Microscopic Monte Carlo Simulation for Oxygen Effect in Ionizing Radiation Induced DNA Damage Computation

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INTRODUCTION

- Oxygen plays a critical role in determining DNA damage generated by ionizing radiation (IR).
  - Existence of oxygen alters the yields of chemical radicals, which is the source of indirect DNA damage.
  - DNA damage may be fixed by oxygen within milliseconds of its occurrence.
- In principle, this oxygen effect can be quantified via the step-by-step microscopic Monte Carlo (MC) simulations.
  - Oxygen is often ignored or treated as constant continuum background in the chemical stage due to the heavy computation cost brought by simulating enormous oxygen molecules.
- Recently, we released an open-source, graphical processing unit (GPU)-accelerated microscopic MC package for IR induced DNA damage calculation, gMicroMC [1] to solve the efficiency issue.

AIM

- Present our recent progress of gMicroMC on realizing the step-by-step simulation of chemical stage with oxygen.
- Study the oxygen effect on the yields of different chemical species.

METHOD

To simulate the oxygen effect, we need to: 1) initialize the oxygen distribution in the target material; and 2) simulate the oxygen involved diffusion and reaction in the chemical stage.

- Initializing the oxygen distribution

- Sampling region R_s : we first have Region of Interest (ROI) for recording radicals within the cellular nucleus. Then, R_s is determined as a box with each dimension length along x, y, z extended r_d from that of ROI, where r_d is the maximum diffusion length of the radicals in water within the duration of chemical stage. R_s is larger than ROI to account for the dilution of oxygen due to diffusion only.
- Counts of oxygen molecules N_{O_2} : it is obtained from oxygen concentration C_{O_2} as $N_{O_2} = C_{O_2} * 760\ mmHg * 1.26 * \frac{\mu M}{mmHg} * V_s * N_A$, where N_A is the Avogadro constant and V_s is the volume of R_s.
- Spatial distribution: N_{O_2} positions were randomly and uniformly sampled within R_s. And each position will be treated as one oxygen molecule.

- Simulating the oxygen-involved chemical stage
- Diffusion: constant diffusion rates were adopted as listed in Table 1.

Table 1. Chemical species and their diffusion coefficients D

Original chemical species in gMicroMC		New chemical species after adding oxygen	
Species	D (x10^9 nm^2s^{-1})	Species	D (x10^9 nm^2s^{-1})
e_h	4.9	O_2	2.4
$OH\cdot$	2.8	HO_2	2.3
$H\cdot$	7.0	O_2^-	1.75
H^+	9.0	HO_2^-	1.4
H_2	4.8		
OH^-	5.0		
H_2O_2	2.3		

- Reaction: To reduce the computational burden, we only considered those reactions with $k > 10^7/(M \cdot S)$ and probability > 0.05, based on data from Ianik's work [3]. Totally, 11 new reactions were added, as listed in Table 2.

Table 2. Summary of chemical reactions.

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

- Oxygen involved chemical stage simulation: 1) Treat all reactions as diffusion-controlled ones and use Brownian-bridge method to find possible reaction [2]; and 2) reduce the searching burden in the many-body problem with the binning method as illustrated in Figure 1 [2].

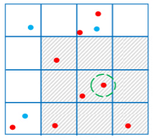

Figure 1. Illustration (2D case) of the binning method used to reduce searching reactant pairs. Circles with different colors represent different molecules. Shaded area represents for the searching area for the molecules with a circle tagged.

- Simulation cases

Chemical stage lasts for 1 μs for simulations listed below.

- Validation: ROI is the first $10 \times 10 \times 10\ \mu m^3$ segment of the track of 5 MeV proton. $C_{O_2} = 21\%$ was considered.
- Oxygen effect: ROI is a sphere with radius $r = 1.5\ \mu m$. 4.5 keV electrons started transport at the center of the sphere. $C_{O_2} = 0$, 3%, 9%, 21% were considered. Results were averaged on 1000 tracks.
- Time performance: radicals from one 4.5 keV electron (~10^3) with different C_{O_2} were simulated with gMicroMC. Equivalent number of radicals from N 4.5 keV electrons were simulated for GEANT4-DNA (with no consideration of oxygen, $N = 100$ equivalent to $C_{O_2} = 3\%$). The ROI is $2 \times 2 \times 2\ \mu m^3$ for both cases.

RESULTS

❑ Validation

- From Figure 2, the time-dependent yield of e_h from our work generally follows the same trend as those from the previous work (Colliaux *et al* 2015 and Boscolo *et al* 2020).
- The depletion rate of e_h from our work was found faster than those from previous work before 10^4 ps, and slower after that.
- Potential reasons:
  1. Brownian bridge method in our package considered the possibility of chemical reaction during the diffusion while other works did not consider this.
  2. As chemical species diffuses away from each other and the local consumption of oxygen, reaction probabilities for e_h related reactions drops quickly while they are not affected in other works since constant continuum oxygen background is used.

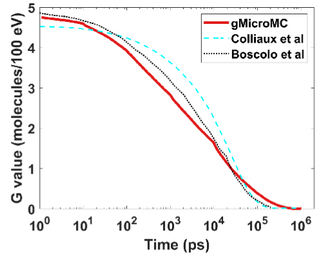

Figure 2. Calculated time-dependent yield of e_h produced by 5 MeV proton under 160 mmHg oxygen

❑ Oxygen effects on yields of different chemical species

From Figure 3 and numerical results shown in Table 2,

- Existence of oxygen reduce mainly e_{aq}^- and $H\cdot$ and the reduction of these radicals increases with increasing oxygen concentration.
- Consequently, the existence of oxygen increase slightly $OH\cdot$ and H_2O_2 for less e_h being involved in consuming $OH\cdot$.
- Toxic HO_2 and O_2^- are generated
- The diffusion time should be long enough to have observable oxygen effect on chemical yields. In this case, the time is around 10 ns.

Table 2. Summary of yields (counts per 100 eV) of different chemical species at 1 μs for different oxygen concentration

	e_h	$OH\cdot$	$H\cdot$	H^+	H_2	OH^-	H_2O_2	HO_2	O_2^-
0%	0.94	2.02	0.87	1.97	0.92	1.01	0.73	0	0
3%	0.46	2.08	0.34	1.97	0.85	0.95	0.77	0.55	0.50
9%	0.12	2.12	0.07	1.98	0.80	0.88	0.79	0.87	0.89
21%	0.00	2.14	0.00	1.97	0.75	0.82	0.82	1.02	1.06

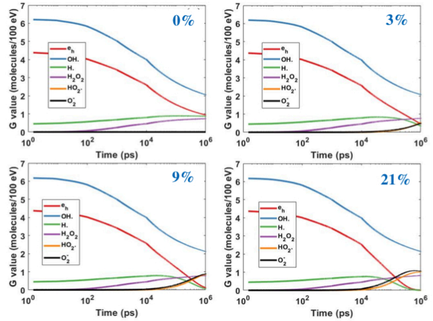

Figure 3. The yields of different chemical species versus time under different oxygen concentration. Results have been averaged on 1000 tracks.

❑ Time performance

The GPU code was executed on one Nvidia Titan Xp GPU (1.58GHz) card while GEANT4 was ran on single core of Intel i7-6850K CPU (3.6GHz). The speedup factor can be **over 1100** for the case with 10^5 molecules. These comparison may be unfair for GEANT4 as it can use multithread to accelerate. However, several GPU cards can be used as well to further speedup GPU program. Hence, GPU MC package shows its advantage over CPU package in doing detailed studies for DNA damage.

Table 3 Time performance with different number of initial molecules for GEANT4-DNA and gMicroMC. Value in parenthesis indicates corresponding oxygen concentration to have same number of molecules.

Number of molecules	GEANT4-DNA	gMicroMC
~ 10^3	61 s	2 s (0)
~ 10^5	70000 s	58 s (3%)
~ 10^6	-	175 s (21%)

CONCLUSIONS

Simulation of chemical stage with oxygen was successfully achieved in our GPU-based MC package gMicroMC with a step-by-step fashion. The introduction of oxygen majorly reduce the yields of hydrated electron e_{aq}^- and hydrogen radical $H\cdot$. The reaction between oxygen and other radicals is in competition with the mutual reactions among other radicals, leading to less reduction of e_{aq}^- and $H\cdot$ by oxygen with a lower initial oxygen.

After adding the new module for oxygen, gMicroMC remains efficient and accurate. As current studies are focused more and more on realistic conditions, GPU MC packages for nanoscopic simulation will be more and more important as shown by the above analysis of time performance. gMicroMC is also open source and welcome anyone who is interested.

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REFERENCES

[1] Tsai MY, Tian Z, Qin N, Yan CC, Lai YF, Hung SH, Chi YJ, Jia X. A new open-source GPU-based microscopic Monte Carlo simulation tool for the calculations of DNA damages caused by ionizing radiation---Part I: Core algorithm and validation. *Medical physics*. 2020.

[2] Tian Z, Jiang SB, Jia X. Accelerated Monte Carlo simulation on the chemical stage in water radiolysis using GPU. *Physics in Medicine and Biology*. 2017;62:3081–96.

[3] Plante I. A Monte–Carlo step-by-step simulation code of the non-homogeneous chemistry of the radiolysis of water and aqueous solutions. Part I: theoretical framework and implementation. *Radiation and Environmental Biophysics*. 2011;50, **389-403.**

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