G4DNA-based Radiochemical Monte Carlo Model to Investigate DNA Damage and FLASH Mechanism

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INTRODUCTION

- **DNA Damage**
  - Single Cell Model: Physical + Chemical Stages
  - Single Cell Model for Gold Nanoparticle Effect Investigation

- **FLASH Mechanism Study**
  - Proton Beam Simulation
  - Oxygen Depletion

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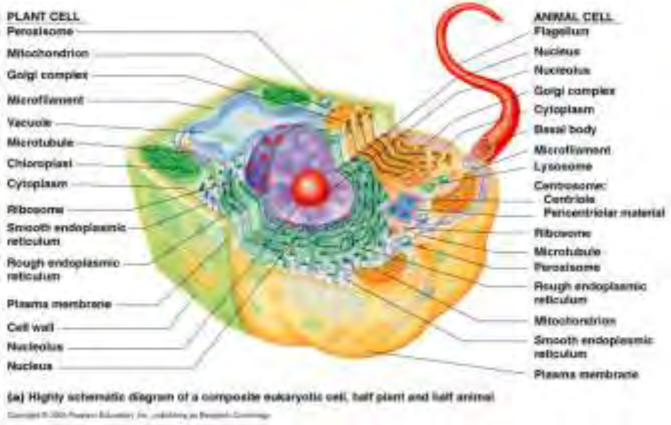
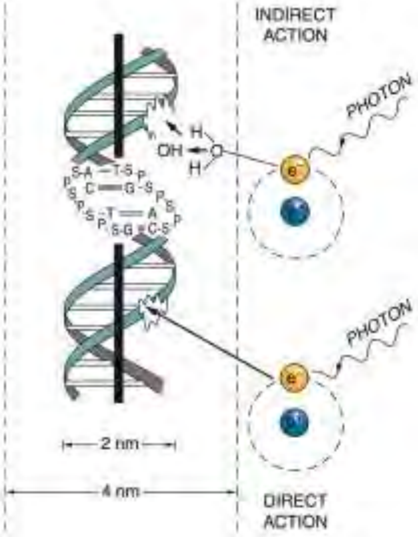
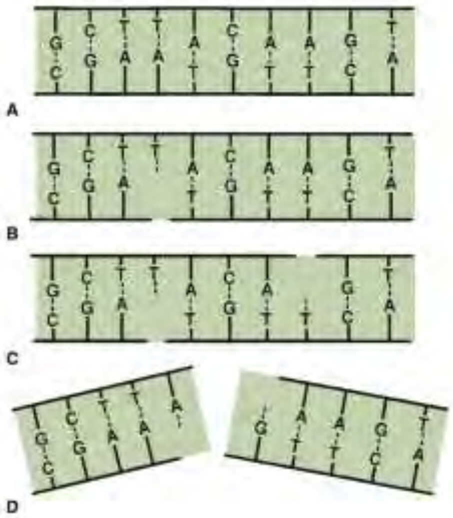
BACKGROUND



Cell, the basic block of plants and animals, also the basic unit in this study.



Direct and indirect actions of radiation to DNA.



Single- and Double- strand DNA breaks caused by radiation.

MICRODOSIMETRY: PHYSICAL MODEL

Modeling gold nanoparticle radiosensitization using a clustering algorithm to quantitate DNA double-strand breaks with mixed-physics Monte Carlo simulation

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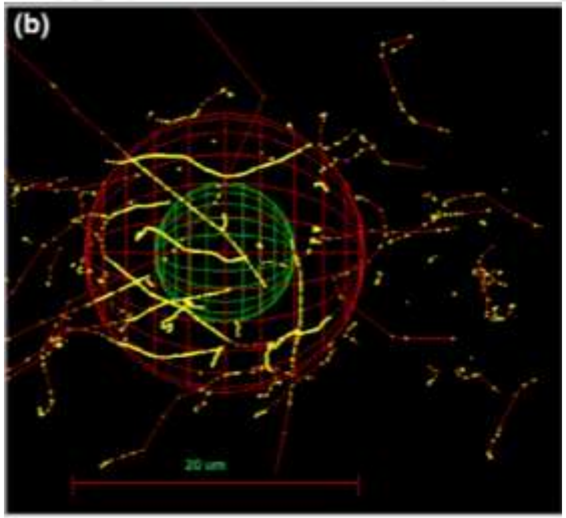
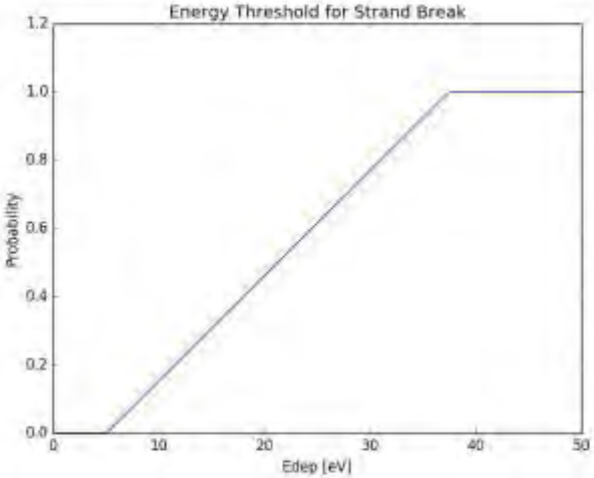
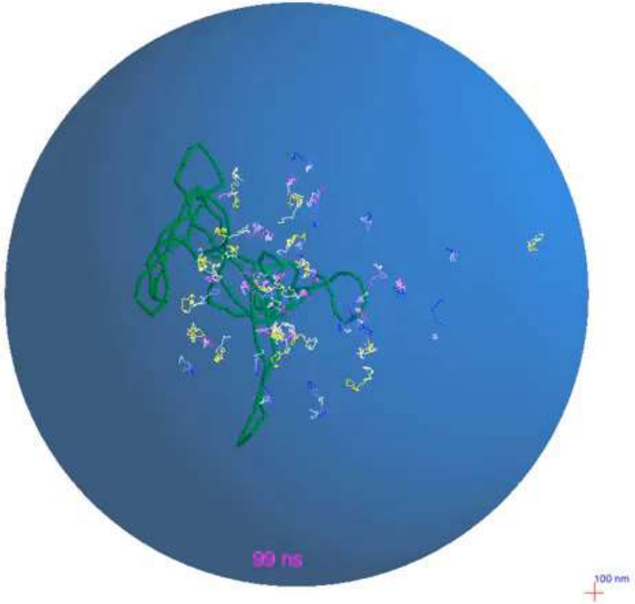
Department of Radiation Oncology, Washington University School of Medicine, St. Louis, MO 63110, USA





GEANT4-DNA CHEMICAL PROCESS



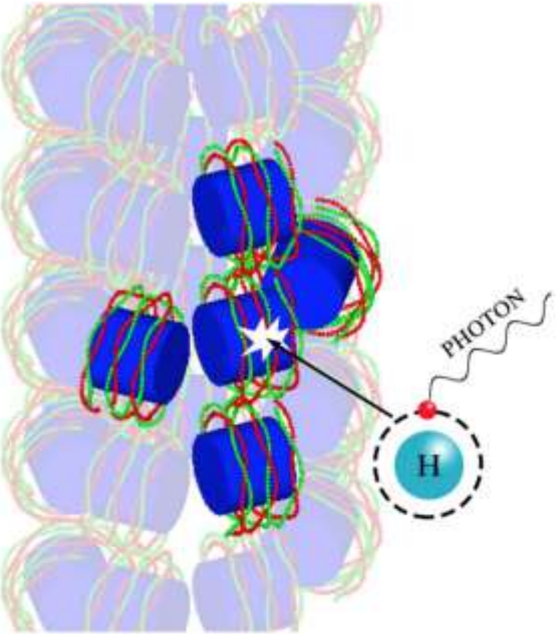
Simulation of water radiolysis in Geant4-DNA

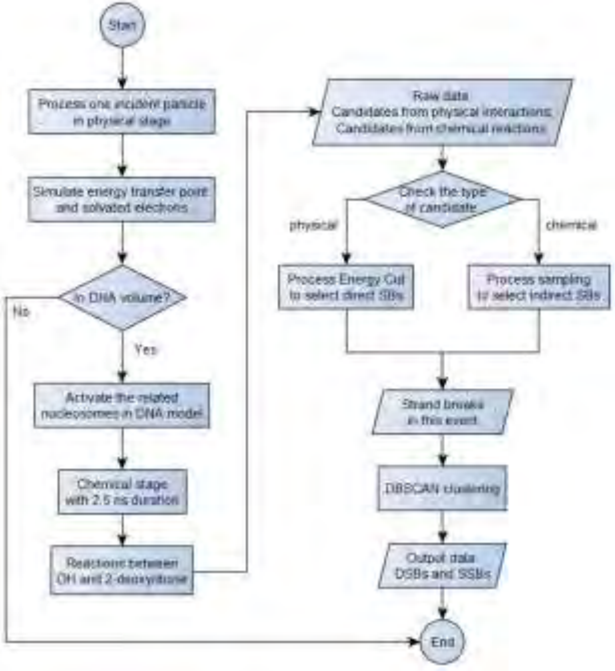
Table 2. Related reactions of the Geant4-DNA chemical module [10] used in the chemical stage simulation.

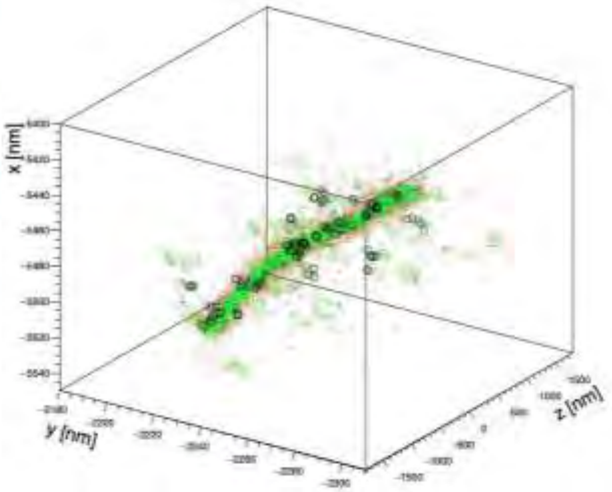
Reaction	Reaction rate (10^9 $M^{-1} \cdot s^{-1}$)
2-deoxyribose + OH· → damaged 2-deoxyribose	2.5
Histone + OH· → Histone	—
H_2 + OH· → H· + H_2O	4.17×10^{-3}
OH· + OH· → H_2O_2	0.44
H· + OH· → H_2O	1.44

Part of reactions in Geant4-DNA chemical module

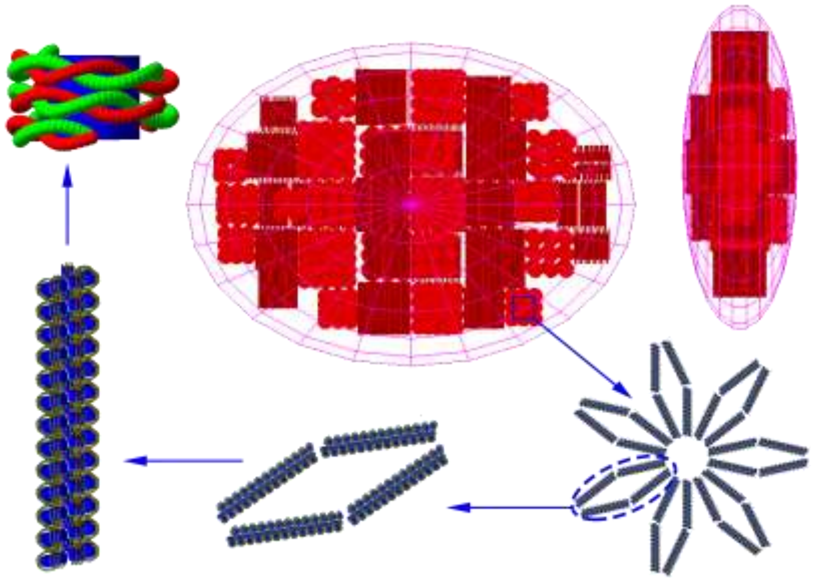
SIMULATION OF DIRECT & INDIRECT EFFECT

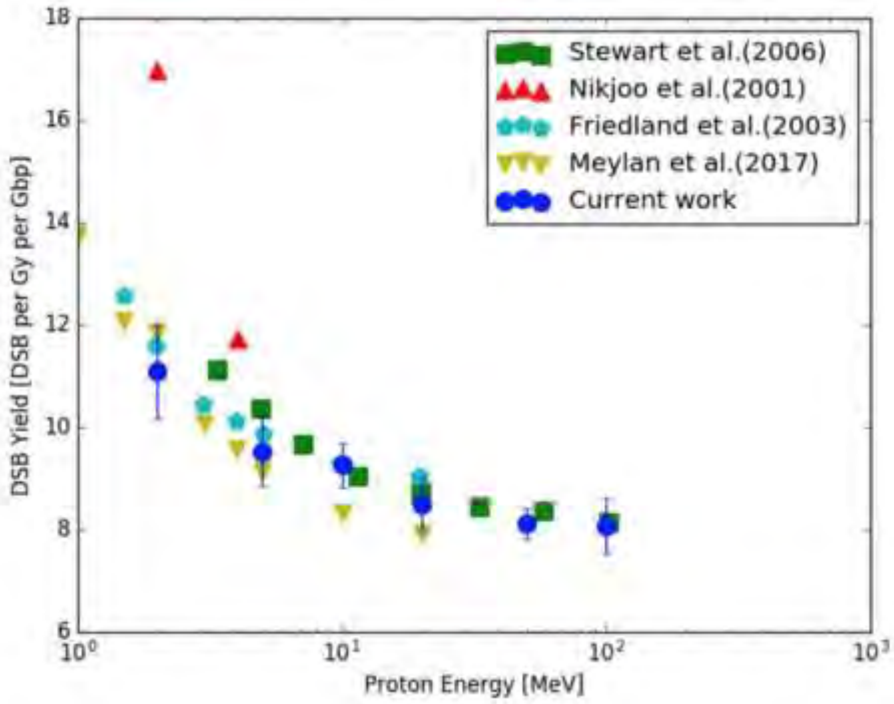






SINGLE CELL MODEL WITH WHOLE NUCLEAR DNA





GOLD NANOPARTICLE EFFECT

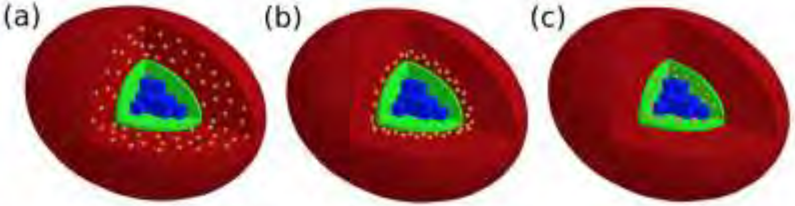


FIGURE 4 Simulation geometry representation of the single cell model that includes the cytoplasm, cell nucleus, detailed DNA geome and individual gold nanoparticles (GNPs) with three different distribution patterns: (a) Uniformly distributed in the cytoplasm. (b) Congregat around the nucleus. (c) Uniformly distributed in the nucleus and outside the chromosome territories

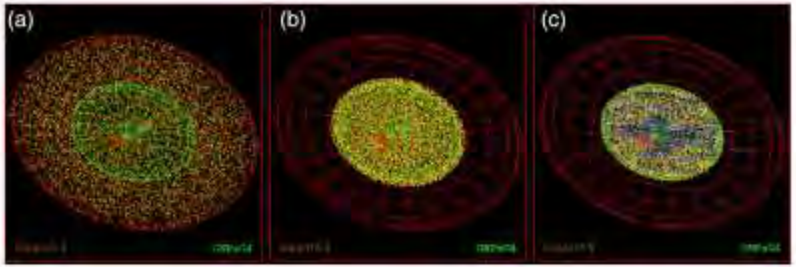
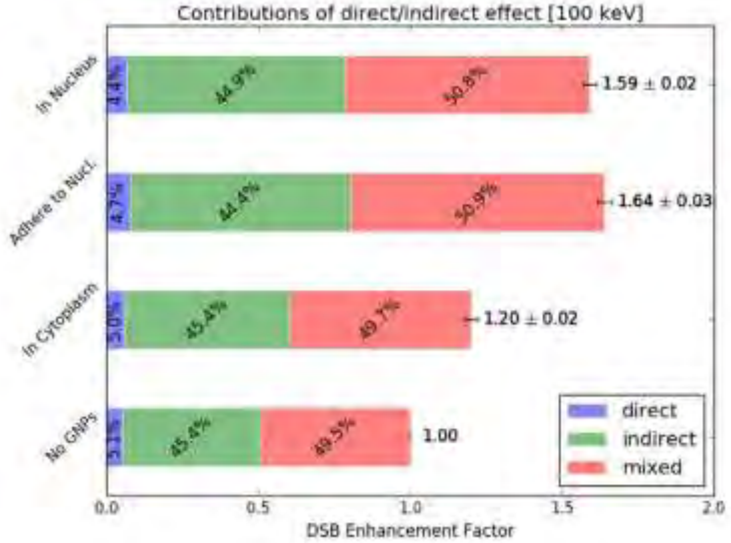
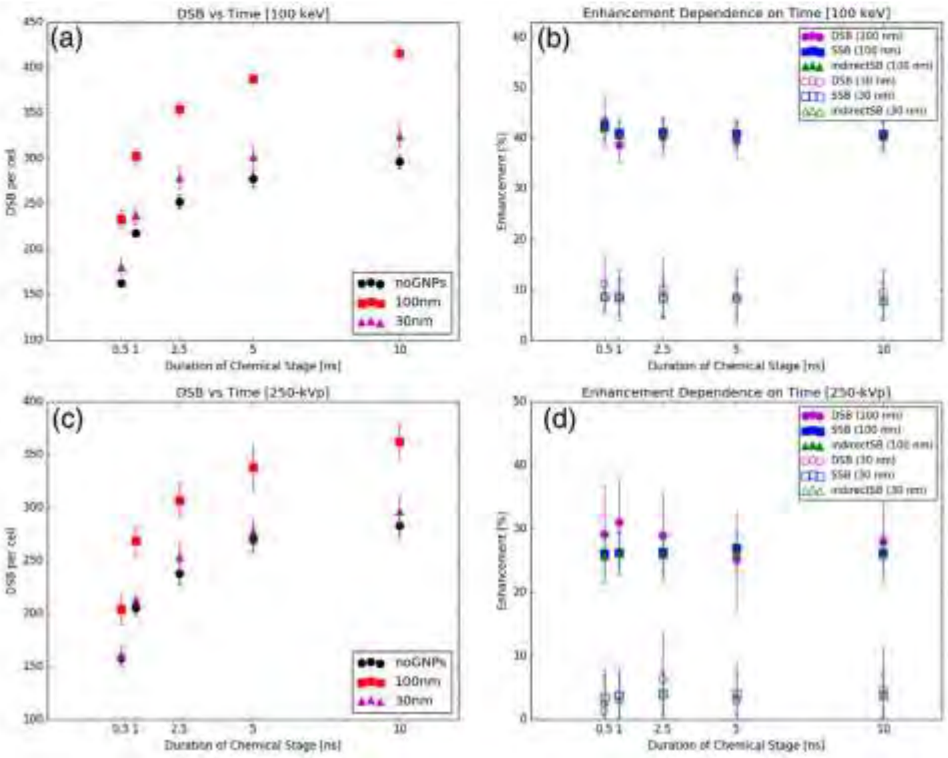


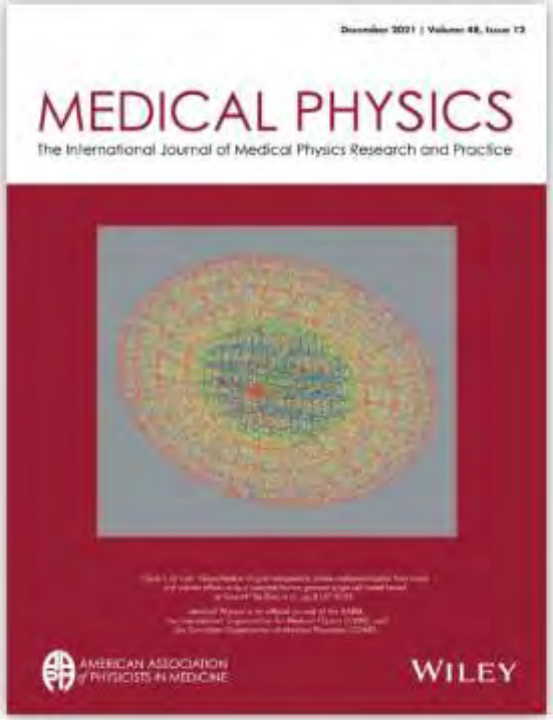
FIGURE 5 (a) Simulation geometry of the single cell model with 12 000 90 nm gold nanoparticles (GNPs) in cytoplasm. (b) Twelve thousand GNPs congregated around the nucleus. (c) Eight thousand two hundred seven GNPs were simulated in the nucleus



DSB enhancement factor with different GNPs locations in 100 keV photon source.

GOLD NANOPARTICLE EFFECT





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- **FLASH Mechanism Study**
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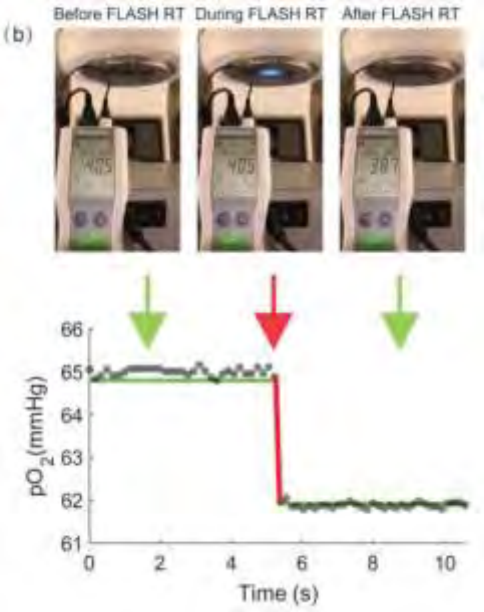
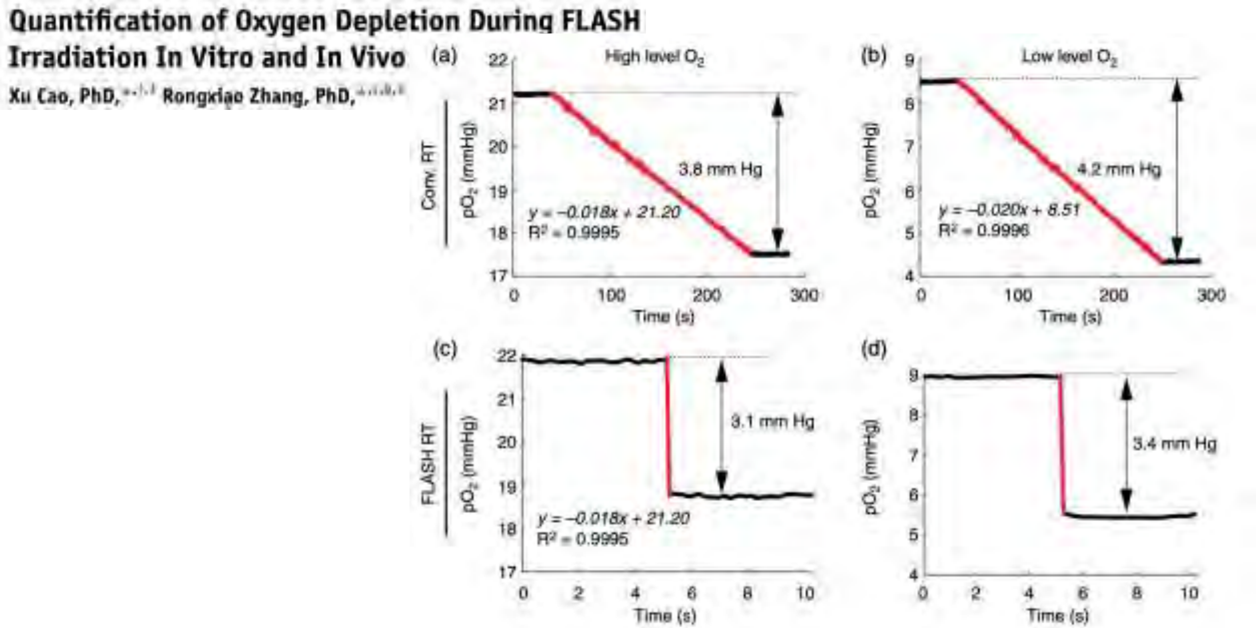
BACKGROUND

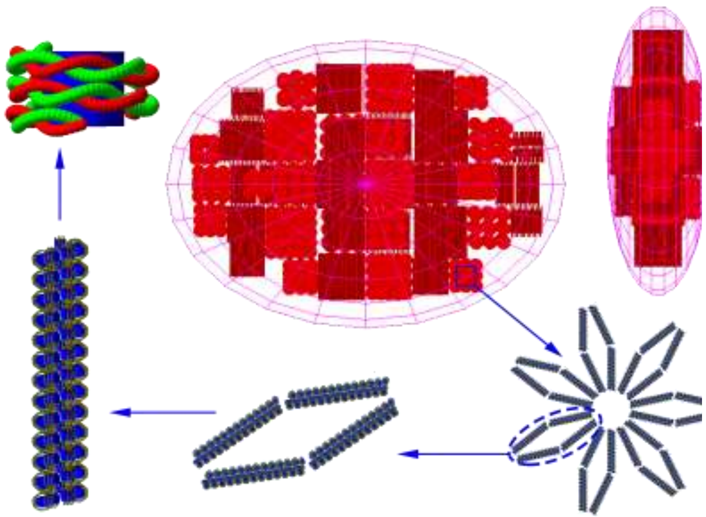
- Hypothetic mechanisms of FLASH effect: The transient oxygen depletion resulting from radiolytic oxygen consumption.
- Published experimental studies show oxygen depletion at different dose rates.

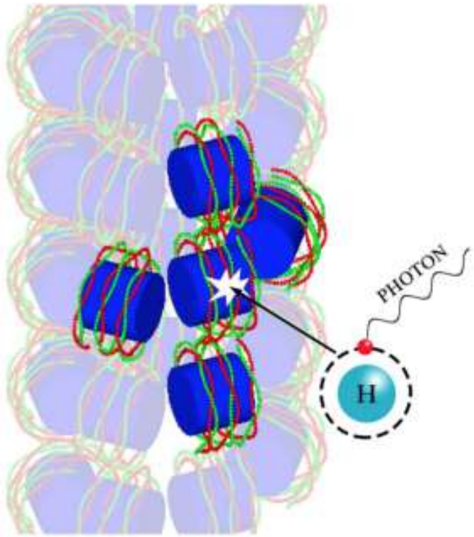




BACKGROUND

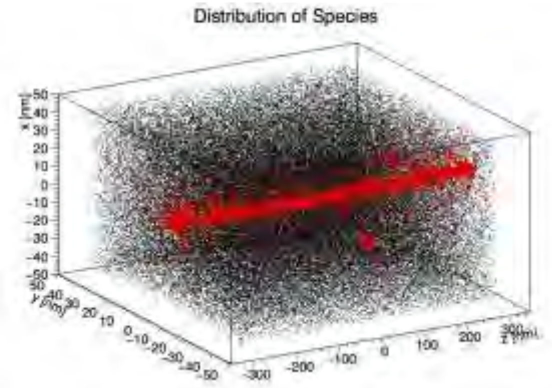
- In our previous study, G4-DNA was used to simulate a single cell model with complete human genome.
- DNA molecules can be simulated as static objects with zero coefficients of diffusion after physical stage.
- Since 2022, G4-DNA included oxygen molecules reactions in chemistry module.

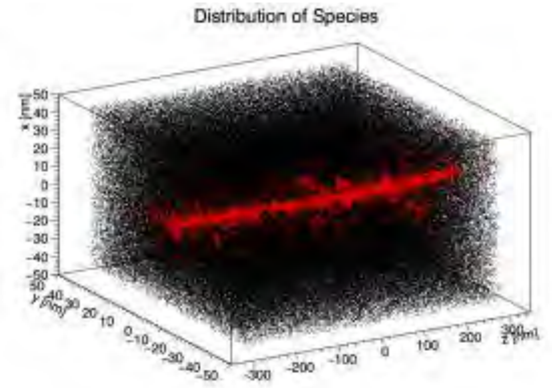




Reaction channels			k_{obs} ($10^{10} L \cdot mol^{-1} \cdot s^{-1}$)
$e_{aq}^- + e_{aq}^-$	→	$2OH^- + H_2$	0.5
$e_{aq}^- + OH^\cdot$	→	OH^-	2.95
$e_{aq}^- + H^\cdot$	→	$OH^- + H_2$	2.65
$e_{aq}^- + H^+$	→	$H^\cdot$	2.11
$e_{aq}^- + H_2O_2$	→	$OH^\cdot + OH^-$	1.41
$OH^\cdot + OH^\cdot$	→	H_2O_2	0.44
$OH^\cdot + H^\cdot$	→	H_2O	1.44
$H^\cdot + H^\cdot$	→	H_2	1.20
$H^+ + OH^-$	→	H_2O	14.3
$H_2 + OH^\cdot$	→	$H^\cdot$	0.00417
$e_{aq}^- + O_2$	→	$O_2^{\cdot -}$	1.74
$e_{aq}^- + HO_2^\cdot$	→	HO_2^-	1.29
$e_{aq}^- + O_2^{\cdot -}$	→	$2OH^- + H_2O_2$	1.29
$OH^\cdot + HO_2^\cdot$	→	O_2	0.79
$OH^\cdot + O_2^{\cdot -}$	→	$O_2 + OH^-$	1.07
$OH^\cdot + HO_2^-$	→	$HO_2^\cdot + OH^-$	0.832
$H^\cdot + O_2$	→	$HO_2^\cdot$	2.1
$H^\cdot + HO_2^\cdot$	→	H_2O_2	1.0
$H^\cdot + O_2^{\cdot -}$	→	HO_2^-	1.0
$H^+ + O_2^{\cdot -}$	→	$HO_2^\cdot$	4.78
$H^+ + HO_2^-$	→	H_2O_2	5.0

MOTIVATION & METHODS

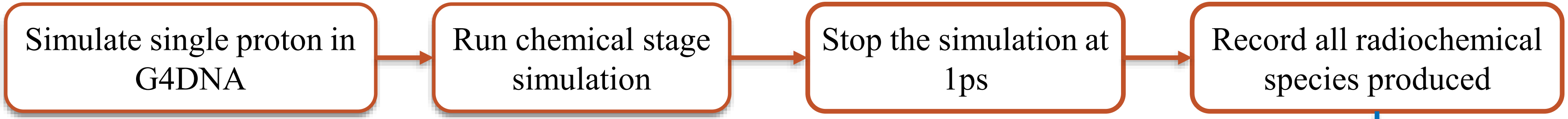




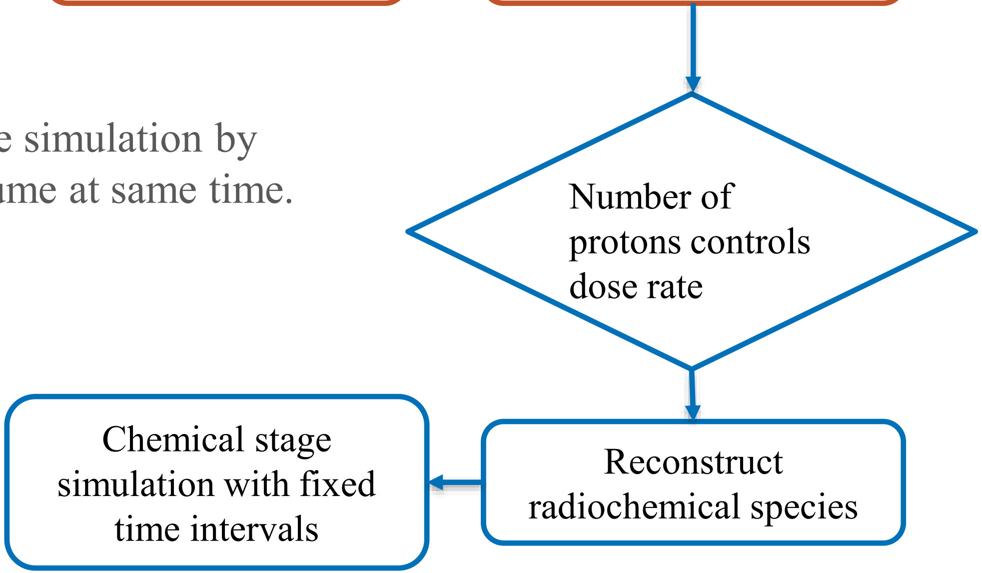
- Developing a G4-DNA radiochemical MC model to investigate the oxygen depletion effect under different dose rates.

- Simulation of water phantom with specific oxygen concentration:
  - **Black points** represent the uniformly distributed O2 molecules in water.
  - **Red points** represent the species from water radiolysis due to a 500 keV proton (ionizing radiation).

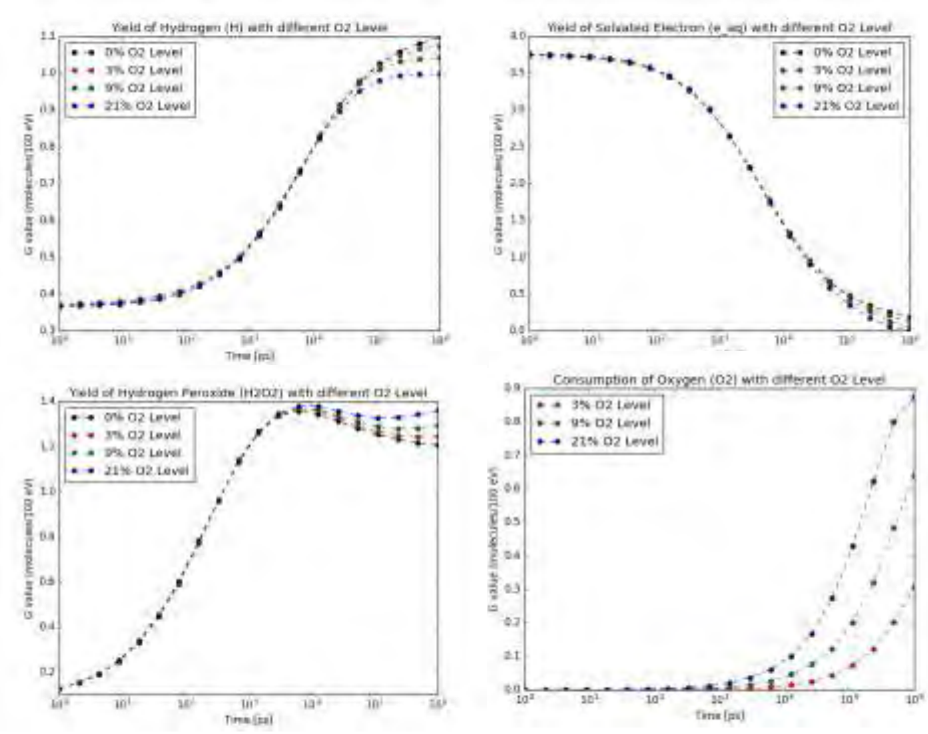
MOTIVATION & METHODS



- Developing a method for the different dose rate simulation by using different number of protons in same volume at same time.
  - Producing inter-track interactions of radicals generated from different proton tracks, which is not an option in G4-DNA.
  - We achieved this by separating the simulation work into two steps.

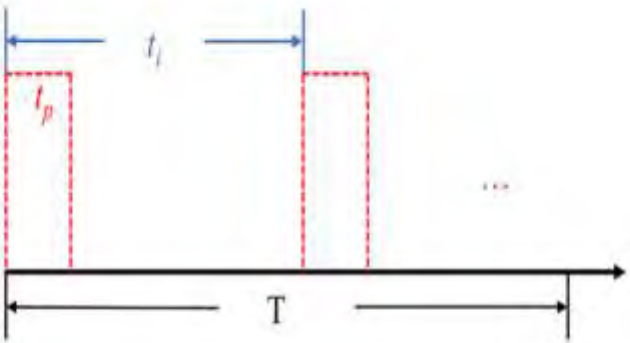


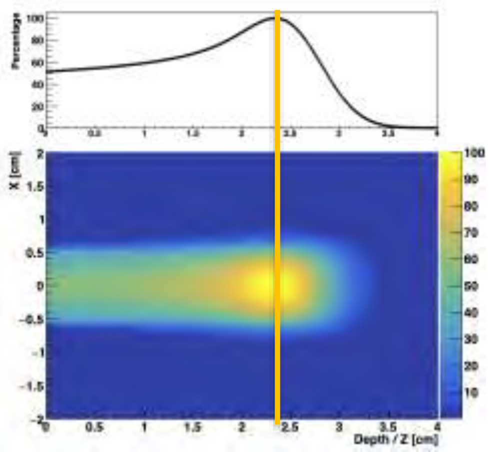
RESULTS: IMPACT OF OXYGEN CONCENTRATION

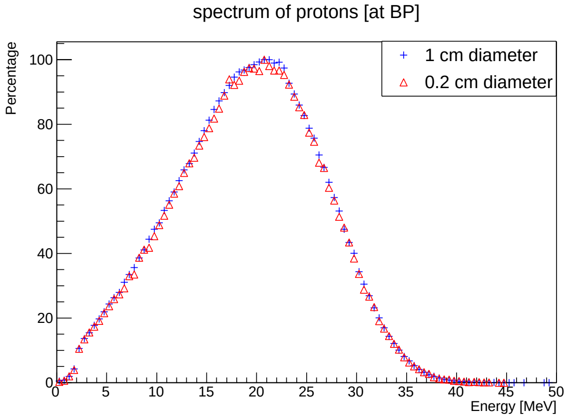


- 500 keV single proton irradiation with different O2 levels.
- Yield of different chemical species as a function of time under different O2 concentrations.
- Impact of O2 presence evident in 1-10 ns after the physical stage.
- Oxygen depletion can also be simulated and collected in this radiochemical MC model.

METHODS: PULSE SIMULATION





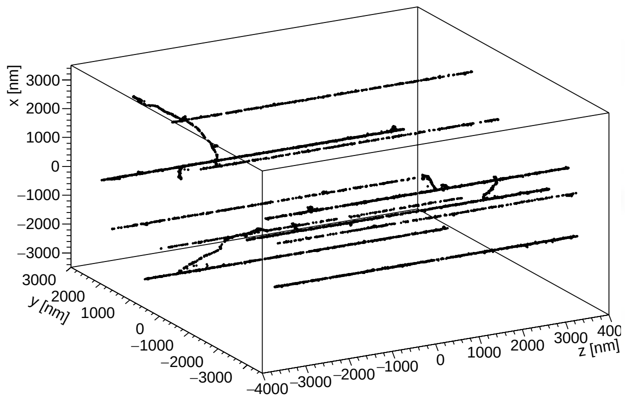


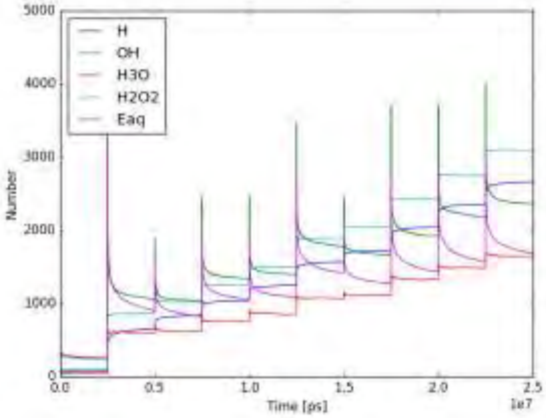
- Pulse structure of the synchrocyclotron (Mevion Hyperscan) at FLASH dose rate. Pulse width t_p is 25 us, and the system was tuned to deliver 750 pulses per second (1.33 ms per pulse). Based on Faraday cup measurement, 39.9 pC per pulse.

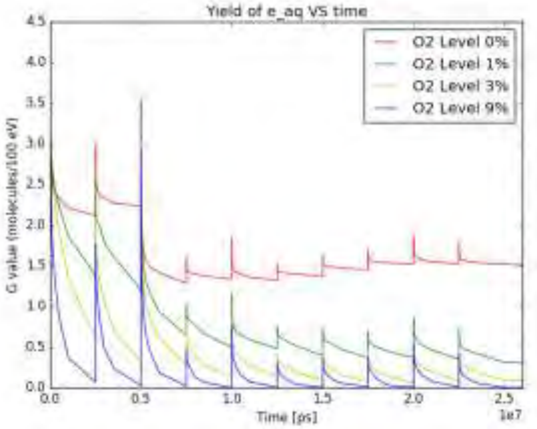
- The spectrum of proton at bragg peak was investigated by MC simulation. Spot size and bragg peak width were match the experimental measurements.

METHODS: PULSE SIMULATION

Radicals from Protons in One Pulse

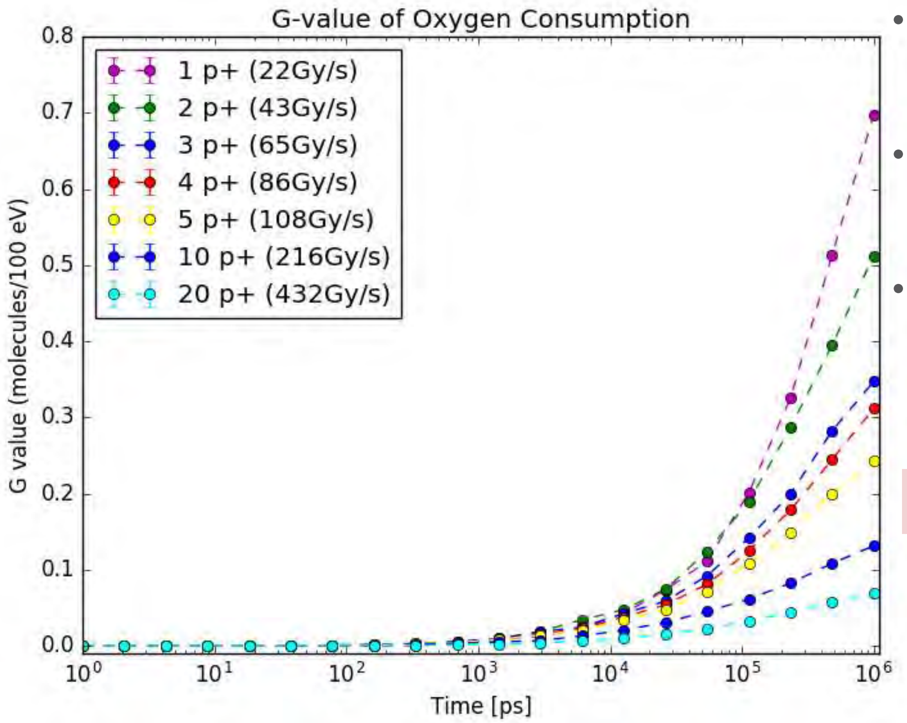




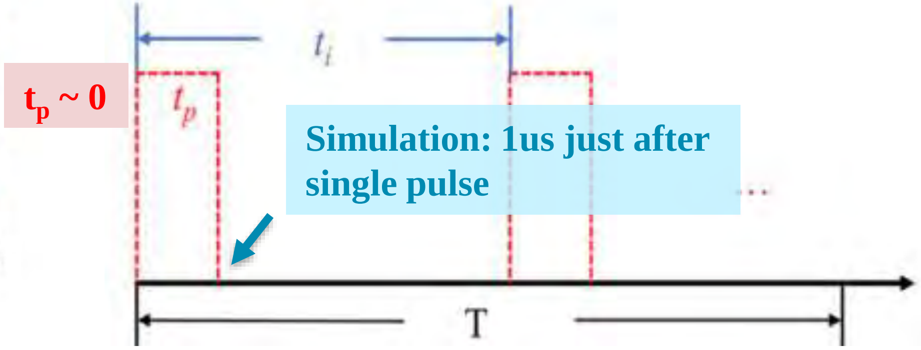


- Considering the computer power and simulation time, a 7x7x7 um3 water phantom was simulated to represent a small voxel at Bragg peak.
- In Mevion's FLASH mode, the average dose rate measured at the Bragg peak is 216 Gy/s. In this dose rate, the number of protons will be 10 in this 7x7x7 um3 water phantom.
- A realistic scenario was simulated by considering the 2.5 us interval time between two adjacent protons, to show the impact of different oxygen concentration.

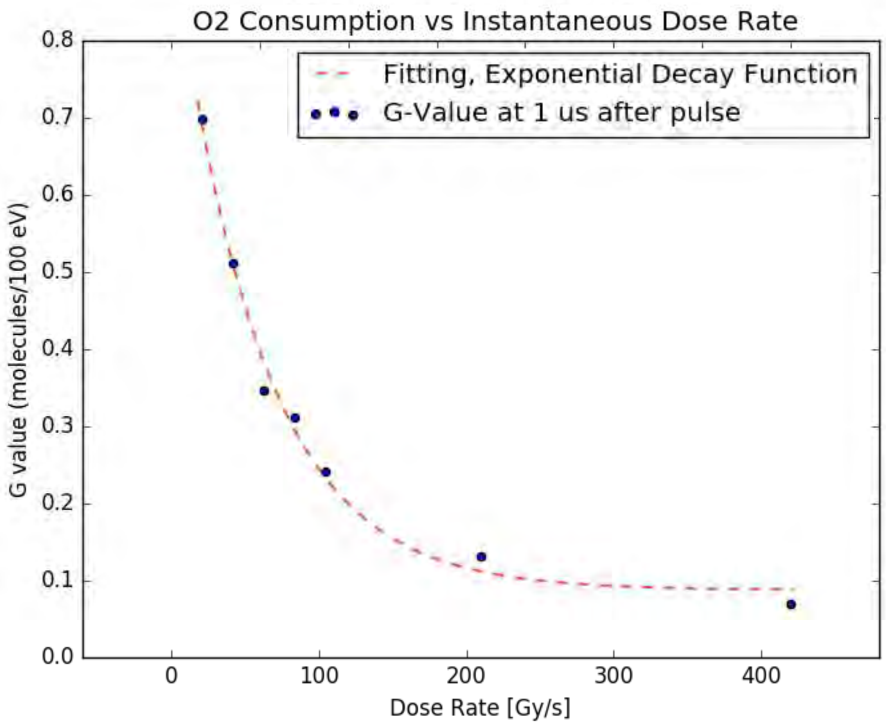
RESULTS: OXYGEN DEPLETION SIMULATION



- A simplified method: Different dose rate was represented by different number of protons.
- 9% O2 level (69mmHg, 86.2uM) was used in this work.
- G-value of Oxygen number decreasing was used to indicate the oxygen depletion capability of different dose rate proton irradiation.



RESULTS: OXYGEN DEPLETION SIMULATION



- The 1us duration time was used in this work to save the simulation time. G-value of O2 depletion at 1us with different dose rate shows an exponential decay in our simulation result.

- At least 35% reduction of the oxygen depletion capability of FLASH irradiation (43 instantaneous dose rate, 2 protons track with same time) was found in our radiochemical simulation model. Self-interactions of radicals from different proton/track was found to be the main reason.

CONCLUSION

- This radiochemical MC model is capable of modeling oxygen depletion to help understand published experimental results.
- The results indicate that oxygen concentration plays an important role.
- The implementation of our model can be used to investigate the FLASH effect by considering a complete and more realistic scenario that can take into account pulse structure differences from different FLASH sources.

ACKNOWLEDGEMENT

My Collaborators:

*Francisco J. Reynoso** — *Tianyu Zhao* — *Hao Yao* — *Arash Darafsheh*

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BARNES JEWISH Hospital

Washington University in St. Louis SCHOOL OF MEDICINE

NCCN National Comprehensive Cancer Network

NCI CCC

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School of Medicine

Radiation Oncology

Thanks

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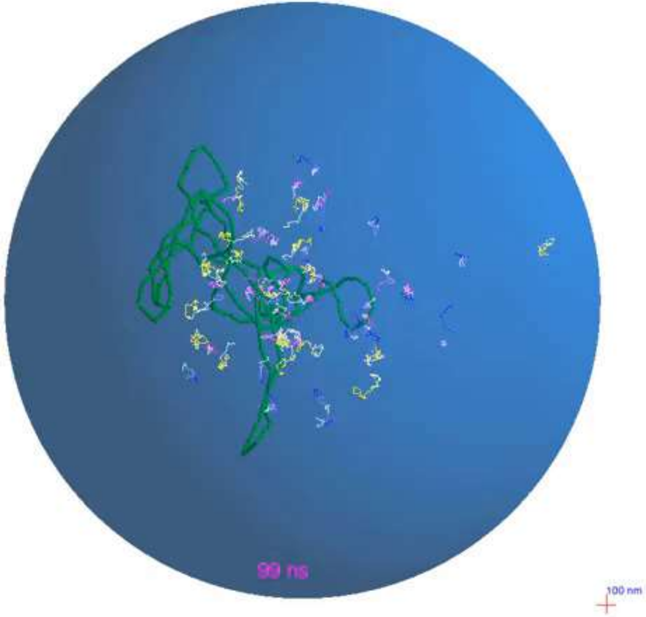
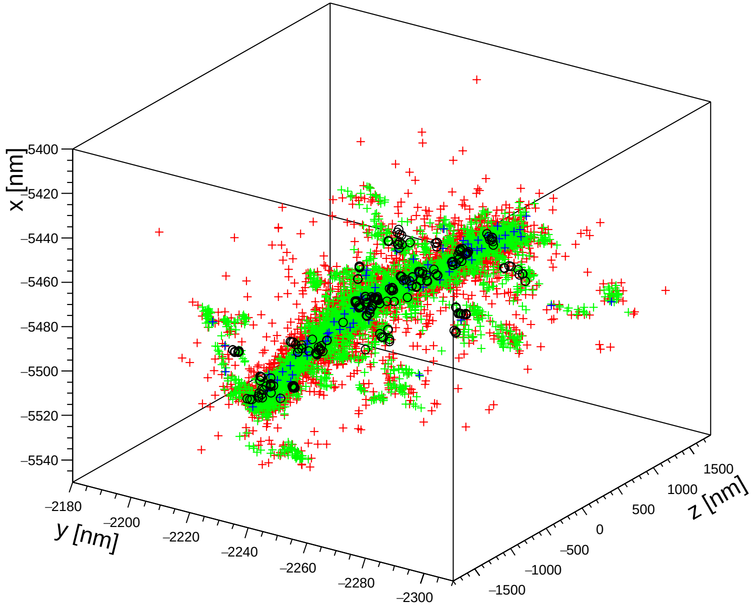
BACKUP

BACKGROUND

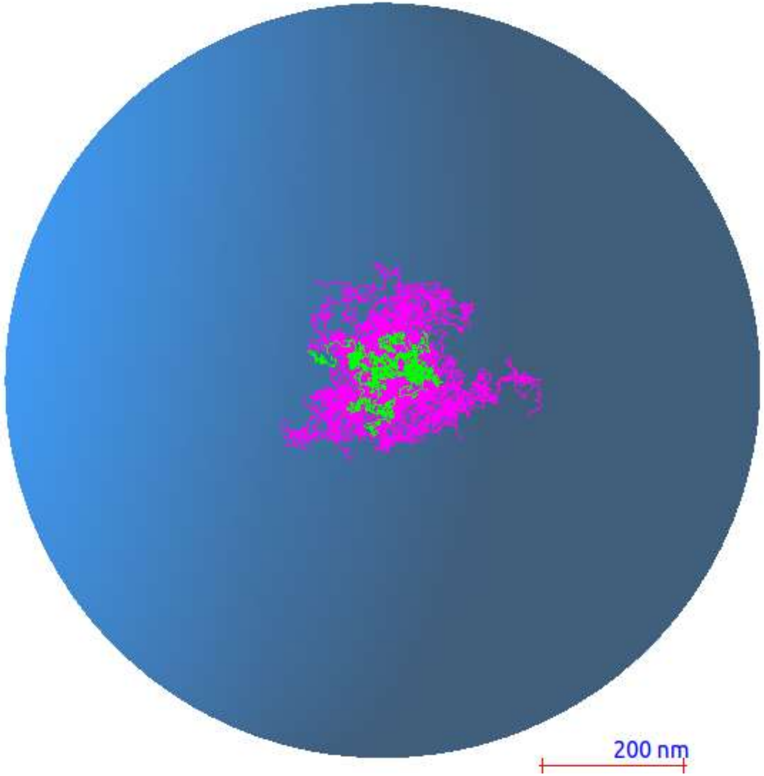


Simulation of water radiolysis in Geant4-DNA



Cross markers (+,+,+) represent the radicals generated @ 1ps after physical process.

OXYGEN DIFFUSION



- O2 and H2O2 simulated at center.
- 1 um water sphere in diameter.
- Chemical stage with 1 us duration.

EXPERIMENTAL MEASUREMENTS

Does FLASH deplete oxygen? Experimental evaluation for photons, protons, and carbon ions

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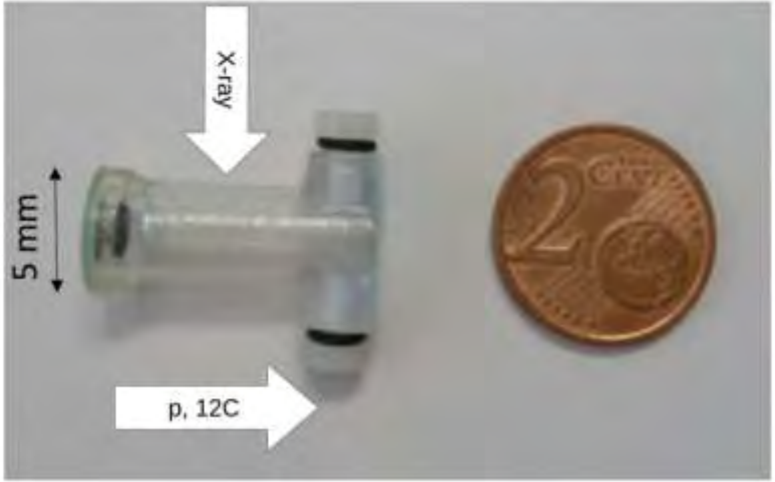
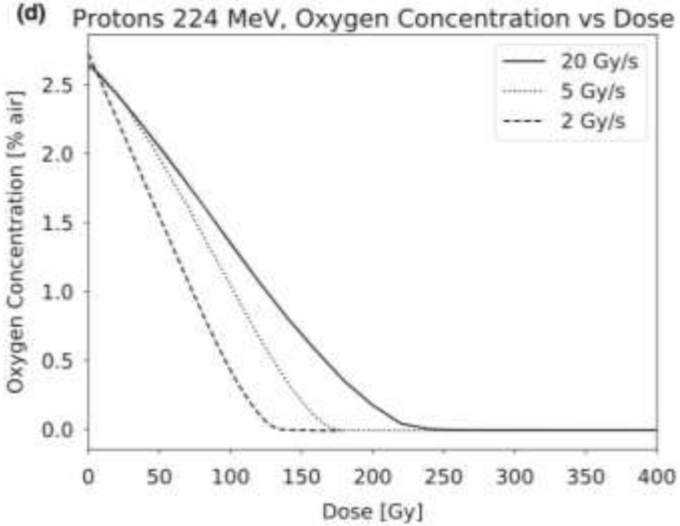
Faculty of Physics and Astronomy, Ruprecht-Karls-University, Heidelberg, Germany





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