

New horizon in
therapy & treatment

FRPT

FLASH RADIOTHERAPY & PARTICLE THERAPY

2021

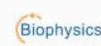
ONLINE CONFERENCE

1-3 DECEMBER 2021

UHDR PROTON BEAM VS. CONVENTIONAL:
HYDROGEN PEROXIDE AS FLASH EFFECT SENSOR

Guillaume Blain, Subatech & Nantes Flash Team, France

J. Vandenborre, D.Villoing, A.Bongrand, G.R. Fois, A.Guertin, F.Haddad, L.Hotouiu, C.Koumeir, R.Labarbe, L.Maigne, V.Métivier, F.Poirier, V.Potiron, N.Servagent, S.Supiot, G. Delpon, Sophie Chiavassa

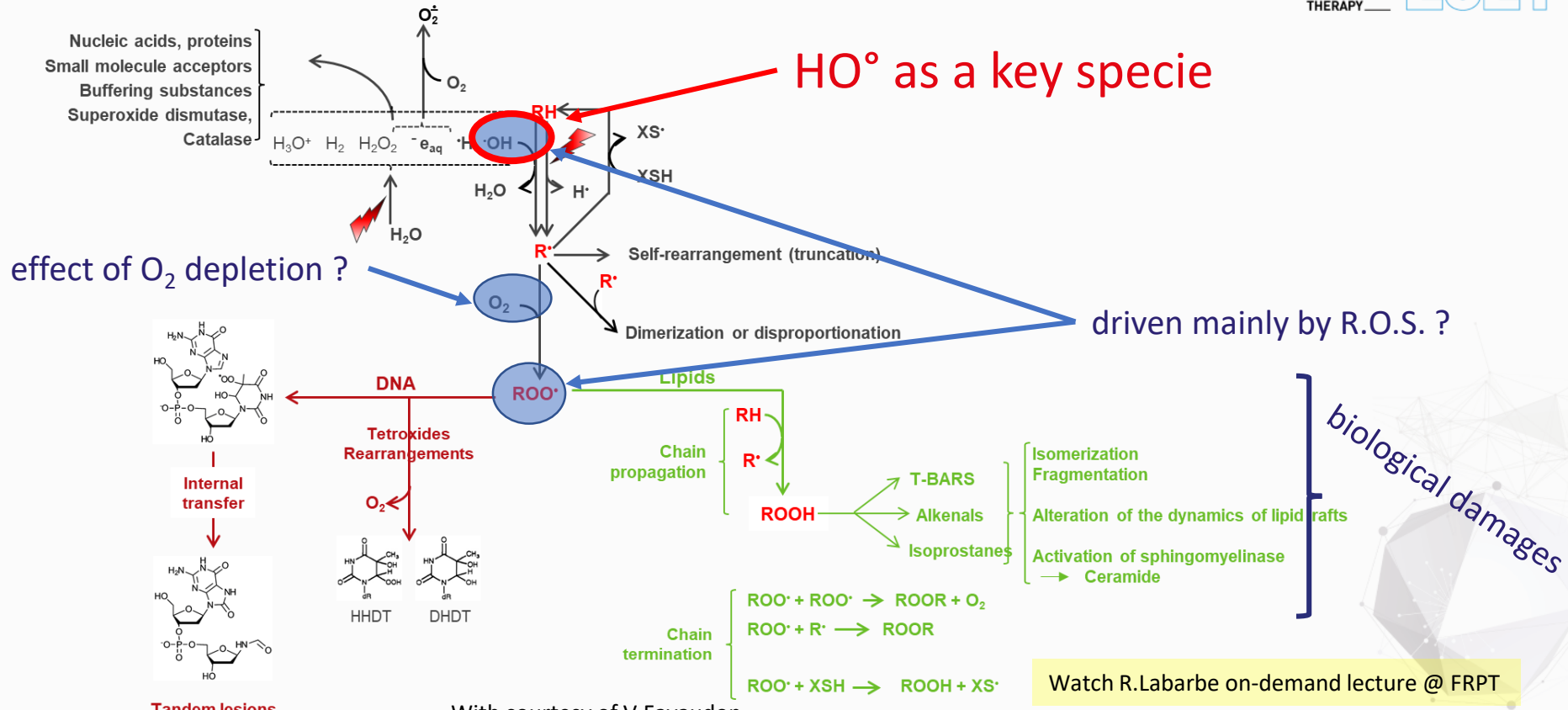


Faculty Disclosure

- Nothing to disclose



FLASH : one effect... several parameters ?

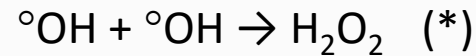
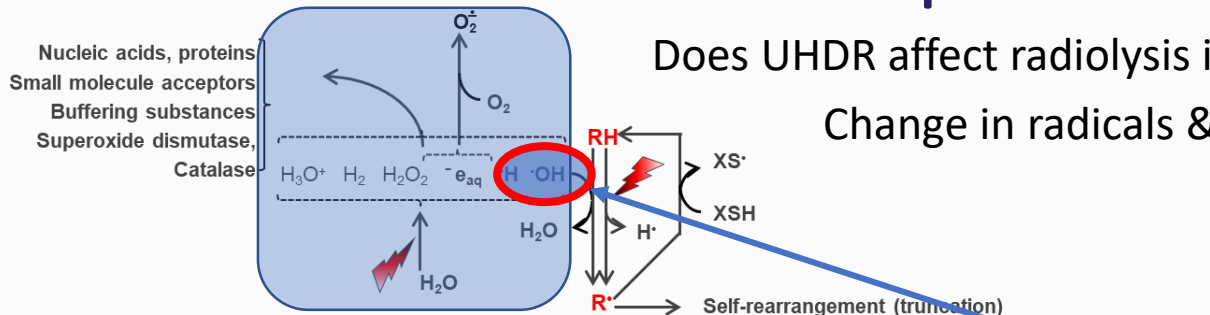


Watch R.Labarbe on-demand lecture @ FRPT

3 **Chromosome breaks – Aneuploidy – Mutations**
Cell death

With courtesy of V.Favaudon
Labarbe et al, Radiotherapy and Oncology 153:303-10, 2020

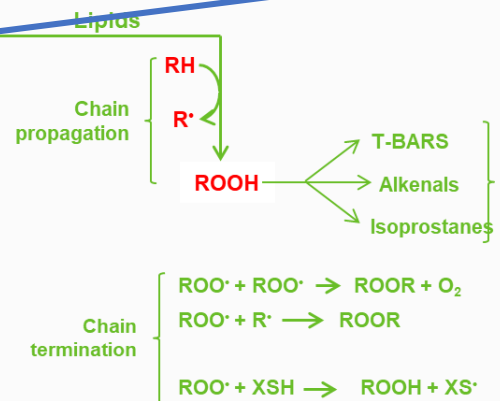
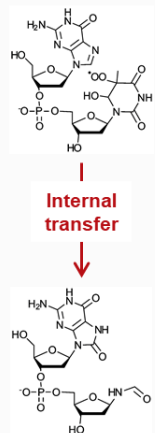
FLASH : one effect... several parameters ?



H_2O_2 as a sensor of HO°

effect of O_2 depletion ?

driven mainly by R.O.S. ?



Isomerization
Fragmentation
Alteration of the dynamics of lipid rafts
Activation of sphingomyelinase
 \rightarrow Ceramide

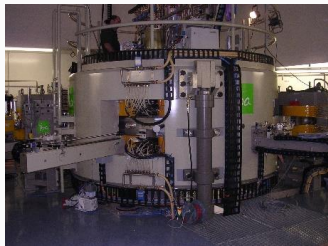
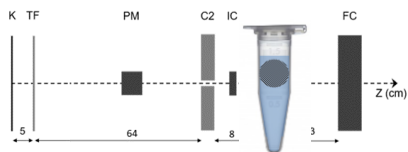
biological damages

Tandem lesions
Chromosome breaks – Aneuploidy – Mutations
Cell death

With courtesy of V.Favaudon
Labarbe et al, Radiotherapy and Oncology 153:303-10, 2020

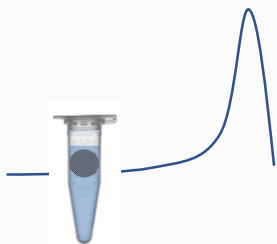
*Hatano, Y., Katsumura, Y., Mozumder, A., 2011. Charged Particle and Photon Interactions with Matter. CRC Press, Boca Raton, USA.

H⁺ beam setups and H₂O₂ measurement

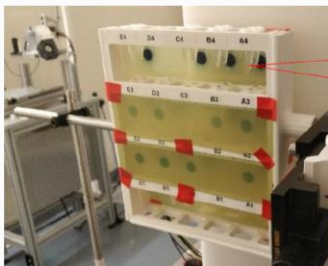


- 68MeV H⁺
- CONV (0,25Gy/s)
- Single pulse UHDR (40Gy to 60kGy/s)
- 1.4mL **pure water**, air, closed cap
- Dosimetry : films, ion.chamber, PM,

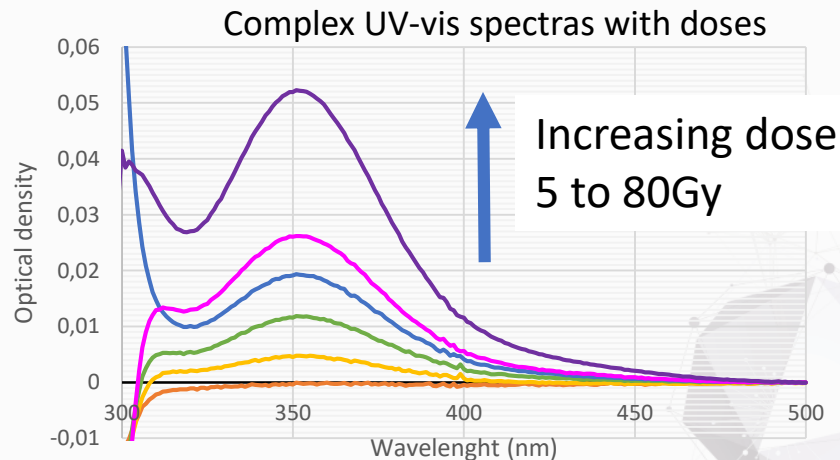
Plateau Irradiation = Zebra fish setup



5

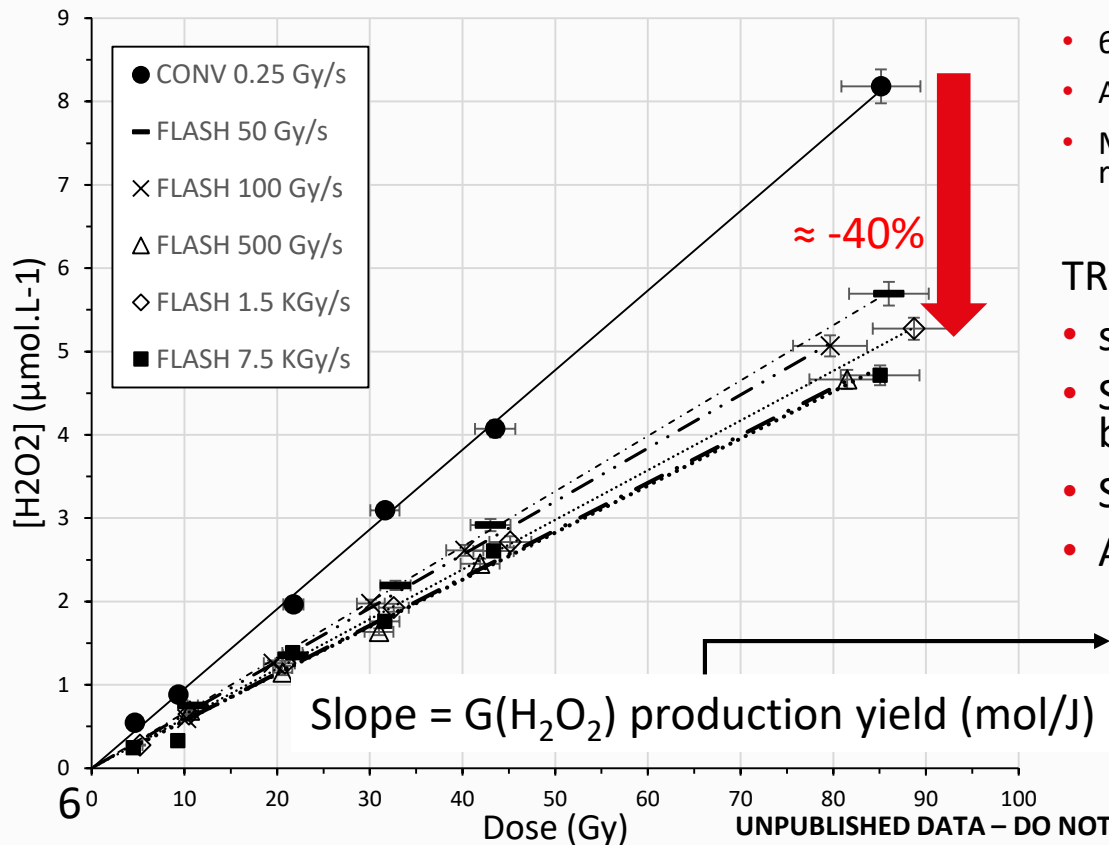


- Post Irr. H₂O₂ measurement
- Ghormley's* tri-iodide protocol
- UV-Vis 350nm band survey



*Ghormley JA, et al. J. Am. Chem. Soc. 76:3351-52, 1954.

H₂O₂ production comparison CONV Vs UHDR



- 68MeV H⁺ , 0.25 to 7.5KGy/s, pure water
- All exp. series replicated twice
- Montay-Gruel exp.* UHDR e⁻500Gy/s conditions reproduced with protons(Δ)

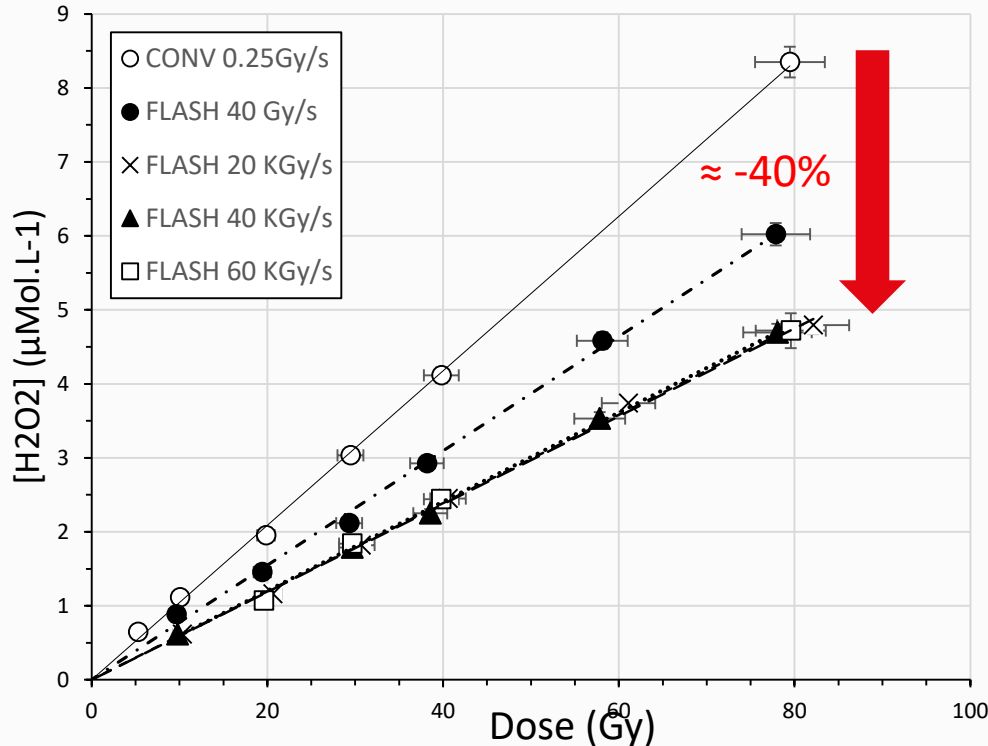
TREND :

- strongly decreased under UHDR beams
- Similar to electron despite of different beam features and measurements
- Stronger decrease with proton
- Already seen from 40 Gy/s

$$G(X)_t = [X]_t / (\text{Dose} \times \rho) \text{ in mol/J}$$

*Montay-Gruel P, Proceedings of the National Academy of Sciences 116:10943-51, 2019

H₂O₂ : what about higher UHDR ?



SAME TREND :

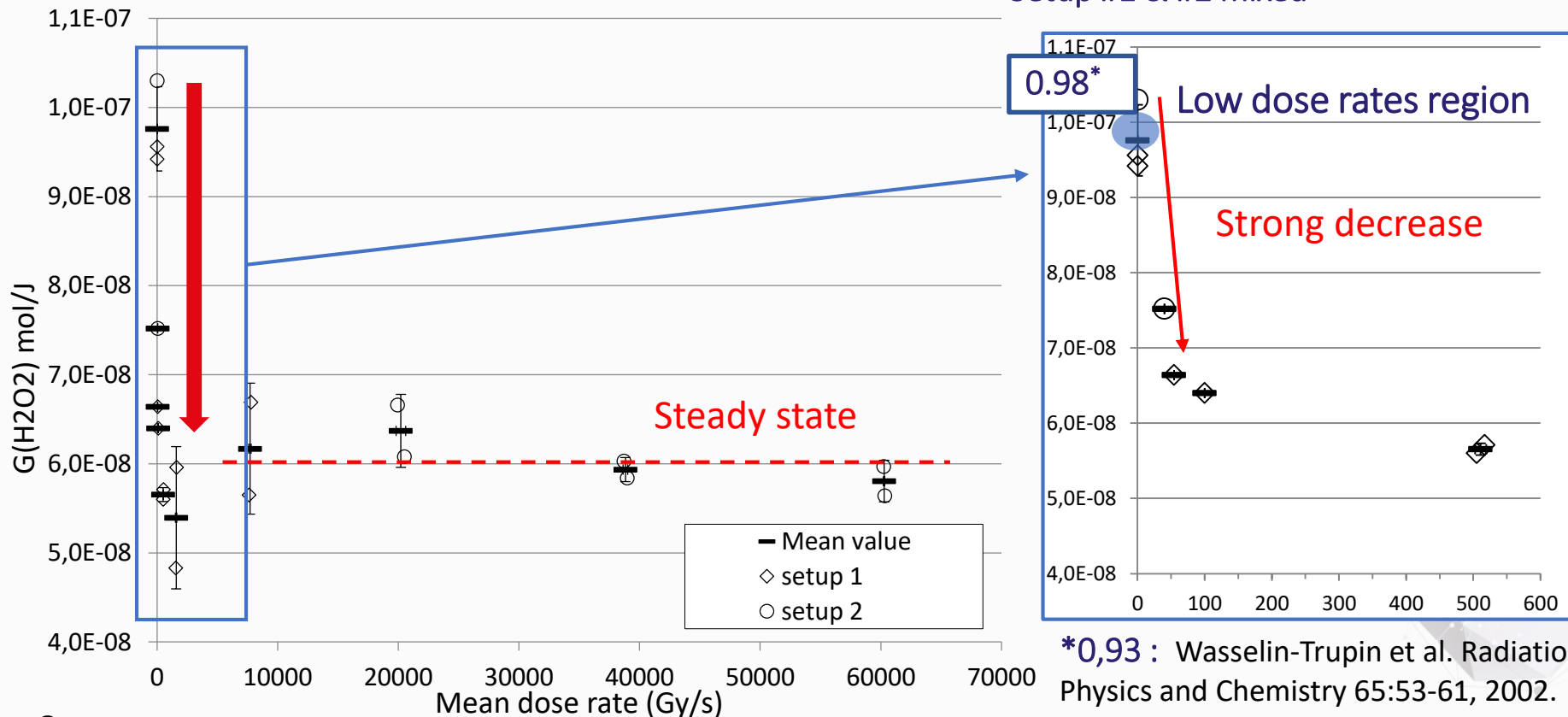
- H₂O₂ production is strongly decreased under UHDR beams

BUT

- Decrease stabilized for greater dose rates up to 60KGy/s

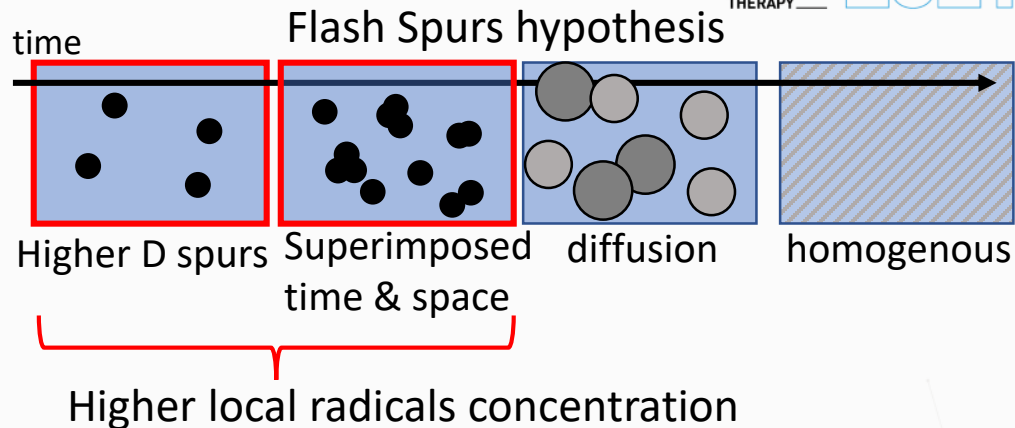
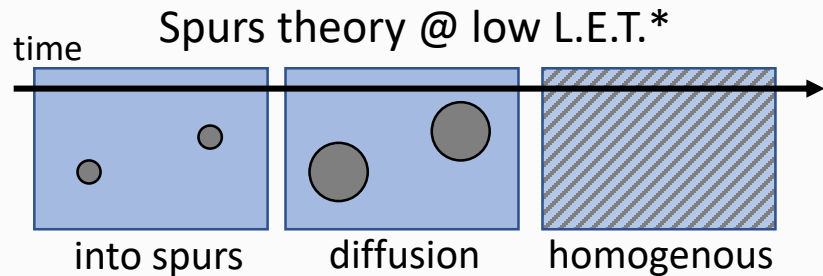
G(H₂O₂) production yields Vs dose rate

Setup #1 & #2 mixed

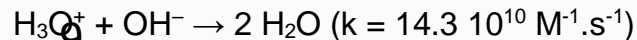
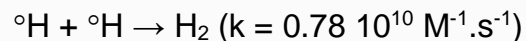
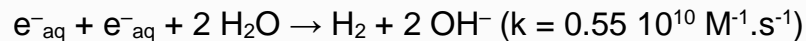
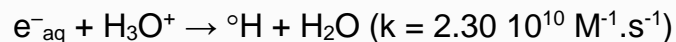
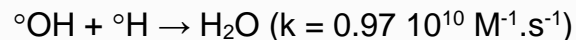
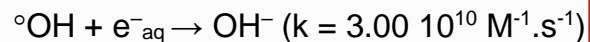
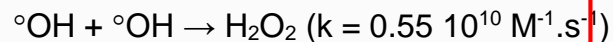


*0,93 : Wasselin-Trupin et al. Radiation Physics and Chemistry 65:53-61, 2002.

An additional early radiolysis step proposal



Reactions inside spurs clusters ($\leq \mu\text{s}$)



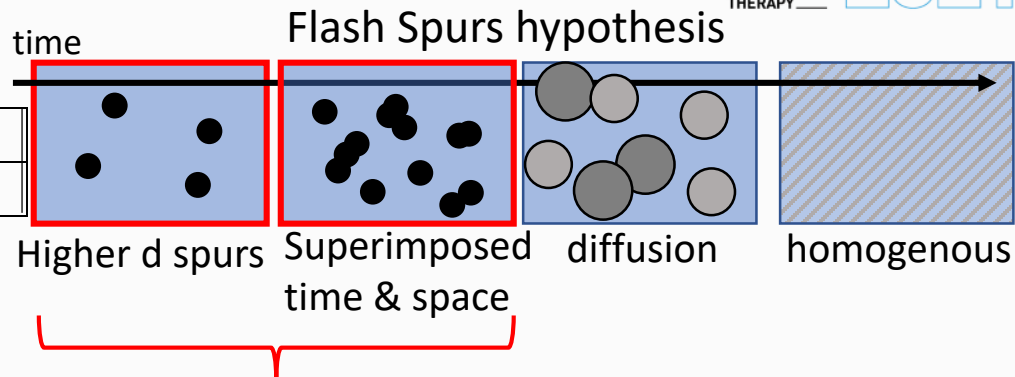
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An additional early radiolysis step proposal

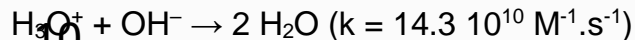
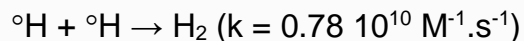
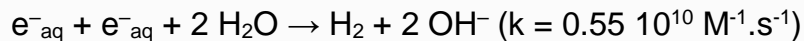
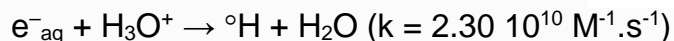
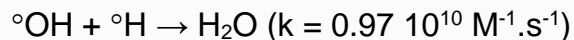
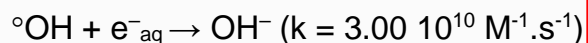
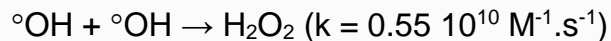
Primary yields inside spurs ($\mu\text{mol/J}$)

Particle	e^-_{aq}	$^{\circ}\text{H}$	$^{\circ}\text{OH}$	H_2	H_2O_2	$^{\circ}\text{HO}_2$	H_3O^+
β, γ	0.44	0.06	0.53	0.02	0.00	0.00	0.44

Atinault, 2008; Laverne, 2000; Laverne and Pimblott, 1991; Pimblott and Laverne, 1997



Reactions inside spurs (μs)



Partial scavenging by e^-_{aq}

Lower $[\text{HO}^{\circ}]$ available to produce H_2O_2

Consistent with lower 7HO-C3CA HO° adduct production observed by Kusumoto*

*in RSC adv., 2020, 10, 3879

Summary

- -40% decrease of H_2O_2 production under UHDR 68MeV H^+ Vs CONV
 - High local radicals concentrations
 - fast kinetics
 - early heterogenous chemistry of radiolysis
 - Consistent with literature
 - Can affect the further steps of proposed FLASH mechanisms ?
- } lower $[\text{HO}^\bullet]$ \rightarrow lower $[\text{H}_2\text{O}_2]$
Less HO^\bullet available for biochemical process

Further investigations in progress

- Measurement of $G(\text{HO}^\bullet)$ and $G(e^\bullet_{\text{aq}})$: Pulsed radiolysis and scavenging
- Beam structure and % O_2 • Steady state understanding
- Geant 4-DNA modelling

Credits



- Proton beams were provided by ARRONAX Cylotron teams
- Pulsing system was designed by F.Poirier
- UHDR and CONV dosimetry was achieved by D.Villoing, C.Koumeir, S.Chiavassa
- Beam line simulation from A.Bongrand, D.Villoing, S.Chiavassa
- Experimental set-up and holder by N.Servagent & Subatech mechanical workshop
- Experimental radiolysis set-up & measurements were by G.Blain & J.Vandenborre
- Radiation chemistry Monte-Carlo Geant4-DNA calculation by G.R.Fois & L.Maigne
- Flash effect mechanism study and discussions, physics, chemistry and biology **by all** including G.Delpon, F.Haddad L.Hotoiu & R.Labarbe... watch his on demand lecture@FRPT



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Thank you for attention

Do you want more ?

- **Details about this work** : completed article submitted in few days

- **About beams** :

PROTON BEAM FLASH ONLINE MONITORING AT ARRONAX CYCLOTRON - Thursday 15h10 Hall C **Charbel KOUMEIR**

- **About dosimetry** :

PROTON BEAM DOSIMETRY AT ULTRA HIGH DOSE RATES: EVALUATION OF THE USABILITY AND THE DOSE RATE DEPENDENCY OF VARIOUS RADIOCHROMIC FILMS - E-poster Station 1 Thursday 17h15 **Daphnée VILLOING**

or

MAXIMIZATION OF THE DOSE HOMOGENEITY IN THE PLATEAU FOR A LOW-ENERGY PRECLINICAL PROTON BEAM LINE - E-poster Station 1 Friday 16h30 **Daphnée VILLOING**

- **About mechanisms** :

A PHYSICOCHEMICAL MODEL TO EXPLAIN THE FLASH EFFECT - on-demand lecture **Rudy Labarbe**