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## Hydrogen Peroxide (H<sub>2</sub>O<sub>2</sub>) production in response to multiple beam irradiation of protons at UHDR

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## Context

The investigation of the **FLASH effect's** underlying **mechanisms** requires pulsed radiolysis studies. To date, **irradiation parameters** that induce such biological effect are improperly defined. Decreases in the **radiolytic yield of H<sub>2</sub>O<sub>2</sub>** at ultra-high doses rate have been reported for electrons [1] and protons [2]. This final species of water radiolysis can be used as a probe to verify hypotheses such as species recombination of tracks or oxygen depletion. To that end, multi-beam studies are relevant. Furthermore, this aspect is primordial for **translational research**, as current treatments often require multiple beams to spare surrounding healthy tissues.

➔ Does multiple beams delivery preserve the effect of UHDR on the production of the reactive oxygen specie (ROS) H<sub>2</sub>O<sub>2</sub>?

## Material and methods

- The **ARRONAX cyclotron** in Nantes delivers protons beam up to 70 MeV, at variable doses rates (0.2 Gy/s to 60 kGy/s) and time structures (millisecond macro-pulses).
- The experimental set-up for proton **radiolysis** [2] with a sample carrier holding designed PEEK radiolysis cells, allows the irradiation of the entire volume of Ultrapure water (Ø = 12 mm, depth = 15 mm) degassed under reconstituted air within the Bragg plateau.
- The **concentration of H<sub>2</sub>O<sub>2</sub>** is determined by UV-visible spectrophotometry (Ghormley method, [3]).
- Orthochromic OC-1 films** [4] were positioned at the cells entrance to ensure targeting and for *in vivo* dosimetry, as shown in Fig.1. Mean and maximum relative differences between film and online dosimetry are 0.5 % and 1.6 %, respectively.

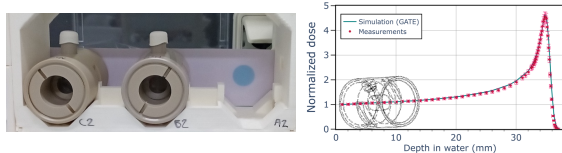


Figure 1. Left: a photograph of two radiolysis cells in front of the OC-1 films, Right: the depth of the radiolysis cell relative to the Bragg curve of 68 MeV protons, measured with a Markus Advanced (PTW) in water.

- 30 Gy** were delivered according to beam structures shown in Fig. 2. The impact of the number of the beams was evaluated in the UHDR mode at **8.6 kGy/s**, by delivering N times the same pulsed beam every 20 seconds but with a reduced duration of dt/N, with N equal to 1 (1x30 Gy), 2 (2x15 Gy), 3 (3x10 Gy), 5 (5x6 Gy) and 10 (10x3 Gy).

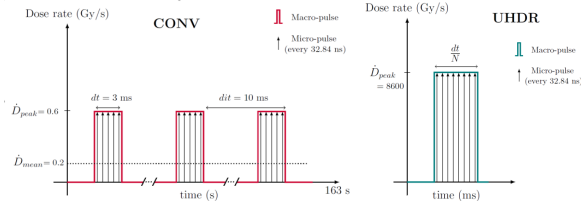


Figure 2. Beam structures used to deliver 30 Gy. For UHDR, dt=3.5 ms.

## Results

Preliminary results (n=1) are presented in Fig. 3.

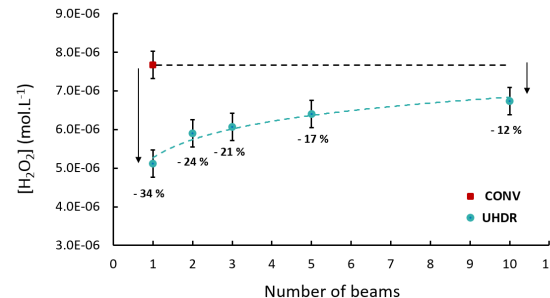


Figure 3. [H<sub>2</sub>O<sub>2</sub>] versus number of beams to deliver 30 Gy with protons under air.

## Conclusion and perspectives

Our study investigated the impact of the number of beams on the concentration of Hydrogen Peroxide (H<sub>2</sub>O<sub>2</sub>) after UHDR proton irradiation:

- The decrease of the H<sub>2</sub>O<sub>2</sub> concentration was **more significant with a single beam** than with multiple beams.
- The delivery of UHDR irradiations with multiple beams allows to obtain a differential effect compared to CONV irradiations but **with a lower amplitude**.
- In addition to the dose rate, the observed effect also depends on the **dose per beam** or the **total duration** of the irradiation.

Subsequent experiments will study the **time delay** between two beams to deepen this finding. Cross-experiments will be carried out with **biological models** (zebrafish embryos).

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