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A simulation-based study on water radiolysis species for $^1$H$^+$, $^4$He$^{2+}$, and $^{12}$C$^{6+}$ ion beams with multiple ionization using Geant4-DNA

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ABSTRACT
Monte Carlo track structure simulation is a powerful method for estimating damage induced by water radiolysis products for cell killing. To investigate the influence of multiple ionization for the formation of water radiolysis products under $^1$H$^+$, $^4$He$^{2+}$, and $^{12}$C$^{6+}$ ion beams, a Monte Carlo simulation based on Geant4-DNA was carried out. The G-value of H$_2$O$_2$ increased monotonically with increasing linear energy transfer up to 200 eV/nm. Above 200 eV/nm, the G-value of H$_2$O$_2$ began dropping, but only when the influence of multiple ionization was considered. This trend is in good agreement with the experimental results. Furthermore, we successfully reproduce the experimental results of G-values of HO$_2^+$, O$_2^-$, and O$_2$. The role of the multiple ionization in the production of H$_2$O$_2$, HO$_2^+$, O$_2^-$, and O$_2$ is also discussed.

INTRODUCTION
Radiation therapy by external beam irradiation is an established treatment option for solid cancer tumors. Heavy-ion therapy is especially effective for deep-seated tumors and hypoxic tumors, compared to proton and conventional x-ray therapies, resulting in high relative biological effectiveness (RBE). Oxygen enhancement ratio (OER) is also an important factor for estimating the effectiveness of radiation therapy. RBE and OER strongly depend on linear energy transfer (LET). Higher values of RBE correspond with high effectiveness, whereas lower values of OER (≥1) indicate less influence of oxygen concentration. In the case of the $^{12}$C$^{6+}$ ion beam, the value of RBE is maximum at a LET of 140 keV/μm (=eV/nm), then drops. The value of OER of the $^{12}$C$^{6+}$ ion beam is about 3 in the low-LET region. The value of OER decreases monotonically with increasing LET and reaches about 1 above 200 eV/nm. In practical terms, the effectiveness of $^{12}$C$^{6+}$ ion beam therapy for hypoxic tumors is higher than that of x-ray because of its high LET. However, the influence of oxygen concentration of tumors on cell killing ability by heavy ions is not negligible. It has also been suggested that changes in oxygen concentration in tumors are important to elucidate the mechanism of oxygen-in-the-track, in which the interaction between water radiolysis products generates oxygen molecules. Water radiolysis products are generated in a certain region, generally known as a “spur,” which might be spherical. Spurs become continuous with increasing LET, consequently forming a cylindrical shape in high-LET regions. Because the value of OER decreases with increasing LET,
above 200 eV/nm, in which a continuous spur can be expected, oxygen molecules are supplied due to reactions between water radiolysis products. It has been noted that the influence of oxygen depletion of hypoxic tumors could be minimized. Namely, we should investigate the role played by reactions between water radiolysis products to explain why the value of OER reduces with increasing LET.

Many researchers have made efforts to clarify the mechanism of reactions between water radiolysis products through experiments and computer simulations. One of the results suggested that multiple ionization plays an important role in generating \( \text{O}_2^− \) and \( \text{HO}_2 \). Additionally, multiple ionization has to be considered to accurately estimate yields of \( \text{H}_2\text{O}_2 \). Indeed, we previously validated the experimental results of the yields of \( \cdot \text{OH} \) and \( \text{e}_\text{aq}^− \) in a wide LET region, including the Bragg peak energy of \( \cdot \text{He}^+ \) and \( \text{C}^{6+} \) ions, using a Monte Carlo simulation based on Geant4-DNA. However, the yield of \( \text{H}_2\text{O}_2 \) had discrepancies between simulation and experimental results. We hypothesized that the discrepancies could be due to the lack of multiple ionization processes. In this study, we aim to understand the contribution of multiple ionization under \( \cdot \text{He}^+ \), \( \text{He}^{2+} \), and \( \text{C}^{6+} \) ion beams, whose roles are not taken into account in the latest version of Geant4-DNA. However, the yield of \( \text{H}_2\text{O}_2 \) had discrepancies limited. We used the ratio \( \sigma = \sigma_\text{di}/\sigma_\text{si} \) from the data sets proposed by Mesungnoen and Jay-Gerin. Details are mentioned in their previous studies. It is an adjustable parameter to reproduce the measured G-value of \( \text{HO}_2 \) strongly affected by multiple ionization. The cross section values of double ionization \( \sigma_\text{di} \) and triple ionization \( \sigma_\text{tri} \) were about one order of magnitude lower than \( \sigma_\text{si} \). We therefore ignored the influence of quadruple ionization as it adds only a minor contribution to the G-value of \( \text{H}_2\text{O}_2 \) and \( \text{O}_2^− \). In the range of LET considered in this work, \( \sigma_\text{si} \) was set as \( \sigma_\text{di} = \sigma_\text{tri} \). Tables I and II show the decomposition reaction schemes and parameters in the physicochemical process.

At the physicochemical stage, water molecules are excited or ionized, resulting in the production of other molecular species such as radicals, ions, and molecules. For the chemical stage, the \textit{G4EmDNAChemistry} constructor with additional reactions was used. The list of reactions and reaction rate constants is shown in Table III. The reactions in Table III are taken from Ref. 13 and modified with the addition of reactions (R1), (R2), and (R3). The reaction rate constants were referred from previous studies. \( \text{HO}_2 \) and \( \text{O}_2^− \) are mainly produced from multiple ionization of water through oxygen atoms formed in their \( ^3\text{P} \) ground state. The ground-state O(\(^1\text{S}\)) atoms will react with themselves or with other species.

### MATERIALS AND METHODS

Geant4-4.10-16 is a simulation toolkit written in C++ language for simulations of passages of particles through matter with the Monte Carlo method. Geant4 has an extension package named Geant4-DNA-17-20 for track structures of charged particles and radiolysis reactions at subcellular scales. We used Geant4-DNA delivered by Geant4 version 10.07.p01 to obtain G-values of water radiolysis products through chemistry simulations with the step-by-step approach. The definition of G-value is the number of species formed or destroyed per unit energy (traditionally 100 eV) absorbed by media. In this work, we follow the radiolysis process from 1 ps to 1 \( \mu \)s under neutral pH conditions at 25 °C.

For the physics stage, we used the \textit{G4EmDNAPhysicsOption}8 physics list implemented in Geant4-DNA. Similar trends can be seen with other physics options, but \textit{G4EmDNAPhysicsOption}8 reproduced experimental results the best. Elastic scattering, ionization, and electronic excitation processes for electrons, protons, neutral hydrogen atoms, and helium atoms with three charged states \( \cdot \text{He}^+ \), \( \text{He}^{2+} \), and \( \text{He}^{3+} \) were taken into account. Sub-excitation processes of vibrational excitation and molecular attachment for electrons and charge exchange process for protons, neutral hydrogen atoms, and charged helium atoms were considered. For heavy ions \( \text{Li}^{6+} \), \( \text{Be}^{9+} \), \( \text{B}^{10+} \), \( \text{C}^{6+} \), \( \text{N}^{14+} \), \( \text{O}^{18+} \), \( \text{Si}^{28+} \), and \( \text{Fe}^{56+} \), we considered an ionization process with effective charge scaling. We obtained the distribution of energy loss of charged particles in water medium through the physics stage of Geant4-DNA simulations. 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 the present study, an air-free water volume of 10 × 10 × 10 mm\(^3\) was set as the target.

Geant4-DNA ver. 10.07.p01 does not provide a multiple ionization process under proton \( \cdot \text{H}^+ \) and heavy ions \( \cdot \text{He}^+ \) and \( \text{C}^{6+} \). It is also not implemented in Geant4 ver. 10.07.p01. We challenged to implement multiple ionization as additional physics, physicochemical, and chemical processes of Geant4-DNA, including calculations of cross sections for double and triple ionization of water. It is based on the \textit{G4DNRuddIonisationExtendedModel} class. The cross section values of double ionization \( \sigma_\text{di} \) were deduced from Rudd’s single ionization cross sections \( \sigma_\text{si} \) for water vapor. Unfortunately, the available information on the cross sections for the double and triple ionization of water is still quite limited. We used the ratio \( \sigma = \sigma_\text{di}/\sigma_\text{si} \) from the data sets proposed by Mesungnoen and Jay-Gerin. Details are mentioned in their previous studies. It is an adjustable parameter to reproduce the measured G-value of \( \text{HO}_2^+ \) strongly affected by multiple ionization. The cross section values of double ionization \( \sigma_\text{di} \) and triple ionization \( \sigma_\text{tri} \) were about one order of magnitude lower than \( \sigma_\text{si} \). We therefore ignored the influence of quadruple ionization as it adds only a minor contribution to the G-value of \( \text{H}_2\text{O}_2 \), \( \text{HO}_2^− \), and \( \text{O}_2^− \). In the range of LET considered in this work, \( \sigma_\text{si} \) was set as \( \sigma_\text{di} = \sigma_\text{tri} \). Tables I and II show the decomposition reaction schemes and parameters in the physicochemical process.

### RESULTS AND DISCUSSION

#### Table I. The branching ratio of dissociation channels used for simulation of the physicochemical stage in liquid water.

<table>
<thead>
<tr>
<th>Reaction STATE</th>
<th>Reaction</th>
<th>Branching Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single ionization state: ( \text{H}_2\text{O}^+ )</td>
<td>( \text{H}_2\text{O}^+ + \cdot \text{OH} )</td>
<td>100%</td>
</tr>
<tr>
<td>Excitation state: ( \text{A1B1} )</td>
<td>( \cdot \text{OH} + \text{H}^+ )</td>
<td>65%</td>
</tr>
<tr>
<td>Excitation state: ( \text{B1A1} )</td>
<td>( \text{H}<em>2\text{O} + \cdot \text{OH} + \text{e}</em>\text{aq}^− )</td>
<td>55%</td>
</tr>
<tr>
<td>Excitation state: ( \text{Ry} )</td>
<td>( \text{H}<em>2\text{O}^+ + \cdot \text{OH} + \text{e}</em>\text{aq}^− )</td>
<td>50%</td>
</tr>
<tr>
<td>Dissociate attachment</td>
<td>( \cdot \text{OH} + \cdot \text{OH} + \text{H}_2 )</td>
<td>15%</td>
</tr>
<tr>
<td>Dissociate attachment</td>
<td>( \cdot \text{OH} + \cdot \text{OH} + \text{H}_2 )</td>
<td>30%</td>
</tr>
<tr>
<td>Dissociate attachment</td>
<td>( \cdot \text{OH} + \cdot \text{OH} + \text{H}_2 )</td>
<td>50%</td>
</tr>
<tr>
<td>Dissociate attachment</td>
<td>( \cdot \text{OH} + \cdot \text{OH} + \text{H}_2 )</td>
<td>100%</td>
</tr>
</tbody>
</table>

#### Table II. Reaction rate constants in liquid water.

<table>
<thead>
<tr>
<th>Reaction RATE</th>
<th>Reaction</th>
<th>Rate Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction ( \text{R1} )</td>
<td>( \text{H}_2\text{O}_2 + \cdot \text{OH} )</td>
<td>100%</td>
</tr>
<tr>
<td>Reaction ( \text{R2} )</td>
<td>( \cdot \text{OH} + \cdot \text{OH} + \text{e}_\text{aq}^− )</td>
<td>55%</td>
</tr>
<tr>
<td>Reaction ( \text{R3} )</td>
<td>( \text{H}_2\text{O} + \text{H}_2\text{O}_2 )</td>
<td>30%</td>
</tr>
<tr>
<td>Reaction ( \text{R4} )</td>
<td>( \cdot \text{OH} + \cdot \text{OH} + \text{H}_2 )</td>
<td>50%</td>
</tr>
<tr>
<td>Reaction ( \text{R5} )</td>
<td>( \cdot \text{OH} + \cdot \text{OH} + \text{H}_2 )</td>
<td>100%</td>
</tr>
</tbody>
</table>

#### Table III. Reaction rate constants in liquid water.

<table>
<thead>
<tr>
<th>Reaction RATE</th>
<th>Reaction</th>
<th>Rate Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction ( \text{R1} )</td>
<td>( \text{H}_2\text{O}_2 + \cdot \text{OH} )</td>
<td>100%</td>
</tr>
<tr>
<td>Reaction ( \text{R2} )</td>
<td>( \cdot \text{OH} + \cdot \text{OH} + \text{e}_\text{aq}^− )</td>
<td>55%</td>
</tr>
<tr>
<td>Reaction ( \text{R3} )</td>
<td>( \text{H}_2\text{O} + \text{H}_2\text{O}_2 )</td>
<td>30%</td>
</tr>
<tr>
<td>Reaction ( \text{R4} )</td>
<td>( \cdot \text{OH} + \cdot \text{OH} + \text{H}_2 )</td>
<td>50%</td>
</tr>
<tr>
<td>Reaction ( \text{R5} )</td>
<td>( \cdot \text{OH} + \cdot \text{OH} + \text{H}_2 )</td>
<td>100%</td>
</tr>
</tbody>
</table>
Triple ionization state: $\text{H}_2\text{O}^{3+}$
- $\text{H}^+ + \text{H}^+ + \text{O}^+$ → $2\text{H}_2\text{O}^+ + \text{O}^+(\text{P})$
- $29\%$
- $d_{\text{O}^+ - \text{H}^+} = 1.20$
- $2\text{H}_2\text{O}^+ + \text{O}^+(\text{P})$
- $16\%$
- $d_{\text{H}^+ - \text{O}^+} = 1.20$
- $2\text{H}_2\text{O}^+ + \text{O}^+(\text{P})$
- $100\%$
- $d_{\text{O}^+ - \text{H}^+} = 1.20$

*OH in the track core of the impacting ions because of the very high local concentration of radicals. The following reactions (R1), (R2), and (R3) have been added to consider the above estimation. These reaction rate constants are based on the data of Hatano et al.\(^{22}\)

R1: $\bullet \text{OH} + \text{O}^+(\text{P}) \rightarrow \text{HO}_2^+$
- $2.02 \times 10^{10}$ (dm$^3$ mol$^{-1}$ s$^{-1}$)

R2: $\text{O}^+(\text{P}) + \text{O}^+(\text{P}) \rightarrow \text{O}_2$
- $2.2 \times 10^{10}$ (dm$^3$ mol$^{-1}$ s$^{-1}$)

R3: $\text{HO}_2^+ + \text{O}^+(\text{P}) \rightarrow \text{O}_2 + \bullet \text{OH}$
- $2.02 \times 10^{10}$ (dm$^3$ mol$^{-1}$ s$^{-1}$)

**RESULTS AND DISCUSSION**

The ratio of double-to-single ionization cross sections $\alpha = \sigma_{\text{dd}}/\sigma_{\text{si}}$ is referred to as Meesungnoen’s value (Fig. 1). The value of $\sigma_{\text{dd}}/\sigma_{\text{si}}$ decreases monotonically with increasing $E_{\text{ion}}/Z$, where $E_{\text{ion}}$ is the ion energy per nucleon and $Z$ is the projectile charge state. This means that the influence of double ionization increases monotonically with increasing LET. Using these values of $\sigma_{\text{dd}}/\sigma_{\text{si}}$ in our simulation of the radiolysis of pure neutral water with $^1\text{H}^+$, $^4\text{He}^2+$, and $^{12}\text{C}^{6+}$ ion beams, we then calculated the G-values of $\text{H}_2\text{O}_2$ and $\text{HO}_2^+ + \text{O}^-$ as a function of LET.

Figure 2 shows the LET dependence of the G-values of $\text{H}_2\text{O}_2$ at 1 μs after irradiation. The simulated G-values and experimental results are shown in colored and black symbols, respectively. Solid and dotted lines represent the trends obtained by Genat-DNA simulation with and without the multiple ionization processes, respectively. In the case of experiments around Bragg peak energies, incoming ions completely stop in the irradiation cell. Thus, energies of incoming ions (i.e., LET) vary drastically. Around the Bragg peak region, the number of water radiolysis species $N$ is estimated by the integration over the ion trajectory. Generally, $N$ increases monotonically with the energy of incident ions $E_{\text{ion}}$. The G-value can be evaluated from the differential value at certain energies. Significant differences of G-values of $\text{H}_2\text{O}_2$ for the $^1\text{H}^+$ ion beam are not observed, whether or not multiple ionization is taken into account. The simulated G-value for the $^4\text{He}^2+$ ion beam is in better agreement with experimental data obtained by Wasselin-Trupin et al.\(^{36}\) than Pastina and LaVerne,\(^{37}\) Burns and Sims,\(^{38}\) and Anderson and Hart.\(^{39}\) A similar trend is seen in the G-value of $\text{H}_2\text{O}_2$ for $^{12}\text{C}^{6+}$ ion beams. The increasing behavior of G-value is slowing down above 50 eV/nm, when we consider the role of the multiple ionization. The simulated G-values for the table.
The ratio of double-to-single ionization cross sections $\sigma_{di}/\sigma_{si}$ for $^4$He$^{2+}$ (dotted red line), $^{12}$C$^{6+}$ (dashed green line), and $^{12}$C$^{6+}$ (dashed-dotted blue line) ion beams reported by Meesungnoen and Jay-Gerin is also shown for the sake of comparison (solid black line).

The G-value of $^1$H$^2$O$_2$ rises monotonically up to 200 eV/nm and then decreases. Above 200 eV/nm, the simulated G-values for the $^{12}$C$^{6+}$ ion beam are significantly smaller than the experimental results reported by Pastina and LaVerne.

To reproduce experimental results using the simulation around Bragg peak energies, we adopt the differential values of the number of water radiolysis species $N$ over the ion trajectory at the energy of incident ions $E_0$ to the G-values and plotted them as a function of the track average LET, which is defined as

$$\text{LET} = E_0 \int_0^E (dE/dx) \, dE.$$  

The G-value of $^1$H$_2$O$_2$ for full stop condition of the $^{12}$C$^{6+}$ ion beam is also represented in Fig. 2 (dashed-dotted magenta line). Experimental data presented by Anderson and Hart, Burns and Sims, Pastina and LaVerne, LaVerne et al., and Wasselin-Trupin et al. are used for comparison with simulated LET dependence of G-values.
processes reported by Meesungnoen and Jay-Gerin\textsuperscript{11} and Gervais et al.,\textsuperscript{12} respectively. The G-values of $\text{HO}_2^- + \text{O}_2^-$ for $^1\text{H}^+$ ion beams evaluated in the present study are between the previous simulations. Also, the present G-values of $\text{HO}_2^- + \text{O}_2^-$ for $^4\text{He}^{2+}$ and $^{12}\text{C}^{6+}$ ion beams are higher than the previous results at the same LETs. At the same LET, the G-value of $\text{HO}_2^- + \text{O}_2^-$ for lighter ions is higher than those of heavier ones. This is because the velocity of lighter ions is slower than that of heavier ones, thereby higher local energy deposition at the close location from the ion path can be expected by lighter ions.\textsuperscript{40,41} Our simulation results for $^{12}\text{C}^{6+}$ ion beams are higher than the experimental results under $^{36}\text{S}^{16+}$ and $^{40}\text{Ar}^{18+}$ ion beams. This finding would support the reliability of our simulation. The simulated G-values increase monotonically with increasing LET, rising more rapidly
above 200 eV/nm, where the G-value of H₂O₂ begins dropping. In fact, ⋅OH reacts not only with O(3P) but also with HO₂ (⋅OH + HO₂ → O₂). Therefore, above 200 eV/nm, the consumption of ⋅OH by the reaction with O(3P) (R1) and HO₂ (R5) is competitive processes with the generation of H₂O₂ by the reaction between ⋅OHs (R4). As a result, the G-value of H₂O₂ reduces above 200 eV/nm. This result is reasonable because the biological effectiveness increases due to the radiation-induced oxygen produced along the ion trajectory in the high-LET region.

Figure 4 shows the LET dependence of several chemical reactions with and without the multiple ionization processes at 1 μs after irradiation. H₂O₂ is formed along the ion path by reaction (R4) (see the reaction list below). At LET above 200 eV/nm, the ground-state O(3P) atoms are inert to water molecules. However, O(3P) atoms efficiently react with ⋅OH (R1) in the track core of heavy ions, at which relatively high concentrations of water radiolysis products can be expected. O₂ is generated by the reaction of HO₂ with ⋅OH (R5),

\[ \text{HO}_2^+ + \cdot \text{OH} \rightarrow \text{O}_2 + \text{H}_2\text{O} \quad 7.9 \times 10^8 \text{ (dm}^3\text{ mol}^{-1}\text{ s}^{-1}), \]  
\[ \cdot \text{OH} + e_{aq} \rightarrow \text{OH}^- \quad 2.95 \times 10^{10} \text{ (dm}^3\text{ mol}^{-1}\text{ s}^{-1}), \]  
\[ \cdot \text{OH} + e_{aq} \rightarrow \text{OH}^- + \cdot \text{OH} \quad 1.1 \times 10^9 \text{ (dm}^3\text{ mol}^{-1}\text{ s}^{-1}), \]  
\[ \text{H}_2\text{O}_2 + e_{aq} \rightarrow \text{OH}^- + \cdot \text{OH} \quad 1.74 \times 10^9 \text{ (dm}^3\text{ mol}^{-1}\text{ s}^{-1}). \]
By competing with reaction (R4), reactions (R1) and (R5) cause a decrease in the number of H₂O₂ generated and an increase in the number of HO₂ + O⁻ formed in the high-LET region. It was also confirmed that the reactions of e⁻ with •OH (R6) and H₂O₂ (R7) contribute to the reduction of H₂O₂. The contribution of reaction (R6) decreases with increasing LET because other radical–radical reactions (e.g., •OH + •OH → H₂O₂ and H⁺ + •OH → H₂O) increase. With multiple ionization, the contribution of reaction (R6) is lower than that without multiple ionization. This finding implies that •OH reacts with O(^1P) (•OH + O(^1P) → HO₂). Also, as LET increases, the contribution of reaction (R7) increases, resulting in a decrease in H₂O₂. Among the reactions considered in this study, reaction (R7) has the largest reaction rate constant 1.1 × 10¹⁰ dm³ mol⁻¹ s⁻¹ among the direct reactions with H₂O₂. The contribution of reaction (R7) with multiple ionization is slightly lower than that without multiple ionization. However, the contribution of reaction (R7) is significant because the G-value of H₂O₂ starts decreasing above 200 eV/nm. Atomic oxygen O(^1P) with the ground state is produced by multiple ionization. It is clear that the multiple ionization processes play an important role in the formation of HO₂ and O²⁻ through the generation of atomic oxygen with the ground-state O(^1P). Therefore, the reaction probabilities of reactions (R1) and (R5) increase, resulting in the facilitation of the generation of HO₂ and O²⁻. Furthermore, under the multiple ionization processes, O₂ is consumed by secondary reactions, for instance, by reactions (R8) and (R9).

Figure 5 shows the time dependence of G-values of water radiolysis species for a 12 MeV ¹²C⁶⁺ ion beam with the multiple ionization processes. The G-values of e⁻ with H₂O, and •OH decrease monotonically with time. That of H⁺ also decreases with time. With the reduction of H⁺, the G-value of O₂ increases. This trend would be related to the H⁺ + •OH → HO₂ reaction. The formation of O₂ can be seen by the intra-track reaction in the high-LET region. In ns after irradiation, the G-value of O₂ decreases with time due to the reaction with H⁺ (H⁺ + O₂ → HO₂) and e⁻ (e⁻ + O₂ → O²⁻). These reactions contribute the formation of HO₂ and O²⁻. H₂O₂ increases with time up to several ns and then slowly drops. The G-value of OH⁻ increases gradually and becomes almost constant above 1 ns. The G-value of O(^1P) is smaller, but it is certainly formed at the early chemical stage. The O(^1P) produced decreases with time. This trend would be related to the formation of O₂. Finally, we confirm the formation of O²⁻ and HO₂ in the chemical stage.

Whereas discrepancies are observed between simulations without multiple ionization and experiments, the G-value of H₂O₂ agrees with experimental results by adding the multiple ionization processes. We have also succeeded in reproducing experimental results of the G-value of HO₂ + O⁻ by implementing the multiple ionization processes. These results support the importance of multiple ionization in the radiolysis of water under high-LET irradiation.

CONCLUSION

The role of multiple ionization in water influencing the G-values of the radiolytic free radical and molecular species, including O₂, was investigated using a Monte Carlo code based on Geant4-DNA. Considering the multiple ionization processes of water molecules, the G-values of H₂O₂ and HO₂ + O⁻ were calculated as a function of LET. The simulated G-value of H₂O₂ increased monotonically with increasing LET up to 200 eV/nm, then dropped. This trend was in agreement with experimental results. Additionally, we succeeded in reproducing the G-value of HO₂ + O⁻. O(^1P) generated by multiple ionization effects, which lead to the reaction with •OH (•OH + O(^1P) → HO₂). A reduction of H₂O₂ yield in the high-LET region above 200 eV/nm can be explained by the consumption of the •OH radicals by other radical–radical reactions due to multiple ionization. Furthermore, under the multiple ionization processes, O₂ is consumed by secondary reactions. The consumption of O₂ and the role of multiple ionization are crucial to explain the FLASH effect.

ACKNOWLEDGMENTS

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

REFERENCES


