Investigating the oxygen depletion effect in FLASH radiotherapy using GPU-based fast Monte Carlo simulations

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INTRODUCTION

- FLASH radiotherapy (RT), which delivers ionizing radiation at an ultrahigh dose rate (> 40Gy/s), is gaining increasing attention. It was found a better normal tissue sparing and a same or better tumor control probability, compared to the conventional RT at the same dose level.
- Oxygen depletion effect is one of the most popular hypothesis to explain FLASH RT effect. However, it remains controversial. It is almost impossible to detect this effect experimentally limited by the current technology, while results from phenomenological modeling is vulnerable with the empirical parameters selected.
- In principle, a step-by-step simulation via the Monte Carlo (MC) technique can be a good way to quantify the oxygen depletion effect in FLASH RT. However, it can be extremely time-consuming to simulate the oxygen chemical reaction with the CPU-based MC packages. Hence, almost no CPU-packages support this simulation functions.
- Recently, we can realize the step-by-step simulation of the oxygen depletion effect within our open source, GPU-accelerated MC package, gMicroMC [1].

AIM

- In this work, we present our progress on applying the step-by-step oxygen depletion simulation via gMicroMC to quantify its impact in FLASH RT.

METHOD

- The details of implementing the step-by-step simulation of oxygen depletion effect in gMicroMC were given in another Blue Ribbon ePoster No. 53114.
- In this study, we used the chemical reaction channels and rates from Plante's paper [2], with the channels also listed in Table 1. Totally, 21 reactions were simulated.

Table 1. Summary of chemical reactions.

Original reactions in gMicroMC	New reactions with oxygen
$e_h + e_h \rightarrow 2OH^- + H_2$	$e_h + O_2 \rightarrow O_2^{\cdot -}$
$e_h + OH^\cdot \rightarrow OH^-$	$e_h + HO_2^\cdot \rightarrow HO_2^-$
$e_h + H^\cdot \rightarrow OH^- + H_2$	$e_h + O_2^{\cdot -} \rightarrow 2OH^- + H_2O_2$
$e_h + H^+ \rightarrow H^\cdot$	$OH^\cdot + HO_2^\cdot \rightarrow O_2$
$e_h + H_2O_2 \rightarrow OH^\cdot + OH^-$	$OH^\cdot + O_2^{\cdot -} \rightarrow O_2 + OH^-$
$OH^\cdot + OH^\cdot \rightarrow H_2O_2$	$OH^\cdot + HO_2^- \rightarrow HO_2^\cdot + OH^-$
$OH^\cdot + H^\cdot \rightarrow H_2O$	$H^\cdot + O_2 \rightarrow HO_2^\cdot$
$H^\cdot + H^\cdot \rightarrow H_2$	$H^\cdot + HO_2^\cdot \rightarrow H_2O_2$
$H^+ + OH^- \rightarrow H_2O$	$H^\cdot + O_2^{\cdot -} \rightarrow HO_2^-$
$H_2 + OH^\cdot \rightarrow H^\cdot$	$H^+ + O_2^{\cdot -} \rightarrow HO_2^\cdot$
	$H^+ + HO_2^- \rightarrow H_2O_2$

- Simulation setup
- Spatial distribution (Figure 1)

We randomly sample electrons with energy E_k in a sphere with radius R, which is equal to the radius of Region of Interest (ROI) r plus the maximum travel distance of the electron. Only radicals produced inside ROI will be considered in the chemical stage simulation. Oxygen is uniformly distributed inside a cube with a dimension of $d = 2(r + 0.3)\ \mu m$. Oxygen regeneration is ignored because of the very short pulse ($1\ \mu s$). Oxygen numbers are determined from the oxygen concentration C_{O_2} as $N_{O_2} = C_{O_2} * 760\ mmHg * 1.26 * \frac{\mu M}{mmHg} * d^3 * N_A$, where N_A is the Avogadro constant. Oxygen concentration levels of 0.01%, 0.1%, 0.5%, 1%, 3%, 9%, and 21% are considered.

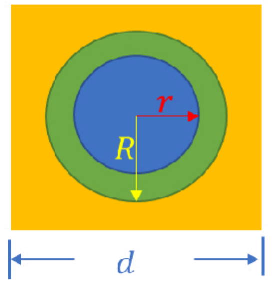

Figure 1. Illustration of the simulation geometry. Blue area (r): ROI. Green area (R): source particles to be sampled in. Orange area (d): oxygen to be sampled in.

- Temporal distribution

Temporally, a beam pulse width of $1\ \mu s$ is used to sample the electrons. The initial electrons are uniformly sampled within the pulse until the instantaneous dose rate D_i in the beam pulse reaches predefined values of $10^6\ Gy/s$, $10^7\ Gy/s$ and $10^8\ Gy/s$.

- Energy and others

Specifically in this work, $E_k = 4.5\ keV$ and $0.3\ keV$ are considered. The $4.5\ keV$ is used to represent radiation cases with primary particles being electrons and photons, while the $0.3\ keV$ is intended to show cases of primary proton and heavy ions, the energies of secondary electrons of which are usually of hundreds of eVs. The cutoff energy for the physical stage is $7.5\ eV$. Default values in gMicroMC for physicochemical stage are used [1]. The duration for chemical stage is $2\ \mu s$ to ensure full reaction between chemical species.

- Evaluation metrics

Time-dependent yields of radicals, oxygen consumption rate (OCR), residual C_{O_2} were used for the quantification for different instantaneous dose rate D_i. $OCR = \Delta G(O_2) * \rho / N_A$ with ρ the density of the medium and $\Delta G = \Delta N(O_2)/E_r$, where E_r is the total deposited energy in the ROI and $\Delta N(O_2)$ is the change of the number of oxygen molecules.

RESULTS

❑ Time-dependent yields of radicals (Figure 2)

- At both oxygen levels, yields of superoxide radicals are similar between that with a dose rate of $10^6\ Gy/s$ and $10^7\ Gy/s$ ((a1) vs. (b1), and (a2) vs. (b2)). It then drops quickly at the dose rate of $10^8\ Gy/s$, compared to the other lower dose rates. It indicates that competition between different chemical reactions can happen when dose rate is too high to cause overlap between different tracks.
- A higher initial oxygen ($C_{O_2} = 3\%$) leads to a higher yield of superoxide radicals compared to the lower concentration ($C_{O_2} = 0.1\%$), indicating more oxygen consumption.

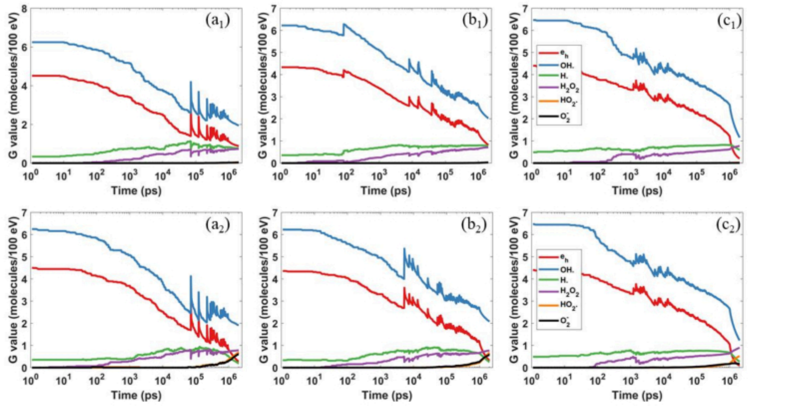

Figure 2. Comparison of the yields of chemical species under different dose rates (a) $10^6\ Gy/s$ (b) $10^7\ Gy/s$ and (c) $10^8\ Gy/s$. Top (bottom) row represents 0.1% (3%) oxygen concentration, which corresponds to initial hypoxic(physioxic) condition. The spike represents the inclusion of new radicals by new incoming primary particles. All figures in the same row share the same legend shown in the right.

❑ Calculated OCR (Figure 3)

- OCR drops with increasing dose rates at the same oxygen concentration level;
- OCR drops with decreasing initial oxygen concentration levels when the dose rate is the same.
- Oxygen can not be fully depleted by radiolysis with varying OCR, while it can be fully depleted if a constant OCR at $C_{O_2} = 21\%$ is assumed.

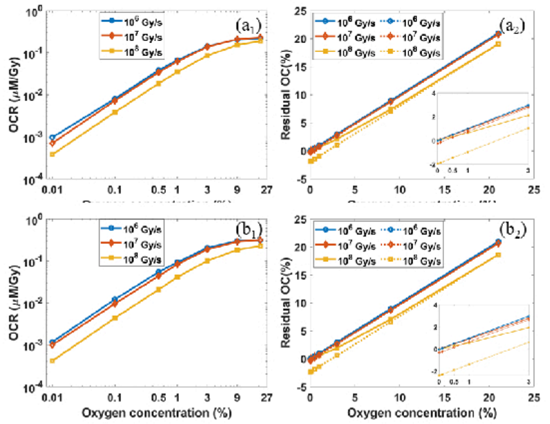

Figure 3. Calculated OCR (left column) and residual oxygen concentration (right column) after one pulse for (a) 4.5 keV (b) 0.3 keV under different initial oxygen concentration.

❑ Residual percentage (Figure 4)

- From left column of Figure 4, a higher dose rate can lead to a higher oxygen consumption since it corresponds a higher initial distributions of chemical radicals;
- From right column of Figure 4, if oxygen regeneration is not considered, a lower dose rate leads to a higher oxygen consumption. This can be explained by the chemical reaction competition effect observed in Figure 2.
- According to the empirical formula for oxygen enhancement ratio (OER), $OER = 1 + 1.63 \times (1 - e^{-0.26 * C_{O_2} * 760})$ [3], we can estimate that OER drops from 1.3 to 1.2 for $C_{O_2} = 0.1\%$ (hypoxia, 0.1% to 0.06%) and from 2.63 to 2.61 $C_{O_2} = 3\%$ (physoxia, 3% to 2.4%) for in Figure 4(b_2) after 30 Gy radiation. The percentage change of OER is only 7.7% and 0.8% for $C_{O_2} = 0.1\%$ and $C_{O_2} = 3\%$, respectively.

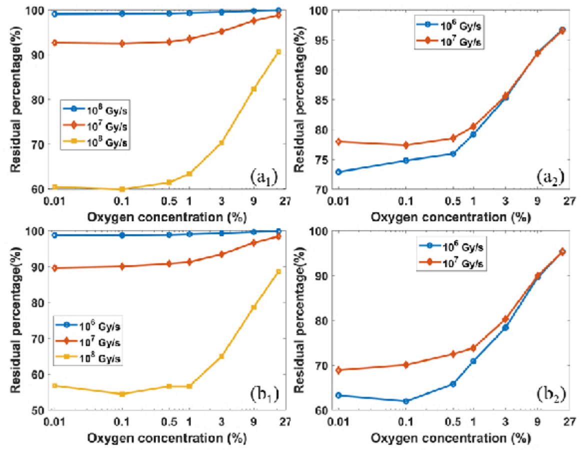

Figure 4. Calculated residual percentage of C_{O_2} under different dose rates for (a) 4.5 keV (b) 0.3 keV. The left and tight column represent the results for a pulse length of 1 μs and an accumulated dose of 30 Gy without considering oxygen regeneration, respectively.

CONCLUSIONS

With the help of GPU in accelerating the chemical stage, we were able to simulate the water radiolysis with the presence of oxygen to study the oxygen depletion effect in FLASH RT. Our simulation showed that the OCR should decrease with increasing dose rate and decreasing initial oxygen concentration, leading to the inability of full oxygen depletion by radiolysis at all tested oxygen concentration level. Without considering oxygen regeneration between pulse, the decreasing percentage of OER brought by the oxygen consumption is only 7.7% and 0.8% for initial hypoxia and physoxia condition after 30 Gy radiation.

We will continue to study the oxygen effect on FLASH RT by considering the oxygen regeneration, DNA repair, etc. so that other factors like the time interval between pulses can be taken into consideration.

ACKNOWLEDGEMENTS

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CONTACT INFORMATION

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