSBs) on opposite strands, a double strand break (DSB) is often created. Since clustering of DNA damage occurs on larger scales, the hierarchical structure of the DNA in the cell, from nucleosomes to chromosomes, can be an important consideration in modeling efforts [24]. Many track structure algorithms model the particle tracks within liquid water then overlay complex biological geometries after the simulation. In TOPAS-nBio, simulations can be performed within the physical volumes (e.g., scoring energy deposition within the sugar-phosphate backbone of a DNA segment). Even though the current track structure medium is limited to water, users still have the ability to assign densities greater than 1 g/cm^3 to specific geometric components. DNA can then be represented by a chain of water structures with the density or the same water equivalent path-length of DNA. TOPAS-nBio will provide the user with dedicated scorers to output quantities such as SSB and DSB yields.

All TOPAS parameter files are order independent and use strict type checking. To illustrate a basic example of the parameter file system for the TOPAS-nBio extension, we generate a simple spherical cell with a central nucleus and 20 mitochondria arranged randomly in the cytoplasm, all composed of liquid water (see Figure 2). In Geant4, all the particles and physical processes required in the simulation are set in the so called physics list. To simplify this process, TOPAS offers users the ability to select premade complete physics lists from Geant4 (reference physics lists), or to select modular lists which consist of a selection of different physics lists as a customized option. The modular physics lists most relevant to TOPAS-nBio are the condensed history low energy electromagnetic processes (in TOPAS called g4em-penelope, g4em-livermore) and the track structure Geant4-DNA processes (g4em-dna). Although Geant4 also offers modular physics lists, TOPAS-nBio again simplifies the use of these advanced features through the use of simple parameter commands to generate complex simulations in a simple manner. We refer the reader to the official TOPAS documentation for further details[1].

2.2. Validation of TOPAS-nBio

In this study, we validate TOPAS-nBio by comparing to a previous Monte Carlo study predicting strand breaks in a simple linear DNA segment for several particles types [11] and

[1] http://topas.readthedocs.org

an experimental study measuring the occurrence of strand breaks within a DNA plasmid from incident protons [12].

2.2.1. Monte Carlo validation study—The Charlton et al. (1989) study [11] modeled direct damage to simple linear DNA strands using electron and ion track structure codes. The Charlton DNA model consisted of a central cylinder of length 1 nm, representing the base-pair volume. The sugar-phosphate backbone was represented by half-cylinders with a full diameter of 2.3 nm, each rotated by 36 degrees around the central base-pair volume. The width of each single base-pair was set to 0.34 nm. Figure 3 shows the geometry of the Charlton DNA model as set up in TOPAS-nBio. The left panel shows a single strand of the Charlton model while the right panel shows the full DNA strand i.e. two strands. All materials in the linear DNA segment were set to water (*G4_WATER*).

A total of 10^4 Charlton DNA segments, each consisting of 54 base-pairs, were randomly distributed in a larger liquid water cylinder of length 1 μm. To ensure that all the secondary tracks from each particle would be fully contained within the volume, the radius of the larger cylinder was determined for each particle using a pre-calculation simulation. With sufficient statistics, the size of the cylindrical container should not affect the final result (event per Gy per target) if the cylinder covers all the tracks laterally. The radii chosen for the incident alpha particles were 2340 nm (20 MeV), 700 nm (10 MeV), 380 nm (6 MeV) and 500 nm (4 MeV, 3 MeV, 1.2 MeV). The radius of the large cylinder for incident protons of energy 2 MeV was set to 440 nm and for electrons of 20 keV to 7160 nm. One million incident particles were simulated for each particle type and the energy deposited in each of the DNA strand volumes was scored in an ntuple.

Following the Charlton study, we model incident alpha particles with energies ranging from 1.2 MeV to 20 MeV. In addition, incident 2 MeV protons as well as electrons of energy 20 MeV were modeled. The radiation beam was set along the central axis of the cylinder. The Geant4-DNA physics models were used to simulate the track structure of all the incident particles and their secondary electrons. To compare with the published simulated results available in Charlton et al. [11], the results were normalized to the event occurrence number per gray per target.

The energy deposited within the DNA segments was used to calculate the number and type of strand break within the segment. A break was considered to occur when the total energy deposited within the sub-volume (sugar-phosphate cylinder) was greater than 17.5 eV. A Matlab (Mathworks Inc.) script was used to categorize the breaks into six different types: SSB, 2SSB, SSB+, DSB, DSB+ and DSB++ (see Figure 4). A SSB occurs when energy greater than the threshold value is deposited in a single strand of the two sugar-phosphate backbone chain. If more than one SSB in the same strand occurs, this was classified as a SSB+. If at least one SSB occurs on each strand with a separation less than $x = 10$ base-pairs, a DSB was scored. If a DSB with an additional SSB on one of the strands occurs, a DSB+ was scored and the presence of two or more DSBs in the segment was classified as a DSB++. In this study we only investigated direct radiation damage effects and indirect damage (e.g., from OH radicals produced in dilute solution) was not modeled.

2.2.2. Experimental data validation study—The second geometry used for the validation study was a circular plasmid DNA model (based on the pBR322 strand [25]). The double helix structure of the DNA molecule was constructed with simple cylindrical volumes following the prescription described in Bernal et al. [26] and is shown in Figure 5. Each base-pair consisted of a central cylinder of length 0.34 nm and diameter 1 nm and was surrounded by two quarter cylinders set directly opposite from each other. The quarter cylinders were rotated by 36 degrees on adjacent base-pairs, to create the twisted double strand around the base-pair volume in the ring. A total of 2000 base-pairs were simulated in a single plasmid ring.

The interactions of protons within the simple plasmid were simulated and compared to the experimental data from Vyšín et al. [12]. In the experimental study, SSB and DSB yields in DNA plasmids after proton irradiation were measured. Dry plasmids were mounted on a glass coverslip and then placed in a plastic petri dish and irradiated in air with protons at the U-120M isochronous cyclotron at the Nuclear Physics Institute of the Czech Academy of Sciences (CAS). Since the proton energies reported in the study are those at the point of impact, i.e. at the plasmid, we first generated a TOPAS phase-space file at the sample position from a simple beam of monoenergetic protons traversing ~ 3 m of air, to match the experimental setup (Kateřina P Brabcová and Václav Štěpán, private communication, August 2016). The energy of the incident proton beam was chosen so that the average proton kinetic energy at the sample (phase-space file) would be the same as those reported in the experimental study (10 MeV, 20 MeV and 30 MeV). The phase-space file was generated on a plane of 30×30 mm^2 and then shrunk to one of 120×120 nm^2 to allow for higher statistics in the plasmid simulation. The shrunken phase-space file was used to simulate damage to the plasmid using TOPAS-nBio. A volume ratio between the original and shrunken phase-space files were used to correct the scored quantities.

In the TOPAS-nBio simulation, the DNA plasmid was simulated on the glass coverslip (thickness 0.15 mm) and within a plastic petri dish (thickness 0.8 mm, diameter 56 mm and length 13 mm). This was to account for any backscatter effects. The exact composition and density for the coverslip and petri dish were unknown and we used generic definitions of both. The density of glass and plastic were set to 2.5 g/cm^3 and 1.5 g/cm^3, respectively. The material surrounding the plasmid was set to air, while the DNA plasmid itself was composed of liquid water. The plasmid was contained in a thin water ring envelope with an outer radius of 110.6 nm, inner radius of 108.2 nm and length of 2.4 nm. The Geant4-DNA track structure processes were used within this water envelope (*G4_WATER*), while condensed history processes were assigned to the air filled spaces, petri dish and coverslip. Irradiating a dry sample in a vacuum eliminates the indirect effects of radiation damage via the production of free radical species. Although the sample irradiated in the experiment was not placed in a vacuum but in air, it was dry, and we expect that free radical production would be low. For this reason, we do not include any of the chemical models in this simulation study. Since the goal of our study is validation of the physical models in TOPAS-nBio, we specifically chose this experimental study using dry samples because of the negligible radiolysis.

The energy deposited within each component of the DNA plasmid (i.e., the sugar-phosphate quarter cylinders) was scored in an ntuple scorer. Both SSB and DSB yields were determined using the same criteria as in the Charlton DNA model case (i.e., with $x = 10$ base-pairs). Since the techniques used in the experimental study did not differentiate between the types of strand break, we simply quantify the simulated damage as a SSB or DSB. A total of one million protons were simulated for each mono-energetic proton beam simulated.

3. Results and Discussion

3.1. Monte Carlo validation study

Figure 6 shows the occurrence of each type of strand break generated in our simulation study, compared to those obtained in the Charlton et al. [11] simulation study for 10 MeV incident alpha particles. In this Figure, events which deposit energy in the DNA segment volume with energy less than the threshold value of 17.5 eV is referred to as a no break. Our results show that TOPAS-nBio generated more low energy events (i.e., no breaks) than those reported in the Charlton et al. study. This is attributed to the difference between the physics processes in the two track structure codes. It can be argued that the Geant4-DNA physics processes have better modeling capabilities for very low energy particles, with the ability to model secondary particles to energies of a few eV [27]. The early models available in the Charlton et al. study could only produce the initial distributions of deposited energy, and the collective excitation, energy or charge transfer into and out of the region of interest was not handled by the electron track code [28] used in that study. Geant4-DNA can additionally handle the transfer of particles between regions and this was taken into account in our simulations by modeling tracks within the physical geometric volumes rather than overlaying volumes on the simulated tracks. Furthermore, the data used in the physics models for Geant4-DNA is based on that for liquid water while the models in the Charlton study are based on gaseous data. Even with the differences between the physical process models for the track structure simulations, the occurrence of breaks show similar trends to the Charlton et al. study. Both simulation studies show that alpha particles are more efficient at producing SSBs than other complex breaks. Both codes also predict that 2SSB and DSB++ are less likely to occur than other types of breaks. Our simulation results however show an increased amount of DSBs and a decreased amount of DSB++ when compared to the Charlton et al. study. Again this may be attributed to differences in the modeling algorithms with TOPAS-nBio more accurately modeling the damage inducing low energy electrons that cause lesions.

Figure 7 compares the frequency distribution of event size in the DNA segments for different energy ranges for TOPAS-nBio (black) to the Charlton et al. study [11] (blue) for different particle types. TOPAS-nBio predicts more low energy events than the study by Charlton et al. [11], which is likely a result of the different physics models. The trends are however very similar, with both algorithms predicting an increase in events for higher energy intervals starting with electrons, to protons, to the higher energy alpha particles, and finally to the lower energy alpha particles.

To illustrate that the observed differences between the Charlton et al. study (MOCA8 code) and TOPAS-nBio may be attributed to the physics modeling, we compared our simulation results to three other track structure algorithms. For this study, we simulate a nucleosome sized cylinder (diameter 10 nm and length 5 nm) and a DNA strand sized cylinder (diameter 2 nm and length 2 nm) with TOPAS-nBio. Each cylinder was irradiated with 500 eV and 1 keV electrons and 10 million histories was generated for each case. The TOPAS-nBio results were compared to data generated from other Monte Carlo track structure tools extracted from Nikjoo et al. [29] (see Figure 8). TOPAS-nBio predicted more low energy deposition events compared to the MOCA8 code, which was utilized in the Charlton et al. study, consistent with our observations. Better agreement is found between Geant4-DNA, CPA100 and OREC simulations than with MOCA8 since the cross sections in MOCA8 are based on data for gaseous water, while the other codes are all based on calculations for liquid water. Even though CPA100 and Geant4-DNA use the same liquid water data in their cross section calculations, differences are observed between the two codes. This was also observed in a previous comparison study of dose point kernel distribution calculations [30].

There is a strong dependence of the threshold energy on the strand break yield. The yield of both double and single strand breaks decrease with an increase in threshold energy [31]. The threshold energy in the sugar-phosphate volume for DNA strand breaks was chosen to match that used by Charlton et al. [11] and was first calculated by Humm and Charlton (1988) [32] based on biological experimental data [33]. Since track structure algorithms are limited to water media, another commonly used threshold energy is 10.79 eV [26, 34] which is based on the ionization threshold of liquid water [35]. Both these values have been shown to be in good agreement with experimental studies [34, 36, 31].

3.2. Experimental data validation

Figure 9 compares the total number of TOPAS-nBio simulated SSB and DSB yields (Mbp^{-1} Gy^{-1}) as a function of linear energy transfer (LET) to the experimental data of proton irradiated dry DNA plasmids from Vyšín et al. [12]. Both the experimental and simulation data show the same trend, an increase in both SSB and DSB yields with increasing LET. Both studies also show that protons are more effective at producing SSBs than DSBs in dry samples.

The experimental data however predict a higher SSB yield and a lower DSB yield than the simulation, thus predicting higher SSB to DSB ratios for all LET values. The experimental measurements predicted SSB=DSB = 24, 42 and 41 for 10 MeV, 20 MeV and 30 MeV protons, respectively. TOPAS-nBio predicted SSB=DSB = 16, 22 and 21 for 10 MeV, 20 MeV and 30 MeV protons, respectively, approximately a factor of 2 less. Differences between the two data sets are most likely due to an oversimplified DNA model geometry or other experimental factors not accounted for in the simulation. The DNA model considered here was a simple circular ring, however plasmids can have many other complex geometries (supercoiled, linear, open-circled) with varying lengths of base-pairs. The Vyšín et al. study reported that all three types of geometries were observed in their study. We also assume in our simulation that the DNA sample was strictly dry, this was however not the case in the experiment with the plasmid being irradiated in air and not a vacuum. Although the effect is

likely to be very small, moisture in the air could potentially lead to the production of free radicals preferentially causing SSBs (single reaction) in the plasmid, unaccounted for in the simulation. The same experimental study also found that the number of SSBs and DSBs increased for irradiation of samples within a dilute solution and did not vary with LET. This suggests that indirect effects would play a role in causing damage to the plasmid in the hydrated case. Furthermore, DSB yield differences could be due to the insensitivity of electrophoresis to count multiple DSBs in close proximity to each other in the plasmid (i.e., where multiple close DSB damage sites would be counted as a single DSB). The enzymatic treatment the samples underwent in the experimental protocol could also affect the yield of strand breaks; this was also not accounted for in our simulation study since the biological mechanism of these effects is not well known.

4. Conclusions

The TOPAS-nBio extension provides users with a powerful and easy-to-use tool for the development of advanced radiobiology Monte Carlo simulations. The extension allows for detailed track information to be correlated within realistic biological volumes. TOPAS-nBio has been designed to facilitate the exchange of ideas between biologists and physicists by making advanced Monte Carlo simulations available to non-experts. Here, we present the first validation study of TOPAS-nBio in simple DNA geometries by comparing our simulation data to other simulation and experimental studies.

In a simple linear DNA model segment we find relatively good agreement with the simulation study in Charlton et al. [11]. Our data predict similar trends to the published simulation study, with similar yields for SSBs and DSBs. However, our model predicts a higher number of very low energy events (< 17:5 eV). We show that this can be explained by the improved physics models used in TOPAS-nBio. TOPAS-nBio uses the Geant4-DNA physics models which are based on data for liquid water, while the original study used models based on water in a gaseous phase. Furthermore, the low energy physics models available in Geant4-DNA are more sophisticated than the early models used in the Charlton et al. study.

In another validation study, we compare published experimental data [12] of the yield of SSBs and DSBs in DNA plasmids to our circular DNA plasmid model. We find that TOPAS-nBio predicts a similar trend to that observed experimentally but the ratio of the yield of SSB to DSB is lower for the simulation study. This is most likely due to unaccountable differences in the simulation and experimental setup (e.g., a simplified DNA model, indirect effects) and the insensitivity of the experimental technique to count multiple types of strand breaks occurring in close proximity to each other. This study shows that TOPAS-nBio is capable of predicting damage to simple DNA plasmids which agrees well with the experimental observations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Perl J, Shin J, Schümann J, Faddegon B, Paganetti H. TOPAS: An innovative proton Monte Carlo platform for research and clinical applications. Med Phys. 2012; 39(11):6818–6837. [PubMed: 23127075]
2. Nikjoo H, Uehara S, Emfietzoglou D, Cucinotta FA. Track-structure codes in radiation research. Radiat Meas. 2006; 41(9–10):1052–1074.
3. Friedland W, Dingfelder M, Kundrát P, Jacob P. Track structures, DNA targets and radiation effects in the biophysical Monte Carlo simulation code PARTRAC. Mutat Res-Fund Mol M. 2011; 711(1–2):28–40.
4. Plante, I., Cucinotta, FA. Computational Intelligence Methods for Bioinformatics and Biostatistics. Berlin, Heidelberg: Springer Berlin Heidelberg; 2012. Multiple CPU Computing: The Example of the Code RITRACKS; p. 12-25.
5. Emfietzoglou D, Papamichael G, Kostarelos K, Moscovitch M. A Monte Carlo track structure code for electrons (~10 eV-10 keV) and protons (~0.3–10 MeV) in water: partitioning of energy and collision events. Phys Med Biol. 2000; 45(11):3171–3194. [PubMed: 11098897]
6. Uehara S, Nikjoo H, Goodhead DT. Cross-sections for water vapour for the Monte Carlo electron track structure code from 10 eV to the MeV region. Phys Med Biol. 1993; 38(12):1841–1858.
7. Agostinelli S, Allison J, Amako K, Apostolakis J, Araujo H, Arce P, et al. GEANT4: A Simulation toolkit. Nucl Instrum Meth A. 2003; 506:250–303.
8. Sempau J, Fernández-Varea JM, Acosta E, Salvat F. Experimental benchmarks of the Monte Carlo code PENELOPE. Nucl Instrum Meth B. 2003; 207:107–123.
9. Incerti S, Douglass M, Penfold S, Guatelli S, Bezak E. Review of Geant4-DNA applications for micro and nanoscale simulations. Phys Medica. 2016; 32(10):1187–1200.
10. Testa M, Min CH, Verburg JM, Schümann J, Lu H-M, Paganetti H. Range verification of passively scattered proton beams based on prompt gamma time patterns. Phys Med Biol. 2014; 59(15): 4181–4195. [PubMed: 25004257]
11. Charlton DE, Nikjoo H, Humm JL. Calculation of initial yields of single- and double-strand breaks in cell nuclei from electrons, protons and alpha particles. Int J Radiat Biol. 1989; 56(1):1–19. [PubMed: 2569005]
12. Vyšín L, Brabcová KP, Štěpán V, Moretto-Capelle P, Bugler B, Legube G, et al. Proton-induced direct and indirect damage of plasmid DNA. Radiat Environ Bioph. 2015; 54(3):343–352.
13. Delage E, Pham QT, Karamitros M, Payno H, Štěpán 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; 192:282–288.
14. 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; 204:159–169.
15. Kam WWY, McNamara AL, Lake V, Banos C, Davies JB, Kuncic Z, Banati RB. Predicted ionisation in mitochondria and observed acute changes in the mitochondrial transcriptome after gamma irradiation: A Monte Carlo simulation and quantitative PCR study. Mitochondria. 2013; 13(6):736–742.
16. Zhang B, Davidson MM, Hei TK. Mitochondria regulate DNA damage and genomic instability induced by high LET radiation. Adv Space Res-Series. 2014; 1:80–88.
17. McNamara AL, Kam WWY, Scales N, McMahon SJ, Bennett JW, Byrne HL, et al. Dose enhancement effects to the nucleus and mitochondria from gold nanoparticles in the cytosol. Phys Med Biol. 2016; 61(16):5993–6010. [PubMed: 27435339]

18. Bernal MA, Bordage M, Brown J, Davidkova M, Delage E, El Bitar Z, et al. Track structure modeling in liquid water: A review of the Geant4-DNA very low energy extension of the Geant4 Monte Carlo simulation toolkit. Phys Medica. 2015; 31(8):861–874.
19. Incerti S, Ivanchenko A, Karamitros M, Mantero A, Moretto P, Tran H, et al. Comparison of GEANT4 very low energy cross section models with experimental data in water. Med Phys. 2010; 37(9):4692–4708. [PubMed: 20964188]
20. Karamitros M, Luan S, Bernal MA, Allison J, Baldacchino G, Davidkova M, et al. Diffusion-controlled reactions modeling in Geant4-DNA. J Comput Phys. 2014; 274:841–882.
21. Karamitros M, Mantero A, Incerti S, Baldacchino G, Barberet P, Bernal M, et al. Modeling Radiation Chemistry in the Geant4 Toolkit. Progr Nucl Sci Technol. 2011; 2(0):503–508.
22. Goodhead DT. Initial Events in the Cellular Effects of Ionizing Radiations: Clustered Damage in DNA. Int J Radiat Biol. 2009; 65(1):7–17.
23. Ward JF. Radiation Mutagenesis: The Initial DNA Lesions Responsible. Radiat Res. 1995; 142(3): 362. [PubMed: 7761586]
24. Alloni D, Campa A, Friedland W, Mariotti L, Ottolenghi A. Track structure, radiation quality and initial radiobiological events: Considerations based on the PARTRAC code experience. Int J Radiati Biol. 2011; 88(1–2):77–86.
25. Bolivar F, Rodriguez RL, Greene PJ, Betlach MC. Construction and characterization of new cloning vehicle. II. A multipurpose cloning system. Gene. 1977; 2:95–113. [PubMed: 344137]
26. Bernal MA, Liendo JA. An investigation on the capabilities of the PENELOPE MC code in nanodosimetry. Med Phys. 2009; 36:620–625. [PubMed: 19292002]
27. Kyriakou I, Šefl M, Nourry V, Incerti S. The impact of new Geant4-DNA cross section models on electron track structure simulations in liquid water. J Appl Phys. 2016; 119(19):194902.
28. Paretzke HG, Turner JE, Hamm RN, Ritchie RH. Spatial distributions of inelastic events produced by electrons in gaseous and liquid water. Radiat Res. 1991; 127(2):121–129. [PubMed: 1946995]
29. Nikjoo, H., Uehara, S. Computational Approaches in Molecular Radiation Biology. Boston, MA: Springer US; 1994. Comparison of various Monte Carlo track structure codes for energetic electrons in gaseous and liquid water; p. 167-185.
30. Champion C, Incerti S, Perrot Y, Delorme R, Bordage MC, Bardiès M, et al. Dose point kernels in liquid water: An intra-comparison between Geant4-DNA and a variety of Monte Carlo codes. Appl Radiat Isotopes. 2014; 83:137–141.
31. Nikjoo H, O'Neill P, Goodhead D, Terrissol M. Computational modelling of low-energy electron-induced DNA damage by early physical and chemical events. Int J Radiati Biol. 2009; 71(5):467–483.
32. Humm, JL., Charlton, DE. DNA damage by Auger emitters. London: Taylor and Francis; 1988. Double strand breakage in DNA produced by the photoelectric interaction with incorporated 'cold' bromine; p. 111-122.
33. Martin RF, Haseltine WA. Range of radiochemical damage to DNA with decay of iodine-125. Science. 1981; 213(4510):896–898. [PubMed: 7256283]
34. Friedland W, Jacob P, Paretzke HG. Simulation of DNA fragment distributions after irradiation with photons. Radiat Environ Bioph. 1999; 38:39–47.
35. Dingfelder M, Hantke D, Inokuti M, Paretzke HG. Electron inelastic-scattering cross sections in liquid water. Radiat Phys Chem. 1999; 53(1):1–18.
36. Nikjoo H, O'Neill P, Wilson WE, Goodhead DT. Computational approach for determining the spectrum of DNA damage induced by ionizing radiation. Radiat Res. 2001; 156:577–583. [PubMed: 11604075]

Highlights

- Validation study of the Monte Carlo simulation Toolkit, TOPAS-nBio, for radiobiology studies.
- We compare TOPAS-nBio simulations in simple DNA geometries to previously published studies.
- We find TOPAS-nBio predicts very similar trends of strand break yields to both comparison studies.

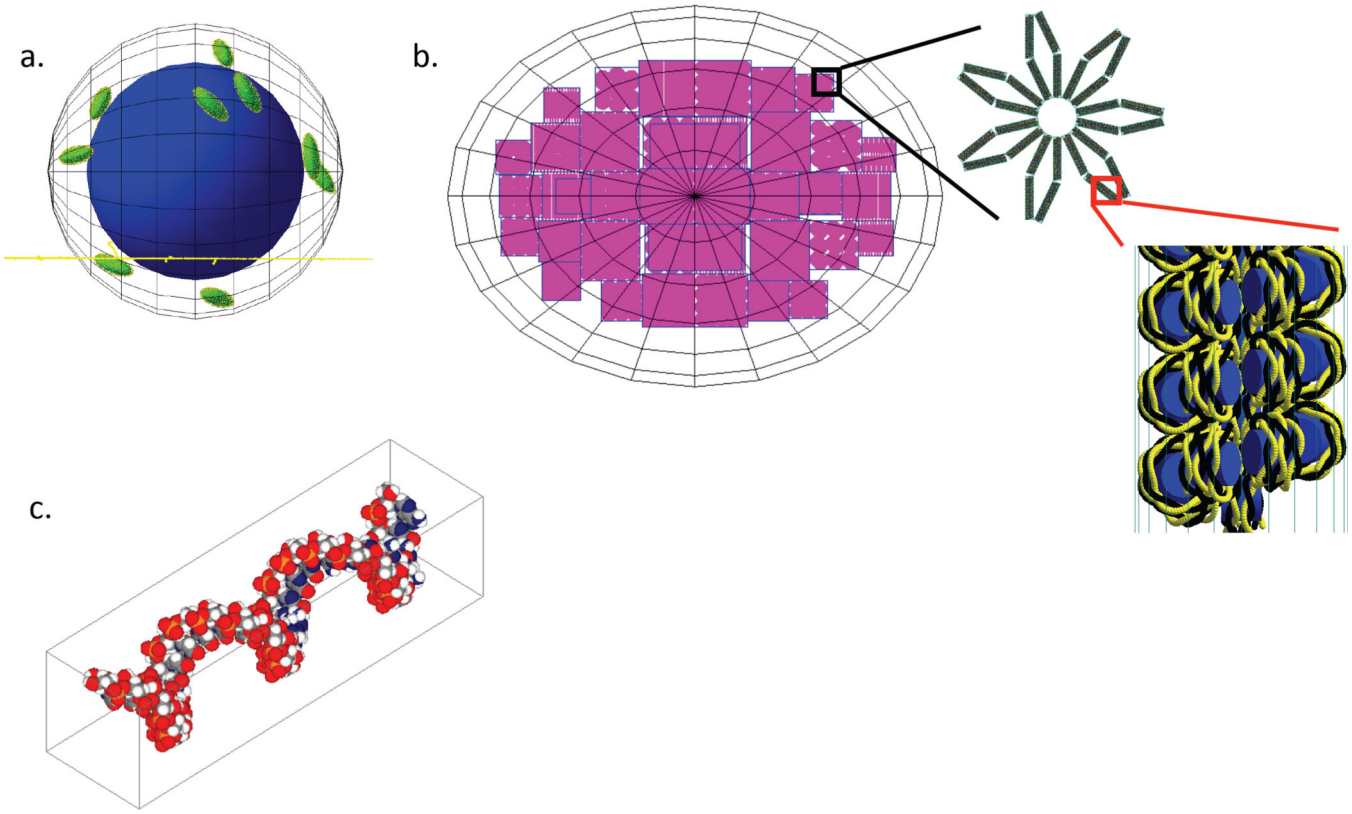

Figure 1.

Visualization of some of the geometries available in TOPAS-nBio: (a) cell with nucleus (blue) and mitochondria (green), (b) nucleus with chromosome territories (pink), chromatin fibers arranged in a flower arrangement and with each fiber comprised of double helix DNA strands wrapped around histone proteins, and (c) RNA strand geometry composed of spheres, representing the atom arrangement of the molecule, taken from the Protein Data Bank (adapted from Geant4-DNA).

```
# TOPAS-nBio example.
# A simple spherical cell with organelles modelled with EM physics.

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d:Ge/World/HLY=1. cm
d:Ge/World/HLZ=1. cm

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s:Ge/MyCell/Parent="World"
d:Ge/MyCell/CellRadius=10. um
s:Ge/MyCell/Material="G4_WATER"
s:Ge/MyCell/Color="black"

#Nucleus
d:Ge/MyCell/Nucleus/NuclRadius=5. um
s:Ge/MyCell/Nucleus/Material="G4_WATER"
s:Ge/MyCell/Nucleus/Color="red"
s:Ge/MyCell/Nucleus/DrawingStyle="solid"

#Mitochondria
b:Ge/MyCell/Mitochondria/random="true"
i:Ge/MyCell/Mitochondria/NbOfMito=20
d:Ge/MyCell/Mitochondria/a=0.5 um
d:Ge/MyCell/Mitochondria/b=0.3 um
d:Ge/MyCell/Mitochondria/c=0.9 um
s:Ge/MyCell/Mitochondria/Material="G4_WATER"
s:Ge/MyCell/Mitochondria/Color="grass"
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s:Ge/MyCell/Mitochondria/DrawingStyle="solid"

Ph/Default/Modules = 1 "g4em-standard_opt0"
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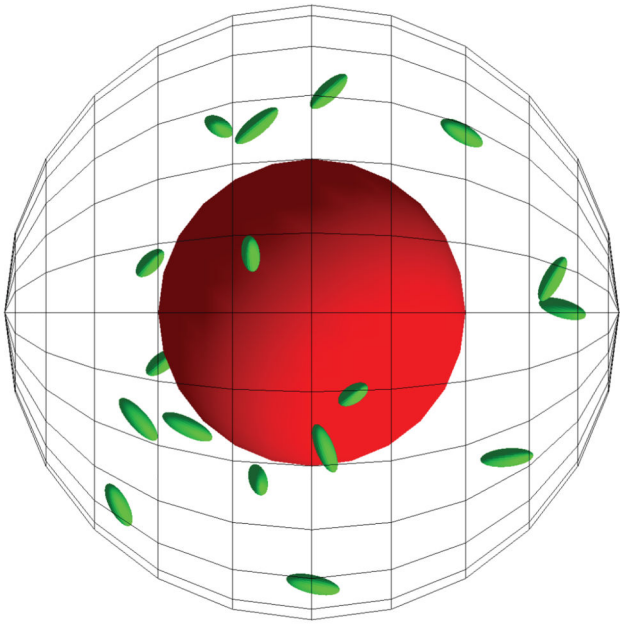

Figure 2.
Example of a TOPAS-nBio parameter file to generate a simulation of a simple spherical cell (also pictured) with organelles.

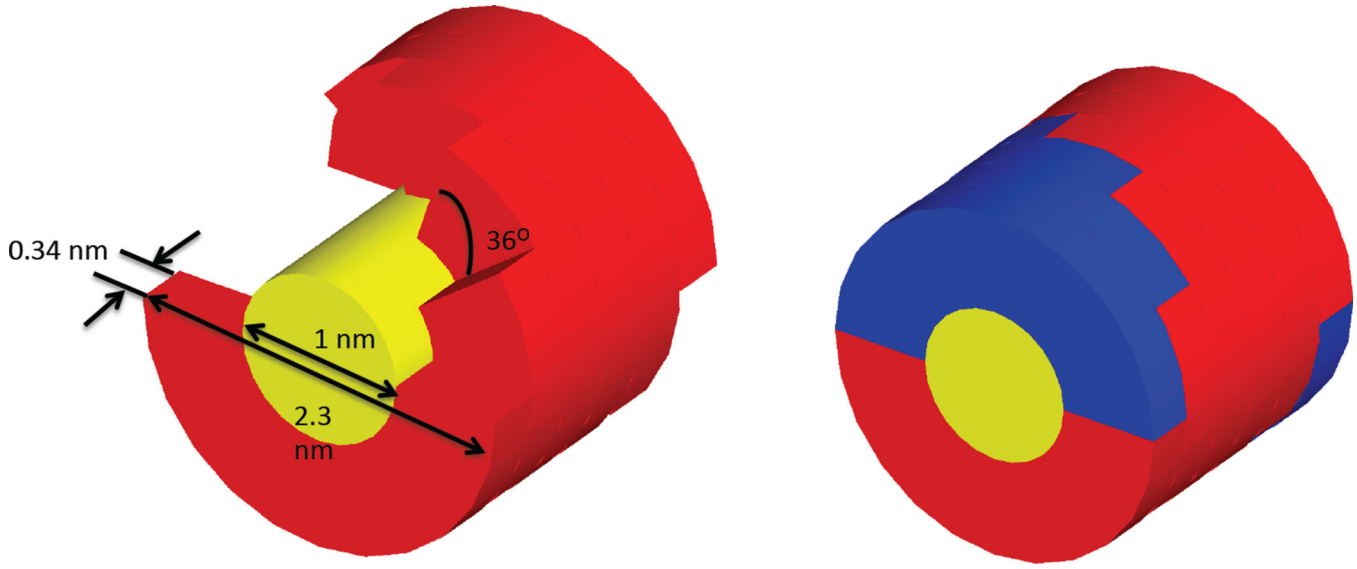

Figure 3.

The Charlton DNA model of a single strand [11]. The base-pair consists of a cylinder of diameter 1 nm surrounded by half-cylinders of outer diameter 2.3 nm, each rotated by 36 degrees, representing the sugar phosphate backbone of the strand. The left panel shows a single strand of the model while the right panel shows the full DNA segment.

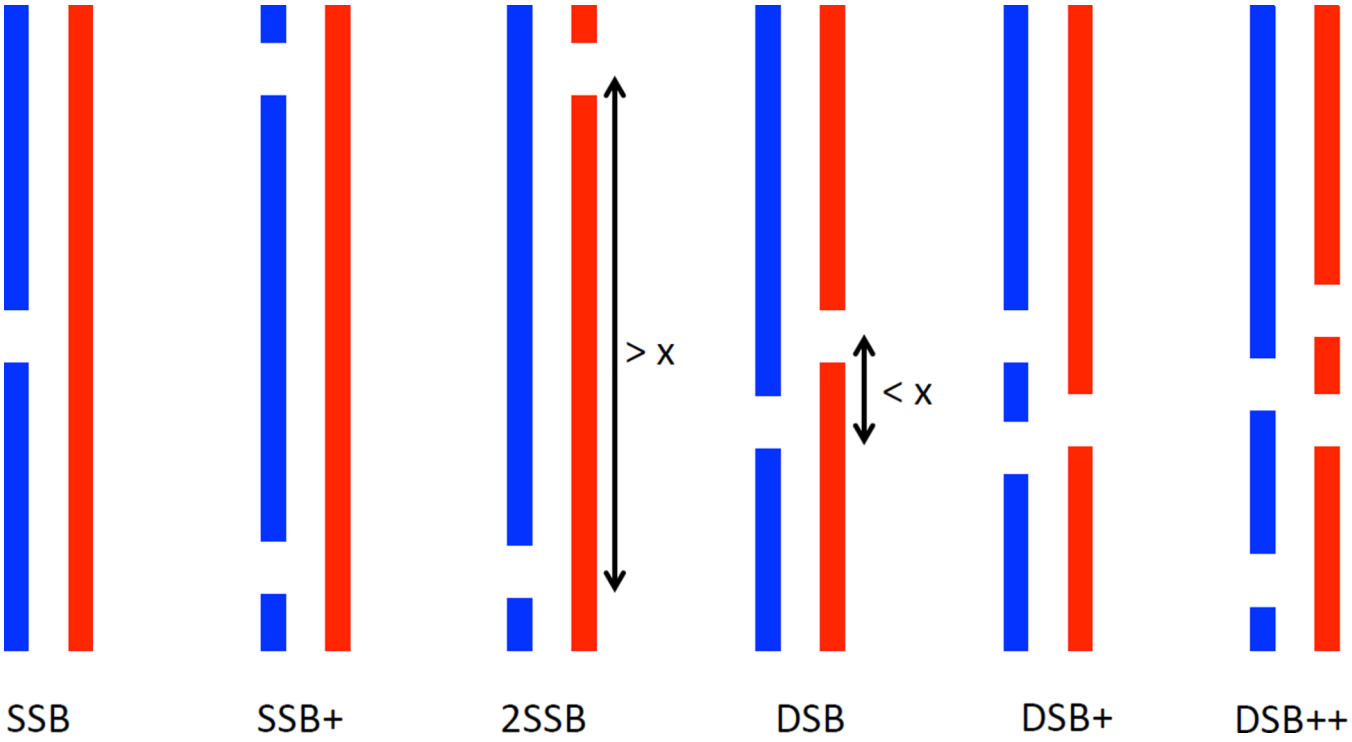

Figure 4.

Classification of strand breaks used in the analysis (adapted from [11]). The separation parameter *x* was set to 10 base-pairs.

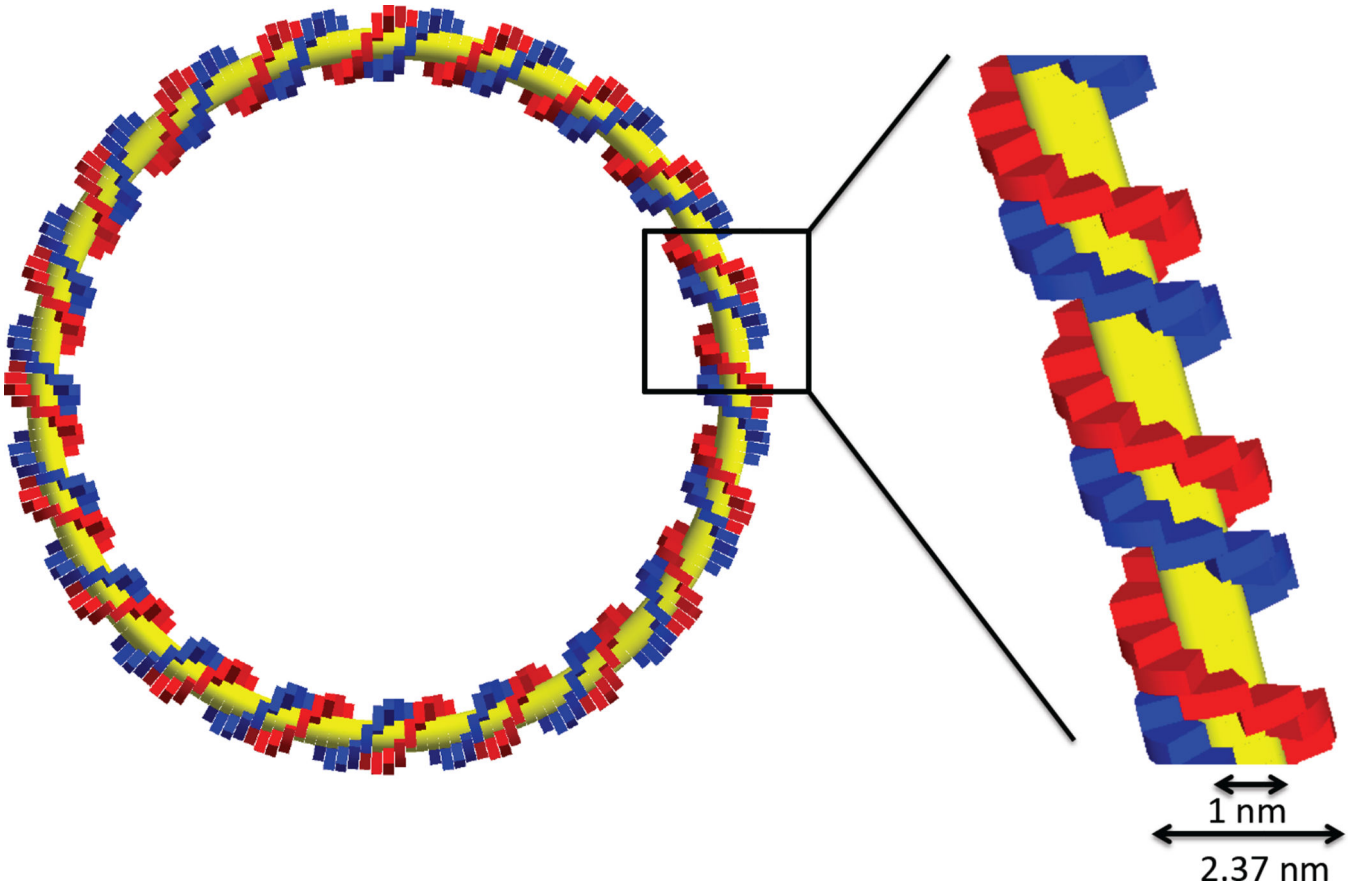

Figure 5.

The circular DNA plasmid model. The base-pair consists of a cylinder of diameter 1 nm (yellow). Two sugar-phosphate strands (red and blue) are wrapped around the central base-pair volume. The length of a single base-pair was set to 0.34 nm.

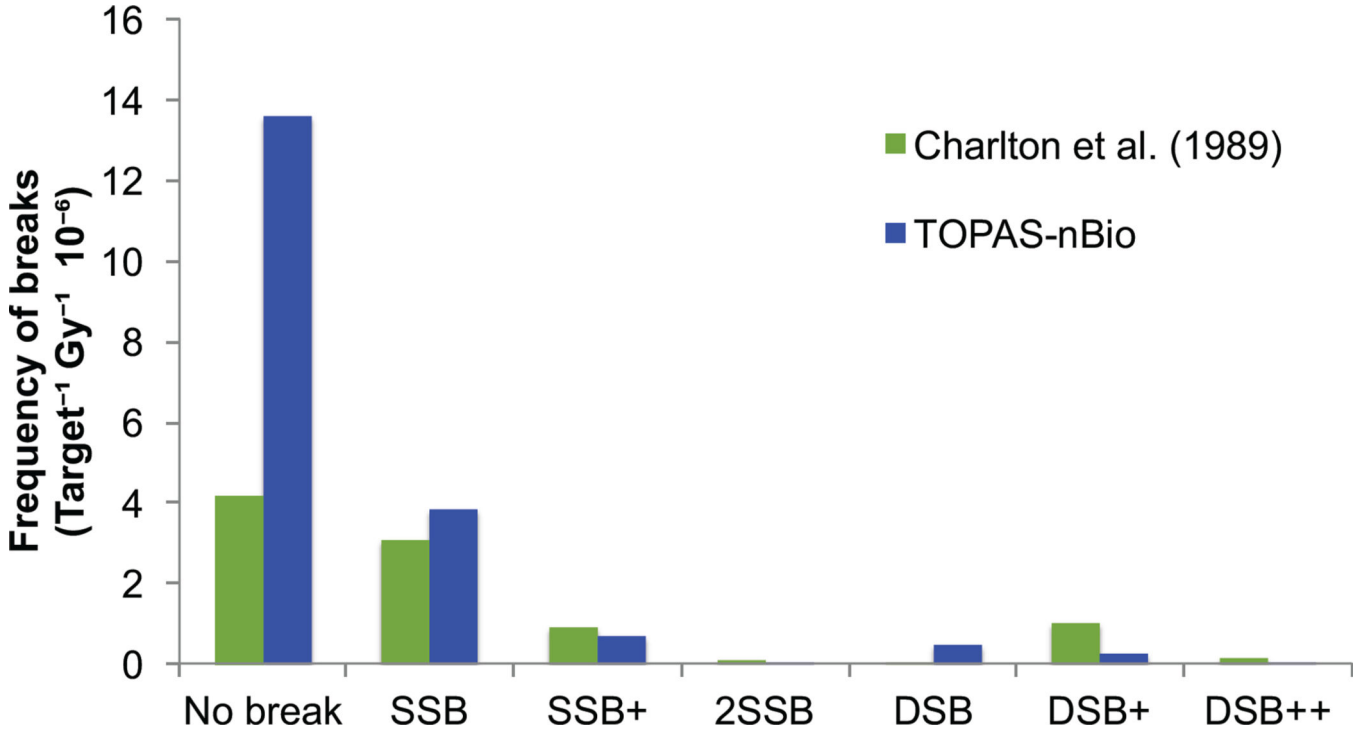

Figure 6.

The frequency of six different types of DNA segment breaks generated from TOPAS-nBio (blue) compared to the Charlton et al. [11] simulation data (green) for 10 MeV incident alpha particles. No break refers to the case where the energy deposited in the segment is less than the threshold value of 17.5 eV. The results of the Charlton et al. study were renormalized according to the event size reported in the paper.

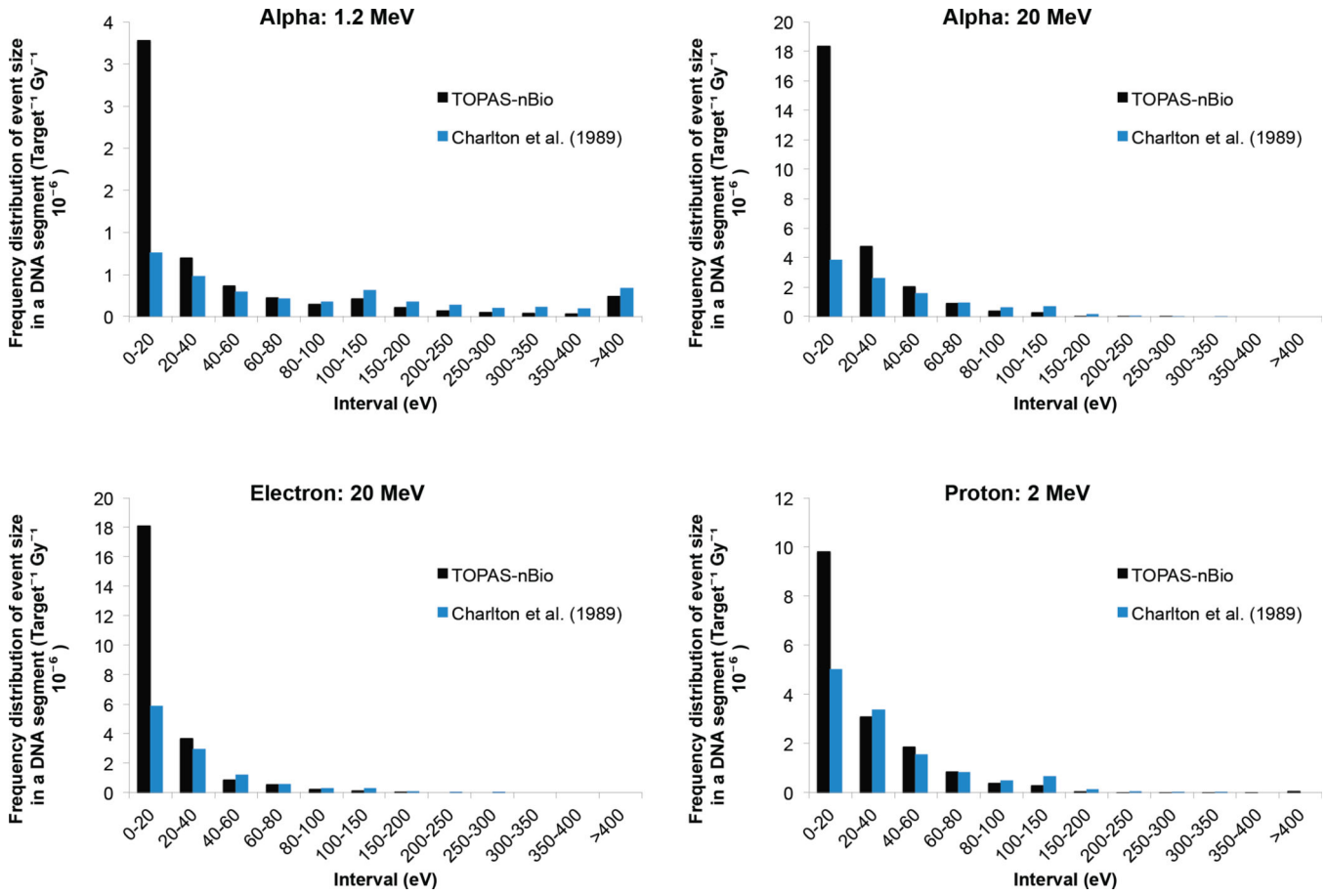

Figure 7.

Comparison of frequency of events (target^{-1} Gy^{-1}) within a DNA target as a function of energy range (eV) for 1.2 MeV and 20 MeV alpha particles, 20 MeV electrons and 2 MeV protons. The results generated with TOPAS-nBio (black) are compared to data from Charlton et al. [11] (blue).

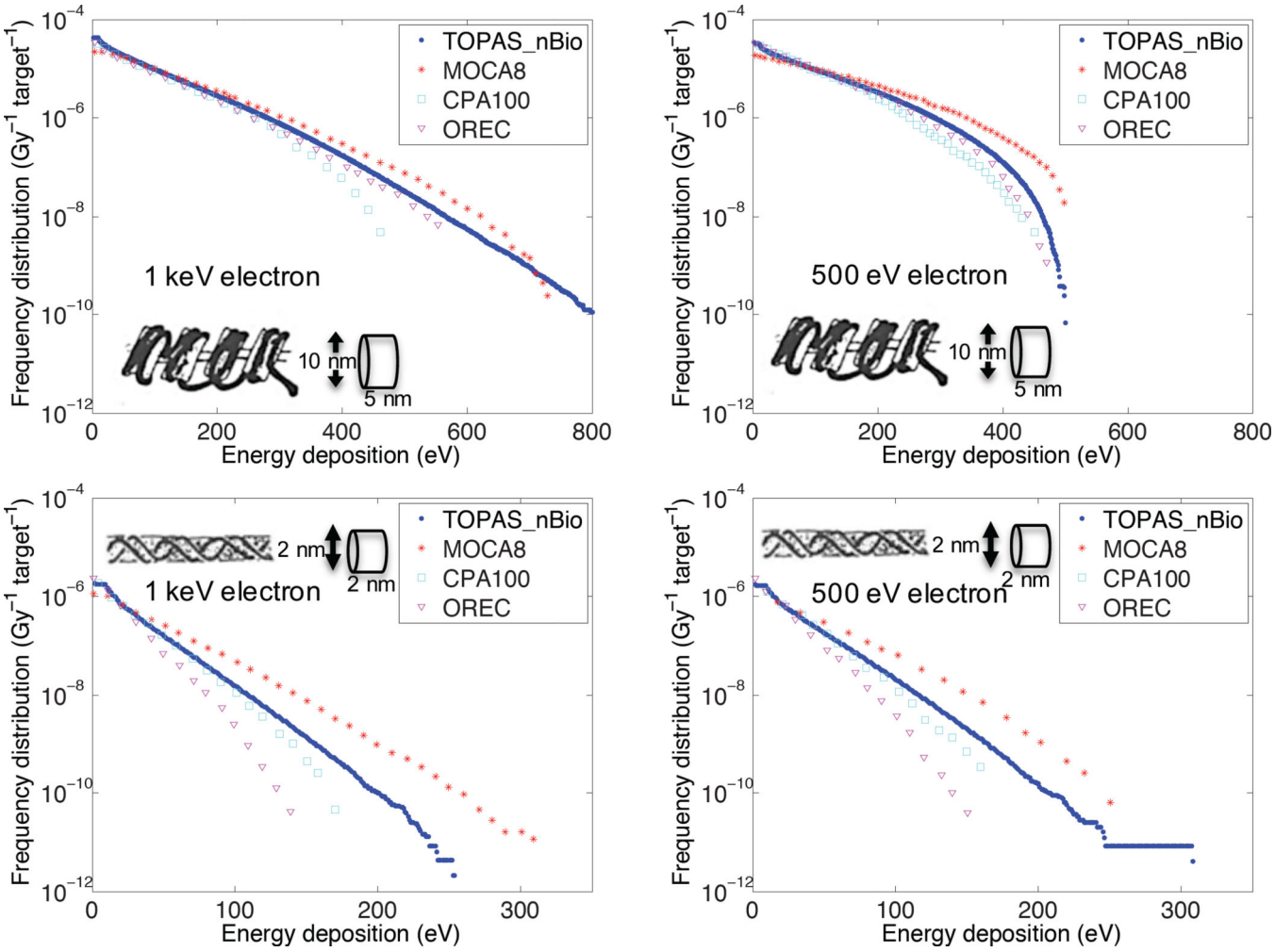

Figure 8.

Frequency of energy deposition in approximately nucleosome-sized (top panel) and DNA-sized (bottom panel) cylinders consisting of liquid water, irradiated with 500 eV and 1 keV electrons. The ordinate gives the absolute frequency of energy deposition E (eV) in a single cylinder randomly positioned, and randomly oriented, in water irradiated with 1 Gy of the given radiation. TOPAS-nBio results are shown in blue while data for the other Monte Carlo track structure codes were extracted from Nikjoo et al. (1994) [29]

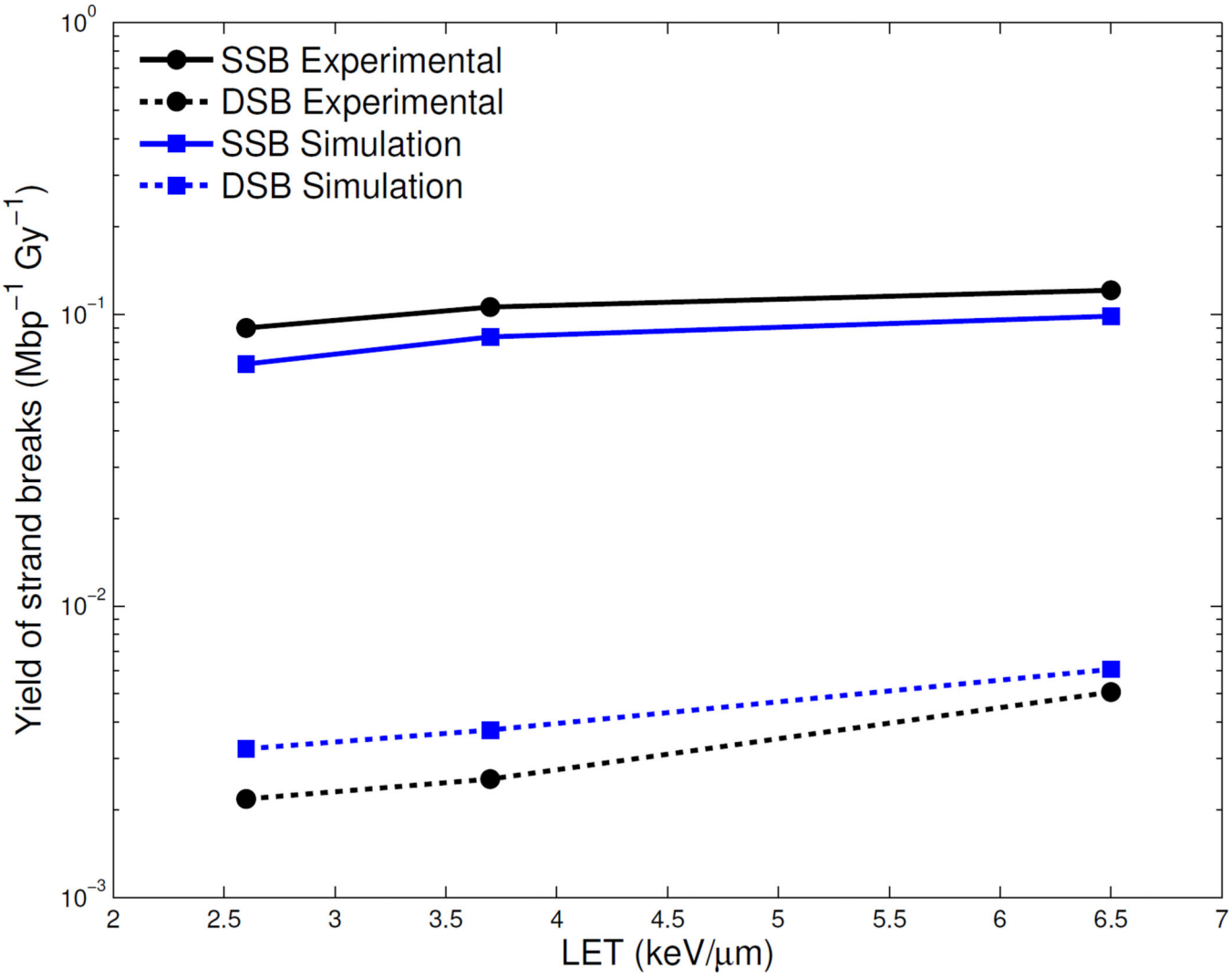

Figure 9.

Frequency of SSBs and DSBs (per Gy per MBp) in a circular DNA plasmid, irradiated by protons, as predicted by simulation (blue) and compared to the experimental data (black) extracted from Vyšín et al. [12].