Quantitative estimation of track segment yields of water radiolysis species under heavy ions around Bragg peak energies using Geant4-DNA

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We evaluate the track segment yield G′ of typical water radiolysis products (e−aq, ·OH and H2O2) under heavy ions (He, C and Fe ions) using a Monte Carlo simulation code in the Geant4-DNA. Furthermore, we reproduce experimental results of ·OH of He and C ions around the Bragg peak energies (< 6 MeV/u). In the relatively high energy region (e.g., > 10 MeV/u), the simulation results using Geant4-DNA have agreed with experimental results. However, the G-values of water radiolysis species have not been properly evaluated around the Bragg peak energies, at which high ionizing density can be expected. Around the Bragg peak energy, dense continuous secondary products are generated, so that it is necessary to simulate the radical–radical reaction more accurately. To do so, we added the role of secondary products formed by irradiation. Consequently, our simulation results are in good agreement with experimental results and previous simulations not only in the high-energy region but also around the Bragg peak. Several future issues are also discussed regarding the roles of fragmentation and multi-ionization to realize more realistic simulations.

Cancer patients can nowadays select several modalities in radiotherapy such as conventional X-ray therapy and particle therapies (e.g., proton therapy, heavy ion therapy and boron neutron capture therapy). The number of patients receiving particle therapy for cancer (mainly proton or C-ion beams) is increasing annually1. There are two major advantages to particle therapy. The first is having a higher quality of life (QOL) compared to other modalities, such as surgical operation and/or chemotherapy. The second is high effectiveness for deep-seated hypoxic tumors. For particle therapies, high ionization density can be expected at the tumor site due to the Bragg peak2, around which a large amount of energies of incoming ions is deposited. The accuracy of dose calculation around the Bragg peak is thus very important for treatment planning. Monte Carlo simulations have recently been adopted as a treatment planning software application for dose calculations. Judgment for patient-specific quality assurance is performed based on the calculation result using a Monte Carlo simulation. For example, PTsim (Particle Therapy Simulation Framework) is a Geant4 based Monte Carlo simulation toolkit for particle therapy, that some institutes use clinically in Japan3. Furthermore, the radiation therapy program based on Geant4, named GATE, is often used in European countries4. Using Monte Carlo simulations, we can accurately calculate dose distributions even in complex geometries, for instance, the human body, only when truly precise physics processes are installed in the computer code. While primary energy transfer induced by ionizing radiation in media occurring in the extremely fast stage (typically 10−18 s)5 can be accurately calculated using a Monte Carlo simulation toolkit, it is tough to simulate the following secondary reactions in the “physicochemical phase”

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simulate G-values of compared to other water radiolysis products but is destroyed by eaq disassembled in solution is being quantitatively clarified. As is well known, the effectiveness of indirect action formed or destroyed by unit energy (conventionally 100 eV), of damaged should therefore be assessed to elucidate the contribution of indirect action.

Many researchers have experimentally evaluated radiation chemical yields (G-values), the number of entities formed or destroyed by unit energy (conventionally 100 eV), of OH, hydrated electrons (eaq) and hydrogen peroxide (H2O2), all of them are typical water radiolysis products under ionizing radiation, using radical scavengers (e.g., coumarin-3-carboxylic acid (C3CA) and phenol). Furthermore, the correlation between generated yields of OH, which efficiently react with DNA molecules, and those of radiolysis product of an amino acid disassembled in solution is being quantitatively clarified. As is well known, the effectiveness of indirect action increases with the increasing of the energy of incoming ions, while the linear energy transfer (LET) decreases. Around the Bragg peak of C ions, the contribution of indirect action is up to 50% for cell killing under humidified air with 5% CO2 at 37 °C. Chemical reactions by water radiolysis products should therefore be taken into account to properly understand the biological effectiveness of cancer treatment with radiation.

In parallel with experiments, the LET dependence of G-values of typical water radiolysis products in the high energy region (> 100 MeV/u) was evaluated using Geant4-DNA. The simulation results were in agreement with experimental results. However, G-values around Bragg peak energies have not been successfully simulated. At the Bragg peak energy region of C ions, the contribution of indirect action for biological effects is still large (~50%). We are now trying to establish a platform that can estimate the therapeutic effects and evaluate biological effects by simulations with reference to the amount of OH obtained experimentally. In this work, we simulate G-values of OH, eaq and H2O2 under heavy ions (He, C and Fe ions) up to 10^6 s using Geant4-DNA. The obtained simulation results are compared to the experimental results around Bragg peak energies and previously obtained ones in the high energy region.

Materials and methods

Experiments. Previously, yields of water radiolysis products (OH, eaq and H2O2) under ion irradiation were evaluated. In this section, we reproduce the derivation process of the yields reported in the previous study.

G-values of OH have been measured using radical scavengers [e.g., phenol and coumarin-3-carboxylic acid (C3CA)] in solution in C3CA (purity 0.98%; Fujifilm/Wako Pure Chemical Industries Ltd., Osaka, Japan) with phosphate buffer was prepared in ultrapure water (Milli-Q Advantage; Merck & Co., Kenilworth, NJ) at 66 mM, pH = 6.8. From these measurements, the number of OH formed per ion track (N) can be computed.

\[
N = \frac{G(OH) \cdot E_0}{100} = \frac{1}{100} \int_0^{E_0} G'(OH) \, dE,
\]

where \(E_0\) is the initial energy of incoming ions. When the experiments are done at several energies, \(N\) can be plotted as a function of the energy of the ions, and a resulting fitting curve can be derived. Then, we can determine the track segment yield \(G'\), that is the yield for an infinitesimal energy loss, defined for one specific energy of ion:

\[
G'(OH) = 100 \times \frac{dN}{dE}.
\]

The so-called "scavenging capacity" of a scavenging reaction is expressed by the product of the rate constant of the reaction and the concentration of the radical scavenger. Its inverse represents the average scavenging time scale. So, adjusting the concentration of probe, the time dependence of the G-value of OH can be reconstructed. The detailed procedures for experiments to evaluate G-values of OH are described elsewhere.

The aqueous solution containing 1 mM sodium nitrate (NaNO3) and 5 mM di-sodium hydrogen phosphate (Na2HPO3) are used for the measurement of eaq. eaq is scavenged by nitrate anion to produce NO3−, which immediately reacts with one of the surrounding water molecules, resulting in the production of nitrogen dioxide (NO2). NO2 then reacts with hydrogen phosphate anion (HPO4^2−) to produce an anion (NO3−), which can easily be determined by applying Saltzman technique with molar extinction coefficient of 42,300 M−1 cm−1 at 540 nm. Furthermore, Ghormley technique has been adopted to evaluate the yield of H2O2. H2O2 is very stable compared to other water radiolysis products but is destroyed by eaq due to intra-track reactions. To minimize the decomposition by intra-track reactions, 2.5 mM NaNO3 aqueous solution was used for measurements. The detailed procedures for experiments are described elsewhere.

In this work, we re-plotted these experimental results. All experiments were done under neutral pH conditions at 25 °C.

Simulations. A Monte Carlo simulation with Geant4-DNA was performed to calculate G-values of water radiolysis products. We used the G4EmDNAPhysics_option8 physics constructor with additional sub-excitation processes of vibrational excitation and molecular attachment for electrons installed in Geant4-DNA ver. 10.05.p01. The G4EmDNAPhysics_option8 physics constructor covers the energy range from 0.5 MeV/u to
10^6 MeV/u for heavy ions (He, C and Fe ions). Furthermore, G4EmDNAChemistry was used for the simulation in the chemical stage. The simulation geometry is a 10 × 10 × 10 mm³ air-free water cube. This is the size determined in consideration of the measurement system. When primary particles have deposited 10 keV of their energies into the water, the charged particle tracking simulation of the physical process was ceased and shifted to the chemical process. We aborted the event when total energy deposition of each event exceeded 10.1 keV in order to simulate large enough numbers of tracks in reasonable calculation times. That means that total energy deposition of each event was always between 10 and 10.1 keV. In Geant4-DNA, we can follow a particle-based approach for the simulation of water radiolysis, where molecular species are modeled as point-like objects diffusing in a continuous liquid water medium. In this work, we follow the radical annihilation process from 1 ps to 1 μs.

When energies of incoming ions were high enough (e.g., 100 MeV, 25 MeV/u and 400 MeV/u for protons, He and C ions, respectively), they could easily go through a water cube of 10 mm thickness. If not, incoming ions are completely stopped in the water cube. In such cases, energies of incoming ions were rapidly lost, meaning that high ionizing density can be expected around the Bragg peak. This implied that water radiolysis products could be abundantly generated along ion tracks. So, considering the issue of calculation time, it is not easy to follow the chemical process around the Bragg peak energy using a CPU-based simulator. In this study, the issue was overcome by a split simulation. The details of the split simulation are discussed in the following section.

Substantial yields of secondary products generated by water radiolysis have been previously evaluated. In this study, we defined additional molecular species shown in Table 1, which are not implemented in Geant4-DNA ver. 10.05.p01, considering the number of atoms, the number of occupied electrons, the electron occupancy (depending on the molecular composition of each molecule), the Van der Waals radius, mass, charge and diffusion coefficient produced in air-free water due to irradiation. The diffusion coefficients related to the newly defined products are listed in the right column of Table 1.

Electronic state of water molecule

| Dissociation channels | Probability |
|-----------------------|-------------|
| All single ionization states | H₂O⁺ + OH | 1 |
| Excitation state: A¹B¹ | OH + H | 0.65 |
| | H₂O + ΔE | 0.35 |
| Excitation state: B¹A¹ | H₂O⁺ + OH + eaq⁻ | 0.55 |
| | OH + OH + H | 0.15 |
| | H₂O + ΔE | 0.3 |
| Excitation state | H₂O⁺ + OH + eaq⁻ | 0.5 |
| Rydberg, diffusion bands | H₂O + ΔE | 0.5 |
| Dissociate attachment | OH + OH⁻ + H₂ | 1 |

Table 1. Diffusion coefficients of the newly defined products from Frongillo et al.

Table 2. Dissociation schemes and branching ratios. This table is recalled from Shin et al.

Dissociation schemes and branching ratios. This table is recalled from Shin et al.15.

Results and discussion

Time dependence of G-value of water radiolysis products. Figure 1 illustrates the schematic view of diffusion of reactive species produced by water radiolysis from 1 ps to 1 μs after the irradiation of 400 MeV/u C ions. Water radiolysis products along the C ion path are denser than those along secondary electron trajectories. The high density of reactive species can be seen around the C ion trajectory. Reactive species then diffuse to distant locations from the ion path. Figure 2a–c show the time dependence of G-values of O₂⁻, eaq⁻ and H₂O₂ after irradiation of 1 MeV electrons. The number of launched ions/electrons was 1000 and the statistical error was around 5%. Our simulation results of reaction of water radiolysis products with newly defined molecules...
Without the reactions represented in Fig. 3. Figure 5 shows the number of reactions related to discrepancy between simulation results (blue) and experimental results becomes significantly smaller than that experimental data. When the role of reactions of added secondary products (Table 1) are taken into account, the Fig. 4 have been calculated with the new reactions added. The time was chosen close to the scavenging ones of 0 to any energies as indicated in Fig. 4a,b. Finally, G-values are calculated from Eq. (2). All results shown in Table 3.

Table 3. Reaction and reaction rate constants. These values are based on the data of Hatano et al. The reaction rate constants for first-order reactions of species O\(^{-}\), HO\(_2\)\(^{-}\) are based on the data reported by Plate.

| Reaction | Reaction rate (dm\(^3\) mol\(^{-1}\) s\(^{-1}\)) | Reaction | Reaction rate (dm\(^3\) mol\(^{-1}\) s\(^{-1}\)) |
|----------|----------------------------------|----------|----------------------------------|
| H + H \rightarrow H\(_2\) | 5.03 x 10\(^{-6}\) | H\(_2\)O\(_2\) + e\(_{aq}\) \rightarrow OH\(^{-}\) + OH | 1.1 x 10\(^{-6}\) |
| H + OH \rightarrow No product | 1.55 x 10\(^{-10}\) | H\(_2\)O\(_2\) + OH \rightarrow HO\(_2\) | 1.27 x 10\(^{-9}\) |
| H + e\(_{aq}\) \rightarrow H\(_2\) + OH | 3.5 x 10\(^{-7}\) | H\(_2\)O\(_2\) + O\(^{-}\) \rightarrow HO\(_2\) + OH | 5.55 x 10\(^{-7}\) |
| H + e\(_{aq}\) \rightarrow H\(_2\) + OH | 2.5 x 10\(^{-10}\) | e\(_{aq}\) + e\(_{aq}\) \rightarrow OH\(^{-}\) + OH + H\(_2\) | 5.0 x 10\(^{-9}\) |
| H + OH \rightarrow e\(_{aq}\) | 2.51 x 10\(^{-7}\) | e\(_{aq}\) + HO\(_2\) \rightarrow H + HO\(_2\) | 2.11 x 10\(^{-9}\) |
| H + O\(_2\) \rightarrow HO\(_2\) | 2.1 x 10\(^{-10}\) | e\(_{aq}\) + O\(_2\) \rightarrow H\(_2\)O\(_2\) + 2OH | 1.3 x 10\(^{-9}\) |
| H + HO\(_2\) \rightarrow H\(_2\)O\(_2\) | 1.0 x 10\(^{-10}\) | e\(_{aq}\) + HO\(_2\) \rightarrow O\(^{-}\) + OH | 3.5 x 10\(^{-9}\) |
| H + O\(_2\) \rightarrow HO\(_2\) | 1.0 x 10\(^{-10}\) | e\(_{aq}\) + O\(_2\) \rightarrow O\(_2\) | 1.74 x 10\(^{-10}\) |
| OH + OH \rightarrow H\(_2\)O\(_2\) | 5.3 x 10\(^{-10}\) | e\(_{aq}\) + HO\(_2\) \rightarrow HO\(_2\) | 1.28 x 10\(^{-9}\) |
| OH + H\(_2\)O\(_2\) \rightarrow HO\(_2\) + H\(_2\)O\(_2\) | 2.87 x 10\(^{-10}\) | H\(_2\)O\(_2\) + O\(_2\) \rightarrow H\(_2\)O\(_2\) | 4.78 x 10\(^{-9}\) |
| OH + H\(_2\) \rightarrow H + H\(_2\)O\(_2\) | 3.28 x 10\(^{-10}\) | H\(_2\)O\(_2\) + OH \rightarrow No product | 1.13 x 10\(^{-10}\) |
| OH + e\(_{aq}\) \rightarrow OH\(^{-}\) | 2.95 x 10\(^{-10}\) | H\(_2\)O\(_2\) + HO\(_2\) \rightarrow H\(_2\)O\(_2\) | 5.0 x 10\(^{-10}\) |
| OH + OH \rightarrow O\(^{-}\) + O\(_2\) | 6.3 x 10\(^{-10}\) | HO\(_2\) + O\(_2\) \rightarrow O\(_2\) + HO\(_2\) | 9.7 x 10\(^{-10}\) |
| OH + HO\(_2\) \rightarrow O\(_2\) | 7.9 x 10\(^{-10}\) | HO\(_2\) + HO\(_2\) \rightarrow O\(_2\) + HO\(_2\) | 8.3 x 10\(^{-10}\) |
| OH + O\(_2\) \rightarrow O\(_2\) + OH | 1.07 x 10\(^{-10}\) | O\(_2\) + H\(_2\)O\(_2\) \rightarrow OH + O\(_2\) | 1.36 x 10\(^{-10}\) (s\(^{-1}\)) |
| OH + HO\(_2\) \rightarrow OH\(^{-}\) + HO\(_2\) | 8.32 x 10\(^{-10}\) | HO\(_2\) + H\(_2\)O\(_2\) \rightarrow HO\(_2\) + OH | 1.36 x 10\(^{-10}\) (s\(^{-1}\)) |
| OH + O\(_2\) \rightarrow HO\(_2\) | 1.0 x 10\(^{-10}\) | H\(_2\)O\(_2\) + OH \rightarrow OH\(^{-}\) + HO\(_2\) | 1.74 x 10\(^{-10}\) |

(e.g., O\(^{-}\), O\(_2\), O\(_2\)\(^{-}\), HO\(_2\), HO\(_2\)) are shown with a solid blue line and those without the reactions are shown with a solid red line (G4EmDNAChemistry). The previously obtained reference data are also plotted. The simulation results are in good agreement with experimental values. The G-values of OH calculated using G4EmDNAChemistry are slightly higher than our simulation result, and closer to experimental data in several cases. This implies that the added reactions act significantly. However, there are variations in experimental results, so that it is difficult to argue if the present simulation with reactions of water radiolysis product with newly defined molecules is appropriate. In comparison with OH, no difference is observed between the two simulations for the G-values of e\(_{aq}\). Furthermore, the G-value of H\(_2\)O\(_2\) with the new reactions added is higher than that without the reactions. Indeed, H\(_2\)O\(_2\) is not directly produced by water radiolysis, meaning that H\(_2\)O\(_2\) is made by radical–radical reaction (e.g., OH + OH \rightarrow H\(_2\)O\(_2\)). Since the G-value of H\(_2\)O\(_2\) with the new reactions is higher than without them, the role played by secondary products seem to be important. Similar results are observed with 400 MeV/u C ions as shown in Fig. 2d–f, with no dramatic changes in G-values.

When incoming ions (or electrons) have high enough energy, no drastic changes in G-value is visible (Fig. 2). But, to properly simulate the experimental results around Bragg peak energies, at which incoming ions are completely stopped in the experimental set-up, we should consider the role played by secondary products added. Around the Bragg peak, many water radiolysis products would be generated along the ion trajectory due to high ionization density. Because of the high ionization density, it is necessary that radical–radical reactions are properly taken into account. Figure 3 shows the G-values of OH for 0.75 MeV/u He ions and 0.83 MeV/u C ions without the reaction of secondary products added (red: G4EmDNAChemistry). The experimental results are also plotted in black symbols. The G-values of OH without the reaction of added secondary products are about twice higher than experimental results. Around the Bragg peak energy (< 6.0 MeV/u), high ionization density is expected compared to the high-energy region and incoming ions would completely stop in the irradiation cell. It is thus very tough to follow the reactions induced by incoming ions by a conventional CPU simulation. To more accurately simulate the G-value around the Bragg peak energy, we performed a split calculation. The number of OH produced was computed for each energy step with an increment of 0.25 MeV/u, and then, integrated from 0 to any energies as indicated in Fig. 4a,b. Finally, G-values are calculated from Eq. (2). All results shown in Fig. 4 have been calculated with the new reactions added. The time was chosen close to the scavenging ones of experimental data. When the role of reactions of added secondary products (Table 1) are taken into account, the discrepancy between simulation results (blue) and experimental results becomes significantly smaller than that without the reactions represented in Fig. 3. Figure 5 shows the number of reactions related to OH as a function of LET of C ions, ranging from 10 eV/nm to 700 eV/nm. The number of reactions is cumulative one up to 1 μs after the irradiation. Among newly added reactions, ‘OH + OH\(^{-}\) \rightarrow O\(^{-}\) + H\(_2\)O\(_2\) and O\(^{-}\) + H\(_2\)O\(_2\) \rightarrow OH + OH\(^{-}\)’ contribute significantly to the reaction with OH. This means that we have to consider roles of newly added reactions to accurately simulate the G-values of water radiolysis products because these reactions contribute the annihilation process of OH.

**LET dependence of reactive species yield.** Figure 6a–c show the LET dependence of G-values of OH, e\(_{aq}\) and H\(_2\)O\(_2\) at 100 ns after irradiation, simulated in this work and compared to experimental data. Overall, G-values of examined reactive species are in good agreement with experimental results (plotted points) in a wide LET range including the Bragg peak energies. In the cases of OH and e\(_{aq}\), the G-value decreases monotonically with increasing LET as shown in Fig. 6a,b. In comparison to this, the G-value of H\(_2\)O\(_2\) increases monotonically.
Figure 1. Chemical evolution of 400 MeV/u carbon ion track in water in the time 1 ps to 1 μs.
with increasing LET, with higher values for lighter ions at the same LET as shown in Fig. 6c. These results remind us that LET is not a universal parameter for describing the G-value. For scaling G-values, $Z_{\text{eff}}/\beta$ (or $(Z_{\text{eff}}/\beta)^2$), where $Z_{\text{eff}}$ is the effective charge of incoming ions and $\beta$ is the velocity of incoming ions normalized by the speed of light in vacuum, has been applied. Indeed, the description of the dependence of G-value is improved compared to that with LET, but $Z_{\text{eff}}/\beta$ has not been recognized as a universal parameter. To universally express

Figure 2. Time dependence of G-values of (a) OH, (b) $e_{\text{aq}}^-$ and (c) $\text{H}_2\text{O}_2$ for 1 MeV electrons, and (d) OH, (e) $e_{\text{aq}}^-$ and (f) $\text{H}_2\text{O}_2$ for 400 MeV/u carbon ions. The solid lines represent the results of Monte Carlo simulations. Sets of reference data36–43 were used for comparison with simulated time dependence of G-values.

Figure 3. Time-dependent OH yields for (a) 0.75 MeV/u helium ions and (b) 0.83 MeV/u carbon ions. Experimental data presented by Ludwig N.17 were used for comparison with simulated time dependence of G-values.
G-values of water radiolysis products in a wide LET range, the electron interaction concept, which the number of interaction induced by secondary electrons governs the radiation induced yields could work well\textsuperscript{7,44,45}. Furthermore, G-values of ·OH for Fe ions by the present simulation are significantly lower than the experimental results. In the experiments, a water equivalent moderator was used for adjusting the incident energy of Fe ions. Under this process, lighter ions, whose LET is smaller than that of Fe ions, could be produced by fragmentation. Considering the influence of lighter ions produced by fragmentation, higher G-values are expected, so it is reasonable that the present simulation result is lower than those of experiments. In the present version of Geant4-DNA, the influence of fragmentation of the ions is not considered. The implementation of the influence of the lighter ions produced by fragmentation would be one of the future issues to properly simulate the contribution of indirect action in the human body\textsuperscript{46}. Moreover, discrepancies between simulations and experiments are confirmed in G-values of H\textsubscript{2}O\textsubscript{2}. The reason of this discrepancy is the implementation of multi-ionization. In agreement with a previous study\textsuperscript{47}, the influence of multi-ionization of air-free water molecules act effectively. Meesunguonen and Jay-Gerin suggested that the multi-ionizations, although less frequent compared to single ionization, especially contributes to the primary HO\textsubscript{2}/O\textsubscript{2}\textsuperscript{−} yield in the high LET region. In Meesunguonen

**Figure 4.** Number of ·OH produced per initial energy as a function of the initial energies of He (a) and C ions (b) 7, 16, 63, 251 and 1000 ns after irradiation.

**Figure 5.** LET dependent number of reactions involving the ·OH at 1 μs after irradiation of a water target with C ions with a LET range of 10 eV/nm to 700 eV/nm. The number of reactions is the cumulative number of reactions up to 1 μs after irradiation.
J. and Jay-Gerin’s code named IONLYS-IRT, cross sections of elastic, phonon and vibrational electron scattering obtained from electron-impact on amorphous ice films have been employed. To take into account the effects of multi-ionization under high-LET heavy-ion irradiation the model has been extended to incorporate double, triple, and quadruple ionization process in single ion-water collisions. In the present simulation using Geant4-DNA, we consider the elastic scattering, ionization, electronic excitation and charge exchange processes for electron, proton and alpha particles. Furthermore, in the cases of heavy ions, only the ionization process is considered. In the absence of multi-ionization, the G-value of \( \text{H}_2\text{O}_2 \) increases monotonically with increasing LET as shown in Fig. 6c. When multi-ionizations are considered, we anticipate that the G-value of \( \text{H}_2\text{O}_2 \) would increase with increasing LET up to 100 eV/nm and then drop. Generally speaking, \( \text{H}_2\text{O}_2 \) is formed by the recombination of two \( \cdot\text{OH} \) (\( \cdot\text{OH} + \cdot\text{OH} \rightarrow \text{H}_2\text{O}_2 \)). As LET increases, radical–radical reactions occur more efficiently. Above 100 eV/nm, it is known that \( \text{O}(^3\text{P}) \) is produced by multi-ionizations process. Since \( \cdot\text{OH} \) reacts not only

**Figure 6.** LET dependent G-values of (a) \( \cdot\text{OH} \), (b) \( \text{e}_{\text{aq}}^- \) and (c) \( \text{H}_2\text{O}_2 \) at 100 ns after irradiation of a water target with different radiation types. Sets of experimental data presented by Maeyama et al.\(^\text{10}\), Yamashita et al.\(^\text{7}\) and Ludwig\(^\text{17}\) were used for comparison with simulated LET dependence of G-values.
with other \( \cdot OH \) but also with \( O(3^P) \) \(( \cdot OH + O(3^P) \rightarrow HO_2)\), \( \cdot OH \)s are consumed by other radical–radical reaction, causing a reduction of yields of \( H_2O_2 \) yield at high LET. However, we do not consider the contribution of the multi-ionization process in our simulation. Therefore, the roles of \( O(3^P) \) are not added. \( H_2O_2 \) is formed not only by the recombination of two \( \cdot OH \)s, but also by the reaction between \( H\cdot \) and \( HO_2\cdot \) \((H\cdot + HO_2\cdot \rightarrow H_2O_2)\), and the reaction between \( H_3O^+ \) and \( HO_2^- \) \((H_3O^+ + HO_2^- \rightarrow H_2O_2)\). The previous simulation performed by Meesunguonen and Jay-Gerin more properly reproduced experimental G-values of \( H_2O_2 \) above 100 eV/nm. The current version of Geant4-DNA does not handle the multi-ionizations process. We are planning to add it into Geant4-DNA in the future. In comparison to \( eaq^- \), the influence of multi-ionizations to the G-value of \( \cdot OH \) is not significant. One of the main processes consuming the \( \cdot OH \) is its interaction with \( eaq^- \). This reaction is a competing process with the interaction of \( eaq^- \) with the \( O^2^- \). However, for the high LET region, \( \cdot OH \) react more efficiently with \( eaq^- \)48. In brief, \( \cdot OH \) are diminished by reactions with \( eaq^- \) in the track core. This explains why the present simulation results of \( \cdot OH \) are in good agreement with experimental results as represented in Fig. 6a. In accordance with previous studies, \( \cdot OH \) and \( eaq^- \) are not affected by the multi-ionization47,49. Furthermore, \( \cdot OH \) react with \( eaq^- \) in the high LET region, dense track on the particle path47,49. Thus, although multi-ionization processes are not considered in the simulation, the present results regarding \( \cdot OH \) and \( eaq^- \) are in good agreement with experimental results. Figure 7 shows a comparison of the simulated G-values of \( \cdot OH \) at 1 \( \mu s \) after irradiation to a previous simulation47 and experimental measurements50. The present simulations (open symbols) are in good agreement with the previous simulations (solid lines) and experimental results (solid symbols). Once again, the present simulations successfully reproduced the experimental results in a wide LET range thanks to the consideration of newly added reactions.

**Conclusions**

In the present study, we simulated the track segment yields (G’) of water radiolysis products (\( \cdot OH \), \( eaq^- \) and \( H_2O_2 \)) under heavy ion irradiation using a Monte Carlo simulation code in the Geant4-DNA in a wide LET range up to 700 eV/nm. To accurately simulate the G’ around the Bragg peak, we addressed two issues. The first issue is roles played by secondary products generated by water radiolysis. The second issue is the long computation time due to the abundantly generated water radiolysis products around the Bragg peak. To save the computation time, we did the split simulation. Consequently, G’ of \( \cdot OH \) and \( eaq^- \) were in good agreement with experimental results in the examined LET range. However, discrepancies of G’ of \( \cdot OH \) between simulation and experiment were seen in Fe ions. This discrepancy suggested that the contribution of lighter particles produced by fragmentation should be considered for a more accurate simulation. At the same LET, G’ of \( \cdot OH \) and \( eaq^- \) of heavier ions were lower than that of lighter ion, especially noticeable from 40 to 100 eV/nm. This finding is consistent with the fact that LET...
is not universal parameter to express the yields of water radiolysis products especially when it come to complex track structure with high energy secondary electron. At this stage $Z_{eff}/\beta$ could be a better parameter. It will be crucial to discuss a parameter that universally describe the $G$ of water radiolysis products. In comparison to $G_{\text{OH}}$ and $G_{\text{H$_2$O$_2$}}$, $G_{\text{aq}}$ of $\text{H$_2$O}_{2}$ did not agree with experimental results above 100 eV/nm even after the consideration of roles of secondary products generated by water radiolysis. This is because the contribution of multi-ionization is not taken into account in the present stage. To have a more realistic simulation, the multi-ionization should be added in the Geant4-DNA in the near future.

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K.B., T.K., and M.I. wrote the main manuscript text. R.O. and S.O. gave advice on the simulation part, and S.O. is a supervisor of the Geant4-DNA project. Q.R., R.B., N.L., C.G., and P.P. provided experimental results and gave advice regarding Figs. 3 and 5. S.K. gave advice on the experiment part. All authors reviewed the manuscript.

Competing interests
The authors declare no competing interests.

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