Ultra-high Dose Rate response modeling and understanding:

where do we stand

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Outline

- The UHDR response (FLASH) understanding challenge and the role of biophysical modeling
  - Radiolytic Oxygen Depletion
  - Inter Track effects
  - Organic Radical Recombination
- Impact of medium, oxygenation, LET
- Role of experiments at XUHDR (Extreme Ultra high dose rate) as with LDPB (Laser Driven Particle beams): What can we learn?

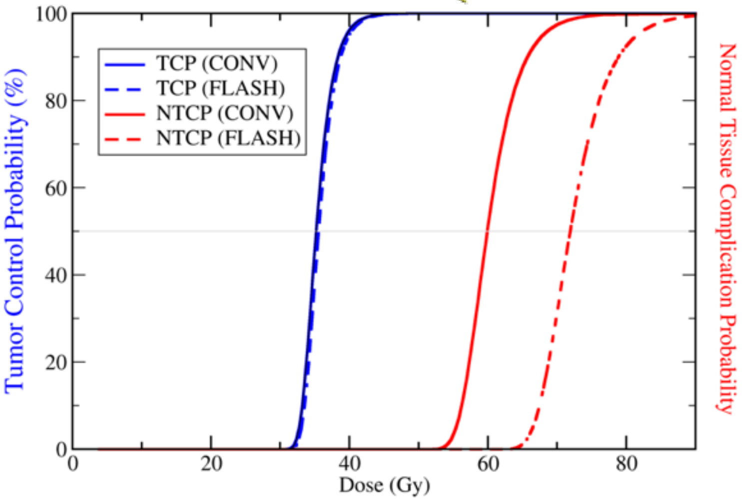
FLASH Effect: what's that

FLASH Radiotherapy, is a novel approach of RT using ultra-high dose rate (>40 Gy/s overall dose rate, for a total irradiation time <100 ms

aiming to get **unchanged tumor control** and **protection in the normal tissue.**

Conventional Irradiation

~0.03 Gy/s

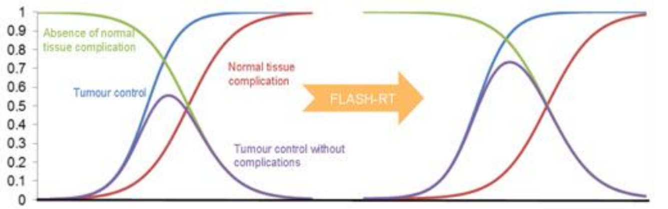


Ultrafast (FLASH) Irradiation

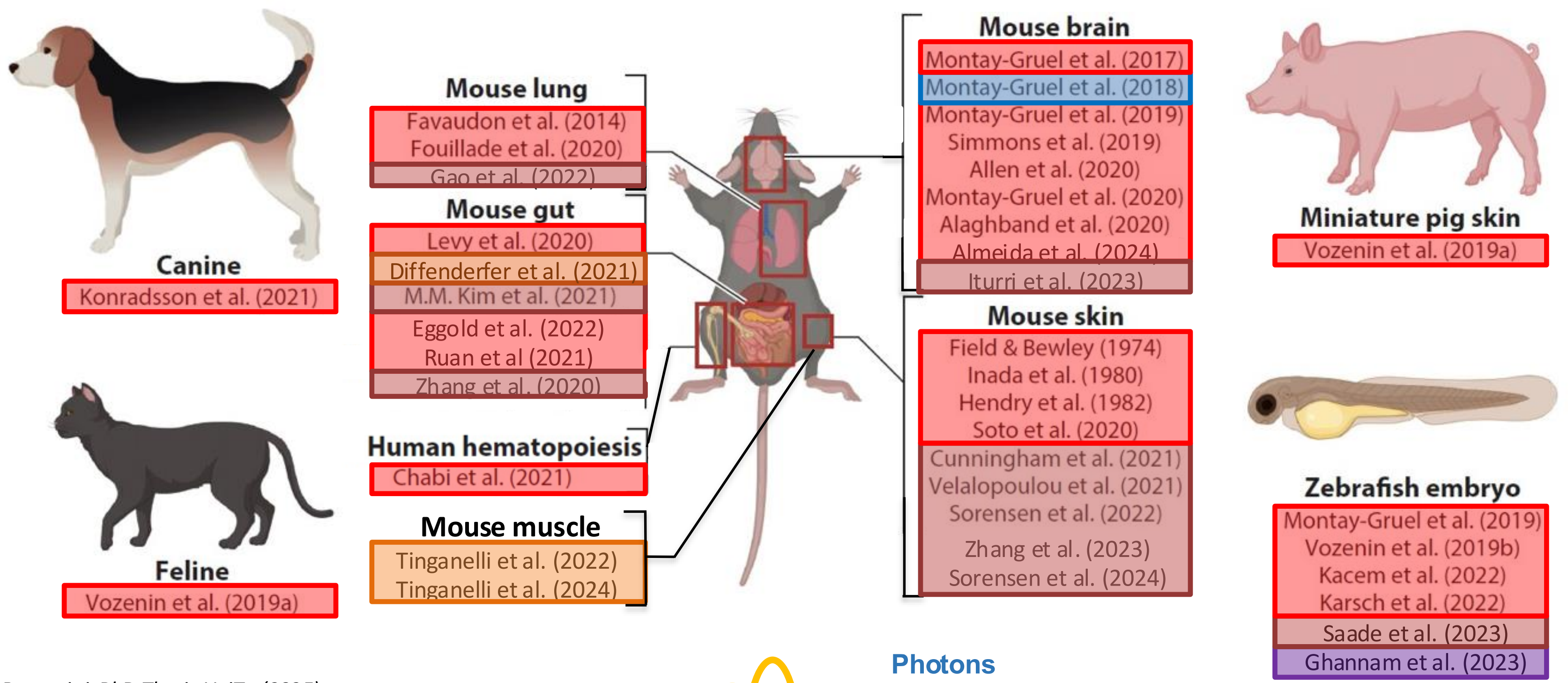
>40 Gy/s

TCPWC=TCP(1-NTCP)

Potential for widening the therapeutic window



The FLASH effect: *in vivo* evidence

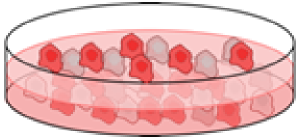


M. Battestini, PhD Thesis UniTn (2025)
Modified starting from C. Limoli, M. C. Vozenin, Annu. Rev. Cancer Biol. (2023)

UHDR beams

Photons
Electrons
Protons
Helium ions
Carbon ions

The “FLASH” effect: *in vitro* evidence*



Clonogenic cell survival

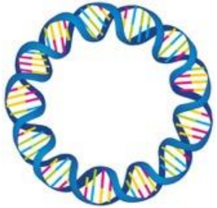
DU145 - Adrian et al. (2020)
Cancer cell lines - Adrian et al. (2021)
H454 - Montay-Gruel et al. (2019)
NS1 - Liljedahl et al. (2022)
IMR90 - Buonanno et al. (2019)
A549, H1437 - Tessonnier et al. (2021)
CHO-K1 - Tinganelli et al. (2021)

DNA damage

MRC5, IMR90 - Fouillade et al. (2020)
PBL (*ex vivo*) - Cooper et al. (2022)
IMR90 - Buonanno et al. (2019)
A549, H1437 - Tessonnier et al. (2021)

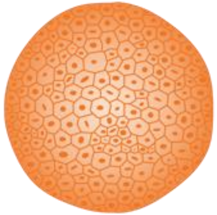
Senescence

IMR90 - Buonanno et al. (2019)



Plasmid DNA damage

pUC19 – Sforza et al. (2024)
pBR322 - Wanstall et al. (2024)



Spheroids

A549 - Khan et al. (2021)

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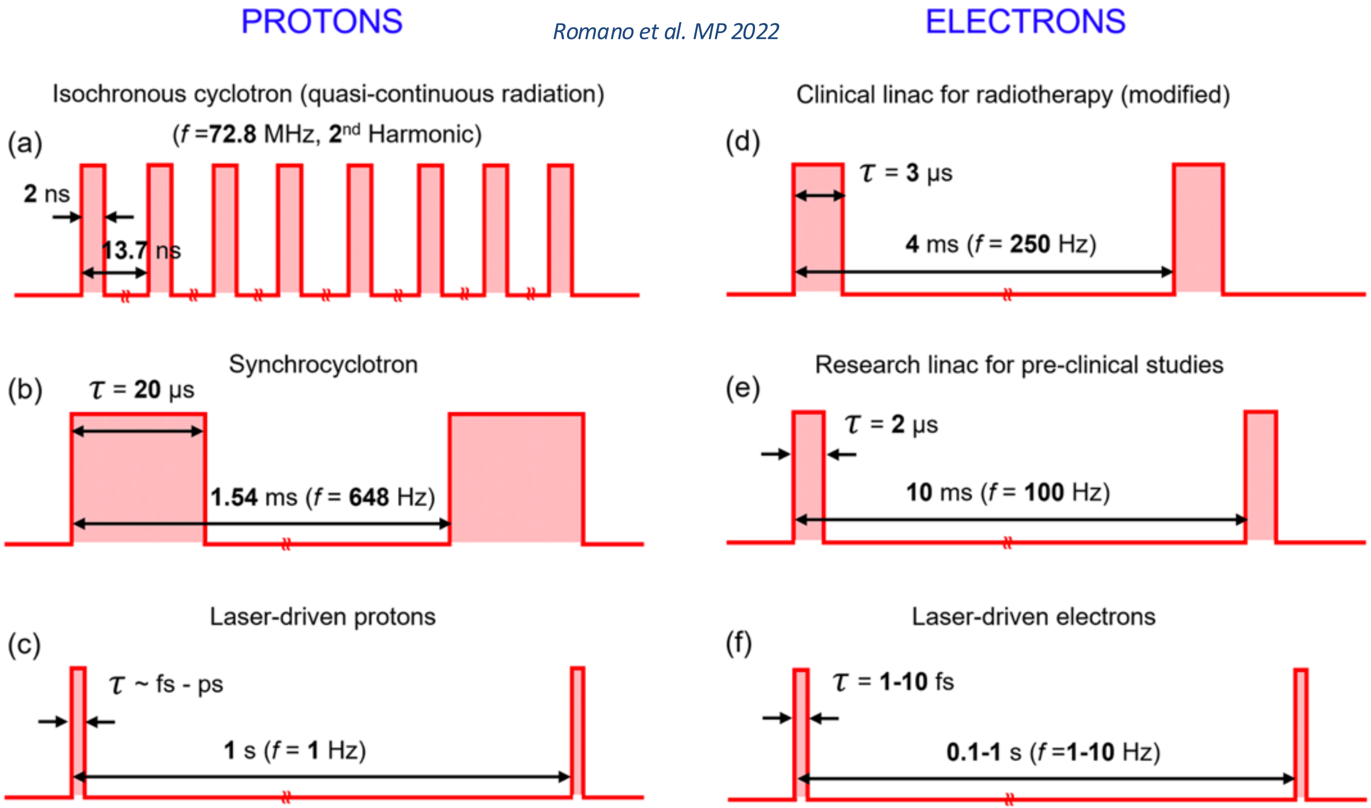
Modified starting from C. Limoli, M. C. Vozenin, Annu. Rev. Cancer Biol. (2023)

UHDR beams

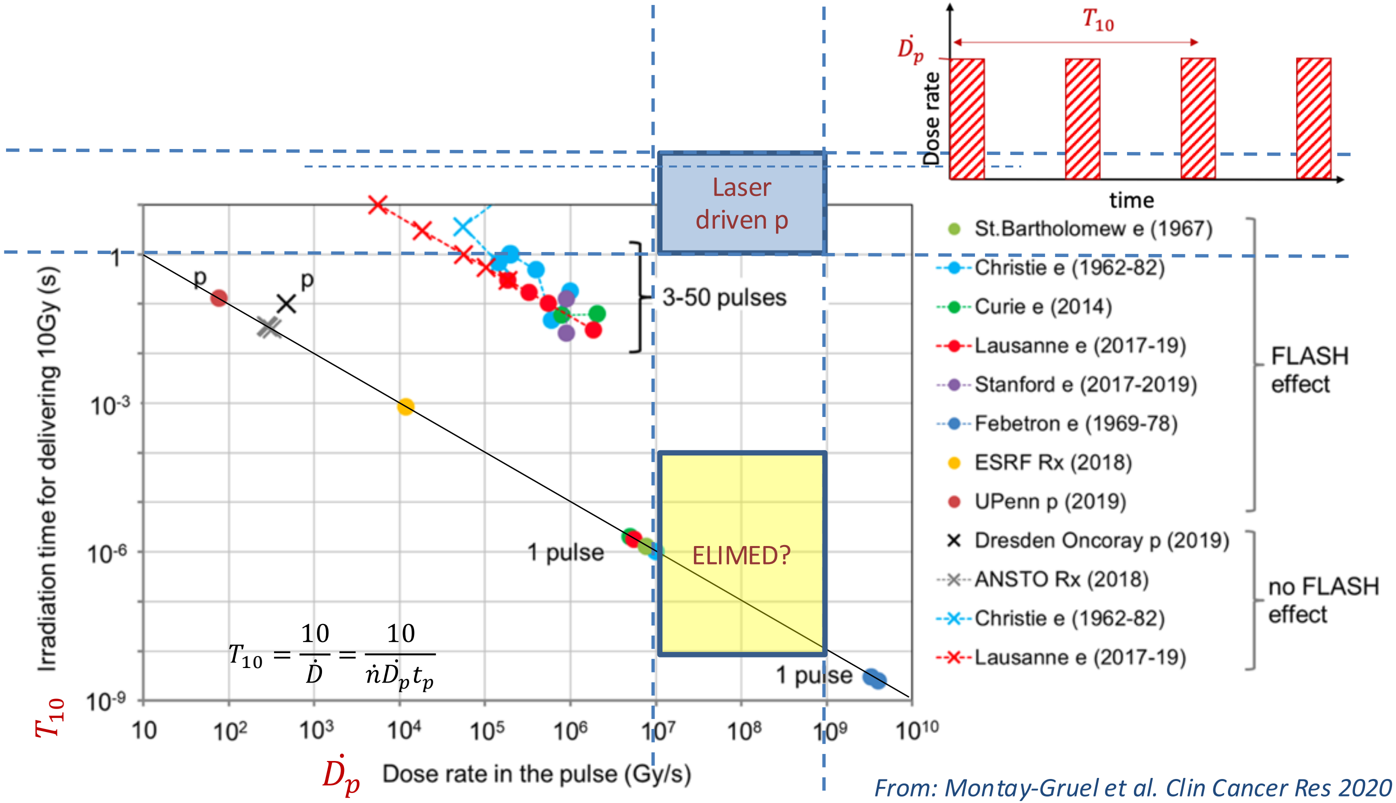
Photons
Electrons
Protons
Helium ions
Carbon ions

*=sparing effect at UHDR

Time structure for different particles

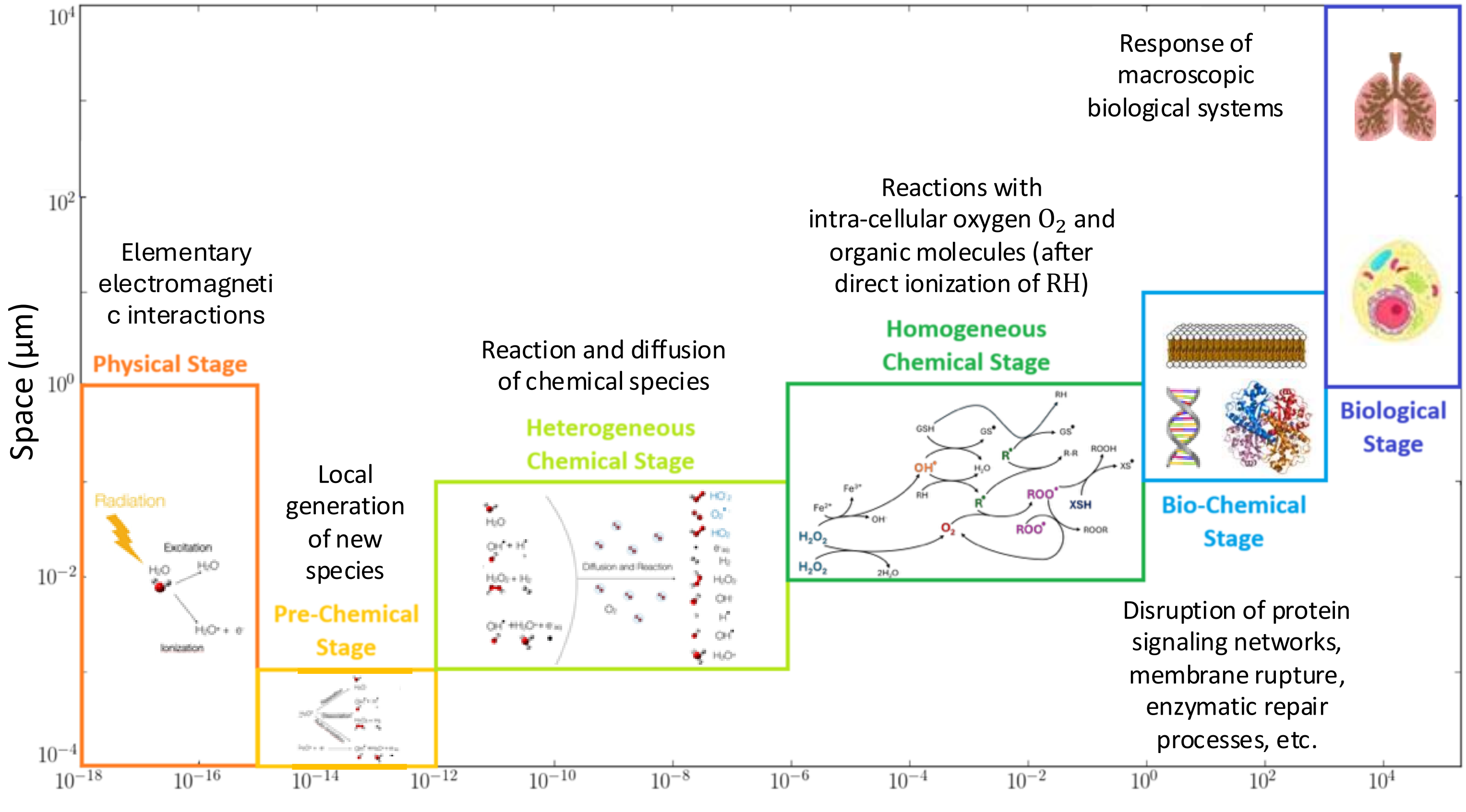


Parameters for observing FLASH/noFLASH



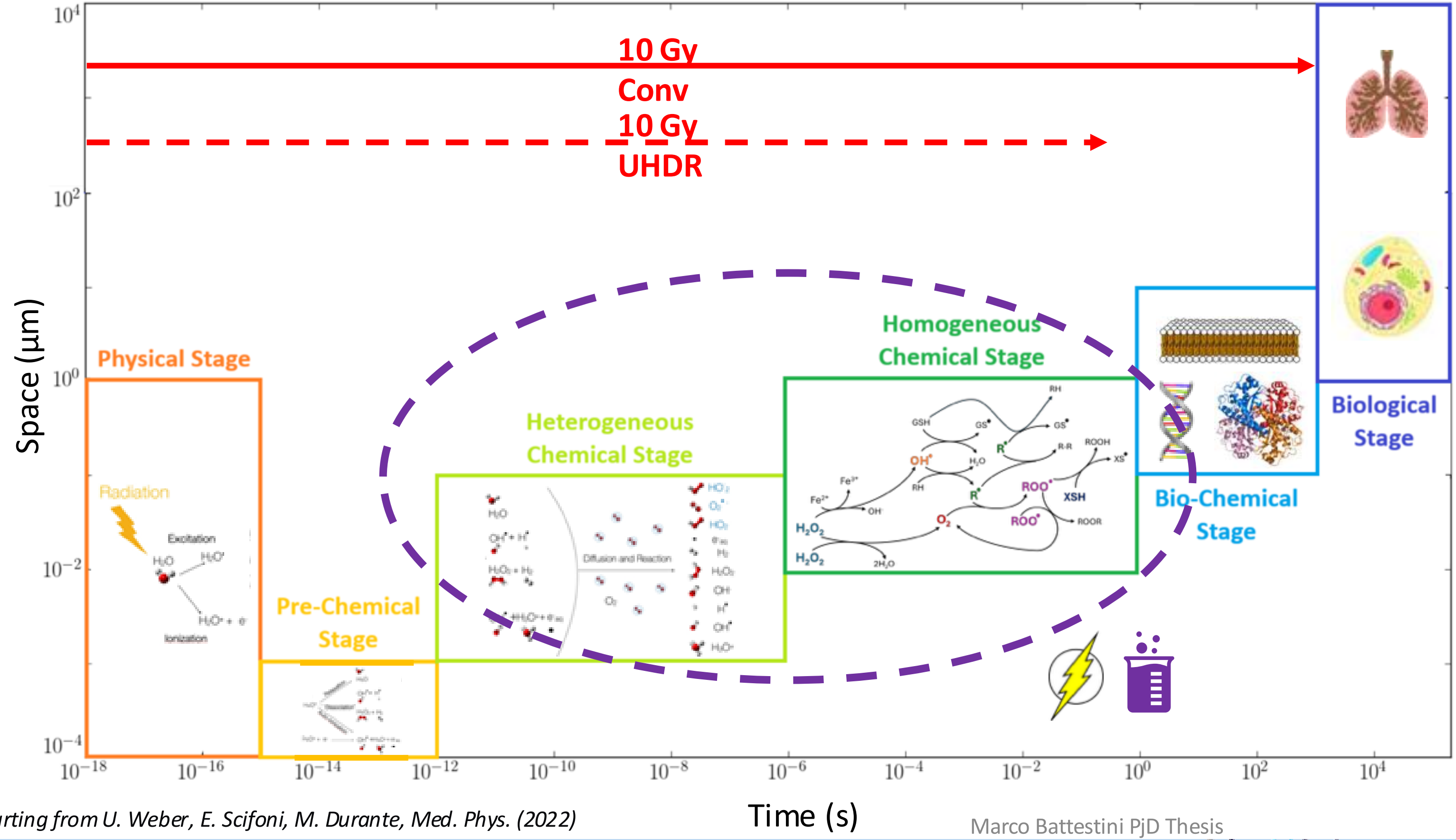
From: Montay-Gruel et al. Clin Cancer Res 2020

Spatio-temporal scales of radiation damage



Modified starting from U. Weber, E. Scifoni, M. Durante, Med. Phys. (2022)

Crucial stages and mechanistic hypotheses of FLASH effect



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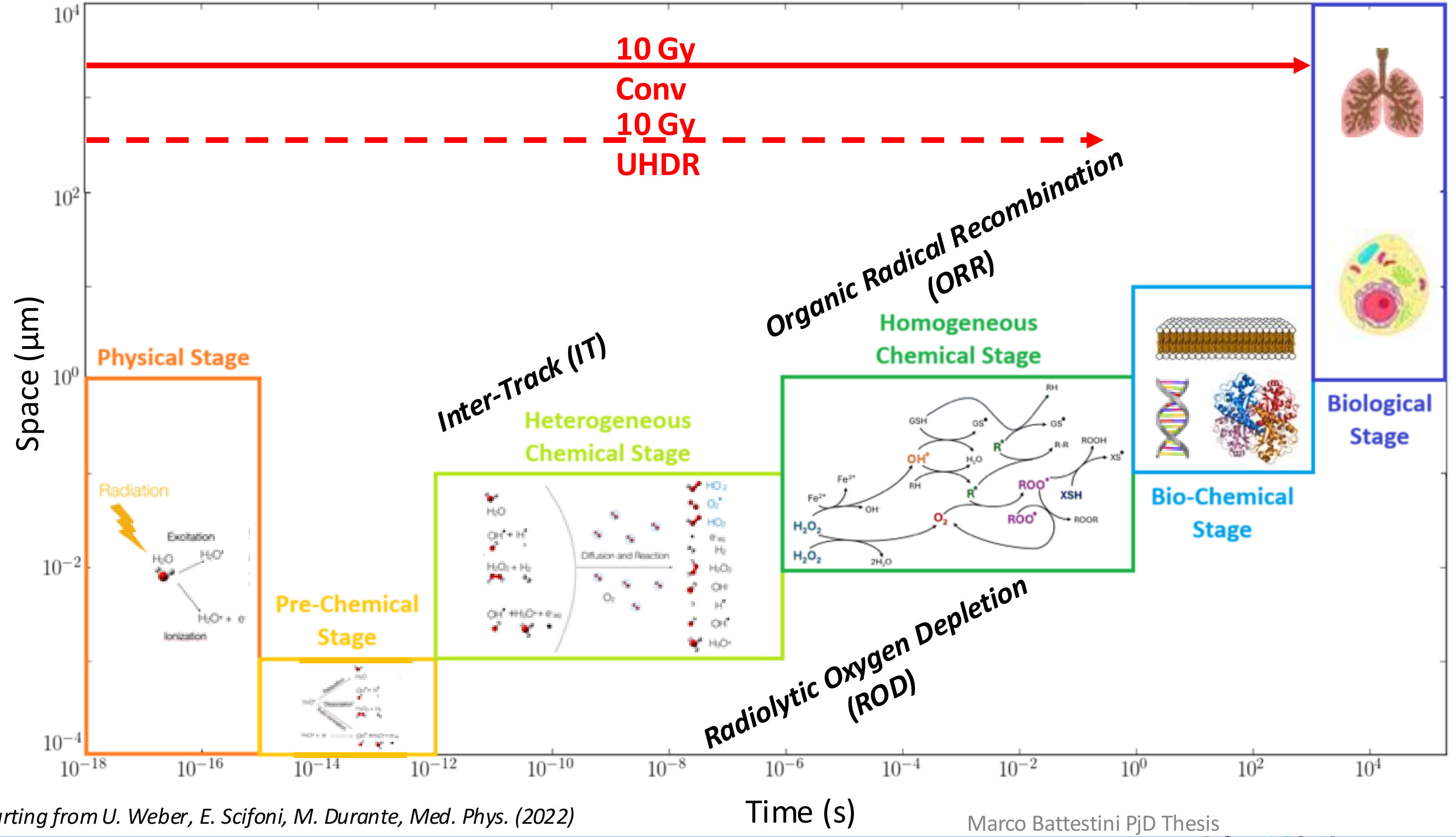
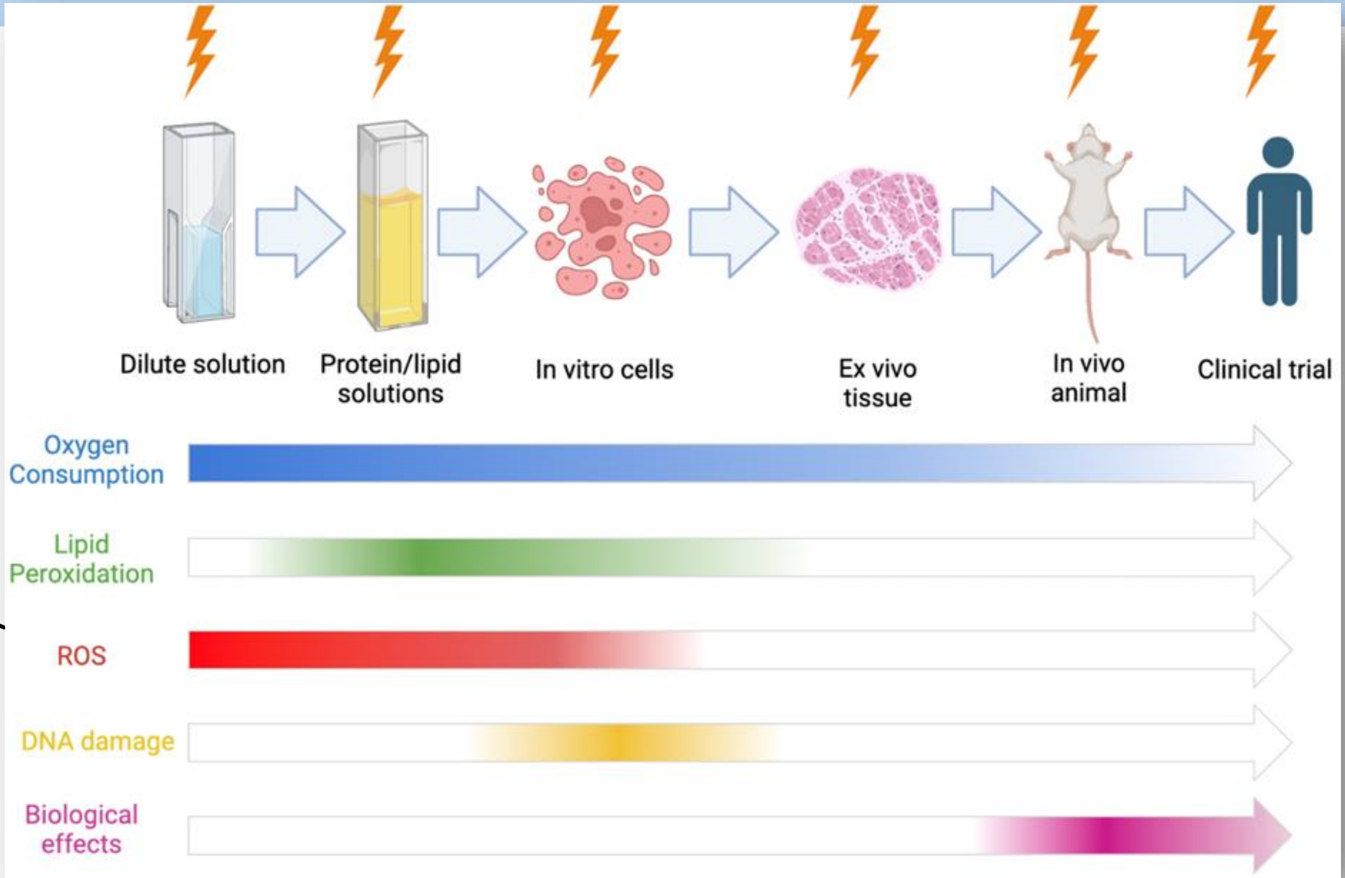
Crucial stages and mechanistic hypotheses of FLASH effect



Modified starting from U. Weber, E. Scifoni, M. Durante, Med. Phys. (2022)

Solution → Translation steps → Human

Assays of Radiation Chemistry Effects



Courtesy of Pogue lab

Sunnerberg, et al,
J. Biomed. Optics 2023

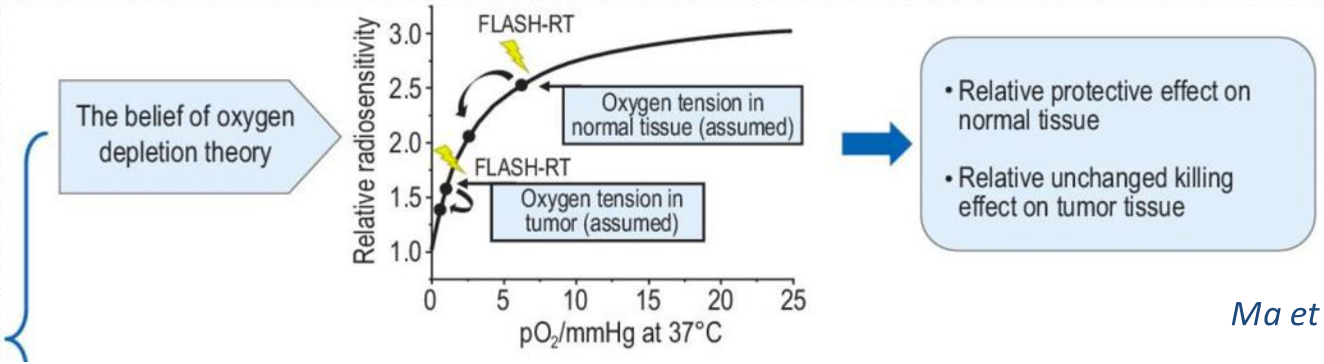
FLASH/UHDR Modeling Studies

Mechanism	Endpoint	Particle	Supported	Reference
ROD	S, δ_{ROD}	e^-	-	[Pratx and Kapp, 2019]
ROD	S, $\overline{RR}$	e^-	yes	[Petersson et al., 2020, Adrian et al., 2020]
ROD	S, dO_2/dD	e^-	yes	[Liew et al., 2021, Liew et al., 2022]
ROD	S, dO_2/dD	e^-	no	[Boscolo et al., 2020, Boscolo et al., 2021]
IT	DNA, ΔG	p, ^4He, ^{12}C	no	[Kreipl et al., 2009]
IT	ΔG	p	yes	[Ramos-Méndez et al., 2020]
-	dO_2/dD, ΔG	e^-, p	-	[D-Kondo et al., 2023, D-Kondo et al., 2025, Shin et al., 2024]
IT	ΔG	e^-, p	yes	[Derksen et al., 2023]
ROD/IT	dO_2/dD, ΔG	p	yes/yes	[Alanazi et al., 2020]
ROD/IT	dO_2/dD, ΔG	e^-	no/yes	[Lai et al., 2021]
IT	$\#_{overlaps}$	p	no	[Thompson et al., 2023]
IT	$\Phi(t)$	e^-	no	[Baikalov et al., 2023]
IT	ROS, NROS	p	yes	[Abolfath et al., 2022, Abolfath et al., 2023]
IT	ΔG	p, ^4He, ^{12}C	no	[Castelli et al., 2025]
ORR	NTCP	e^-	yes	[Labarbe et al., 2020]
ORR	NTCP	e^-	yes	[Espinosa-Rodriguez et al., 2022]
ORR	ΔAUC	e^-, p	yes	[Tan et al., 2023]
-	S	e^-, p, ^4He, ^{12}C	yes	[Battestini et al., 2023, Battestini et al., 2025]

Table 1: *In-silico* FLASH studies in literature. ROD = radiolytic oxygen depletion, IT = inter-track, ORR = organic radical recombination.

M. Battestini PhD Thesis Univ of Trento 2025

The Radiolytic Oxygen Depletion Hypothesis (ROD)

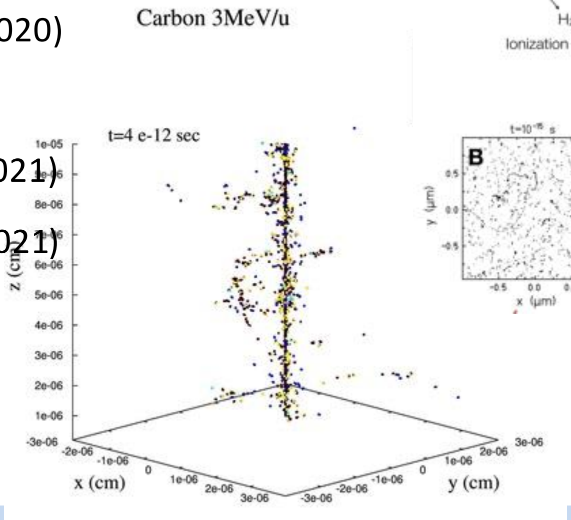


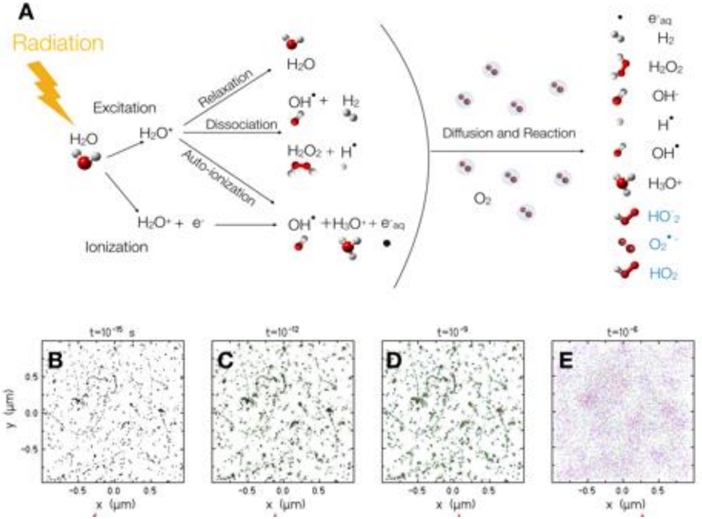
Ma et al. 2024

Monte Carlo Track structure Codes for exploring FLASH Chemistry

Heterogeneous stage (and slightly beyond…)

- TRAX-CHEM (Boscolo et al. 2020)
- TOPASnBIO (Ramos et al. 2020)
- gMicroMC (Lai et al. 2021)
- Geant4-DNA (Tran et al. 2021)
- IONLYS-IRT (Alanazi et al. 2021)
- NASIC (Zhou et al.2021)

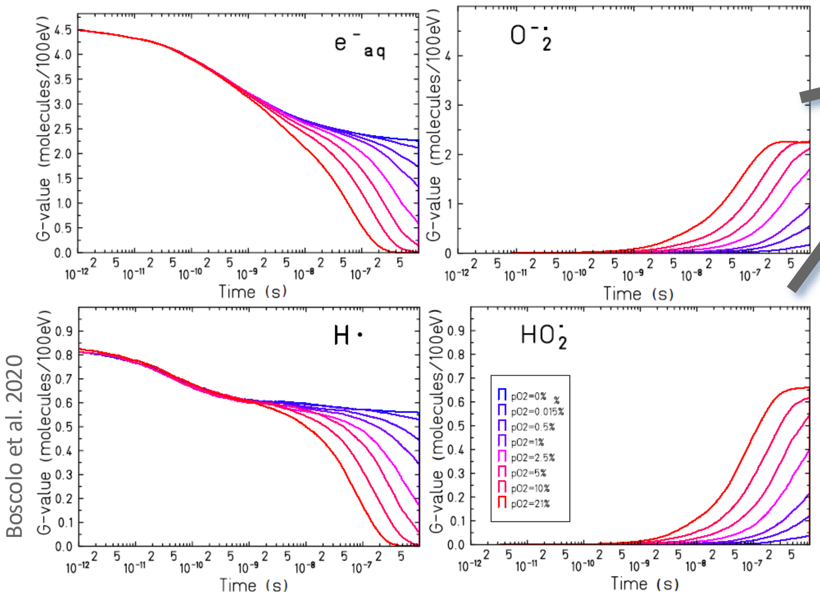


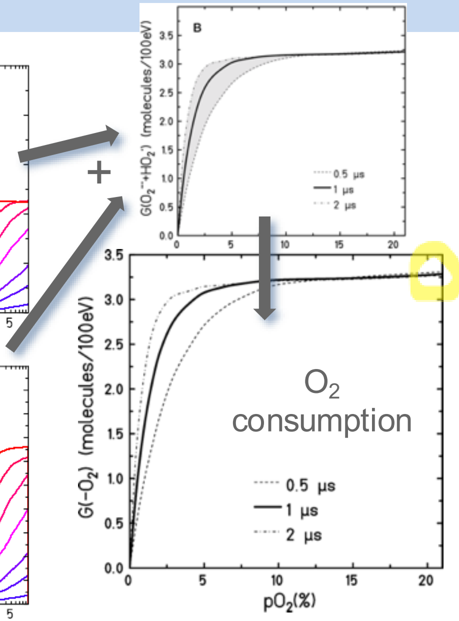


Boscolo et al. 2021 u.r.

TRAX-CHEM predicted oxygen depletion in water

low-LET electrons





3.28 mol./ 100eV = 0.33 μM/Gy **=2.4%/100Gy**

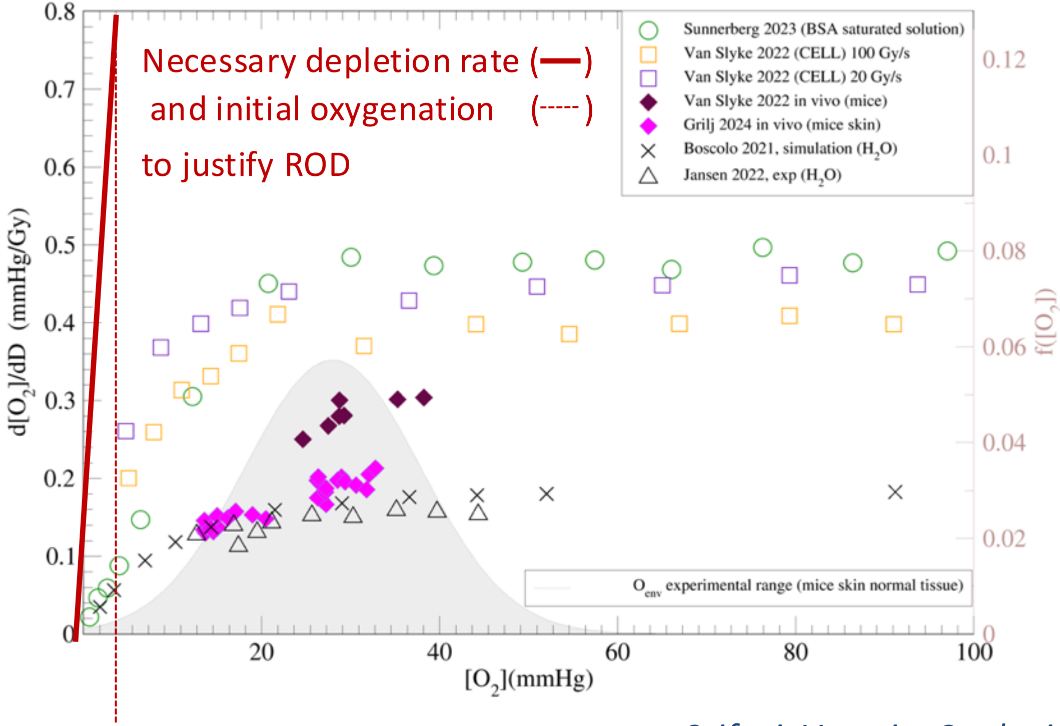
ELSEVIER
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com
Original Article

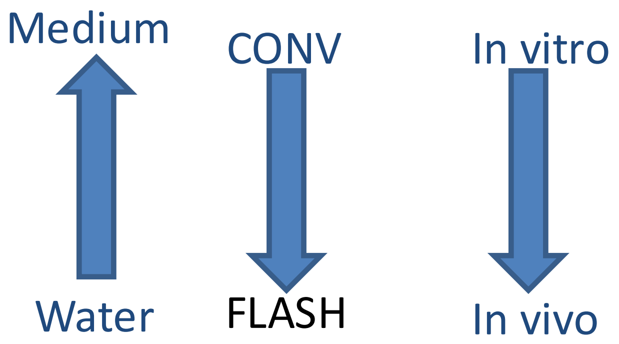
May oxygen depletion explain the FLASH effect? A chemical track structure analysis

Daria Boscolo[a], Emanuele Scifoni[b], Marco Durante[a,c,*], Michael Krämer[a], Martina C. Fuss

Boscolo et al JMS 2020; RO 2021

Summary (Exp&Theor) depletion studies





Scifoni, Vozenin. Cordoni. Fuss, Seco, Radiother Oncol 2025

Summary depletion studies in vivo

Volume 121 • Number 5 • 2025 Letters to the Editor 1399

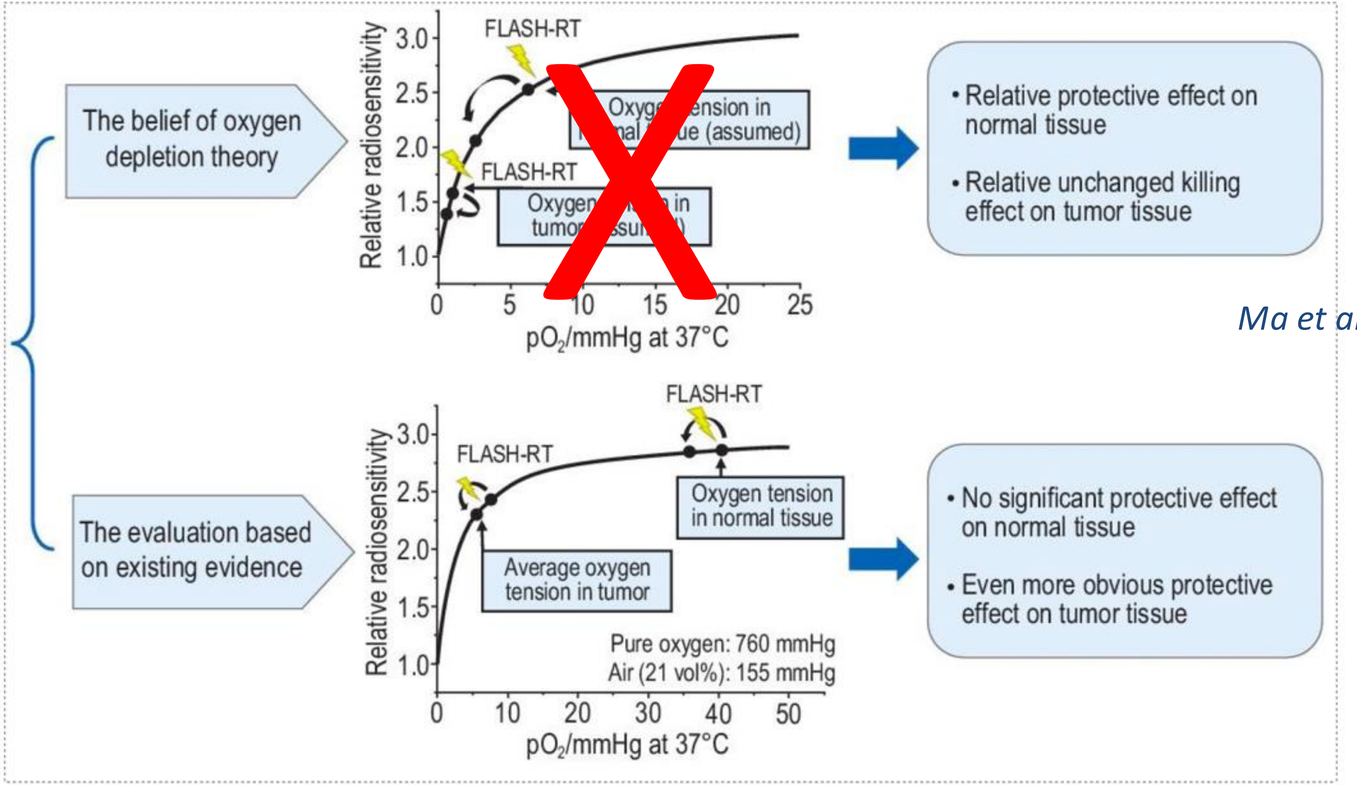
Table 1 Adapted with permission from Boscolo et al[3]: Calculation of absolute FLASH factor (AFF) (as defined in Poulsen et al[1]) for a series of published data with realistic initial oxygenation levels and depletion rates. Rows in italics are relevant to tumor tissues, the others being normal tissues. See Boscolo et al[3] Supplementary Material for details.

Experiment	Dose (Gy)	$pO_{2,env}$ (mmHg)	$pO_{2,fin}$ (mmHg)	AFF=D_{OER}(env)/ $D_{OER,DYN}$
Mouse whole brain[11]	10	25.84	23.79	1.00
Minipig skin[12]	31	40.28	33.36	1.00
Cat, healthy skin/mucosa[12]	33	40.84	37.32	1.00
Cat squamous cell carcinoma[12]	33	14.44	9.65	*1.02*
Mouse lung[13]	17	42.56	38.68	1.00
Lung tumor[13]	17	15.96	13.22	*1.01*
Human patient, healthy skin[10]	15	40.28	36.94	1.00
Human skin lymphoma[10]	15	11.40	9.42	*1.01*

Abbreviation: D_{OER} = oxygen enhancement ratio (OER)—weighted dose.

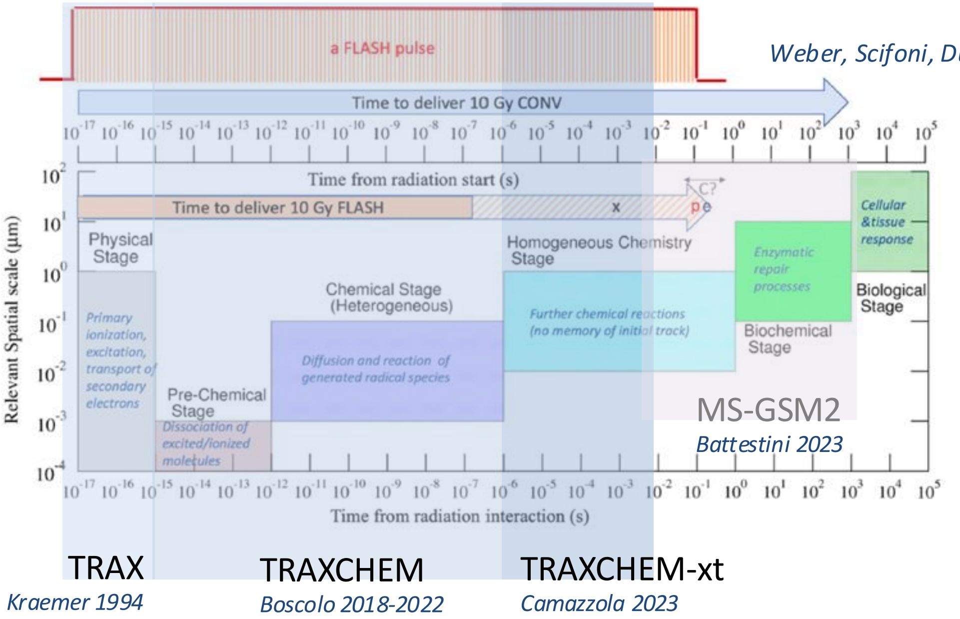
Scifoni, Vozenin. Cordoni. Fuss, Seco, Radiother Oncol 2025

The Oxygen Depletion Hypothesis (ROD)



Ma et al. 2024

The challenge of reaching longer time scales:



TRAXCHEMxt:
Radial Concentrations of Chemical species

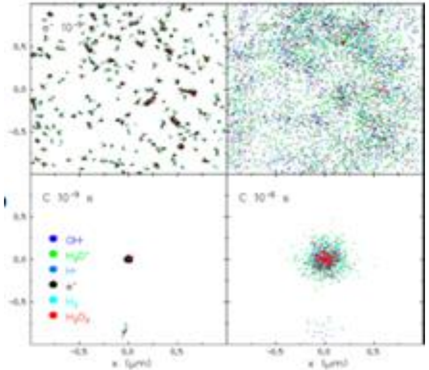
Diffusion development – Matrix approach

Given the boundary value problem (Fick's II law)

$$\partial_t[A] - D\partial_r^2[A] - \frac{D}{r}\partial_r[A] = 0$$

by approximating the derivatives, can recast it in a matrix (M, N) representation

$$M[A_{n+1}] = N[A_n] \rightarrow [A_{n+1}] = M^{-1}N[A_n]$$



Reactions development

Given a simple reaction

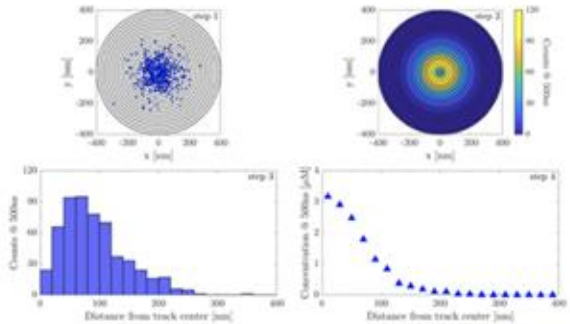
$$A + B \rightarrow C, \text{rate} \frac{d[A]}{dt} = -k_{AB}[A][B]$$

for species A at n^{th} time step dt have

$$\Delta A = -k_{AB}[A_n][B_n]dt$$
$$[A_{n+1}] = [A_n] + \Delta A$$

Camazzola et al. IJMS 2023

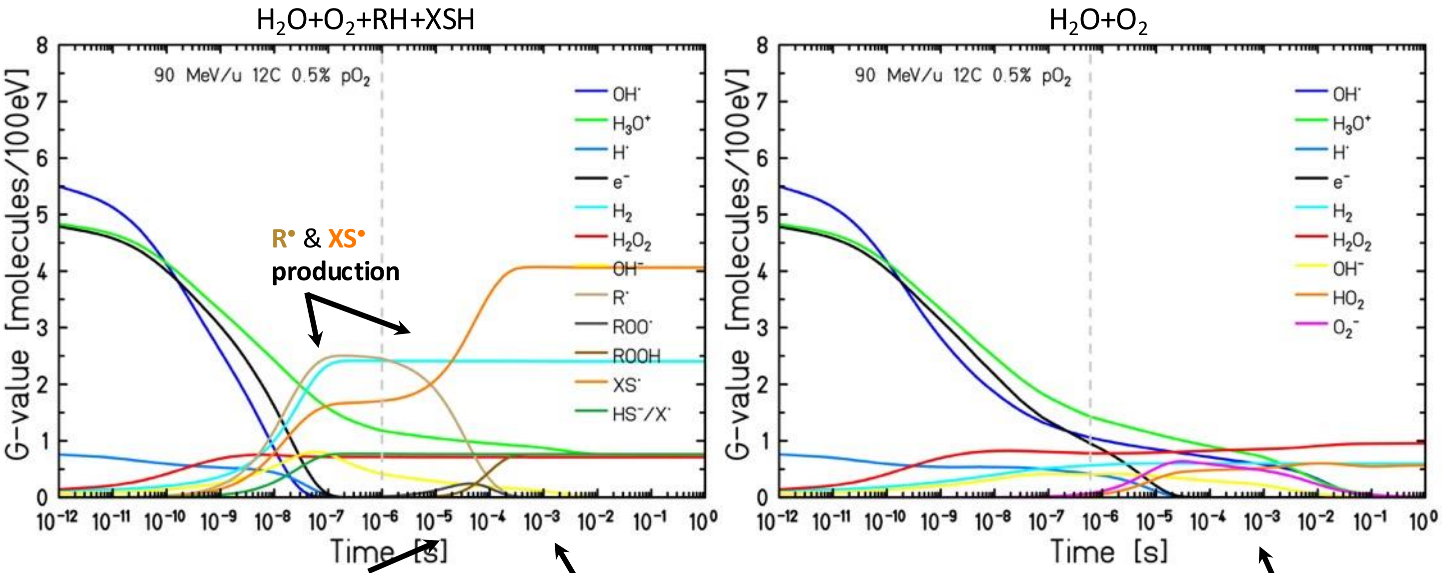
- Phase 2 Transition: New R-D Concentration based model



Extendedn simulation time and impact of . biological medium

Camazzola et al., PMB 2025

<u>G-value</u>: number of radicals/molecules produced per 100 eV of energy deposited

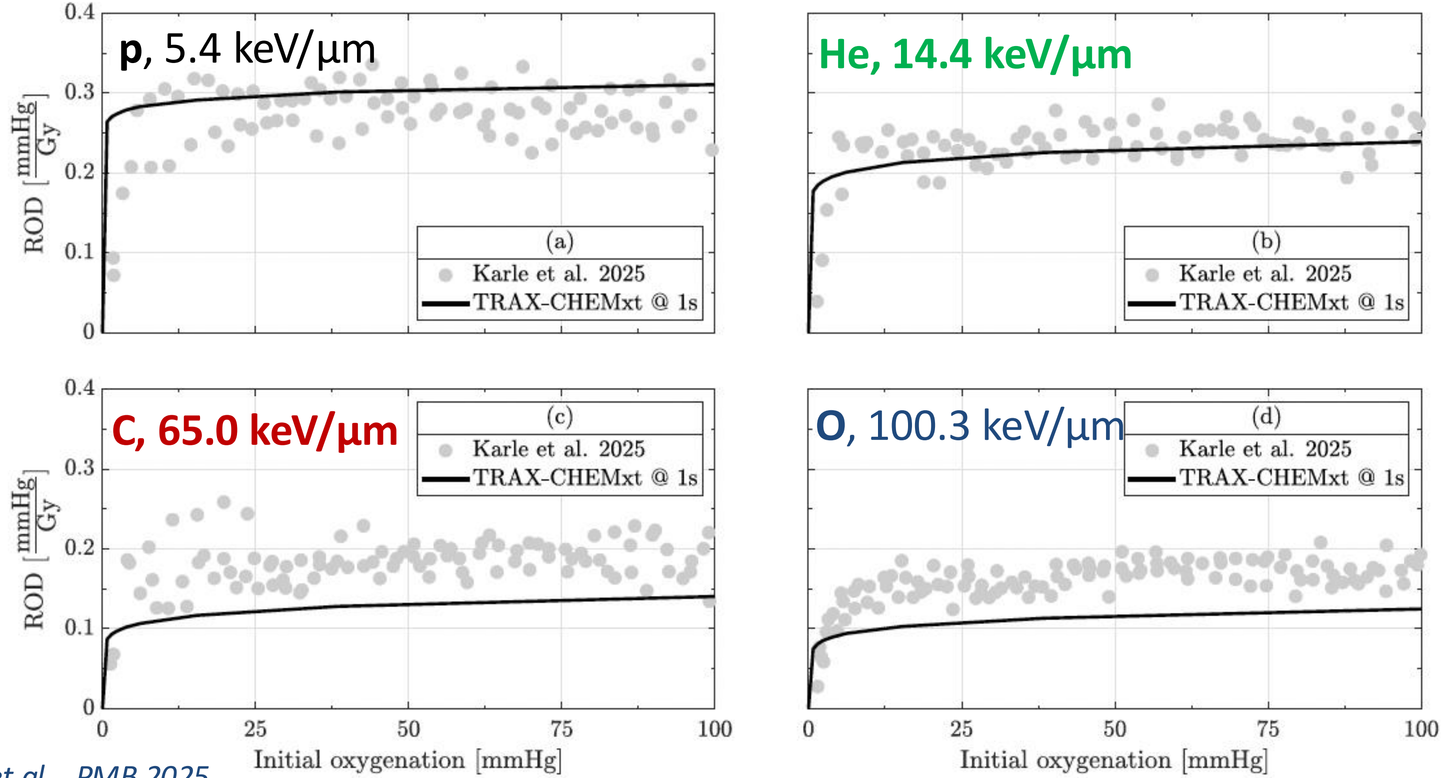


$OH^{\bullet}$, $H^{\bullet}$ & e_{aq}^- **fully consumed**
→ Biological environment already in Monte Carlo!

Long-lasting reactions, **ROOH production**

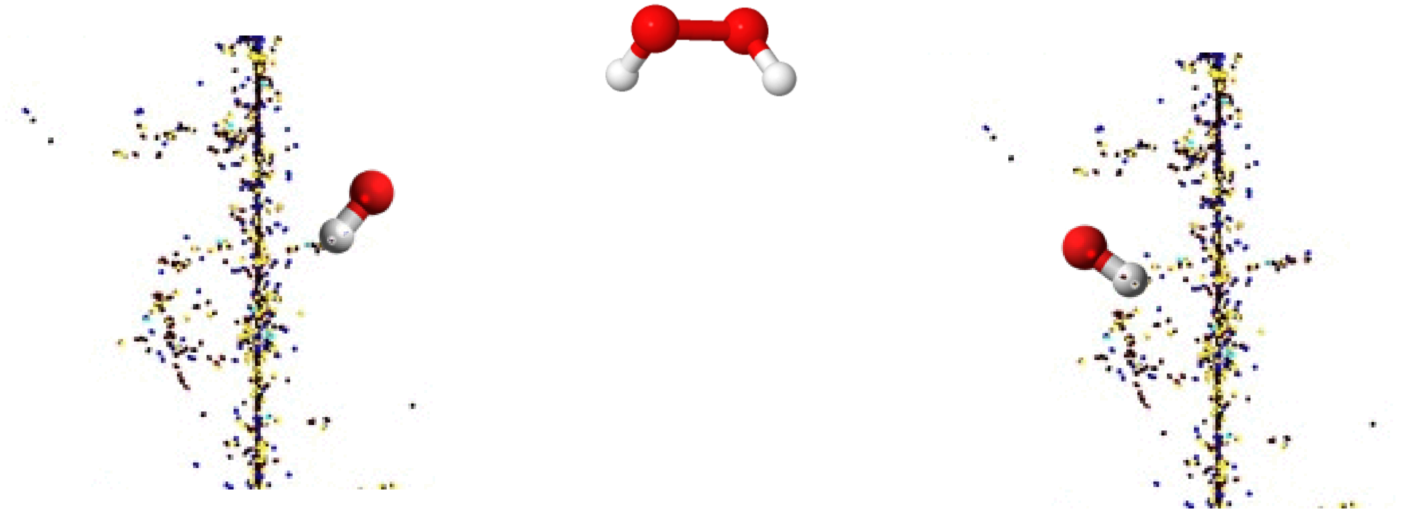
Long-lasting reactions

O_2 Depletion versus LET (in medium)



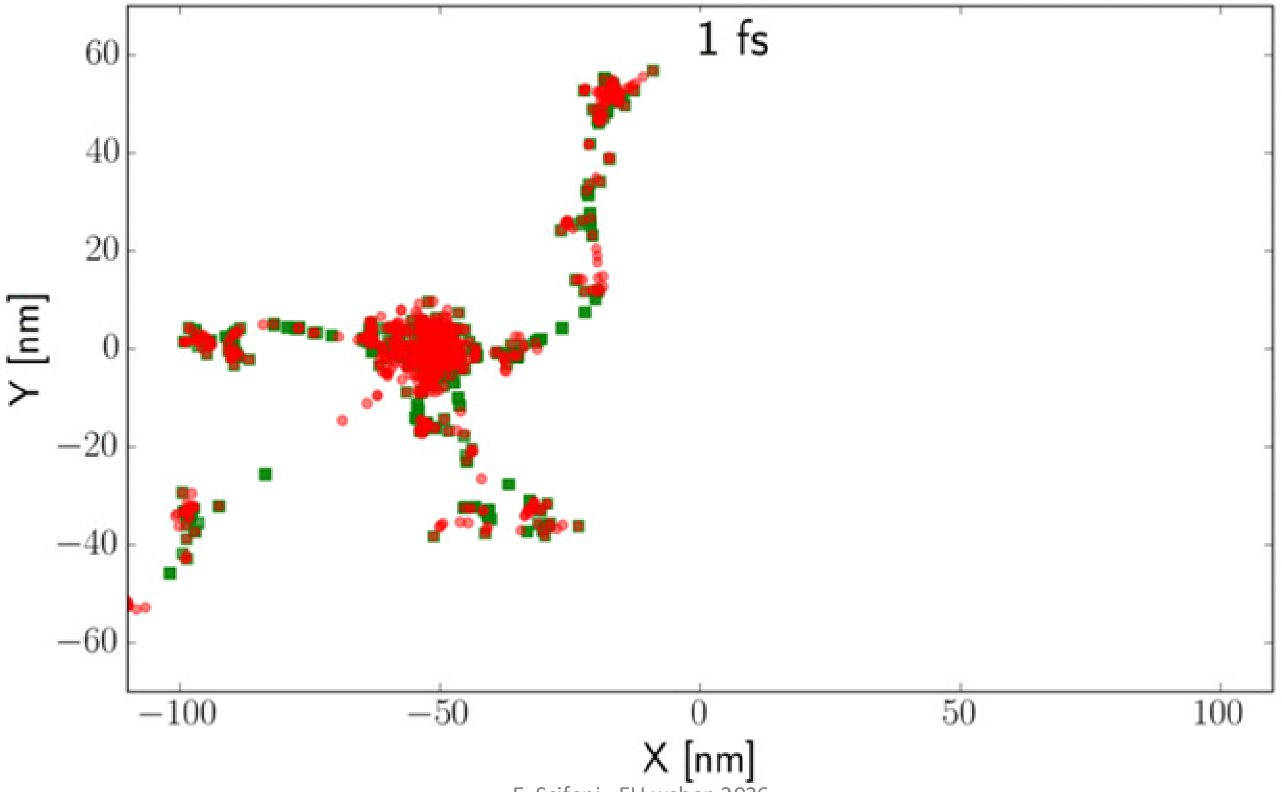
Camazzola et al., PMB 2025

Intertrack effects



INTERTRACK phenomena

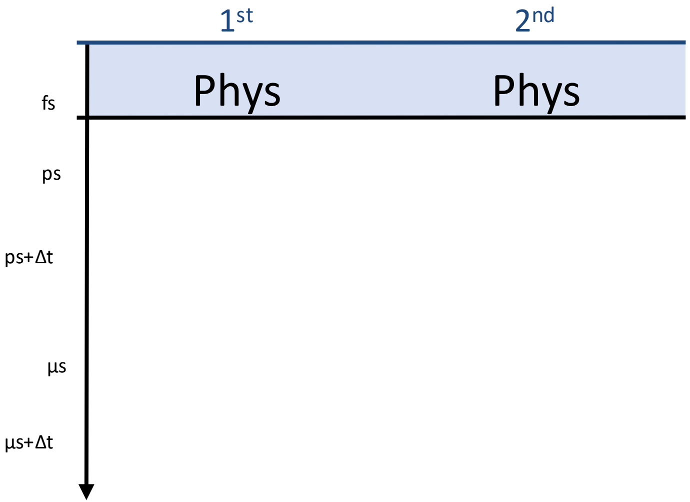
2 Projectile Δx = 100 nm and Δt = 1 ns



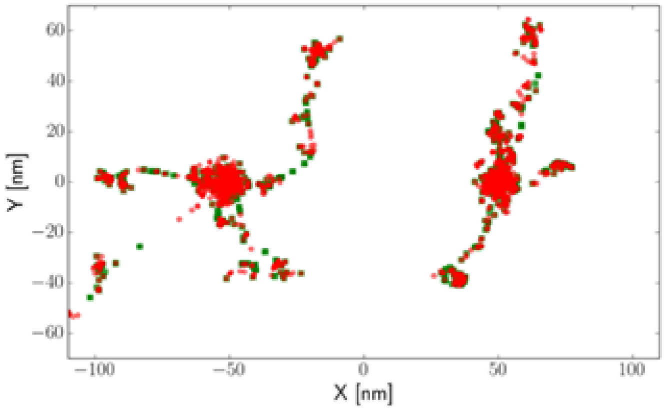
Castelli IJMS 2025

Implementation and study of Intertrack interaction

INTERTRACK



Example: 2 Proj. Δx = 100 nm ; Δt = 1 ns



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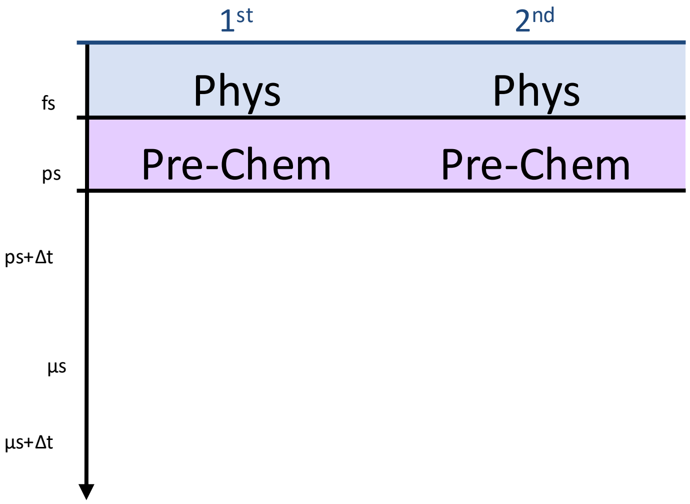

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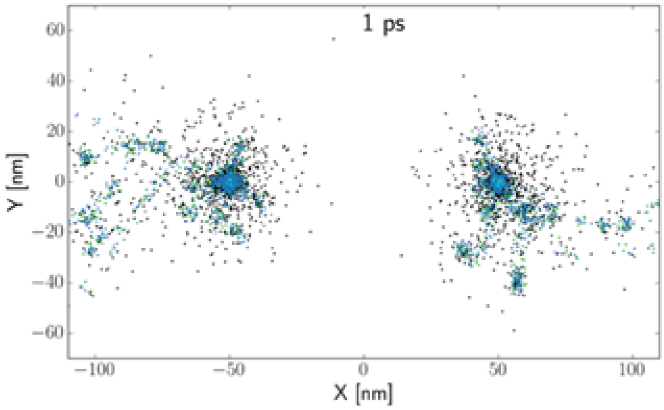

Implementation and study of Intertrack interaction

INTERTRACK:

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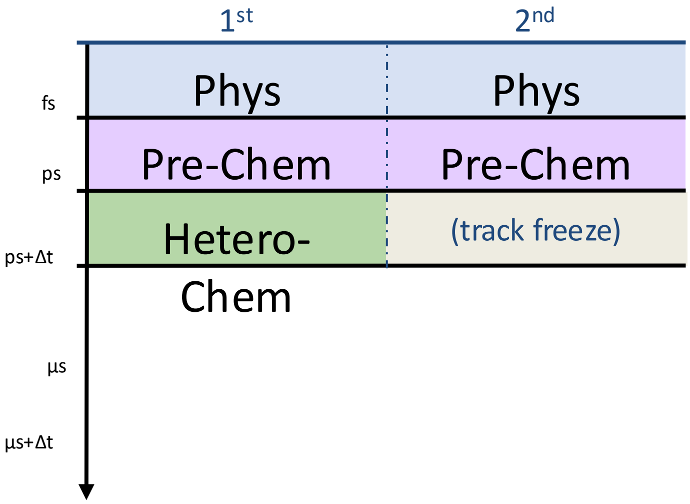

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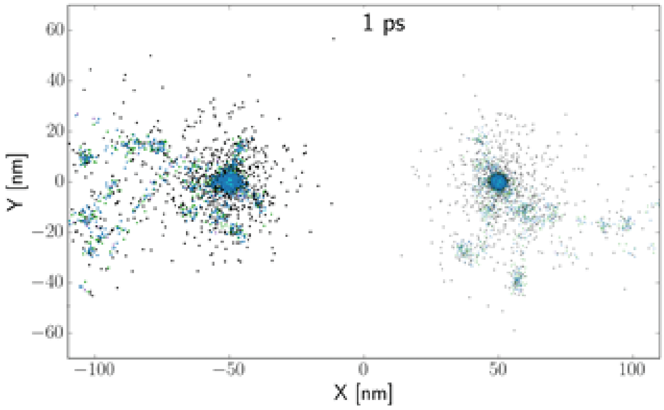

Implementation and study of Intertrack interaction

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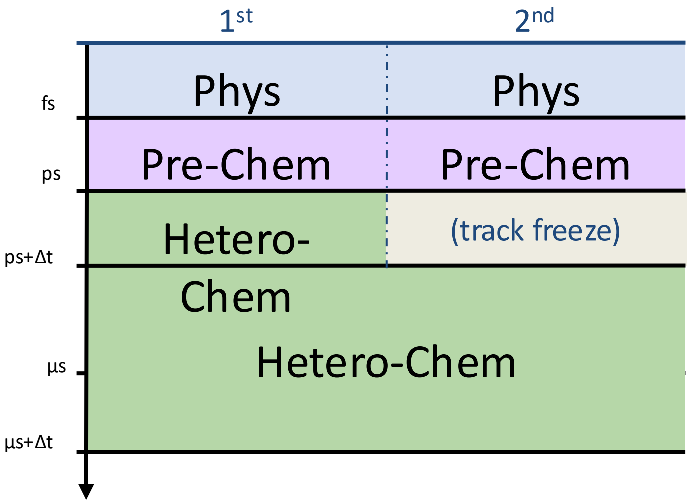

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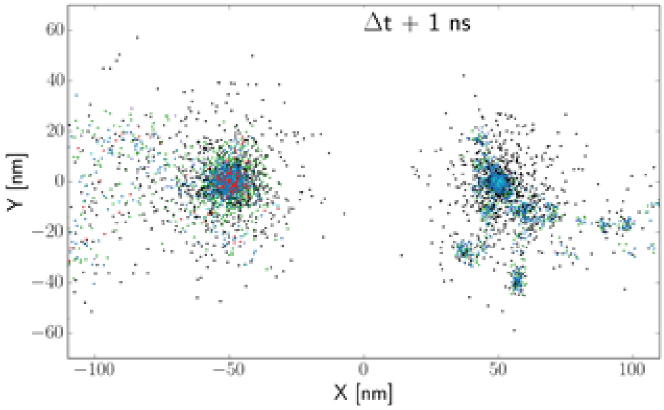

Implementation and study of Intertrack interaction

INTERTRACK

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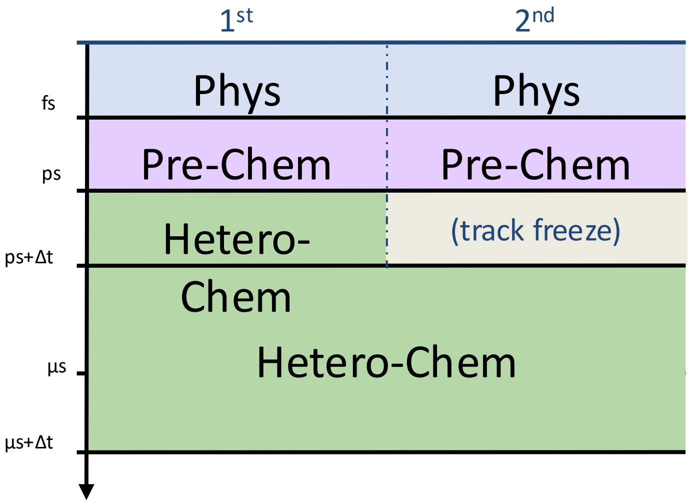
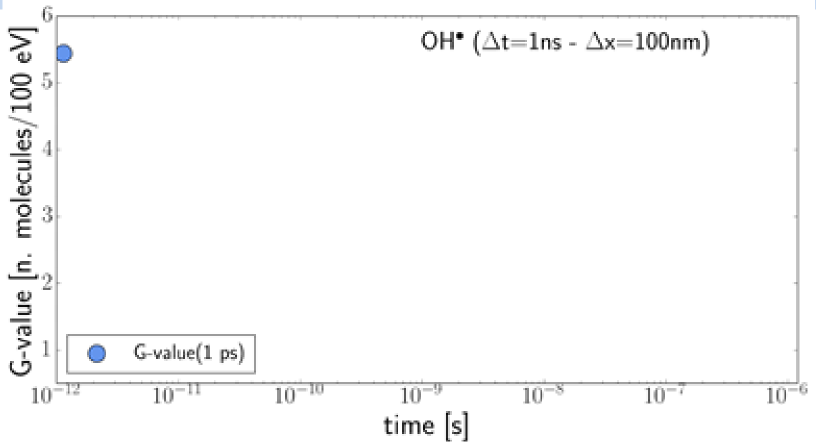
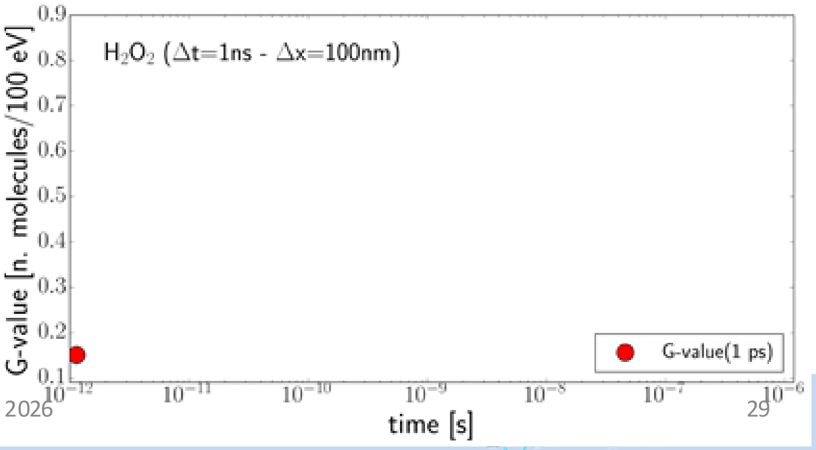


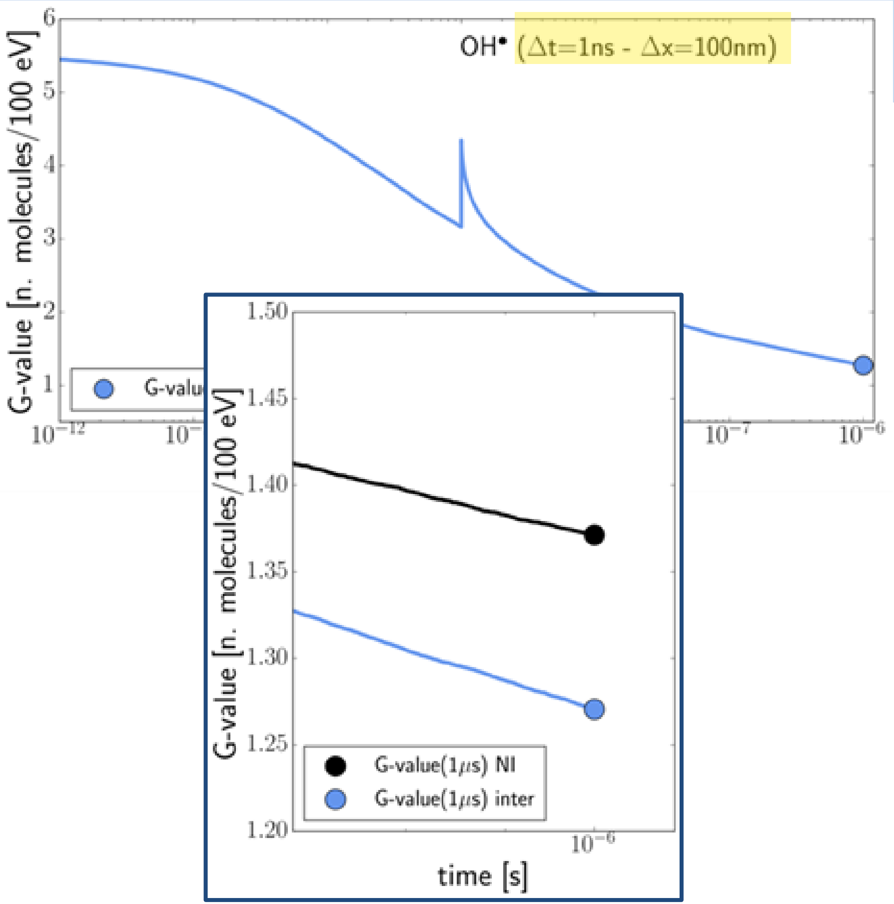
$$\text{G-value}(t) = \frac{N(t)}{E(t)[100eV]}$$





Radicals Plots interpretation

Castelli IJMS 2025



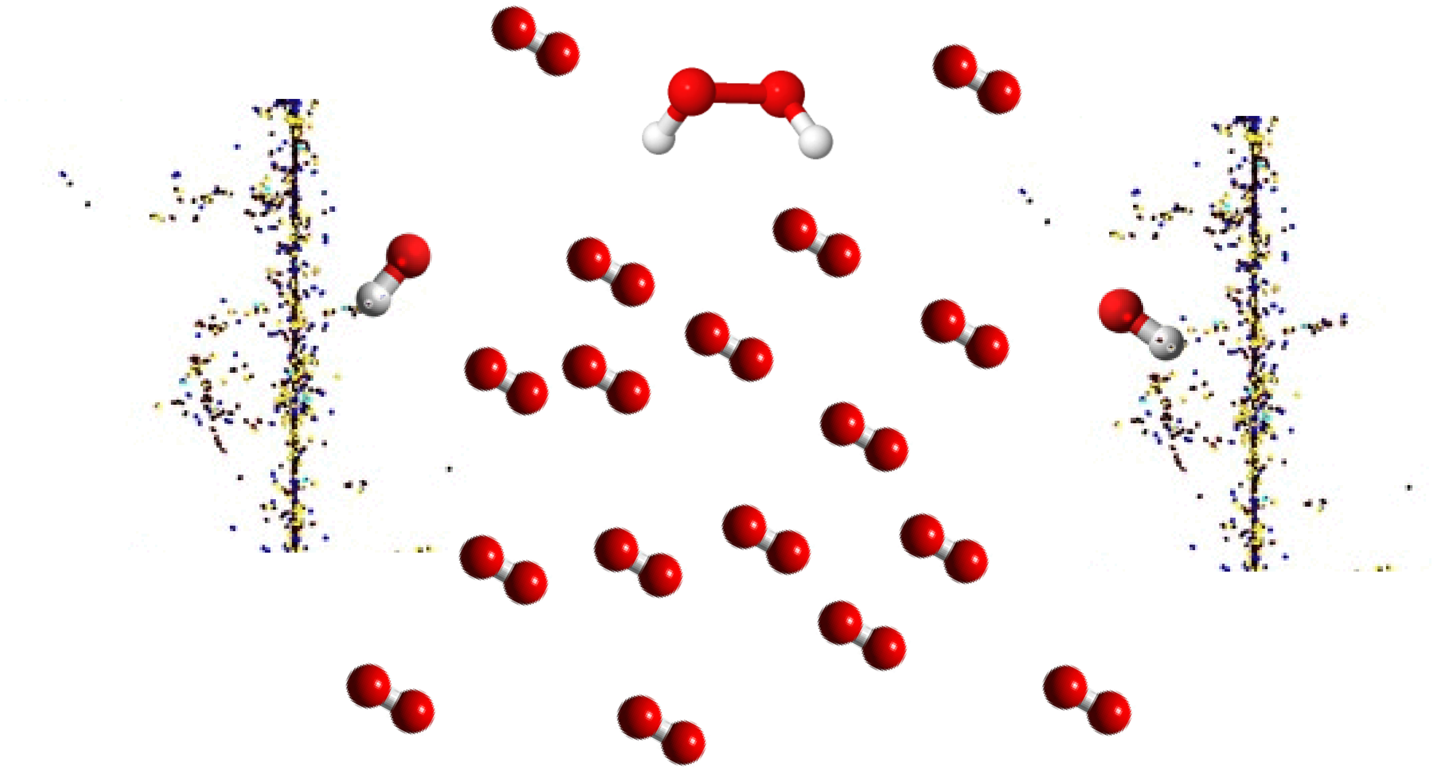
$$\Delta G\text{-value}_{\mu s} = \frac{G\text{-value}_{inter}(\mu s) - G\text{-value}_{NI}(\mu s)}{G\text{-value}_{NI}(\mu s)}$$

$\Delta G\text{-value}_{\mu s}$ (Δt; Δx)= (1.26-1.36)/1.36 = -7.4 %

(Carbon 240 MeV/u) OH•

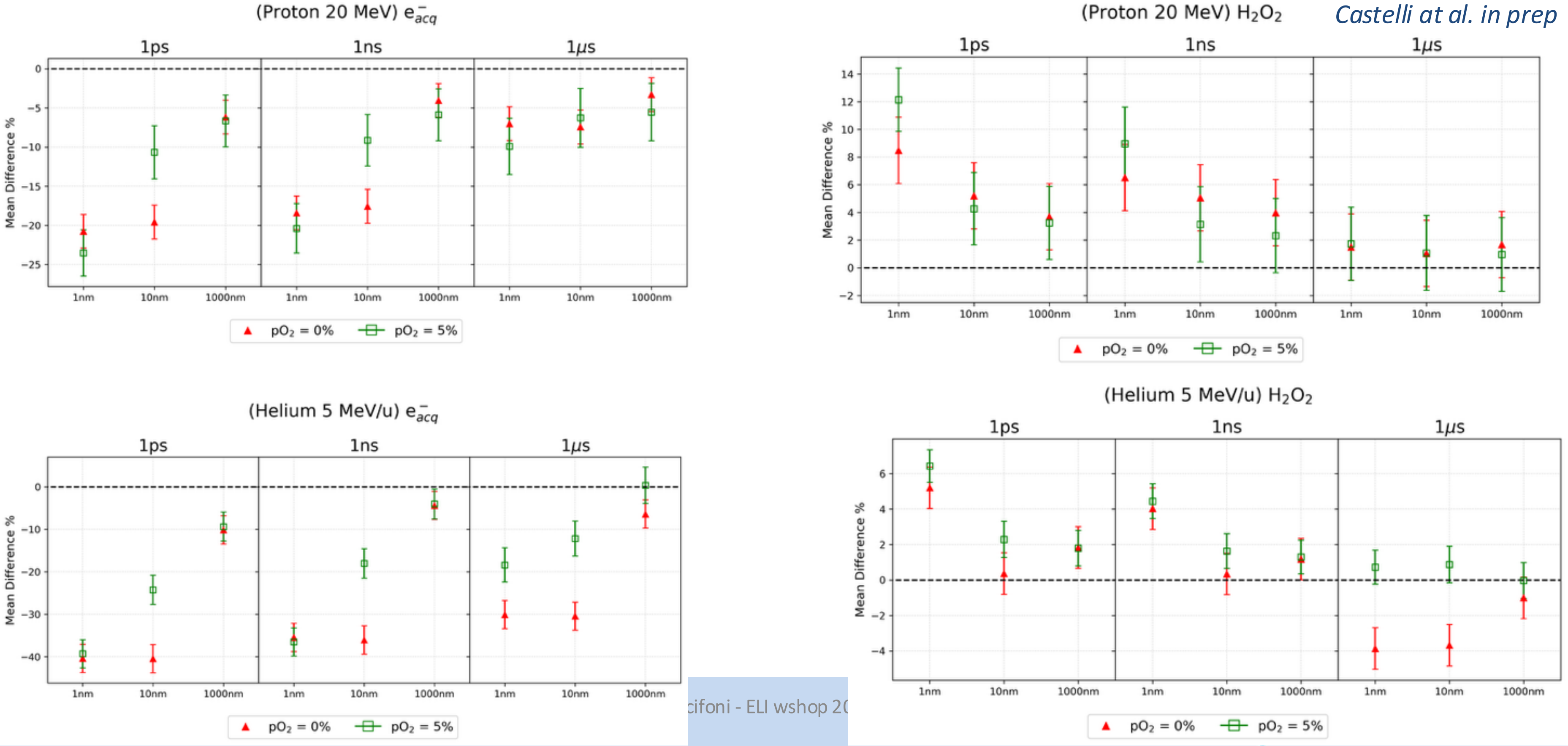
Δx [nm] \ Δt [ps]	10^6	$7\cdot10^5$	$3\cdot10^5$	10^5	10^4	10^3	10^2	10	1
10^3	-0.7	-0.1	-0.6	-0.4	-1.2	-1.8	-4.6	-4.0	-3.7
10^2	-5.6	-5.6	-6.5	-6.6	-7.4	-7.4	-9.7	-9.6	-9.3
10	-7.5	-8.4	-12.4	-15.6	-21.1	-22.4	-25.0	-25.1	-24.3
1	-7.4	-8.8	-12.0	-15.7	-22.5	-27.6	-30.4	-31.2	-30.5
0	-7.4	-7.9	-12.2	-16.2	-23.1	-27.6	-31.0	-31.3	-29.9

Intertrack effects in the presence of Oxygen



Impact of Oxygenation on Intertrack

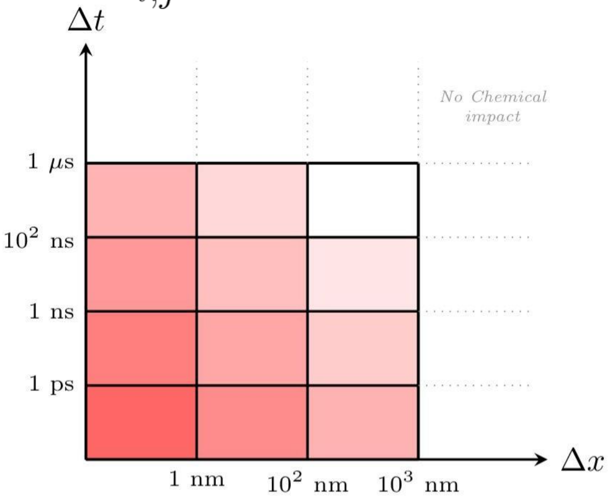
Castelli at al. in prep



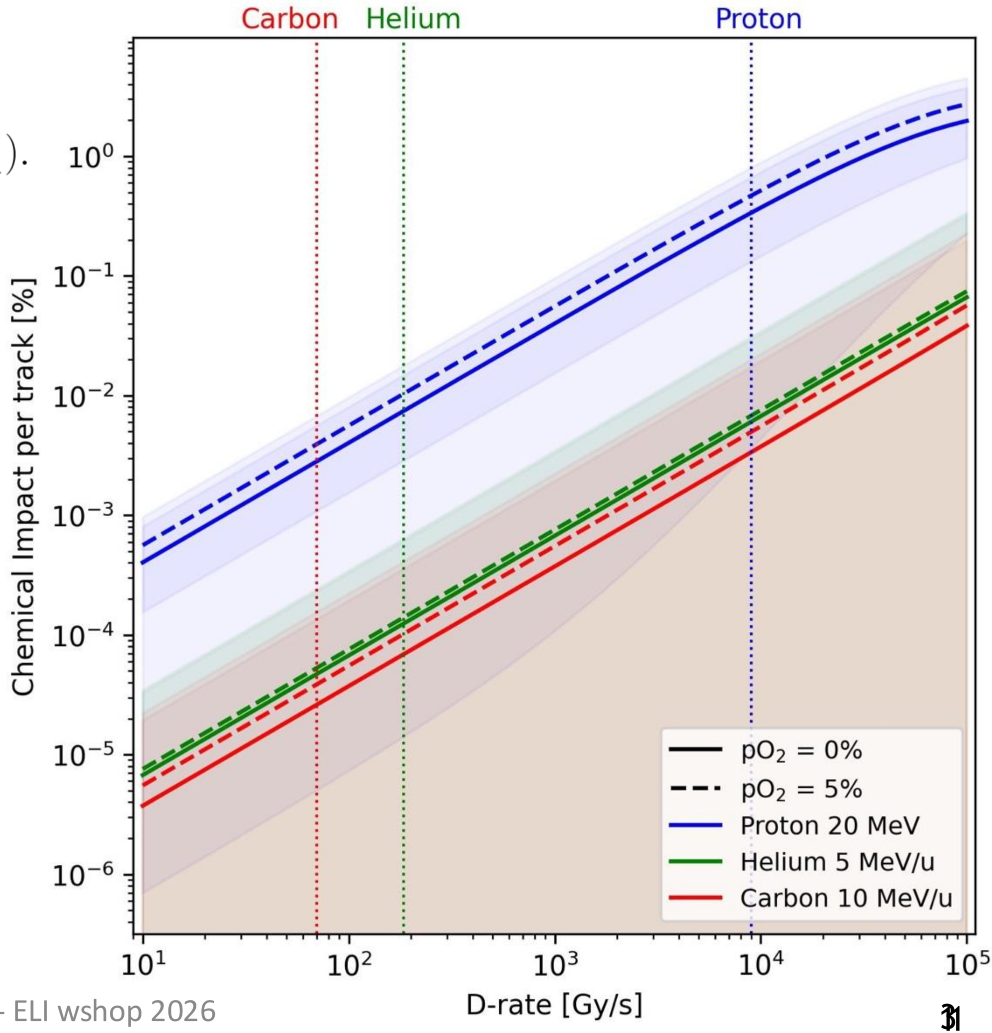
Chemical Impact estimation

$$\Pr(\Delta x_i, \Delta t_j) = P(\Delta x_i, \Delta t_j) - P(\Delta x_{i-1}, \Delta t_j) - P(\Delta x_i, \Delta t_{j-1}) + P(\Delta x_{i-1}, \Delta t_{j-1}).$$

$$\Delta\mathrm{Chem}_{\mu s} \approx \sum_{i,j} \Pr(\Delta x_i, \Delta t_j) \frac{\delta(\Delta x_i, \Delta t_j)}{\mu_{\mathrm{ref}}}$$



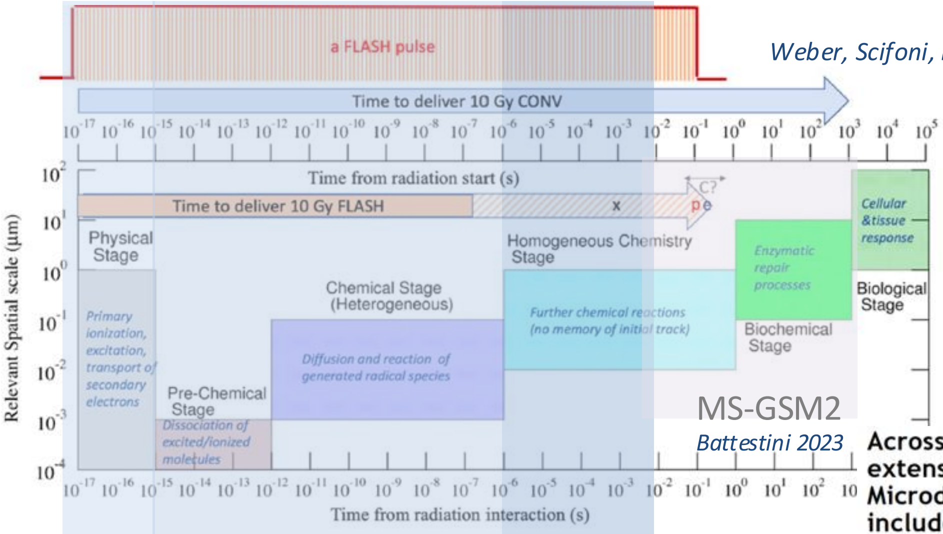
- Proton 20 MeV very **small effect**
- Helium 5 MeV/u **no effect**
- Carbon 10 MeV/u no effect



Castelli to be subm. to Radiat.Res.

FLASH and Spatio-temporal Scales of Radiation Damage

Weber, Scifoni, Durante 2021



MS-GSM2
Battestini 2023

Across the stages: a multiscale extension of the Generalized Stochastic Microdosimetric Model (MS-GSM 2) to include the Ultra-High Dose Rate (UHDR)

Marco Battestini[1, 2], Marta Missiaggia[3, 2], Andrea Attili[4], Francesco Tommasino[5, 2], Chiara La Tessa[3, 2], Francesco Giuseppe Cordoni[6*], Emanuele Scifoni[2]

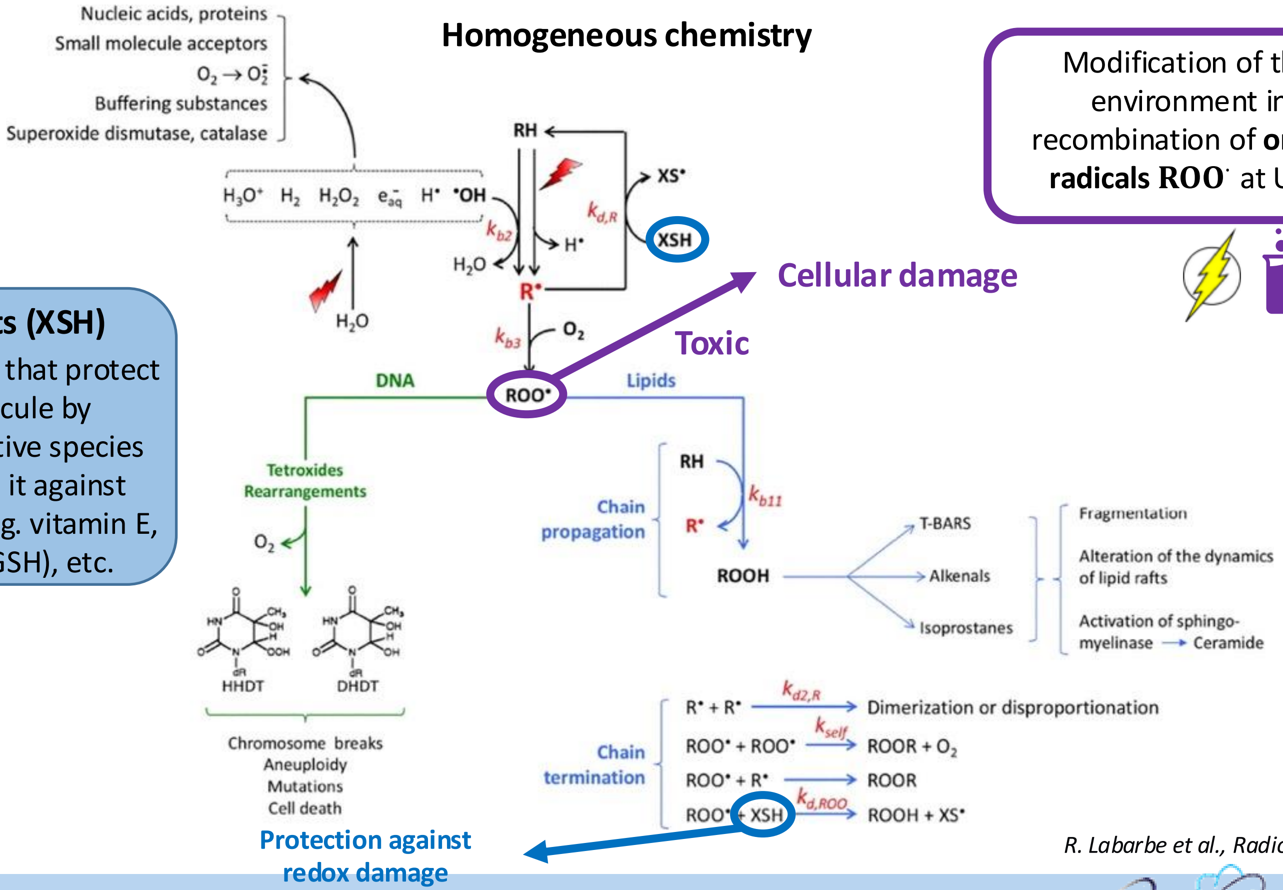
TRAX
Kraemer 1994

TRAXCHEM
Boscolo 2018-2022

TRAXCHEM-xt
Camazzola 2023

Organic radical recombination (ORR) hypothesis

Homogeneous chemistry



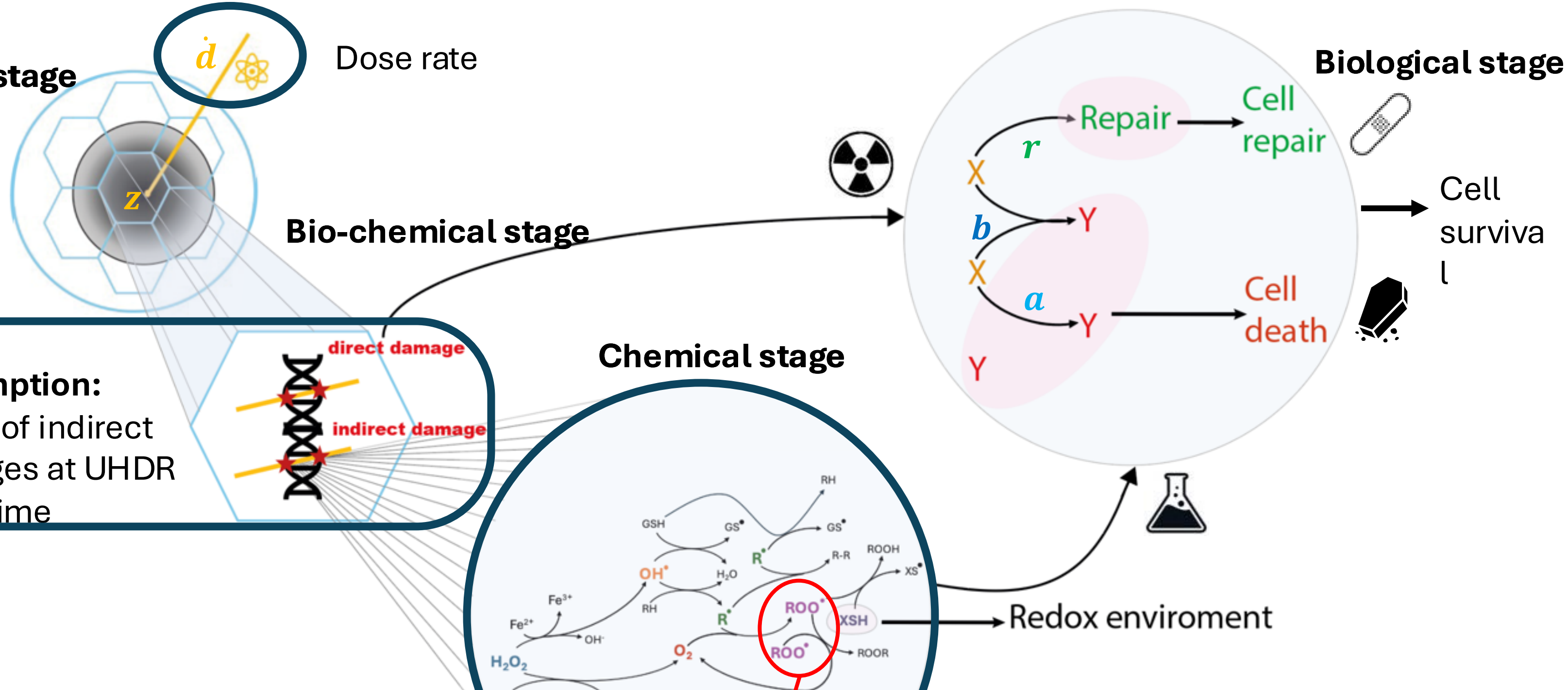
Modification of the chemical environment induced by recombination of **organic peroxyl radicals $ROO^\cdot$** at UHDR regime

Antioxidants (XSH)

Chemical species that protect the biomolecule by scavenging reactive species and preserving it against redox damage. E.g. vitamin E, glutathione (GSH), etc.

R. Labarbe et al., Radiother. Oncol. (2020)

The Multiscale Generalized Stochastic Microdosimetric Model (MS-GSM^2)



Assumption:
reduction of indirect DNA damages at UHDR regime

M. Battestini et al., Front. Phys. (2023)
M. Battestini et al., Radiother Oncol. (2024)

The main idea of MS-GSM^2 for FLASH studies

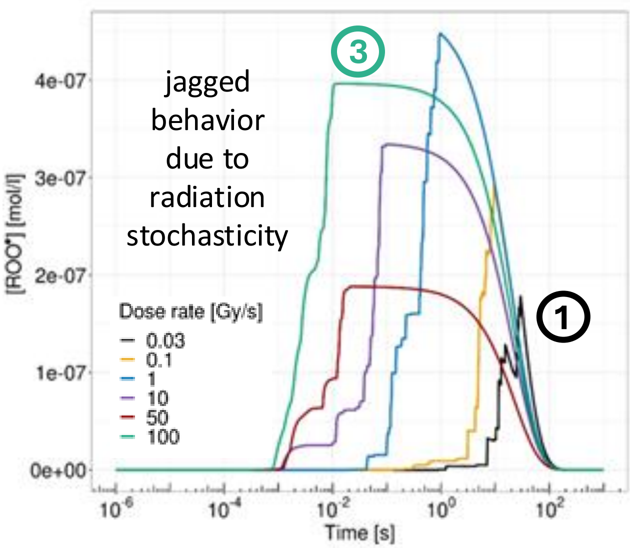
Reactions → $f(\xi)$; Production → $\rho G_\xi \frac{dD(t)}{dt}$

$$\frac{d[\xi]}{dt} = f(\xi) + \rho G_\xi \frac{dD(t)}{dt}$$

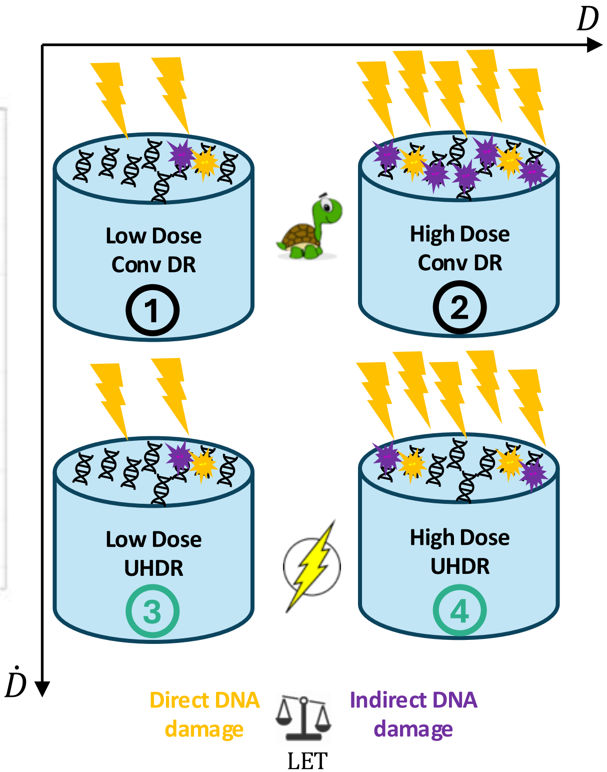
$k_{ij} \cdot [\xi]_i \cdot [\xi]_j$ $\quad \left[\frac{\#\ \text{molecules}}{100\ \text{eV absorbed}}\right]$

$$\begin{cases} \frac{dD(t)}{dt} = \dot{D}, & t \le T_{irr} \\ \frac{dD(t)}{dt} = 0, & T_{irr} < t \le T_{sim} \end{cases}$$

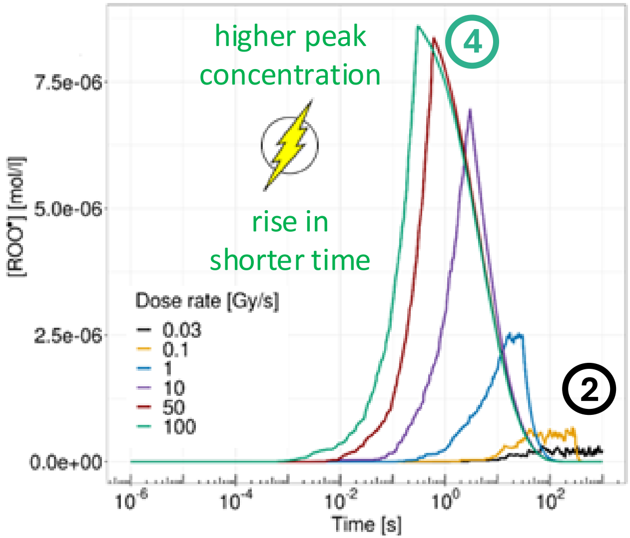
1 Gy



Damage formation



30 Gy

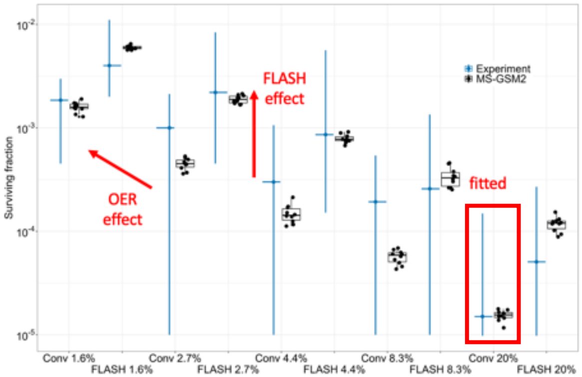


M. Battestini et al., Front. Phys. (2023)

M. Battestini et al., Radiother. Oncol. (2025)

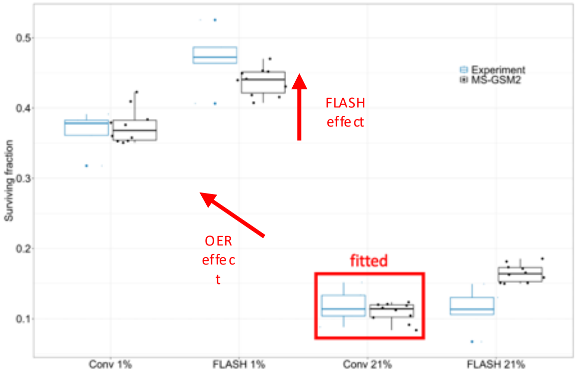
Validation with *in vitro* UHDR experiments

Electrons (10 MeV)



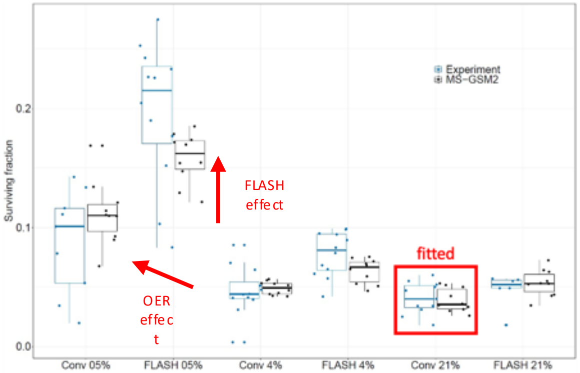
Exp: Adrian et al., Br. J. Radiol. (2020)

Helium ions (56 MeV/u)



Exp: Tessonnier et al., Int. J. Radiation Oncol. Biol. Phys. (2022)

Carbon ions (280 MeV/u)



Exp: Tinganelli et al., Int. J. Radiation Oncol. Biol. Phys. (2022)

Radiotherapy and Oncology xxx (xxxx) 110895

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.elsevier.com

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Journal logo

Original Article

A multiscale radiation biophysical stochastic model describing the cell survival response at ultra-high dose rate under different oxygenations and radiation qualities

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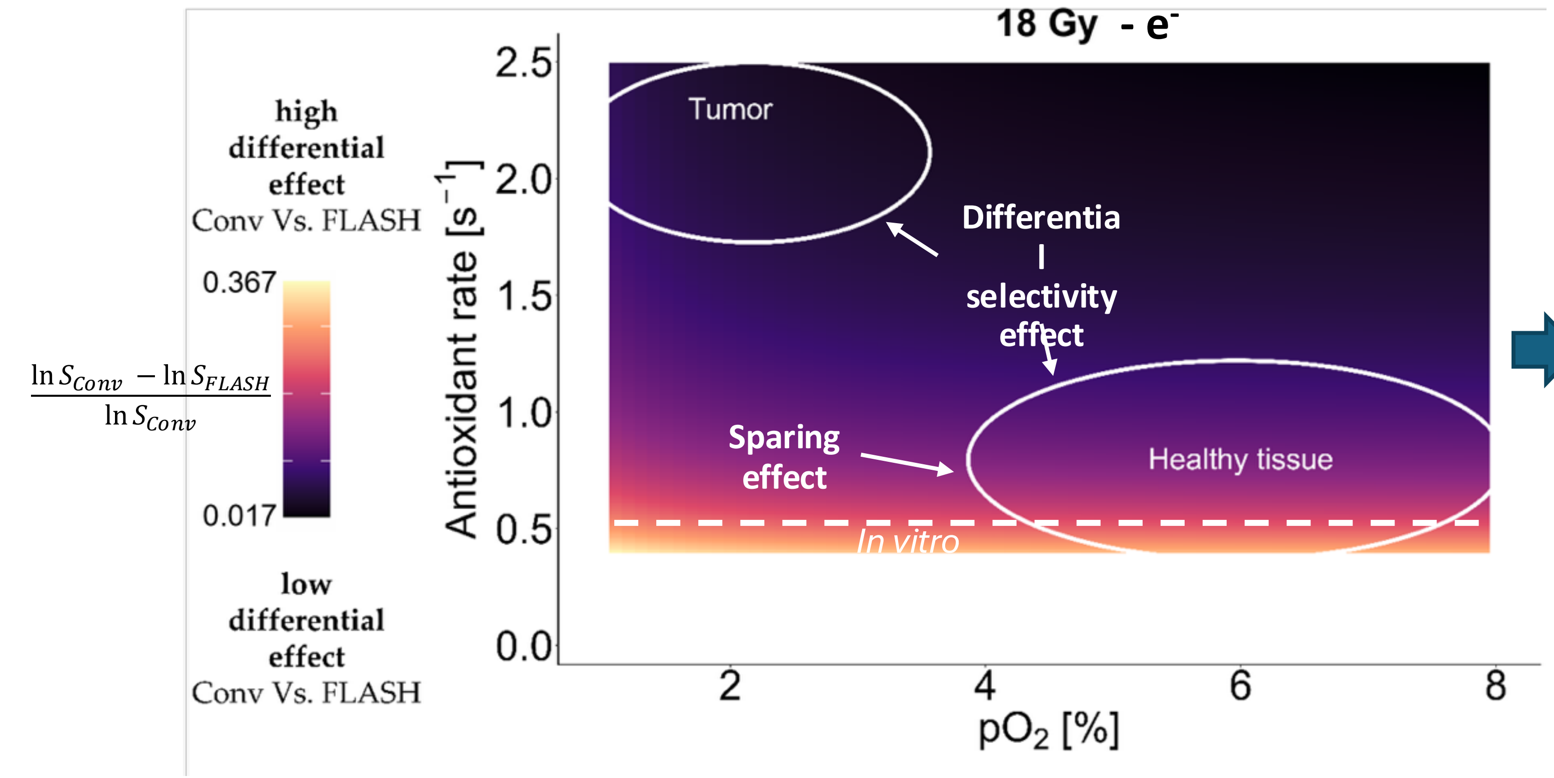
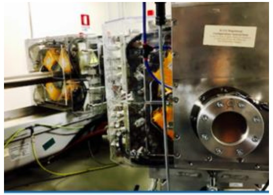
Investigation of the FLASH differential effect



The antioxidant activity modulates the FLASH effect

M. Battestini et al., Radiother. Oncol. (2025)

X-UHDR possibilities @ELIMED?

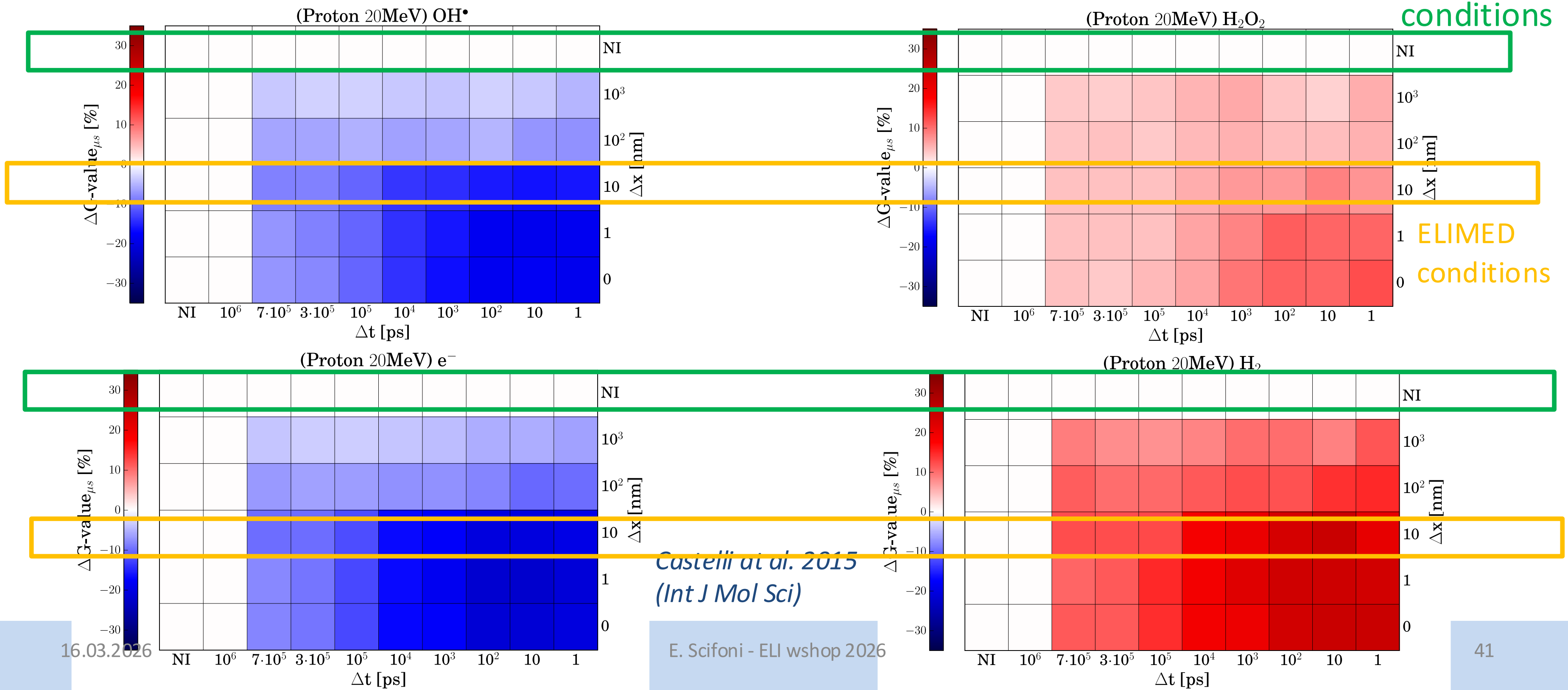


	TRENTO (TPBL-TIFPA) (and most pFLASH in the word)	ELIMED
Energy (MeV/u)	225	20-40
LET (keV/µm)	0.5	1 - 2
Current on target (nA)	0.1 - 390	E07
Pulse width	~100 ms	~30 ns
Intensity p/s	4 E09 - 2.4 E12	E15
Dose rate (instantaneous) on 1cm^2 (Gy/s)	0.1 - 300	E07
Modality	UHDR	XUHDR
Average distance bw 2 tracks in 1 µs	20 µm	0.05 µm

$$\bar{d} = 1/\sqrt{F\left(\dot{D}\tau_{chem}\right)}$$

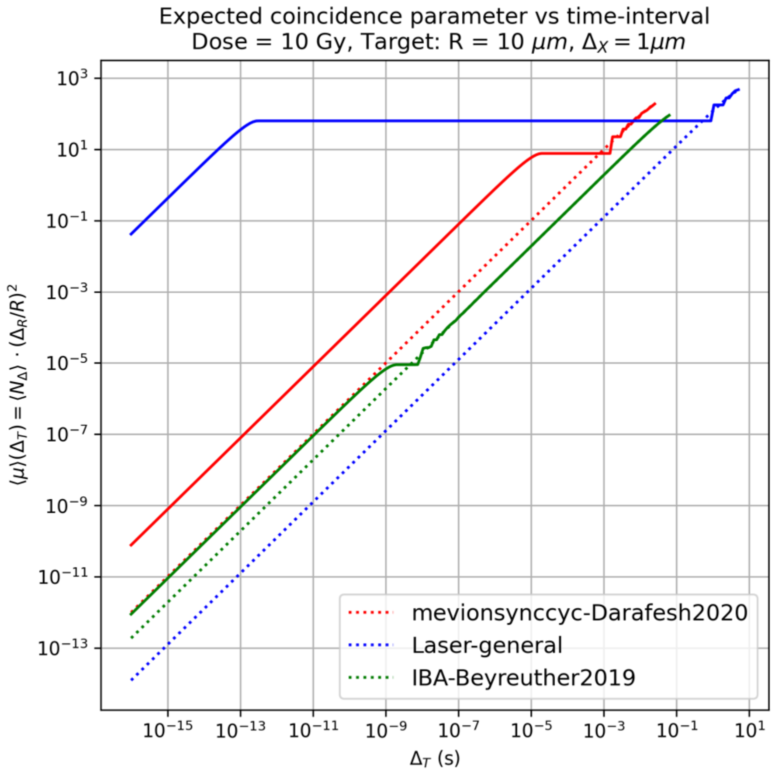
Proton ΔGs for given s/t separation

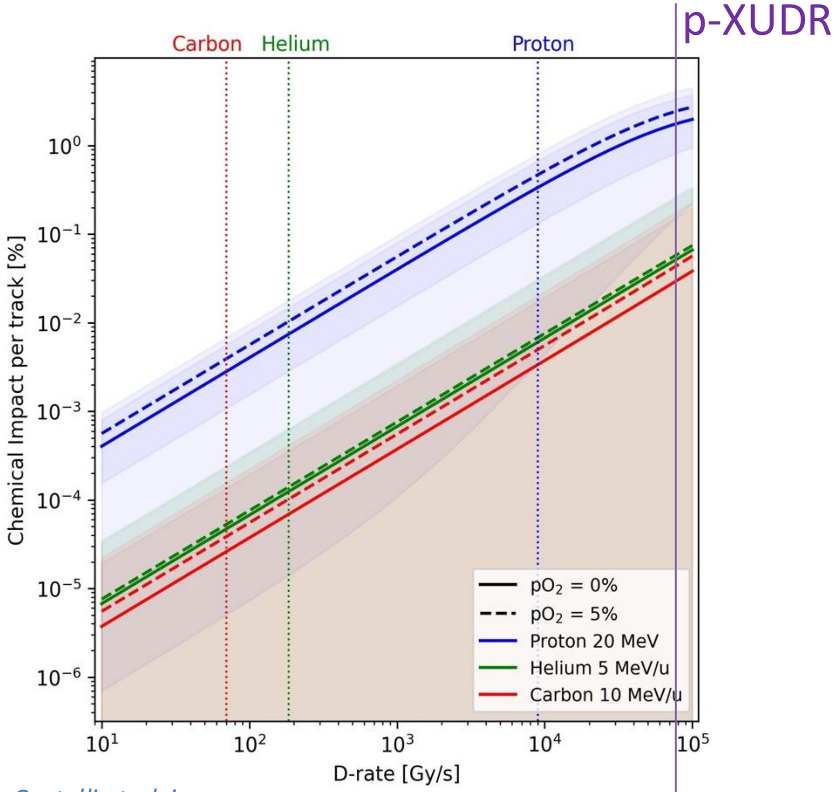
ΔG-value$_{\mu s}$=(G-value$_{\mu s}$(Δx,Δt)-G-value$_{\mu s}$(NI))/G-value$_{\mu s}$(NI)



Castelli at al. 2015 (Int J Mol Sci)

Intertrack accessible at X-UHDR





Castelli et al. in prep

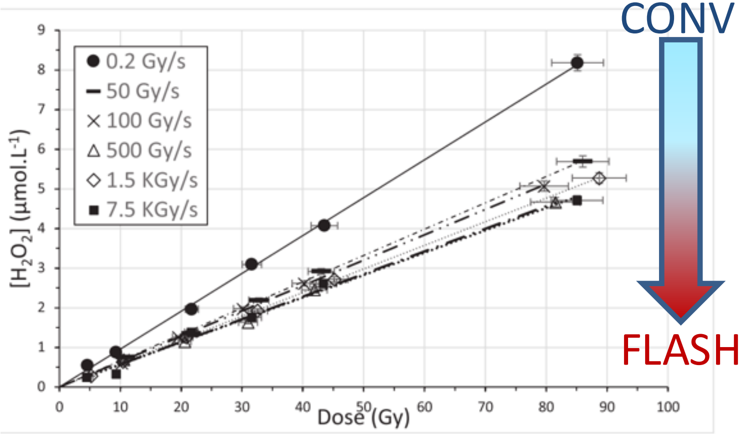
Questions possibly addressed:

- Is p-XUHDR behaviour different from p-UHDR
- Can we understand basic radiation chemistry mechanism?
- Dynamical range: where is the “safe” limit of getting FLASH with protons? Implications for TPS
- Is FLASH depending on the Radiation Quality? Proton experiments in identical rate conditions, as electrons, differing only for particle type

The mystery of the H_2O_2 yield

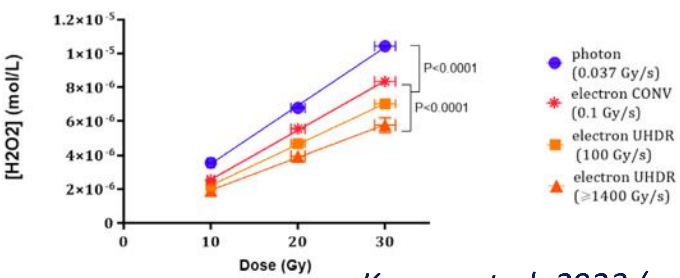
or: Can we understand complex phenomena (FLASH) if we still don't get the simple ones ($G_{H_2O_2}$ vs $\dot{D}$ in water…)?

CONV



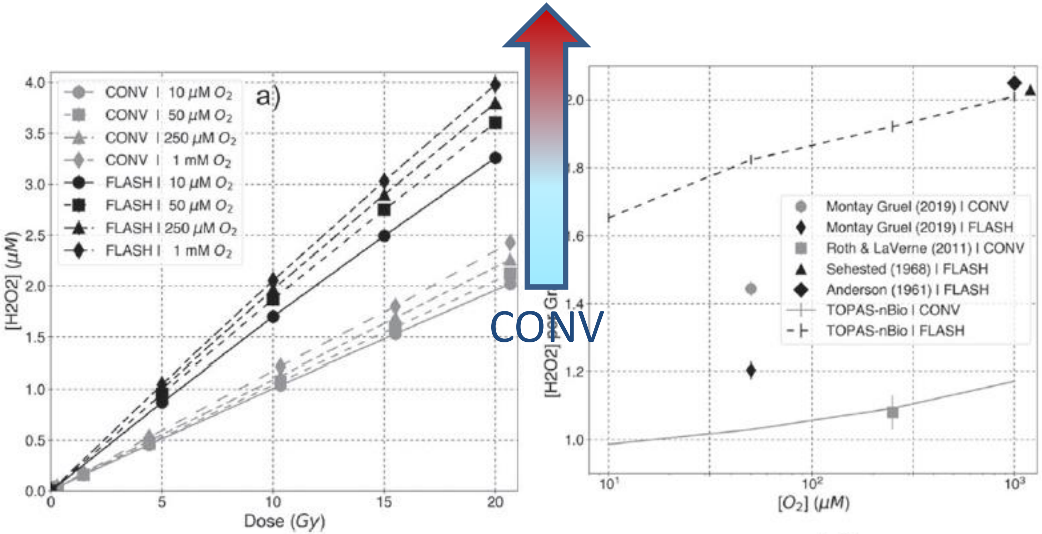
FLASH

Blain et al. 2022 (exp)



Kacem et al. 2023 (exp)

FLASH



CONV

Kondo et al. 2023

Opposite D/t effect found in several experiments and most simulations (already in simple water environment)

Summary

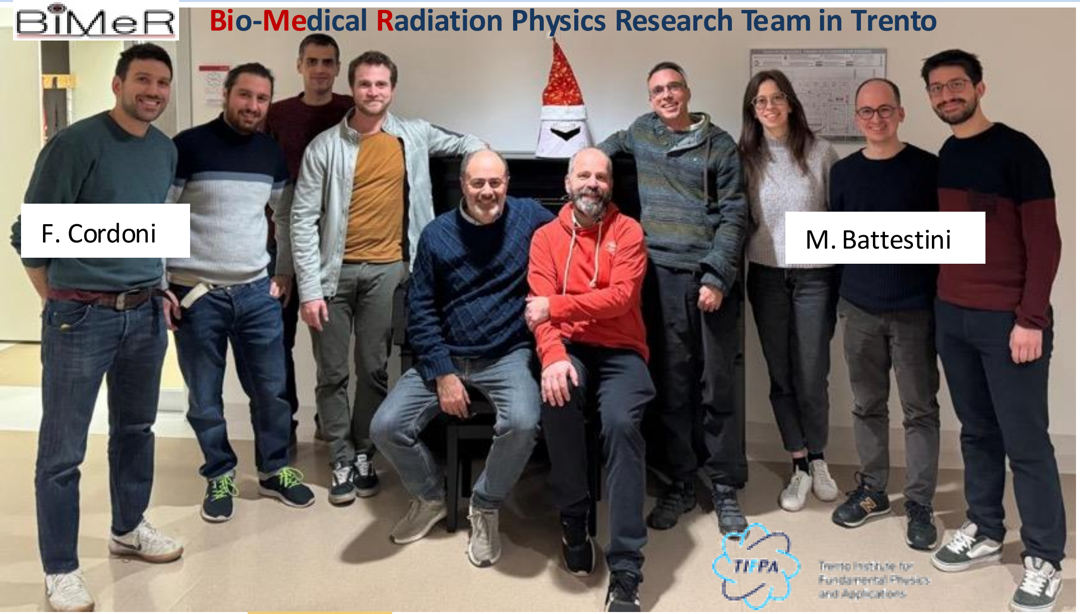
- FLASH RT mechanism remains a fundamental challenge

- Multiscale modeling allows to provide several insights in the mechanism.
- A recent model reproduces most in vitro UHDR data suggesting a potential new interpretation

- Track structure based models are describing the interaction beween tracks in a broad range of spatiotemporal conditions, medium and oxygenation.
- The multitrack feature evidences a clear range in time and space where intertrack may occur, which is extremely limited in typical p-FLASH experiments.

- XUHDR beams like LDPB may open useful possibility of experimental investigations providing proton tracks in close spatiotemporal proximity and in conditions comparable to e-FLASH,thus providing mechanistic insights even before getting to the full FLASH conditions (ADR)

Acknowledgments



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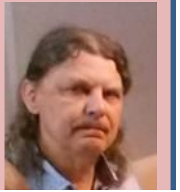

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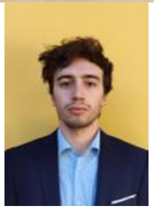

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IV FLASH WORKSHOP

Understanding FLASH Radiotherapy: the role of oxygen and beyond

July 1-3, 2026, Trento (Italy)

TOPICS

Spatio-temporal Features of FLASH Effects
Oxygen and Microenvironment in FLASH
Radiation Chemistry and Physics of the Mechanisms
Biophysical Modeling of UHDR Radiation response
Dosimetry of UHDR Pulse Structure

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https://4thflashworkshop.unitn.it

Call for Abstracts

We invite researchers, particularly young scientists and students, to submit abstracts for the **4th FLASH Workshop**, which will be held **Trento, Italy, 1st–3rd July 2026**. This Workshop brings together experts in the field of **ultra-high dose rate (UHDR)** radiation to fost discussions on the **mechanistic understanding** of the **biological response** following **FLASH irradiation**.

Abstract submissions are welcome on the following **topics**:

- FLASH Radiobiological Mechanism – In Vivo and In Vitro Studies
- UHDR Radiation Chemistry – Experimental
- UHDR Biophysical Modelling and Computational Radiation Chemistry
- UHDR Dosimetry
- Towards FLASH Biological Treatment Planning

We encourage contributions from **students** and **early-career researchers**. Accepted abstracts will be presented during the Workshop ar may be considered for **plenary sessions** and **poster presentations**.

Submission Instructions:

Please prepare your **abstract** using the **template** provided below and submit it in **PDF format** to flash.workshop@unitn.it.

The **submission deadline** is 31st March 2026.

https://4thflashworkshop.unitn.it