Experimental and simulated H_2O_2 radiolytic yields in ultra-pure water under UHDR proton irradiation

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ABSTRACT

Background/Aim: Ultra-high-dose-rate (UHDR, >40 Gy/s) irradiation can enhance the tolerance of healthy tissue. To investigate water radiolysis in proton irradiations, we developed a model of ultra-pure water samples experiments at the ARRONAX facility (IBA Cyclone 70 XP, Nantes, France) for dose rates ranging from 0.2 Gy/s to 6 kGy/s.

Methods: A proton beamline reproducing purified water irradiation experiments was modelled using GATE 10 and delivered in the plateau region of the Bragg peak. Beam delivery was verified using OC film dosimetry. Using Geant4-DNA, radiolysis calculations were performed in micrometric cubic water volumes, accounting for O_2 (21% and 1%) and CO_2 (0.041%). Experimental and simulated $G(H_2O_2)$ were compared at dose rates from 0.2 to 150 Gy/s under different O_2 conditions.

Results: The gamma index evaluation demonstrated a good agreement between the measured and simulated dose distributions. Under aerated conditions, the simulated $G(H_2O_2)$ was 2.05, consistent with the experimental value of 1.98 at a conventional dose rate, increasing the dose rate reproduced the expected decrease in $G(H_2O_2)$, closely matching experimental trends. Under deaerated conditions, $G(H_2O_2)$ decreased from 1.58 at 0.28 Gy/s to 1.21 at 42 Gy/s.

Conclusion: The simulations show the main pattern of radiolysis at different oxygen levels and dose rates, confirming their support for experiments.

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INTRODUCTION

The underlying mechanism of the FLASH effect from physics to biology hasn't been explained yet, despite studies investigating **UHDR (Ultra High Dose Rate)** therapy (> 40 Gy/s) and its tissue-sparing effect [1]. The production of reactive oxygen species during water radiolysis following radiation exposure is crucial. Monte Carlo simulations can reproduce radiolytic species evolution up to 15 minutes post-irradiation under different beam intensities and pulse durations. To that purpose, we reproduced UHDR **proton irradiations** at **ARRONAX (IBA Cyclone 70 XP, Nantes, France) using GATE 10 and Geant4-DNA** water radiolysis simulations.

METHODS AND MATERIALS

• Experimental setup

• The **ARRONAX cyclotron** produces H^+ (65.7 MeV, range in water: 39 mm) at dose rates ranging from 0.2 Gy/s to 6 kGy/s, as described in Figure 1.
• $G(H_2O_2)$ as a final endpoint, was quantified using **the Ghormley triiodide protocol**.
• Film dosimetry (OC-film) for alignment and homogeneity was evaluated using gamma index analysis (2mm/2%).

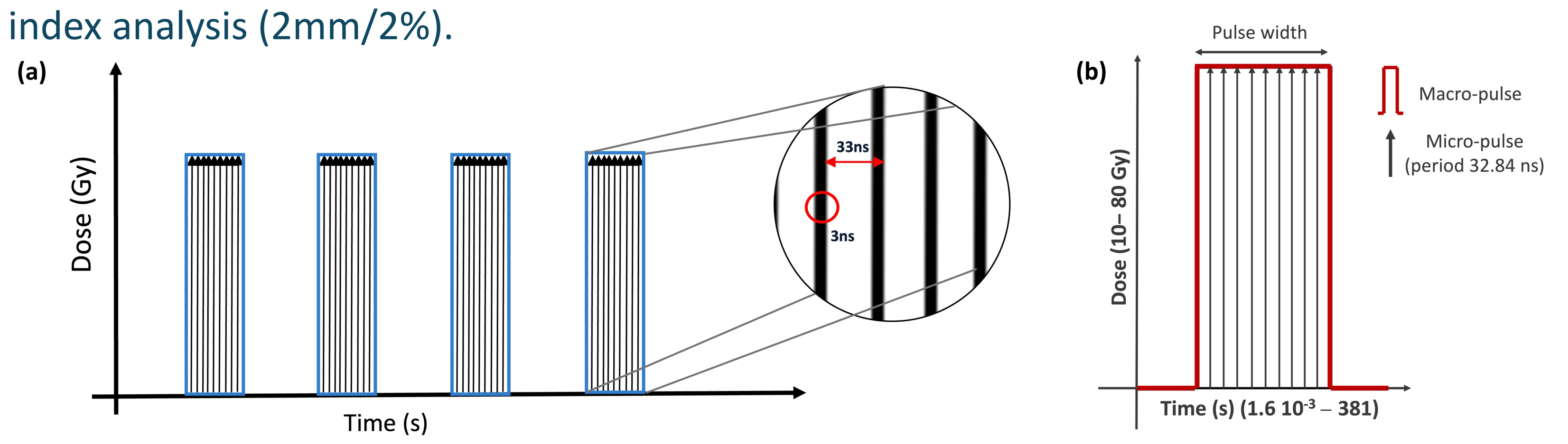


Figure 1. (a) Schematic of a macro pulse composed of a bunch of micro pulses separated by 33 ns
(b) single pulse structure in this work

• Simulation setup

• Figure 2 shows experimental beamline geometry reproduced in **GATE 10**, with plateau region of Bragg curve identified based on a LET value in Figure 2.

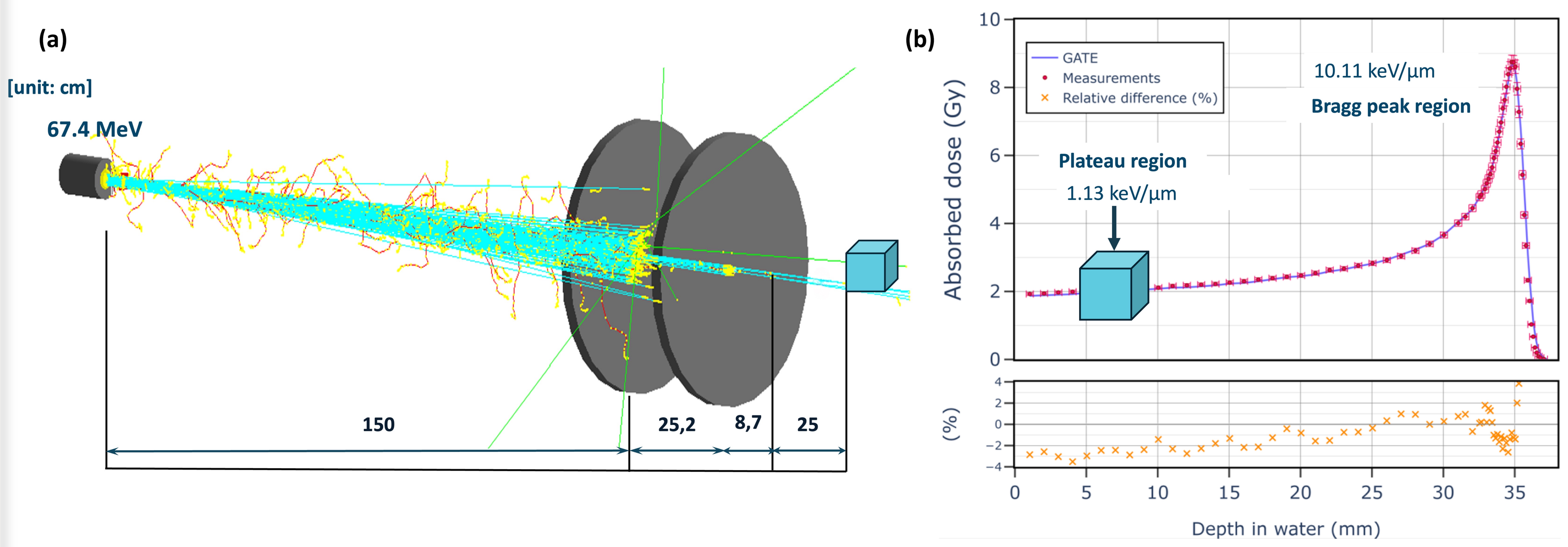
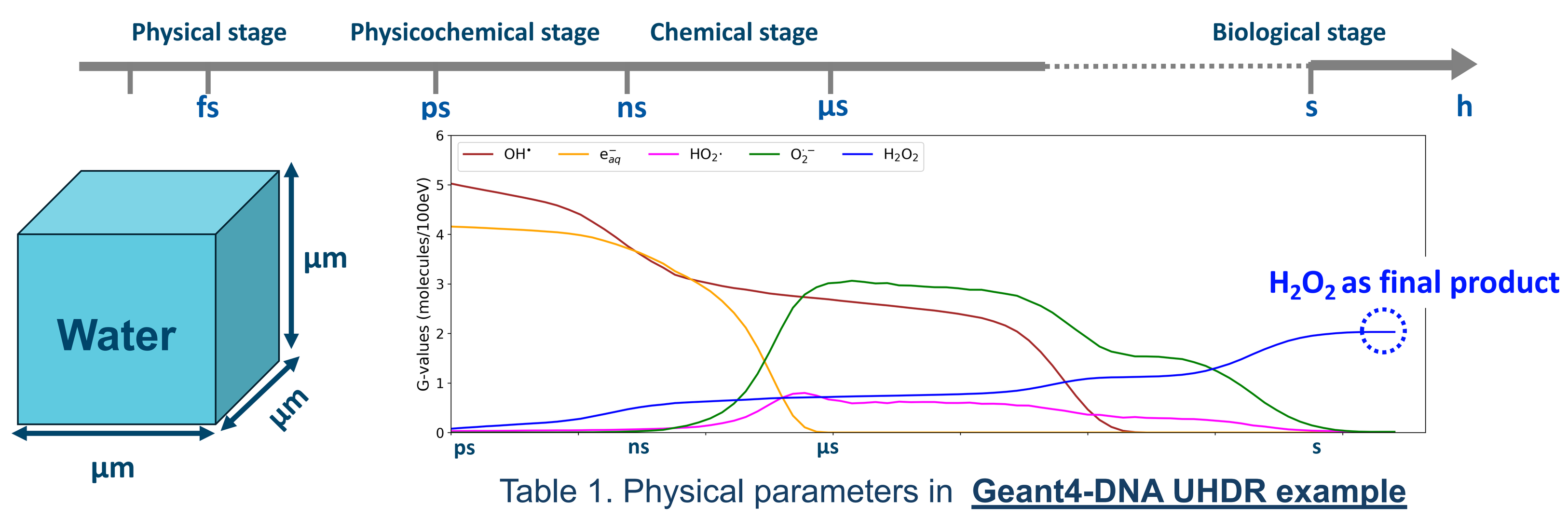


Figure 2. (a) Simulated ARRONAX proton beamline (b) Simulated LET profile in liquid water

• Water radiolysis was simulated using **Gean4-DNA (v11.4.0)** , see Table 1 for parameters



Parameters
• G4EmDNAPhysics_option2
• G4EmDNAChemistry_option 3
• O_2 levels: 0.04% – 21%
• CO_2 levels: 0.042%
• pH level: 5.5 ± 0.3

Table 1. Physical parameters in **Geant4-DNA UHDR example**

Dose rate condition	Dose (Gy)	Number of particles	Pulse duration (ms)	Mean dose rate (Gy/s)
CDR (3.2 μm)	0.01	1.34±0.02	50	0.2
	0.4	25.92±0.42		8
UHDR (1.6 μm)	2	32.80±0.78		40
	2.5	40.60±1.13		50
	5.5	87.73±1.38		110

Results

• Beam quality assurance

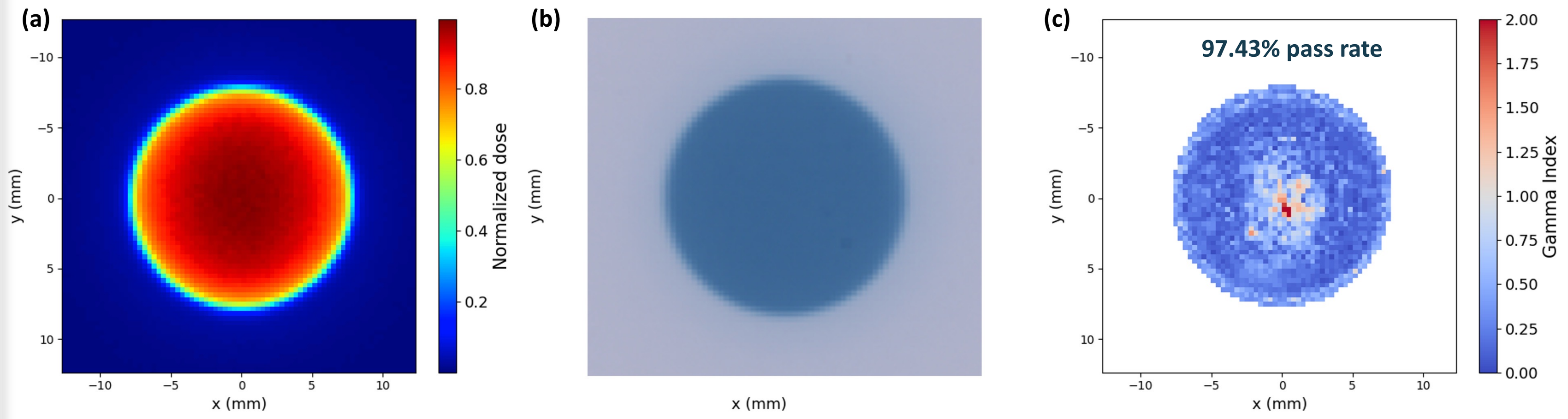


Figure 3. (a) Simulated film, (b) OC-film, and (c) gamma-index map (2mm/2%)

• Comparison of simulated G-value with measurements

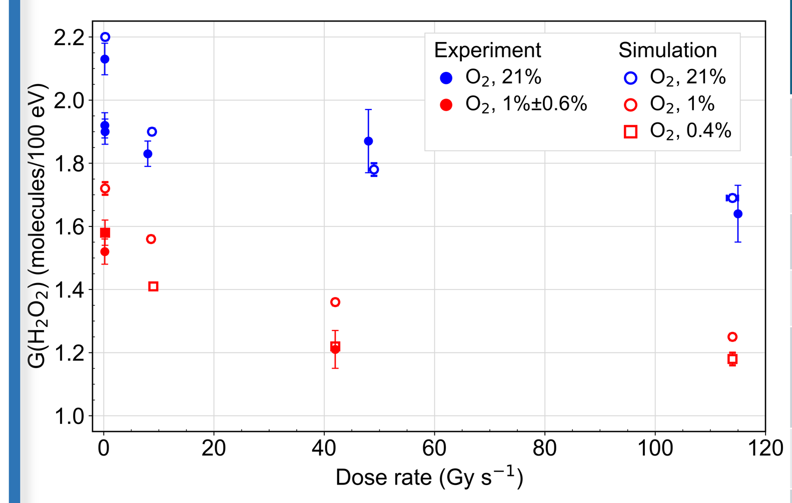


Figure 4. Experimental and simulated of $G(H_2O_2)$ as a function of the dose rate up to 115 Gy/s, under aerated and deaerated conditions.

Table 2. Water radiolysis reactions

Reaction ID	Reaction	Reaction rate (L/mol·s)
R1	$e^-_{aq} + O_2 \longrightarrow O_2^{\cdot -}$	2.3 10^{10}
R2	$H^{\cdot} + O_2 \longrightarrow HO_2^{\cdot}$	1.3 10^{10}
R3	$O_2^{\cdot -} + H^+ \rightleftharpoons HO_2^{\cdot}$	5 10^{10} (pKa=4.8)
R4	$HO_2^{\bullet} + HO_2^{\bullet} \rightarrow H_2O_2 + O_2$	9.80 10^5
R5	$O_2^{\bullet -} + O_2^{\bullet -} + 2H_2O \rightarrow H_2O_2 + O_2 + 2HO^-$	1.0 10^2
R6	$H_2O_2 + e^-_{aq} \rightarrow HO^{\bullet} + HO^-$	1.1 10^{10}
R7	$H_2O_2 + H^{\bullet} \rightarrow HO^{\bullet} + H_2O$	3.50 10^7
R8	$e^-_{aq} + CO_2 \rightarrow CO_2^-$	0.77 10^{10}
R9	$e^-_{aq} + O_2 \rightarrow O_2^{\bullet -}$	2.30 10^{10}

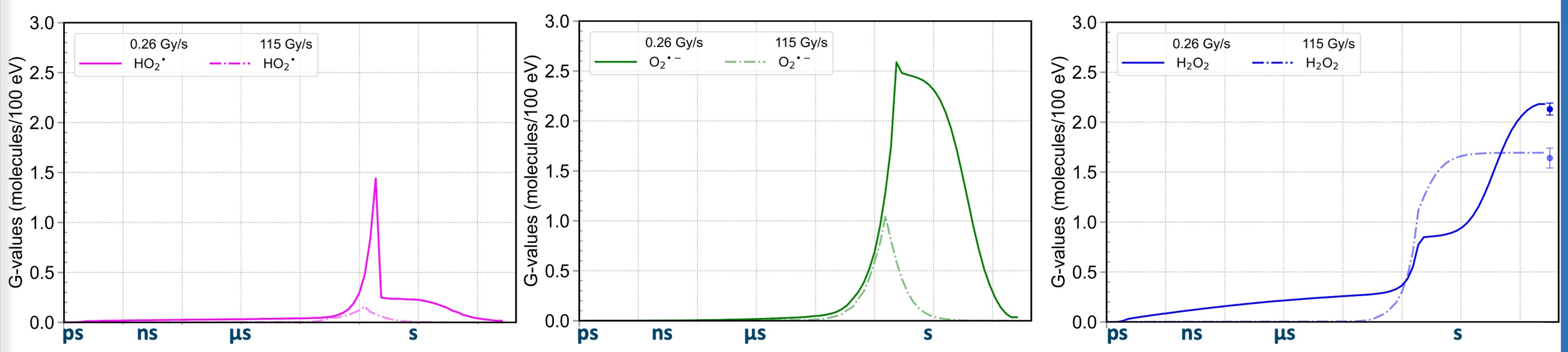


Figure 5. The simulated of G-values as a function of time under different dose rates

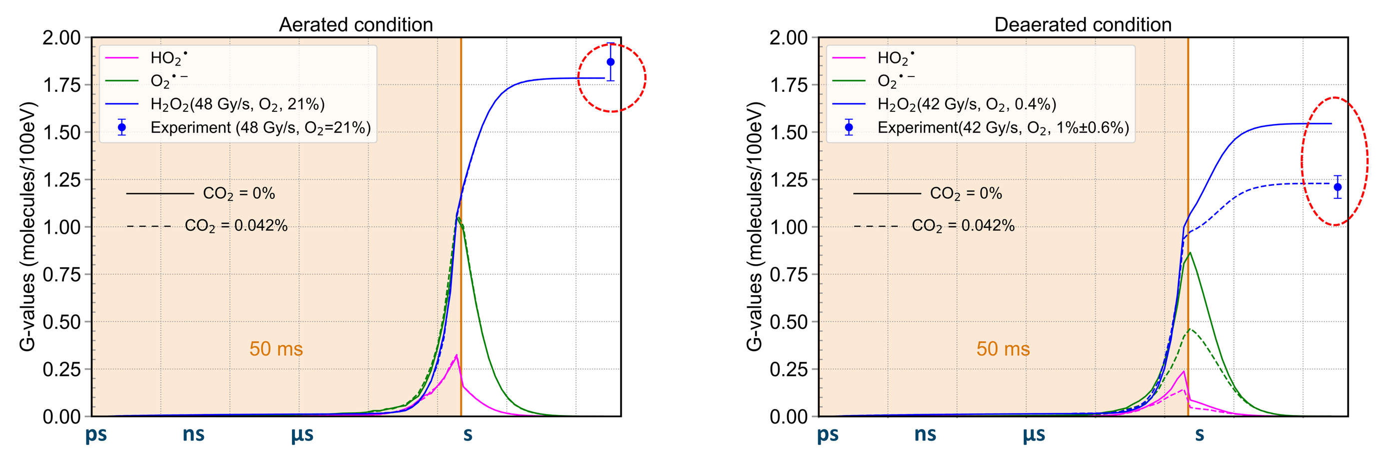


Figure 6. Impact of CO_2 on radical formation

• $G(H_2O_2)$ decreases with increasing dose rate for all O_2 leavels in Figure 4 and 5.
• Under 21% O_2 , the life time of e^-_{aq} and $H^{\cdot}$ (R1 and R2) are shorted, contributing to R4 and R5 in Table 2. Under 0.4% O_2 conditions, $G(H_2O_2)$ can be consumed through R5 to R7. In addition, $O_2^{\bullet -}$ formed via R3 equilibrium plays an important role at pH 5.5.
• In Figure 6, competition from CO_2 is negligible under aerated conditions. However, under deaerated conditions, CO_2 can effectively scavenge e^-_{aq} via R8 and 9.

Conclusion

Both experiments and simulations show an oxygen dependent decrease in $G(H_2O_2)$ under UHDR conditions. Simulations indicate an impact of the CO_2 content at physiological level. For future work, we aim to investigate the role of hydrated electron in the CO_2 and O_2 effects through time resolved radicals' measurement.

[1] Favaudon V, Caplier L, Monceau V, Pouzoulet F, Sarayath M, Fouillade C, Poupon MF, Brito I, Hupé P, Bourhis J, Hall J, Fontaine JJ and Vozenin MC. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Science translational medicine 6, 245, 2014.