Investigation of the direct DNA damages irradiated by protons of different energies using geant4-DNA toolkit

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ABSTRACT

Background: The total yields of direct Single-Strand Breaks (SSBs) and Double-Strand Breaks (DSBs) in proton energies varying from 0.1 to 40 MeV were calculated. While other studies in this field have not used protons with energy less than 0.5 MeV, our results show interesting and complicated behavior of these protons. Materials and Methods: The simulation has been done using the Geant4-DNA toolkit. An atomic model of DNA geometry was simulated. Simulations were performed with a source in the Z-axis direction at the cell nucleus entrance with protons at energies of 0.1−1 MeV in 0.1 MeV steps, 5 MeV, and 10−40 MeV in 10 MeV steps. Results: The calculated SSB yields decreased from 60.08 (GbpGy)^−1 for 0.1 MeV proton energy to 49.52 (GbpGy)^−1 for 0.5 MeV proton energy, and then it increased to 54.35 (GbpGy)^−1 in 40 MeV. The DSB yields decreased from 4.32 (GbpGy)^−1 for 0.1 MeV proton energy to 1.03 (GbpGy)^−1 for 40-MeV protons. The DSB yields for energies less than 0.5 MeV was about 56%, and for the other energy levels, it was 44%. As for SSB yields, 35% of the breaks arose from protons with an energy of fewer than 0.5 MeV and 65% from higher energies. Conclusion: It was found that the proton ranges with an energy less than 0.5 MeV are smaller than the cell size (10 μm), and 100% of the energy is deposited in the cell region. Then protons with these energies are the best choice to increase the number of DSBs.

Keywords: Monte Carlo simulation, proton, SSB yield, DSB yield.

INTRODUCTION

Realizing radiation effects produced by charged particles through biological target is of great interest in treatment by radiation. Radiation therapy requires investigation of radiation cellular level effects and dose deposition originated from them on the nanoscale. The effects on human DNA by ionizing radiations are classified as direct and indirect damages. Direct damage is related to the direct action of particles (primary or secondary) on biological targets through ionization or excitation. Regarding strand breaks, DNA damages due to direct effects have been calculated and reported in different studies. In the exertion of indirect effects, the radiation interacts with water that fills most of the cell volume. This results in free radicals, which are highly reactive atoms or molecules, each with an unpaired electron. Free radicals can attack critical targets that consist of DNA and they also

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break their strands (6). Most DNA damages due to the direct or indirect effects involve Single-Strand Breaks (SSBs) and Double-Strand Break (DSB). If two SSBs on opposite strands occur within ten base pairs, a DSB occurs (7-10). DSBs are considered as the most critical type of damage. They induce damages to chromosomes and lead to cell death. The DSB damage is more severe and may wrongly repair, which can result in cell death. The DNA molecule is a sensitive target to investigate biological effects regarding ionizing radiation in biological cells (11,12). The development of a geometrical model is the first step that should be considered for modeling DNA damages. In the Monte Carlo simulation of DNA damages, some different configurations of DNA structures have been used. The models are of three different types, including linear cylinder, volumetric, and atomic models. The linear model is the simplest model that uses geometric cylindrical shapes to construct a DNA structure. In the volumetric model, the bases, sugar-phosphate groups, and the other parts of the DNA molecule are simulated using different shapes. A few of the researchers who reported their results based on this model include Humm and Charlton (13) and Nikjoo et al. (14). DNA strands are considered in detail in the atomic model, and atoms are simulated with spheres that are based on the Van der Waals radius of atoms. The concept of LET (Linear Energy Transfer) was introduced by the ICRU to compare the energy deposition events for different types of radiation (15). LET (keV/μm) is defined as the average energy transferred from radiation to a medium (for example tissues) per unit length of the path traveled by the radiation (15,16). The radiation biological effects strongly depend on the LET, and that higher-LET radiation has a more significant effect on the cancer cell. One of the commonly used methods to study these effects in detail is based on Monte Carlo simulations performed by the track structure codes. Monte Carlo (MC) techniques are powerful tools for predicting the distribution of direct and indirect damages in cells due to ionizing radiation. Researchers use different simulation methods to study the radiation biological effects. There are different MC codes available to be used in simulations in the DNA size. They include the Geant4-DNA extension of the Geant4 toolkit (17-20), PENEOPE (21,22), PARTRAC (23,24), ETRACK (25), CPA100 (26,27), EPOTRAN (28), EGSnc (29), and some others. The incident proton energy interval is 60-250 MeV, when these protons pass through different tissues, their energy lowers, and when they arrive in the cell nucleus, they will be so low energy. In the tissue and cell region, there are different range of energies, especially low energies. These low energy particles are important for destroying cancer cells. In this study, the Geant4-DNA toolkit was used to simulate protons with different delivered energies from 0.1 MeV to 40 MeV for calculating direct DNA damages. An atomic geometrical model was also defined based on Van der Waals radii. Then the number of SSBs, DSBs and the deposited doses were determined. The investigation proceeds with the calculation of the proton range in the cell region, LET values, SSB and DSB yields, and the Total Strand Break (TSB). The TSB is simply the sum of SSB and DSB yields (i.e., TSB = SSB + DSB). The purpose of this study is to calculate breaks caused by different proton energies. As various studies have not investigated the breaks caused by protons below the 0.5 MeV, part of our study focused on this region of energy. In the end of the article, the effect of threshold energy values on SSB and DSB yields were shown.

MATERIALS AND METHODS

This section is organized into two parts. The first part explains the Geant4 Monte Carlo toolkit, and the second part introduces the simulated model of the cell nucleus and the methods of calculating DNA breaks.

The Geant4 Monte Carlo toolkit

The simulation in this study has been done using the Geant4-DNA toolkit for particle transport through the water. The GEANT4-DNA project is a new set of electromagnetic processes that serve to track low-energy electrons, protons, alpha particles, and several ions. The
The range of particles in different energy levels and the deposited energy are calculated using the SRIM code and the Geant4 toolkit, respectively. Different types of damages, including base damage and strand breaks, were induced by radiation. The knowledge of the accurate position of strand breaks is necessary to realize the complexity of the damage. In this respect, two different groups of strand breaks, including SSB and DSB, were evaluated. At first, the SSBs, DSBs, and the deposited doses per event were determined. At the beginning of processing any events, it contains primary particles. These primaries are pushed into a stack. When the stack becomes empty, the processing of an event is over. G4Event class represents an event. Then DNA damage yields were calculated by equation 2:

$$D_{SSB} (SSB) \text{ yield} = \frac{\text{Number of SSBs (SSBs)}}{\text{Dose (Gy)} \times \text{total number of base pairs (bp)}}$$

The break yields were expressed in units of (Gy Gbp)$^{-1}$. When energy deposition exceeds the threshold energy, an SSB occurs within the cell. The energy threshold in Geant4-DNA is the same as the first excitation value of water; it is 8.23 eV in this study. Other energy threshold values, such as 10.79 eV, 12.61 eV, and 17.5 eV have been reported in other studies.\(^{(21, 34-37)}\) The threshold energy was changed in this study to see its influence on the strand break yields. Simulations were performed with a source in the Z-axis direction (perpendicular to the cell) at the cell nucleus entrance with mono-energetic protons hitting at energies of 0.1-1 MeV in 0.1 MeV steps, 5 MeV, and 10-40 MeV in 10 MeV steps. The number of primary particles used in this simulation for proton source included $10^6$ particles. We should emphasize that all outputs were presented in per source particle.

**RESULTS**

**SSB and DSB values for protons at different energy levels**

The number of DNA strand breaks (SSBs and DSBs) and the deposited dose per event, including their error bars (the error bars are so
As figure 1 shows, the number of SSBs and DSBs is increased as the energy increases from 0.1 MeV to 0.5 MeV. Beyond 0.5 MeV, a decrease in the number of breaks is observed. The trend of the deposited dose per event is similar to that of the SSBs and DSBs. It starts from about 0.02 Gy at 0.1 MeV to the maximum value of 0.08 Gy at 0.5 MeV. After 0.5 MeV, the dose decreases to 0.002 Gy at 40 MeV.

To find the trend of the figures, we calculated the range of protons inside the cell nucleus for different energy levels by the SRIM code. Also, the energy deposit due to protons with different energies was calculated by the Geant4 toolkit. Table 1 shows the range of protons, energy deposition, and strand break yields as a function of proton energy. The SRIM code calculated the range of protons inside the cells, energy deposition, and the yields of both SSB and DSB as a function of proton energy. The SRIM code calculated the range of protons at different energy levels inside the cell nucleus.

As table 1 shows, for protons with the energy of less than 0.5 MeV, the range is less than the cell size (10 μm). Thus, the total energy of the particles is deposited in the cell region. For energies more than 0.5 MeV, the range is bigger than the cell size, and the energy deposition reduces. It is interesting that, for protons with the energy of less than 0.5 MeV, the total proton energy is deposited inside the cells, whereas for 40-MeV protons, the energy deposition is about 0.001 of the whole energy. The range of 40-MeV protons is 1462 times bigger than the cell size, and most of the energy is deposited outside the cell region. For protons with the energy of less than 0.5 MeV, no calculation has been reported yet. Cell size has an important role in such a calculation. The LET values are calculated based on the results of table 1 by using equation 1. Figure 2 shows these calculations as well.

| Energy (MeV) | Range (μm) | Energy deposition (keV) | SSB (GbpGy$^{-1}$) | DSB (GbpGy$^{-1}$) | DSB/SSB |
|--------------|------------|------------------------|--------------------|-------------------|---------|
| 0.1          | 1.43       | 100.00                 | 60.08              | 4.32              | 0.072   |
| 0.2          | 2.79       | 199.94                 | 58.74              | 4.22              | 0.072   |
| 0.3          | 4.54       | 299.72                 | 58.69              | 3.96              | 0.068   |
| 0.4          | 6.68       | 399.38                 | 58.67              | 3.66              | 0.064   |
| 0.5          | 9.2        | 498.78                 | 56.02              | 3.32              | 0.059   |
| 0.6          | 12.07      | 485.72                 | 49.52              | 2.38              | 0.048   |
| 0.7          | 15.26      | 413.24                 | 50.99              | 2.15              | 0.042   |
| 0.8          | 18.27      | 368.70                 | 51.99              | 1.98              | 0.039   |
| 0.9          | 22.52      | 332.85                 | 52.11              | 1.88              | 0.036   |
| 1            | 26.55      | 300.40                 | 52.53              | 1.79              | 0.034   |
| 2            | 354.39     | 81.84                  | 54.38              | 1.16              | 0.021   |
| 5            | 1200       | 45.99                  | 54.37              | 1.03              | 0.019   |
| 10           | 4170       | 24.81                  | 54.35              | 1.03              | 0.019   |
| 20           | 8690       | 17.09                  | 54.35              | 1.03              | 0.019   |
| 30           | 14620      | 45.98                  | 54.35              | 1.03              | 0.019   |

The LET values for the protons with the energy interval of 0.1 MeV- 40 MeV were found to be about 72.96- 0.0031 keV/μm. Figure 3 depicts the DSB yields and the DSB-to-TSB ratio as a function of the primary proton energy.
The effect of threshold energy on DNA damages

Table 2 shows the calculated break yields induced by mono-energetic 0.1 MeV protons with different threshold energies often used in theoretical studies.

Table 2. Total calculated SSB and DSB yields corresponding to different threshold energies.

| Threshold energy (eV) | DSB (Gy Gbp)$^{-1}$ | SSB (Gy Gbp)$^{-1}$ | DSB/SSB | SSB/SSB | DSB/TSB |
|-----------------------|---------------------|---------------------|---------|---------|---------|
| 8.23                  | 3.43±0.21           | 60.10±0.13          | 1       | 1       | 0.07    |
| 10.79                 | 1.26±0.11           | 29.12±0.09          | 0.292   | 0.484   | 0.04    |
| 12.61                 | 0.73±0.09           | 21.02±0.01          | 0.169   | 0.349   | 0.03    |
| 17.5                  | 0.004±0.001         | 0.91±0.002          | 0.001   | 0.015   | 0.01    |

**DISCUSSION**

In this study, an atomic model of DNA was simulated, and the number of simple and complex damages, as well as SSB and DSB yields were calculated. The number of SSBs and DSBs and the amount of the dose increased in the energy interval of 0.1 MeV-0.5 MeV. Beyond 0.5 MeV, however, the trend reversed, and those values decreased. The ratio of the LET values of 0.1 MeV to 0.5 MeV was about 1.35, and that for 40 MeV was about 23163. These LET values were calculated based on the energy deposition and the range of protons in the cell nucleus.

Different studies have used different methods to calculate LET values. Some studies have calculated LET values at the center of the cell (38-40) or in the cell entrance (41). Figure 2 shows that an increase in energy leads to a decrease in the LET. In general, as also found in other studies like (42, 43), Figure 3 suggests that DSB yields decrease once energy increases. The variation of DSB yields with proton energy is more than 100% (from 1.03 to 4.32 (Gy Gbp)$^{-1}$). The experimental results obtained by Belli et al. showed the values 4.74 (Gy Gbp)$^{-1}$ for 11 keV/μm and 5.77 (Gy Gbp)$^{-1}$ for 31 keV/μm (44). Our results for these two LETs are about 50% lower than Belli results. This difference comes from the including of indirect breaks in their calculations that we did exclude them in our calculations. It is important to emphasize that the researchers only calculated direct damages, and their results did not address indirect ones. The ratio of breaks from direct and indirect effects, as reported in some studies, is about 35/65 for the cobalt source (45). The ratio of DSB yields from the proton energy of 0.1 MeV to 0.5 MeV is about 1.3, whereas it is about 4.19 for 0.1 MeV and 40 MeV protons. For higher energy levels, DSBs go to a constant value because most of their energy is deposited outside the cell region. DSB yields at 0.1 MeV are about 4.2 times bigger than those at 40 MeV. Low energies, especially those less than 0.5 MeV, account for the majority of damages. The ratio of DSB to TSB varies from 0.065 (at 0.1 MeV) to 0.02 (at 40 MeV). As found in other studies such as (36), figure 4 suggests that for energies higher than 0.5 MeV, the SSB yields increase when the energy is increased. For proton energies less than 0.5 MeV, the trend is interesting, which is ignored by other studies. SSB yields at 0.5 MeV lose about 18% of their value at 0.1 MeV, but the trend changes beyond this energy; they increase for about 9% in comparison with their value at 0.5 MeV. Direct SSB and DSB yields seem to be constant beyond 5 MeV. Based on figure 4, most of the breaks are of the SSB type, and they vary from about 0.93 (at 0.1 MeV) to 0.98 (at 40 MeV) of the total strand breaks. The SSB-to-TSB ratio increases with an increase in energy. The last results were related to the different threshold energy to see
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the effect of this value on break yields. The total yields of SSB and DSB are decreased when the threshold energy is increased. The decreasing rate of DSB is faster than that of SSB; the ratio of DSB at the threshold energy of 10.79 eV to that at the threshold energy of 8.23 eV is about %29. For SSB, this ratio is about %48. The ratios of DSBs at 10.79 eV, 12.61 eV, and 17.5 eV to 8.23 eV were 0.29, 0.17, and 0.001 respectively. For SSB yields, the corresponding ratios were 0.48, 0.35, and 0.015. It shows that different studies should consider this value, and its effect on the break yields is so much.

CONCLUSION

In this study, Geant4-DNA simulations were done to evaluate the direct damages caused by primary protons in the energy interval of 0.1–40 MeV. The trend of DSB yields decreased from 4.32 to 1.03 (GbpGy)−1 in the energy interval of 0.1 MeV to 40 MeV. The situation was different for the SSB yields. At energy levels lower than 0.5 MeV, the SSB yields decreased from 60.08 (GbpGy)−1 to 49.52 (GbpGy)−1 and Beyond that the yields was increased. Therefore, as the LET increased, for energy less than 0.5 MeV, the proton ranges were bigger than the cell size. The absolute yields of the SSBs tended to decrease, whereas that of the DSBs increased. Generally speaking, the cell size has an important role in calculations.

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