TOPAS-nBio Simulation of Radiation Chemistry Following FLASH Irradiation Including Reactions of Biological Importance

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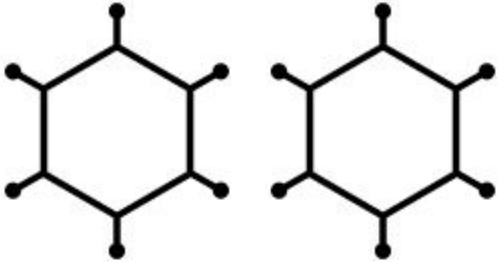
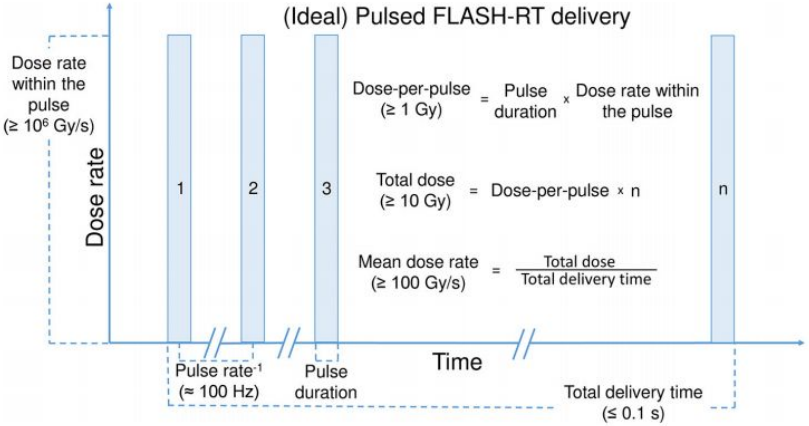
Presentation outline



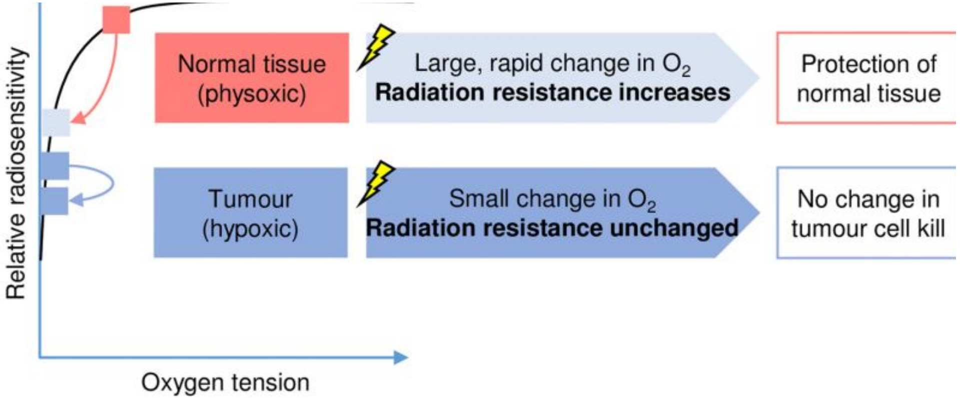
1. Introduction
2. Purpose
3. Methods
4. Results

Electron FLASH methodology
Oxygen depletion hypothesis

- Delivering **≥ 10 Gy dose** in a limited number of 1-2 Gy pulses
- Overall time ≤ **100 ms**
- These high dose rates of irradiations have been shown to reduce radiation damage of healthy tissues, but not the tumor



- **Oxygen depletion** is one of the most commonly mentioned hypothesis to elucidate the FLASH effect
- **In healthy tissues,** the O_2 is depleted in a great extent, so that cells ares made transiently hypoxic and thus radioresistant
- In **tumor cells**, the O_2 difference is much smaller, therefore the TCP is maintained at similar level than in conventional radiotherapy CONV-RT

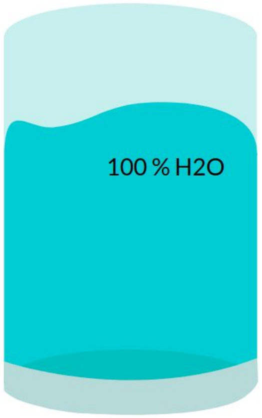


R. Labarbe et al. (2020) “A physicochemical model of reaction kinetics supports peroxyl radical recombination as the main determinant of the FLASH effect”, Radiotherapy and Oncology 153: 303
J. D. Wilson et al. (2020) “Ultra-High dose Rate (FLASH) Radiotherapy: Silver Bullet or Fool’s Gold?”, Front. Oncol. 9: 1563

Purpose

- Does the addition of biologically relevant moieties change the final O_2 concentration under FLASH vs. CONV conditions?

Pure water model



FLASH irradiation

$$e_{aq}^{-} + O_2 \rightarrow O_2^{\bullet -}$$

$$H^{\bullet} + O_2 \rightarrow HO_2^{\bullet}$$

$$O_2^{\bullet -} + HO_2^{\bullet}(+ H^{+}) \rightarrow O_2 + H_2O_2$$

$$2^{\bullet}OH \rightarrow H_2O_2$$

$$O_2^{\bullet -} + {}^{\bullet}OH + H^{+} \rightarrow O_2 + H_2O.$$

Adapted from: Wardman P. Radiotherapy Using High-Intensity Pulsed Radiation Beams (FLASH): A Radiation-Chemical Perspective. *Radiat Res.* 2020 May 20.

Howard B. Michaels et al. (1978) "A Model for Radiation Damage in Cells by Direct Effect and by Indirect Effect: A Radiation Chemistry Approach", Radiation Res. 74(1): 23

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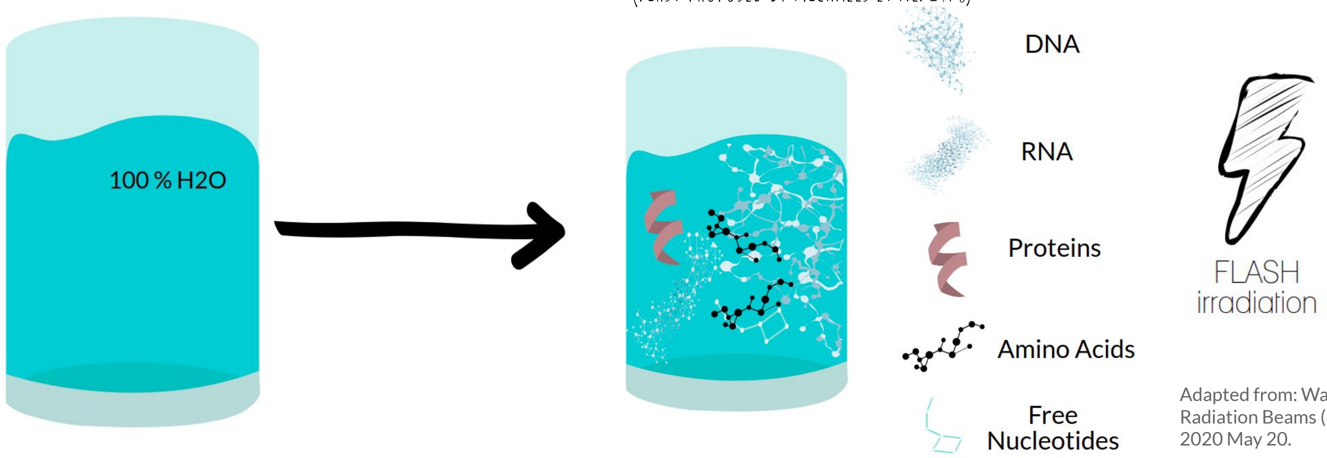
Pure water model

Biological model

(first proposed by Michaels et al. 1978)



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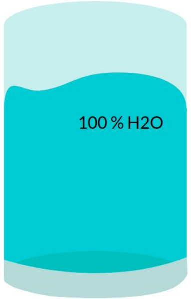
Methods: Introducing biological models into TOPAS-nBio simulations

Model 0



- Pure liquid water model
- Water radiolysis reactions [(1)] and:

$$e^{-}_{aq} + O_2 \rightarrow O_2^{\bullet -}$$

$$H^{\bullet} + O_2 \rightarrow HO_2^{\bullet}$$

Reactions for simulation of radiolysis in pure liquid water.

Reaction	k_{obs} (/M/s)
$e^{-}_{aq} + e^{-}_{aq} \rightarrow H_2 + OH^{-}$	5.5×10^{9}
$e^{-}_{aq} + H_3O^{+} \rightarrow H^{\bullet}$	2.3×10^{10}
$e^{-}_{aq} + H^{\bullet} \rightarrow H_2 + OH^{-}$	2.5×10^{10}
$e^{-}_{aq} + {}^{\bullet}OH \rightarrow OH^{-}$	3.0×10^{10}
$e^{-}_{aq} + H_2O_2 \rightarrow OH^{-} + {}^{\bullet}OH$	1.1×10^{10}
$H_3O^{+} + OH^{-} \rightarrow H_2O$	14.3×10^{10}
$H^{\bullet} + H^{\bullet} \rightarrow H_2$	7.8×10^{9}
$H^{\bullet} + {}^{\bullet}OH \rightarrow H_2O$	1.55×10^{10}
$H^{\bullet} + H_2O_2 \rightarrow {}^{\bullet}OH + H_2O$	9.0×10^{7}
${}^{\bullet}OH + {}^{\bullet}OH \rightarrow H_2O_2$	5.5×10^{9}

[(1)] Pimblott S (1992) *J. Phys. Chem.* **96** 4485–91

[(2)] Howard B and Michaels (1978) *Rad. Res.* **74** 23-34

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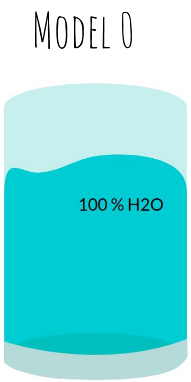

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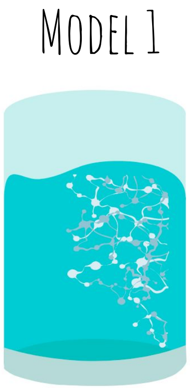

- Model 0 with [2]:

$$DNA + e_{aq} \rightarrow DNA^{\bullet}$$

$$DNA + H^{\bullet} \rightarrow DNA^{\bullet}$$

$$DNA + OH^{\bullet} \rightarrow \text{DNA-OH adduct}$$

$$\text{DNA-OH adduct} + O2 \rightarrow \text{DNA-OO}^{\bullet}$$

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Methods: Introducing biological models to TOPAS-nBio simulations

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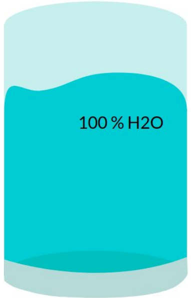

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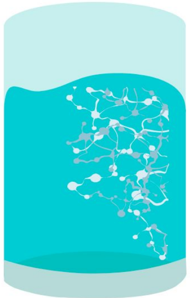
MODEL 1



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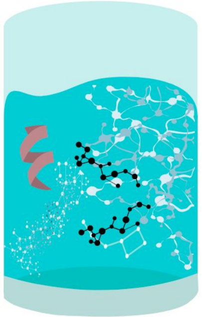
MODEL 2



- Model 0 with [2]:

$DNA + e_{aq} \rightarrow DNA^{\bullet}$
$DNA + H^{\bullet} \rightarrow DNA^{\bullet}$
$DNA + OH^{\bullet} \rightarrow DNA\text{-}OH\ adduct$
$DNA\text{-}OH\ adduct + O2 \rightarrow DNA\text{-}OO^{\bullet}$

$RNA + e_{aq} \rightarrow RNA^{\bullet}$
$RNA + H^{\bullet} \rightarrow RNA^{\bullet}$
$RNA + OH^{\bullet} \rightarrow RNA^{\bullet}$

$Proteins + e_{aq} \rightarrow Proteins^{\bullet}$
$Proteins + H^{\bullet} \rightarrow Proteins^{\bullet}$
$Proteins + OH^{\bullet} \rightarrow Proteins^{\bullet}$

$Amino\ Acids + e_{aq} \rightarrow Amino\ Acids^{\bullet}$
$Amino\ Acids + H^{\bullet} \rightarrow Amino\ Acids^{\bullet}$
$Amino\ Acids + OH^{\bullet} \rightarrow Amino\ Acids$

$Free\ Nu + e_{aq} \rightarrow Free\ Nu^{\bullet}$
$Free\ Nu + H^{\bullet} \rightarrow Free\ Nu^{\bullet}$
$Free\ Nu + OH^{\bullet} \rightarrow Free\ Nu^{\bullet}$

(Nu = Nucleotides)

[1] Pimblott S (1992) *J. Phys. Chem.* **96** 4485–91
[2] Howard B Michaels and John Hunt (1978) *Rad. Res.* **74** 23-34

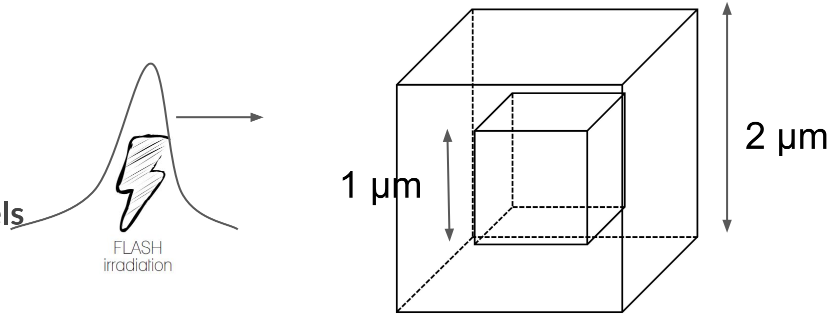
Methods: TOPAS-nBio Monte Carlo track-structure simulations

- An extension of TOPAS tool for sub-cellular simulations.[1]
- Simulates the physical and chemistry stages of water radiolysis.
- The physical and pre-chemical stage of irradiation inherit the parameters provided by Geant4-DNA.[2]
- For chemistry, TOPAS-nBio version for this project uses Independent Reactions Time (IRT) with inter-track simulation capability.[3]

credits:https://gray.mgh.harvard.edu/research/software/258-topas-nbio

Pulse parameters

- The simulations were carried out for **the three different models**
- Total doses **up to 60 Gy** were used in 10 Gy steps[4]
- The system was irradiated by **1 MeV electron beam.**



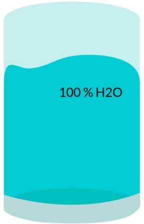
Mode	Dose Rate ($Gy * s^{-1}$)	Dose (Gy)	Pulse frequency (Hz)	Pulse width (µs)	Number of pulses	Treatment time (s)
CONV	0.29	10-60	10	1.0	350-2075	36-210
FLASH	500	10-60	100	1.75-1.9	2-12	0.01-0.11

[1] Schuemann J *et al.*, (2019) *Rad. Res.* **191** 125-138.
[2] Ramos-Méndez J *et al.*, (2018) *Phys. Med. Biol.* **63** 105014 12pp.
[3] Ramos-Méndez J *et al.*, (2020) *Rad. Res.* **194** 351-362.
[4] P. Montay-Gruel et al. (2019) *Proc Natl Acad Sci. USA.* **116**(22):10943-10951

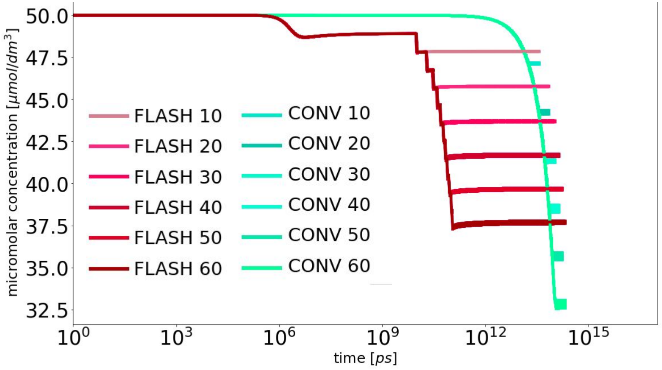
RESULTS

Results: time evolution of O2

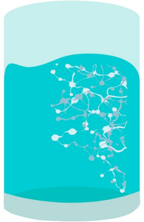
Model 0



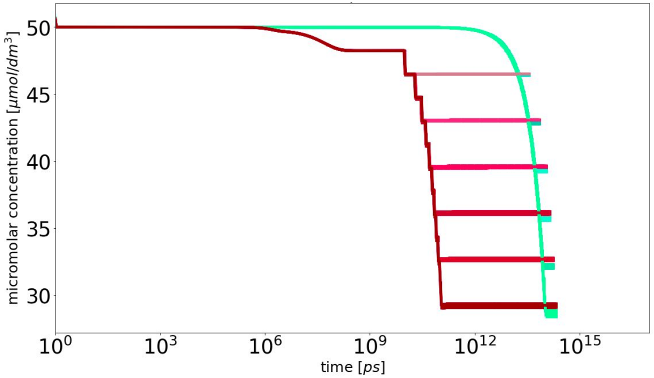
Oxygen depletion Model 0



Model 1



Oxygen depletion Model 1

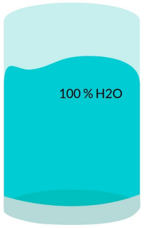


The results for Model2 are still being elaborated

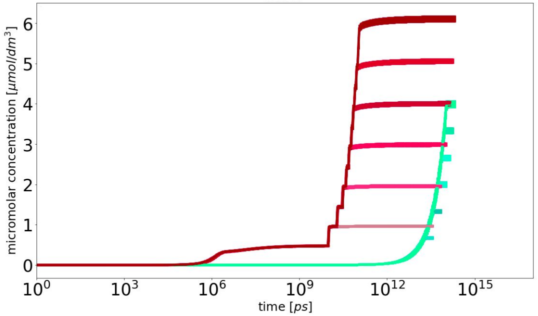
Ramos-Mendez et al., "LET-dependent intetrack yields in proton irradiation at ultra-high dose rates relevant for FLASH radiotherapy" Rad. Res. 194:351-362 (2020).

Results: time evolution of H_2O_2

Model 0



H_2O_2 Model 0



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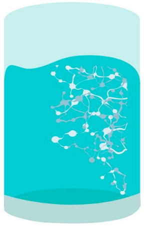
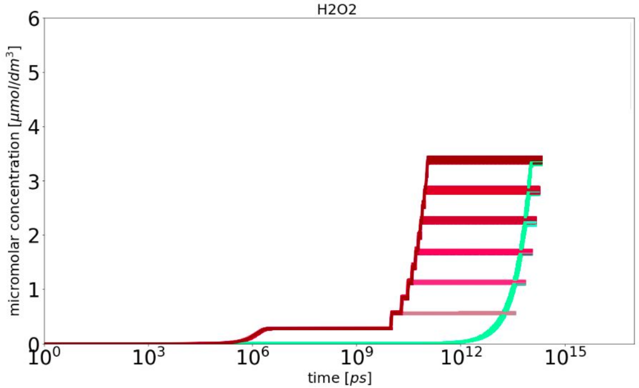
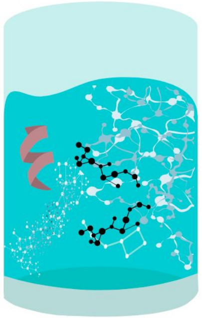


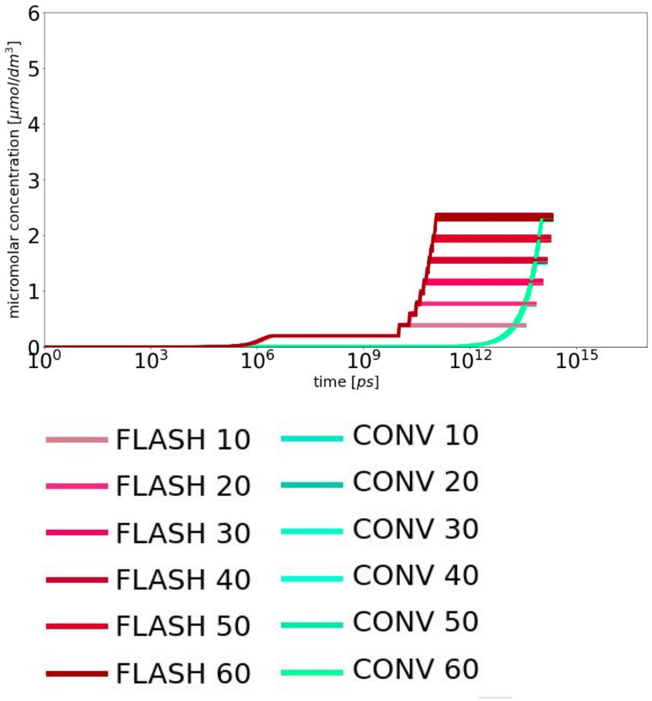
H_2O_2 Model 1



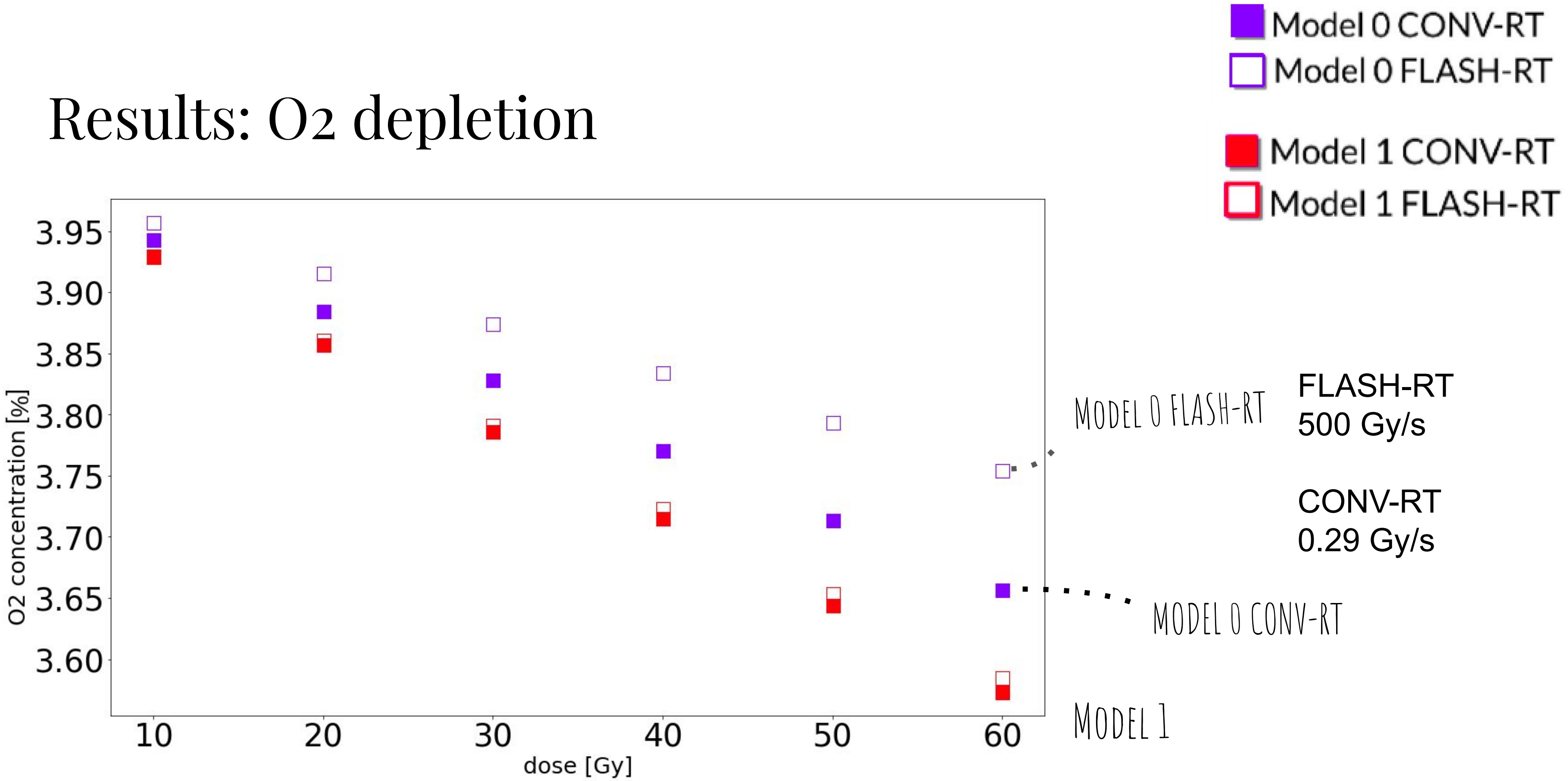
Model 2



H_2O_2 Model 2



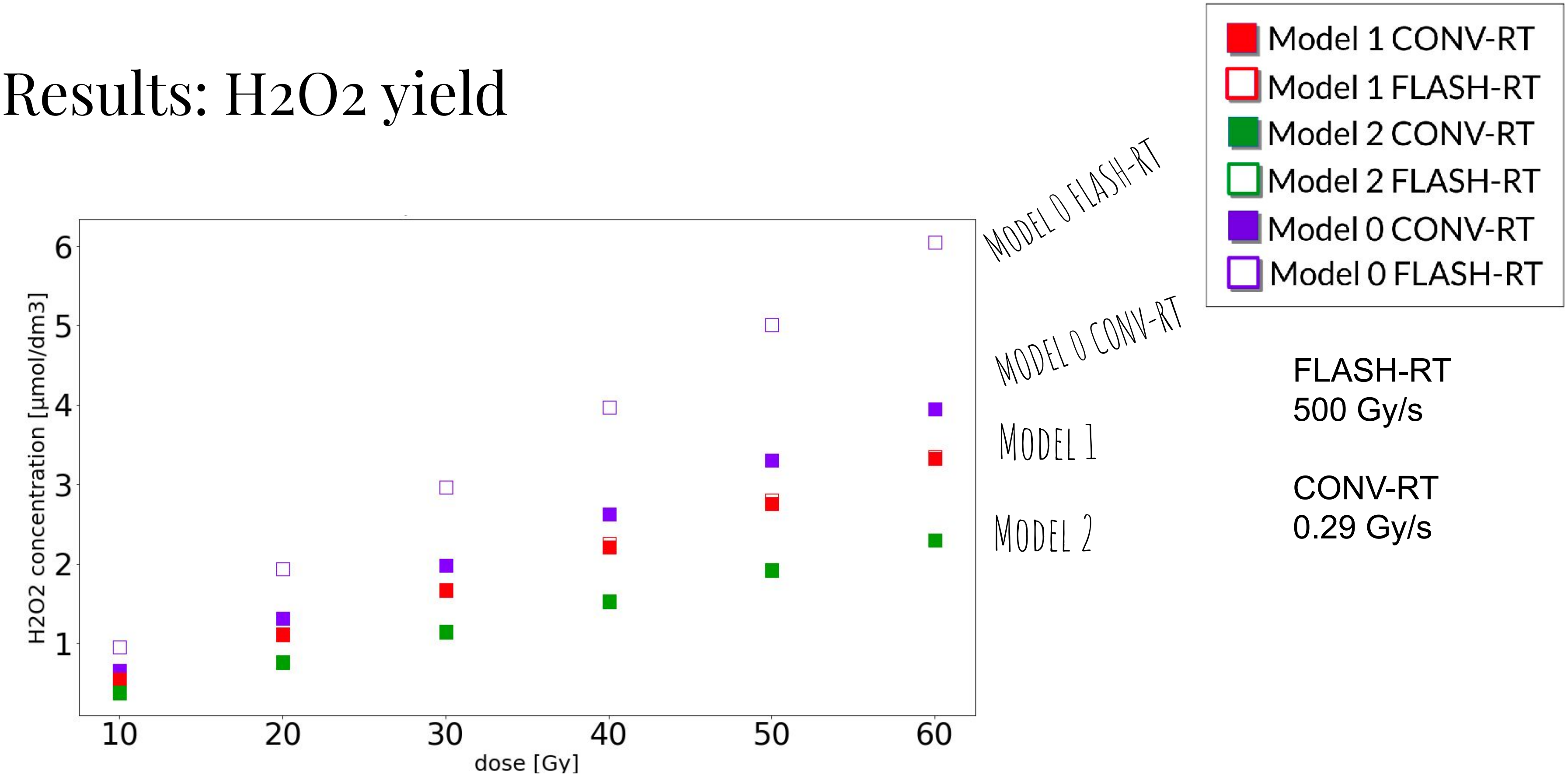
Results: O2 depletion



FLASH-RT
500 Gy/s

CONV-RT
0.29 Gy/s

Results: H_2O_2 yield



FLASH-RT
500 Gy/s

CONV-RT
0.29 Gy/s

Conclusions/summary

SIMULATIONS PERFORMED IN PURE WATER DO NOT REFLECT THE RADIATION CHEMISTRY GOING ON IN BIOLOGICAL SYSTEMS

- In this work we implemented three models to evaluate the chemical yields produced by low and high-dose rates.
- It was found that additional biological material affects significantly the yields compared to a pure liquid water model.
- The addition of a more detail model including more biological material affects the total yield of products like H_2O_2 and O_2.

THANK YOU FOR ATTENTION

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