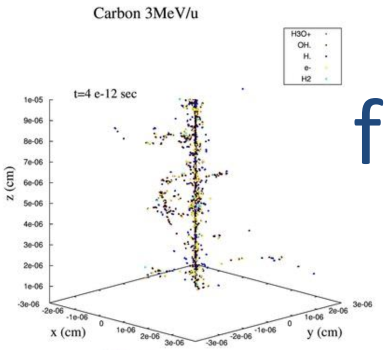
ICTP-IAEA-MAMBA School - Trieste 2025

Particle beam Radiation Biophysics:

from the nanoscale to therapy



Emanuele Scifoni

Bio-Medical Radiation Physics Research Team in Trento

Trento Institute for Fundamental Physics and Applications

UNIVERSITÀ DI TRENTO

Outline

- Introduction
  - Particle beam Radiation: from molecular level interactions to cell killing effects
- Relative effectiveness factors and their modeling
- Ultra high dose rate response: the FLASH radiotherapy puzzle
- Implementing Radiobiology in Treatment Planning
- Summary and Outlook

Bio-Medical Radiation Physics Research Team in Trento

- C. La Tessa, UniTN
- E. Scifoni, INFN
- F. Tommasino, UniTN

- **F. Cordoni,** Tenure Track UniTN (mathematician)
- M. Missiaggia, Postdoc (now@UM)
- A. Taffelli, Postdoc
- L. Castelli, PhD student
- E. Pierobon. PhD student
- **S. Lorentini**, Head of Medical Physics staff @ Trento PTC
- **A. Bisio**, CIBIO (Biologist)
- M. Battestini PhD student
- E. Fogazzi, PhD student
- E. Verroi, Technical Resp Exp Cave

Where are we

Trento

sponsor
Cooperazione Trentina

INFN2024

6° INCONTRO NAZIONALE DI
FISICA NUCLEARE

Sala della Cooperazione
via G. Segantini 10

TRENTO
26 | 28 Febbraio

TOPICS
- DINAMICA DEI QUARK E DEGLI ADRONI
- TRANSIZIONI DI FASE E PLASMA DI QUARK E GLUONI
- STRUTTURA NUCLEARE E DINAMICA DELLE REAZIONI
- ASTROFISICA NUCLEARE
- SIMMETRIE E INTERAZIONI FONDAMENTALI
- APPLICAZIONI, INTERDISCIPLINARIETÀ E NUOVI METODI NELLA FISICA NUCLEARE

COMITATO ORGANIZZATORE
Giuseppina Bisogni (Univ. di Pisa & INFN Pisa)
Giuseppe Eugenio Bruno (Politecnico di Bari & INFN Bari)
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Raffaella De Vita (INFN Genova)
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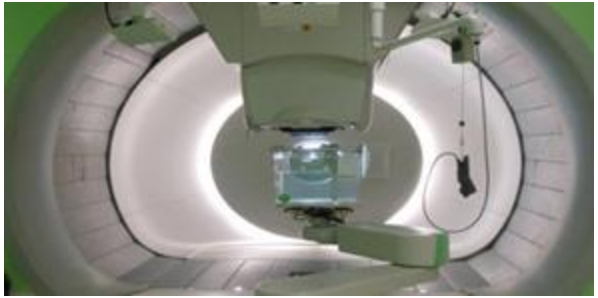
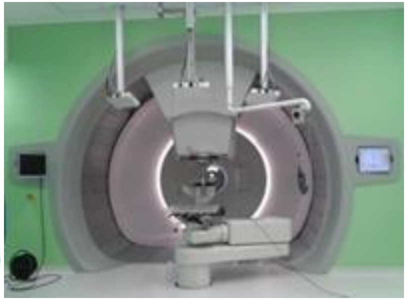
Francesco Tommasino (Univ. di Trento & INFN TIFPA)
Cristina Vaccarezza (INFN LNF)

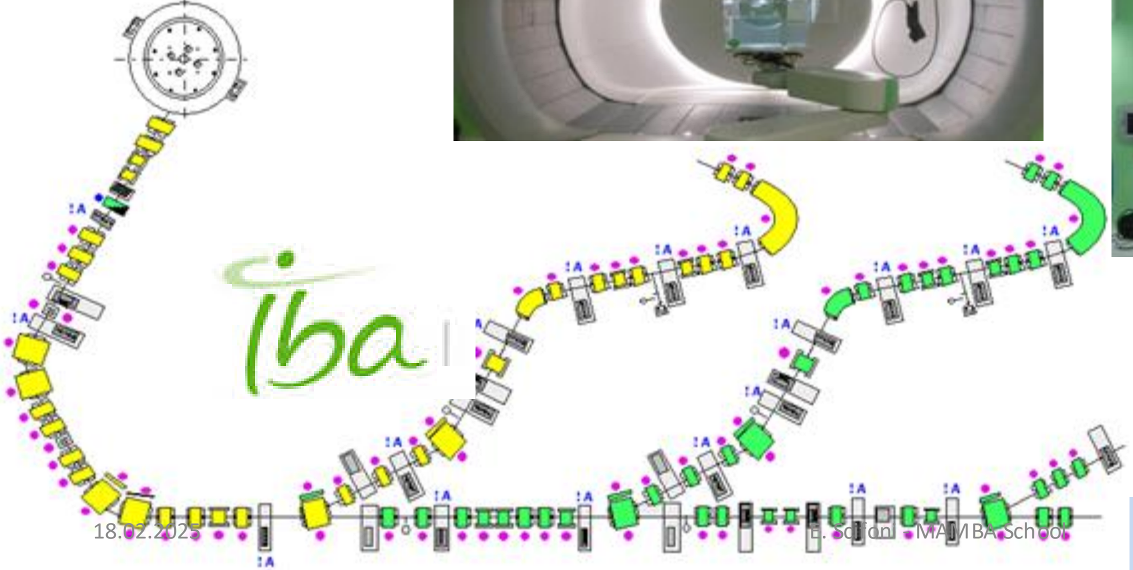
COMITATO ORGANIZZATORE LOCALE
Roberto Senmen Brusa, co-chair (Univ. di Trento & INFN TIFPA)
Emanuele Scifoni, co-chair (INFN TIFPA)
Winfried Leidemann (Univ. di Trento & INFN TIFPA)
Francesco Pederiva (Univ. di Trento & INFN TIFPA)
Alberto Quaranta (Univ. di Trento & INFN TIFPA)
Alessandro Roggero (Univ. di Trento & INFN TIFPA)
Francesco Tommasino (Univ. di Trento & INFN TIFPA)

TIFPA
UniTN/DF

Trento Proton Therapy Center







TIFPA Experimental cave @PTC- Trento

PAC submission
Open to users

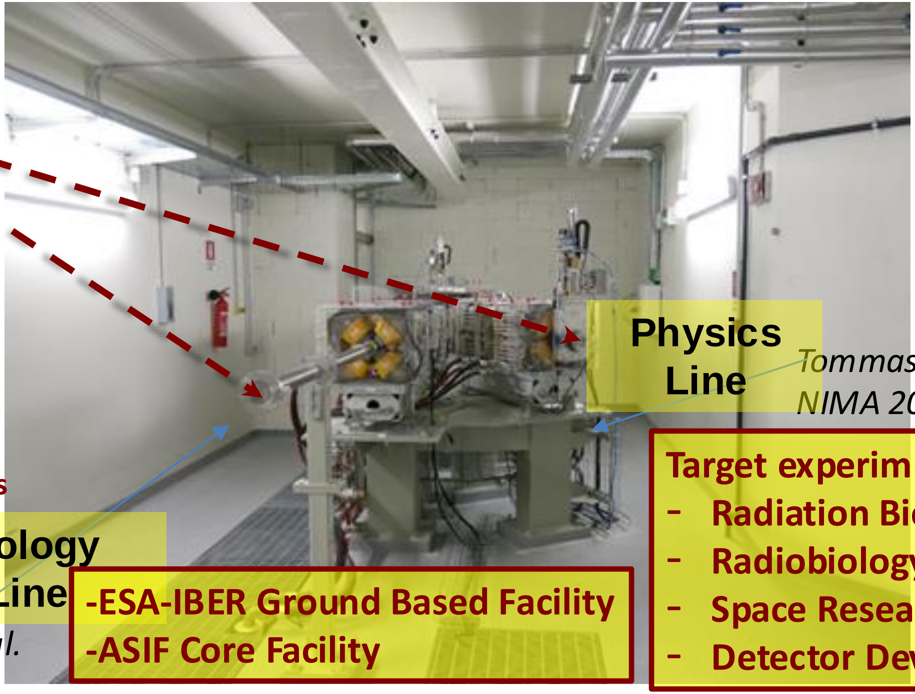
www.tifpa.infn.it/sc-init/med-tech/p-beam-research/

Beam Production:
- Isochronous Cyclotron IBA Proteus 235
- Energy Range: 70-225 MeV
- Beam Current: up to 320 nA
- Typical Efficiency: ≈55%

Two beam lines

Energy range at beam exit: 70 – 225 MeV

100 exp from 2016, by local /external groups



Tommasino et
NIMA 2017

Tommasino et al.
Phys Med 2019

-ESA-IBER Ground Based Facility
-ASIF Core Facility

Target experiments:
- **Radiation Biophysics**
- **Radiobiology**
- **Space Research**
- **Detector Development**

Hadrontherapy in Italy

In Construction/ commissioning

Milano (IEO)

Aviano (CRO)

In Operartion

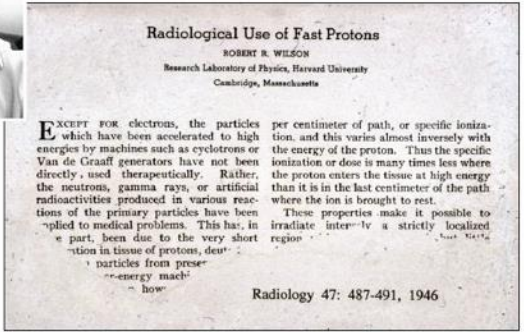
- **p** high E (70-235 MeV)
- **C, p**, possibly in future **He,O,** high E (80-400 MeV/u),
- **p,** low E (up to 62 MeV/u)

Hadrontherapy

- Also called
    - Ion beam therapy
    - (Charged) Particle Therapy

- Radiation Therapeutic option exploiting **charged particle beams** features, physics and radiobiological based

R.R. Wilson, "Foreword to the Second International Symposium on Hadrontherapy," in Advances in Hadrontherapy, (U. Amaldi, B. Larsson, Y. Lemoigne, Y., Eds.), Excerpta Medica, Elsevier, International Congress Series **1144**: ix-xiii (1997).



Radiological Use of Fast Protons

ROBERT R. WILSON

Research Laboratory of Physics, Harvard University
Cambridge, Massachusetts

EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly, used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been plied to medical problems. This has, in e part, been due to the very short tion in tissue of protons, deu particles from prese -energy mach how

per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest.

These properties make it possible to irradiate inter ly a strictly localized region

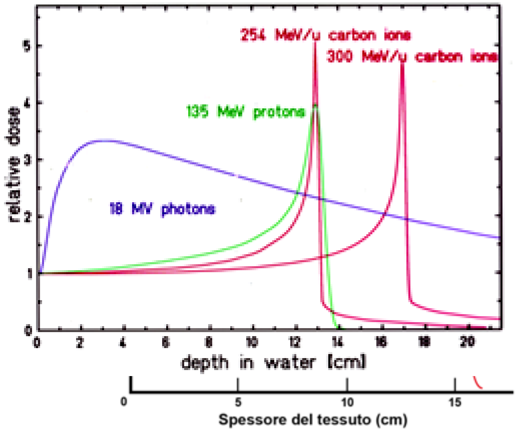
Radiology 47: 487-491, 1946

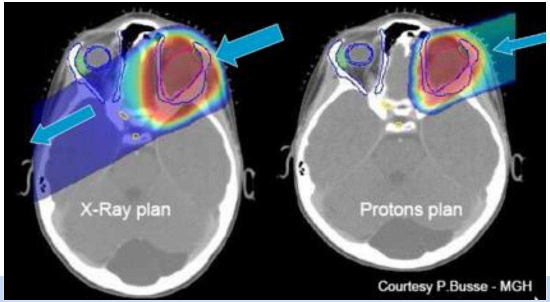
R. Wilson
1946

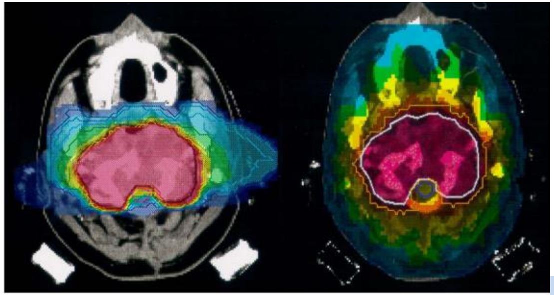
Particle versus Photon radiation

- Protons and other ions deposit less dose in healthy tissue/ OAR
  - Macroscopic **physical** advantages
  - In some cases also **biological** advantages

- Clear advantage for sustainability of a retreatment







C-12, 2 fields

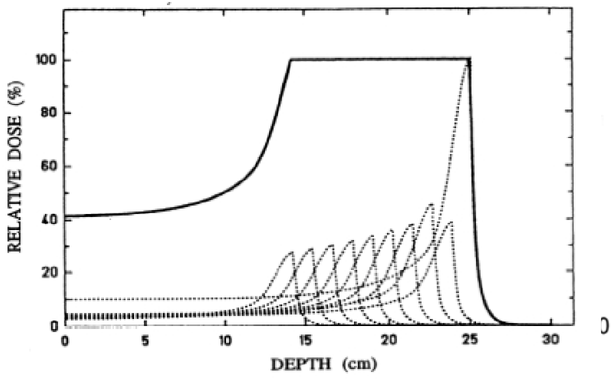
IMRT, 9 fields

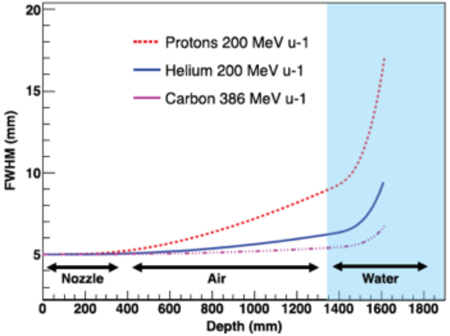
Jäkel, Debus, Heidelberg

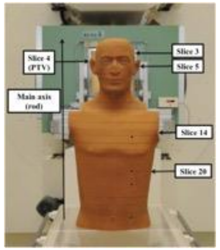
The obvious advantages: Physics

Depth dose

Spread out Bragg peak

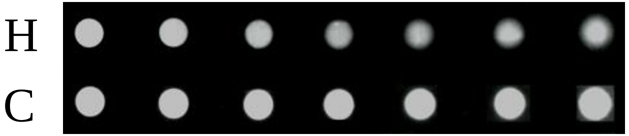


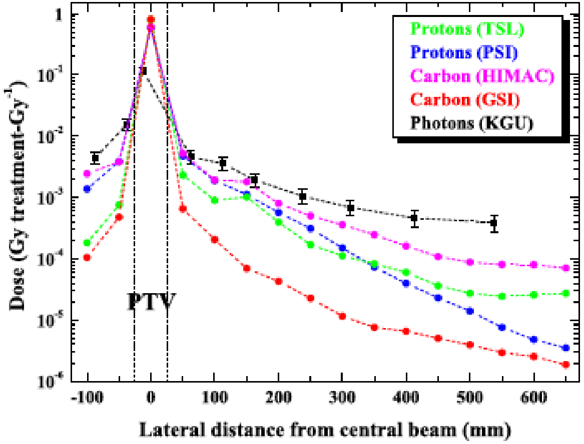




Rovituso et al. PMB 2017

Lateral profile

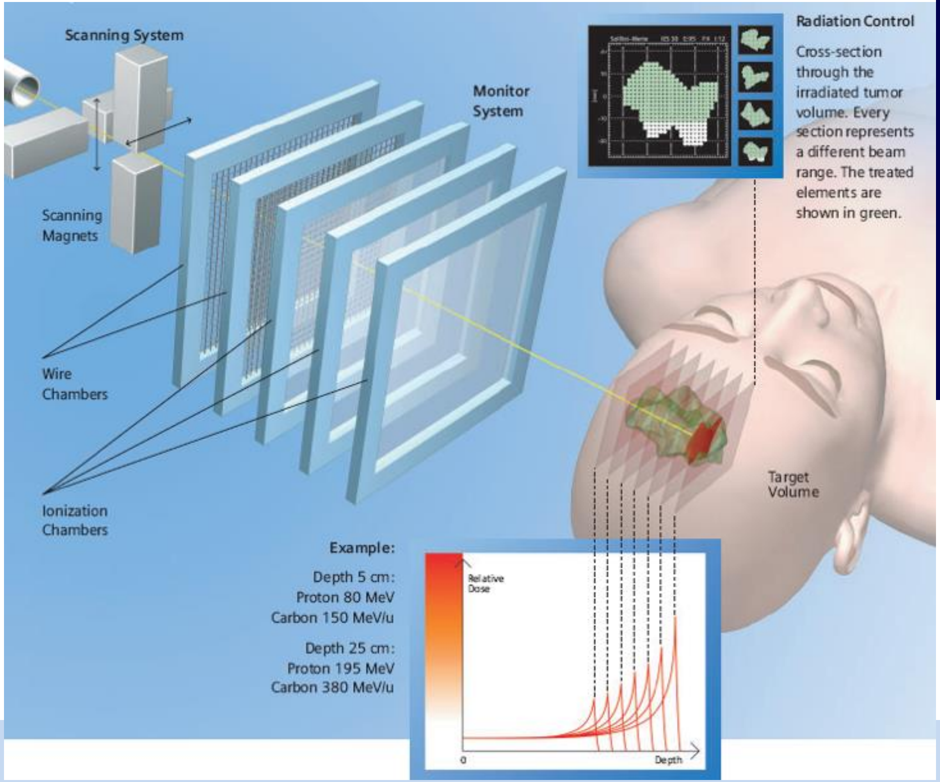




La Tessa et al. Radiother. Oncol. 2012

Dose Delivery

Active (Raster) Scanning



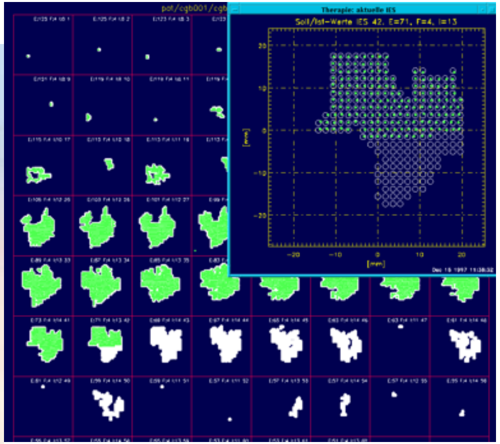
Radiation Control

Cross-section through the irradiated tumor volume. Every section represents a different beam range. The treated elements are shown in green.

Example:

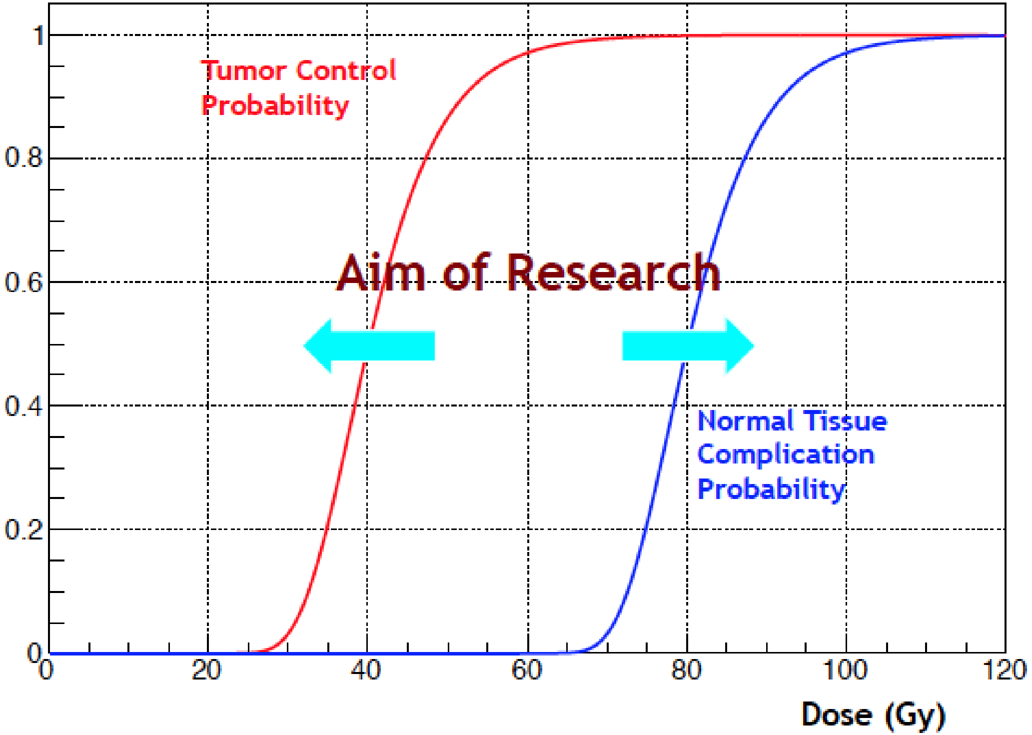
Depth 5 cm:
Proton 80 MeV
Carbon 150 MeV/u

Depth 25 cm:
Proton 195 MeV
Carbon 380 MeV/u

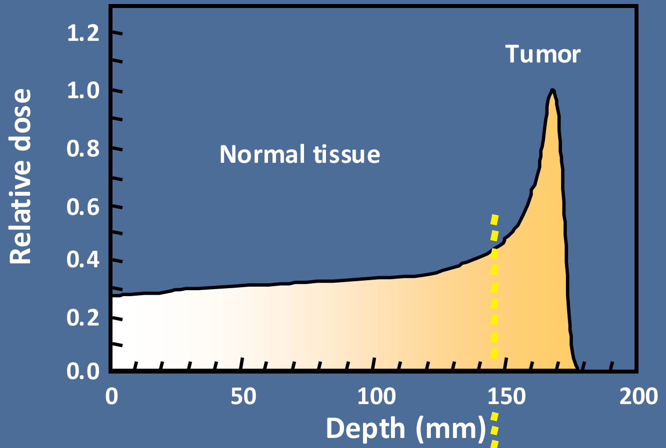


Typically:
p: ~10^9p/s
12C: ~ 10^{8p}/s

Exploiting Hadrontherapy

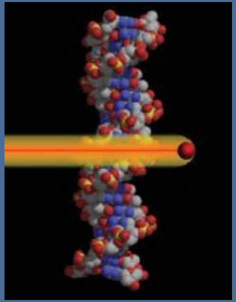


The less obvious: Biology



Durante & Loeffler,

Nature Rev Clin Oncol 2010



			Potential advantages
Energy	high	low	
LET	low	high	
Dose	low	high	High tumor dose, normal tissue sparing
RBE	≈ 1	> 1	Effective for radioresistant tumors
OER	≈ 3	< 3	Effective against hypoxic tumor cells
Cell-cycle dependence	high	low	Increased lethality in the target because cells in radioresistant (S) phase are sensitized
Fractionation dependence	high	low	Fractionation spares normal tissue more than tumor
Angiogenesis	Increased	Decreased	Reduced angiogenesis and metastatization
Cell migration	Increased	Decreased	

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journal homepage: www.sciencedirect.com/journal/ijpt

Particle Beam Radiobiology Status and Challenges: A PTCOG Radiobiology Subcommittee Report

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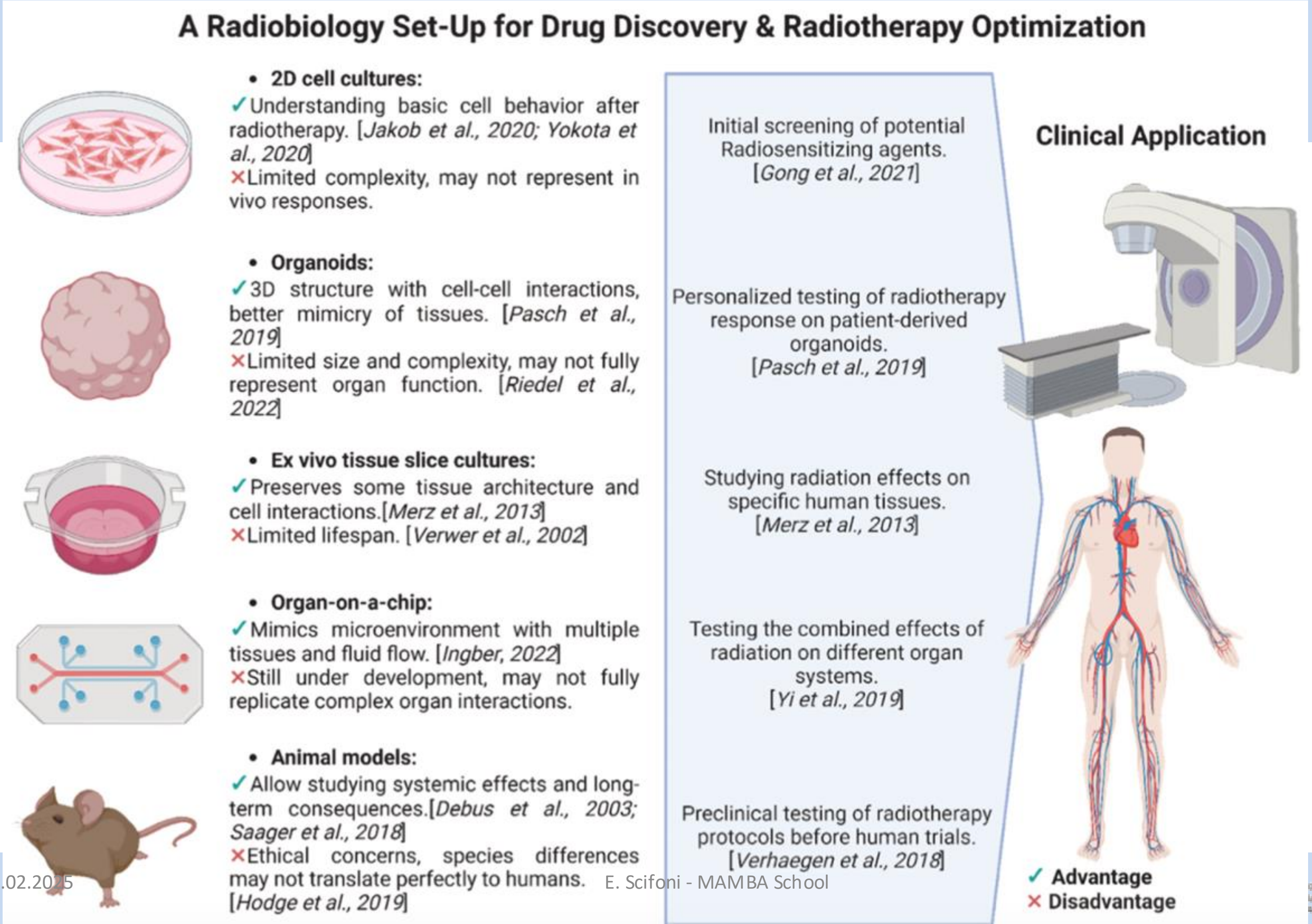


A Radiobiology Set-Up for Drug Discovery & Radiotherapy Optimization

- **2D cell cultures:**

✓Understanding basic cell behavior after radiotherapy. [*Jakob et al., 2020; Yokota et al., 2020*]
×Limited complexity, may not represent in vivo responses.

- **Organoids:**

✓3D structure with cell-cell interactions, better mimicry of tissues. [*Pasch et al., 2019*]
×Limited size and complexity, may not fully represent organ function. [*Riedel et al., 2022*]

- **Ex vivo tissue slice cultures:**

✓Preserves some tissue architecture and cell interactions.[*Merz et al., 2013*]
×Limited lifespan. [*Verwer et al., 2002*]

- **Organ-on-a-chip:**

✓Mimics microenvironment with multiple tissues and fluid flow. [*Ingber, 2022*]
×Still under development, may not fully replicate complex organ interactions.

- **Animal models:**

✓Allow studying systemic effects and long-term consequences.[*Debus et al., 2003; Saager et al., 2018*]
×Ethical concerns, species differences may not translate perfectly to humans. [*Hodge et al., 2019*]

Initial screening of potential Radiosensitizing agents. [*Gong et al., 2021*]

Personalized testing of radiotherapy response on patient-derived organoids. [*Pasch et al., 2019*]

Studying radiation effects on specific human tissues. [*Merz et al., 2013*]

Testing the combined effects of radiation on different organ systems. [*Yi et al., 2019*]

Preclinical testing of radiotherapy protocols before human trials. [*Verhaegen et al., 2018*]

Clinical Application

✓ **Advantage**
× **Disadvantage**

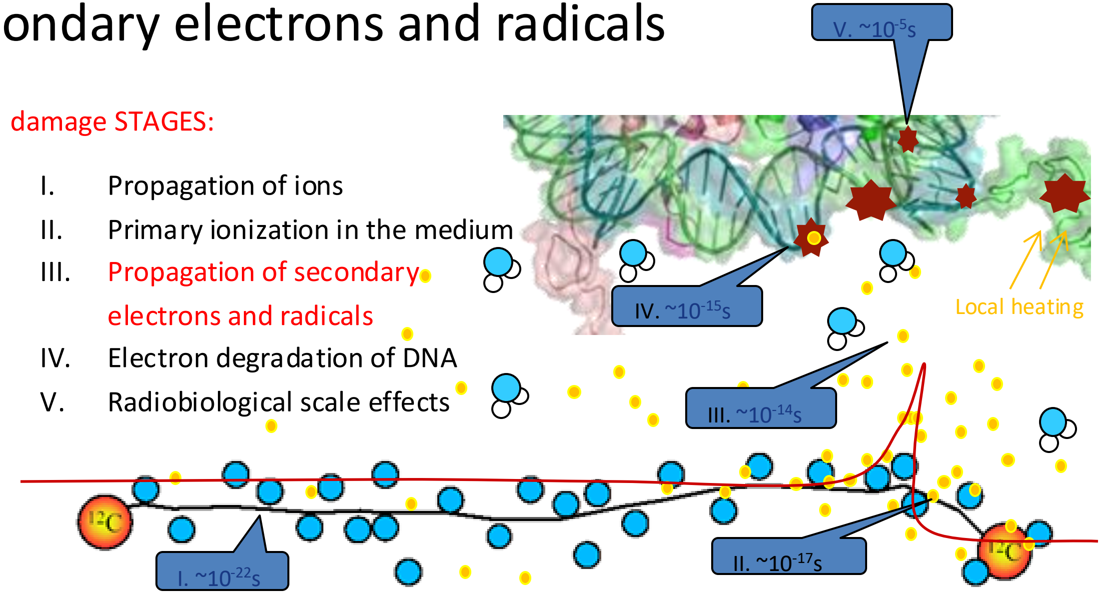
Ahmad
et al. 2024

The mechanism of biological damage with particle beams

La Largest part of the damage comes from secondary electrons and radicals

Ion beam damage STAGES:

I. Propagation of ions
II. Primary ionization in the medium
III. Propagation of secondary electrons and radicals
IV. Electron degradation of DNA
V. Radiobiological scale effects

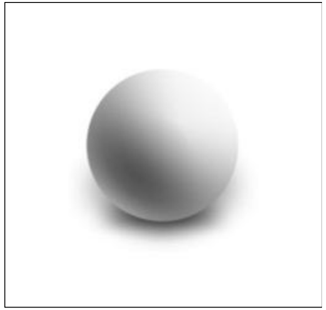


Scifoni et al. COST nanoIBCT EU proposal (2010)

Why we need models in radiation biology?

- To make predictions on different radiation effects on cells/tissue
- To implement in Treatment Planning
- To understand and explain phenomena on physics bases (*computational microscopy*)


“This is not a cow”
--- René Magritte

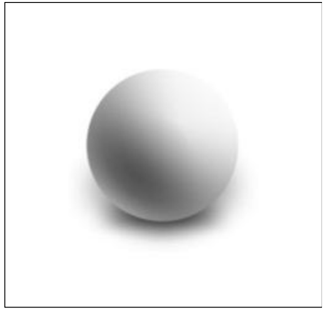

“This is a cow”
--- Anonymous physicist

Courtesy from A.Attili

The basic Idea of Physics based modeling of (radiation induced) Biological effects

- Ignore as much as possible Biology (too complicate for you)
- Spot the differences in Physics
- Work on them as relative factors

“This is not a cow”
--- René Magritte



“This is a cow”
--- Anonymous physicist

Courtesy from A.Attili

Particle beam biophysics

Radiation biophysics attempts to explain on the basis of the pattern of fundamental interactions, **relative factors** of radiation induced biologic effectiveness, e.g.:

- Different Particle type/radiation field : **RBE**

$$RBE = \left.\frac{D(ref = Xrays)}{D(Particle\ Field)}\right|_{same\ effect}$$

- Different medium, environment, oxygenation: **OER**

$$OER = \left.\frac{D(pO_2)}{D(21\%)}\right|_{same\ effect}$$

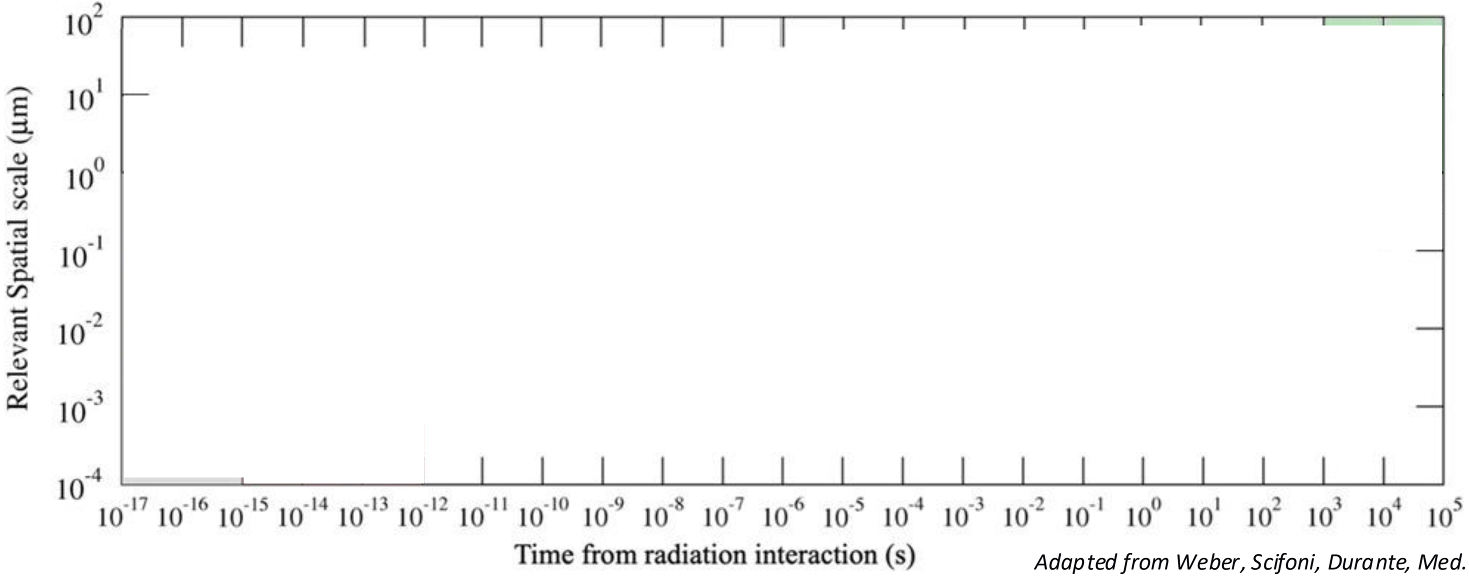
- Impact of Radisensitizer/radioprotector substance: **DEF**

$$DEF = \left.\frac{D([C = 0])}{D([C])}\right|_{same\ effect}$$

- Different dose delivery method (dose rate): **DREF**

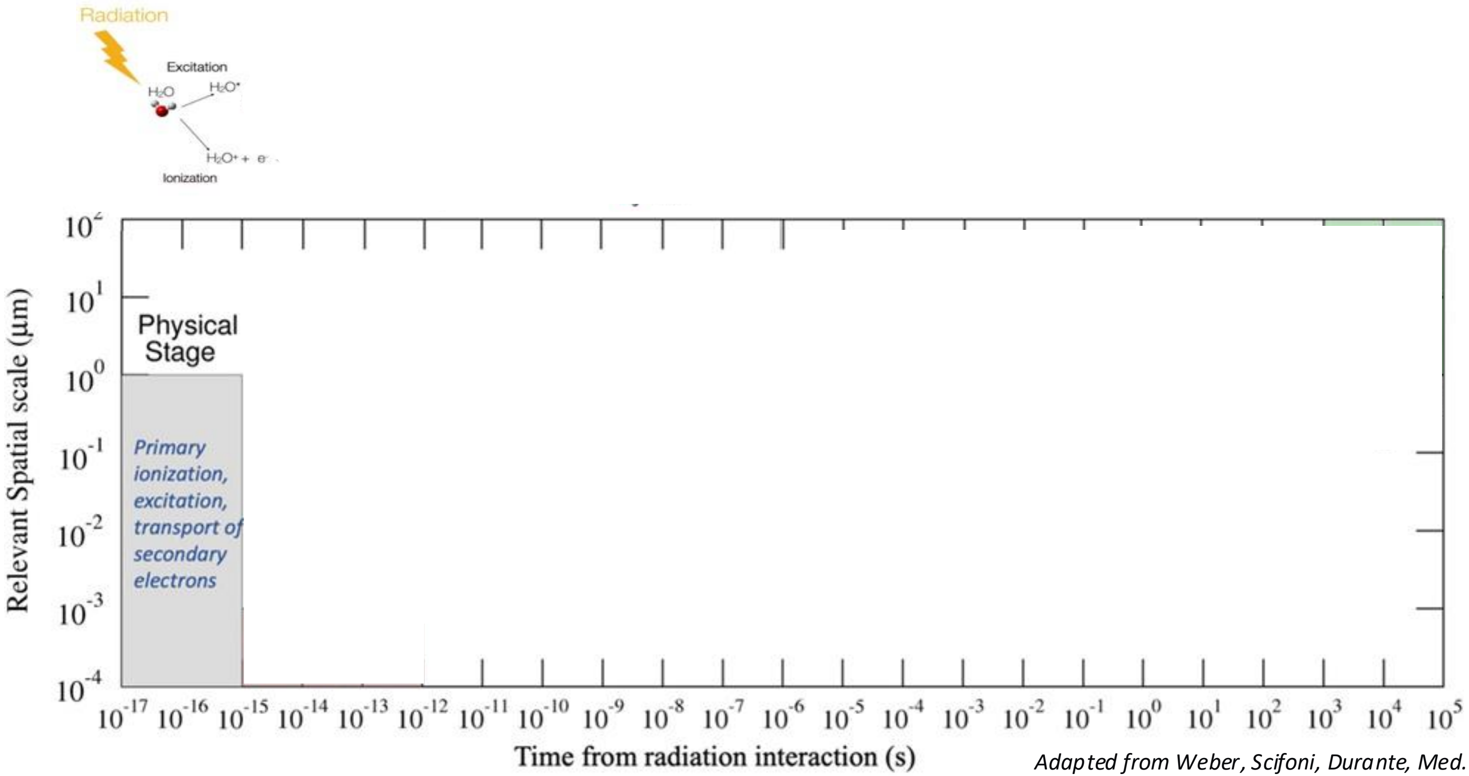
$$DREF = \left.\frac{D(\dot{D})}{D(\dot{D}_{ref})}\right|_{same\ effect}$$

Spatiotemporal scales of radiation damage



Adapted from Weber, Scifoni, Durante, Med. Phys. (2022)

Spatiotemporal scales of radiation damage



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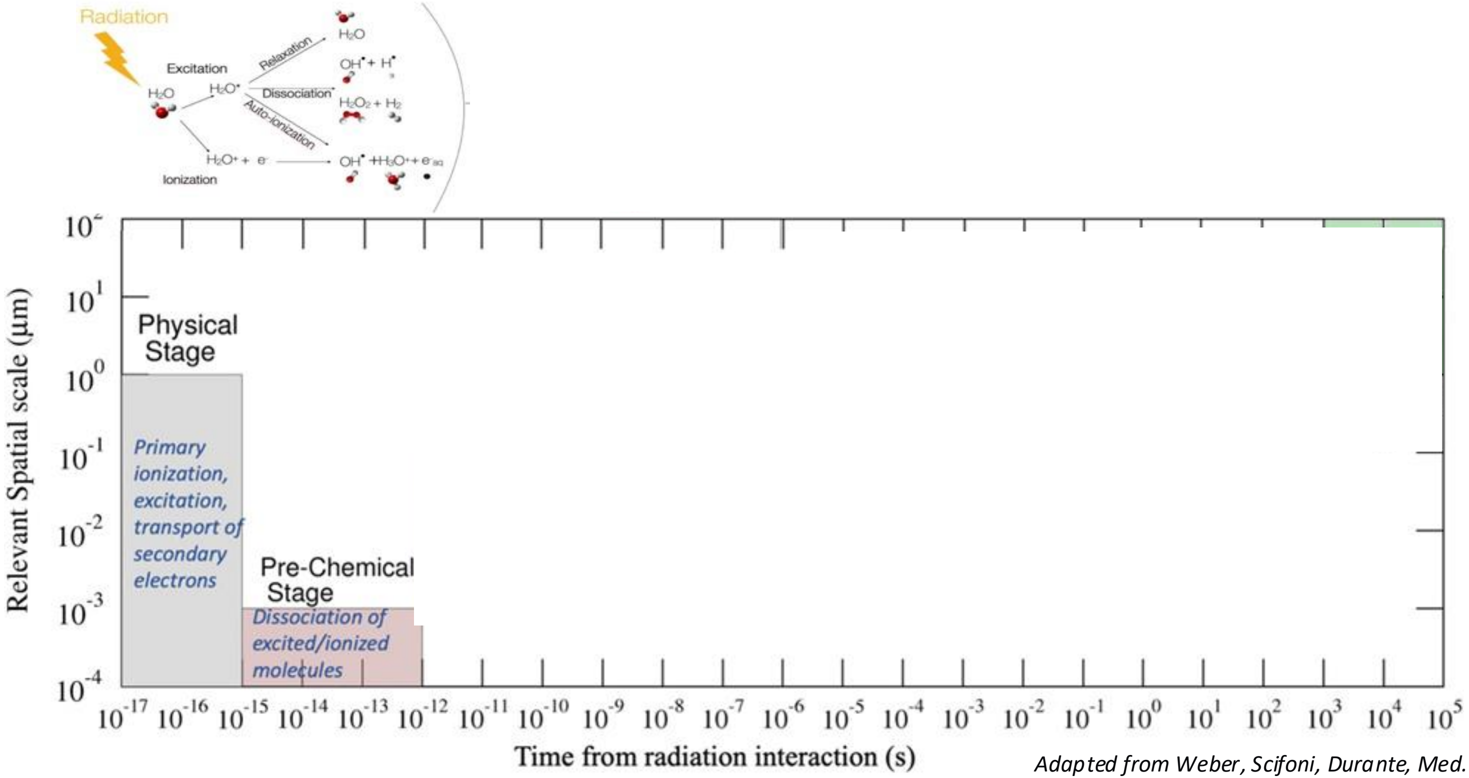

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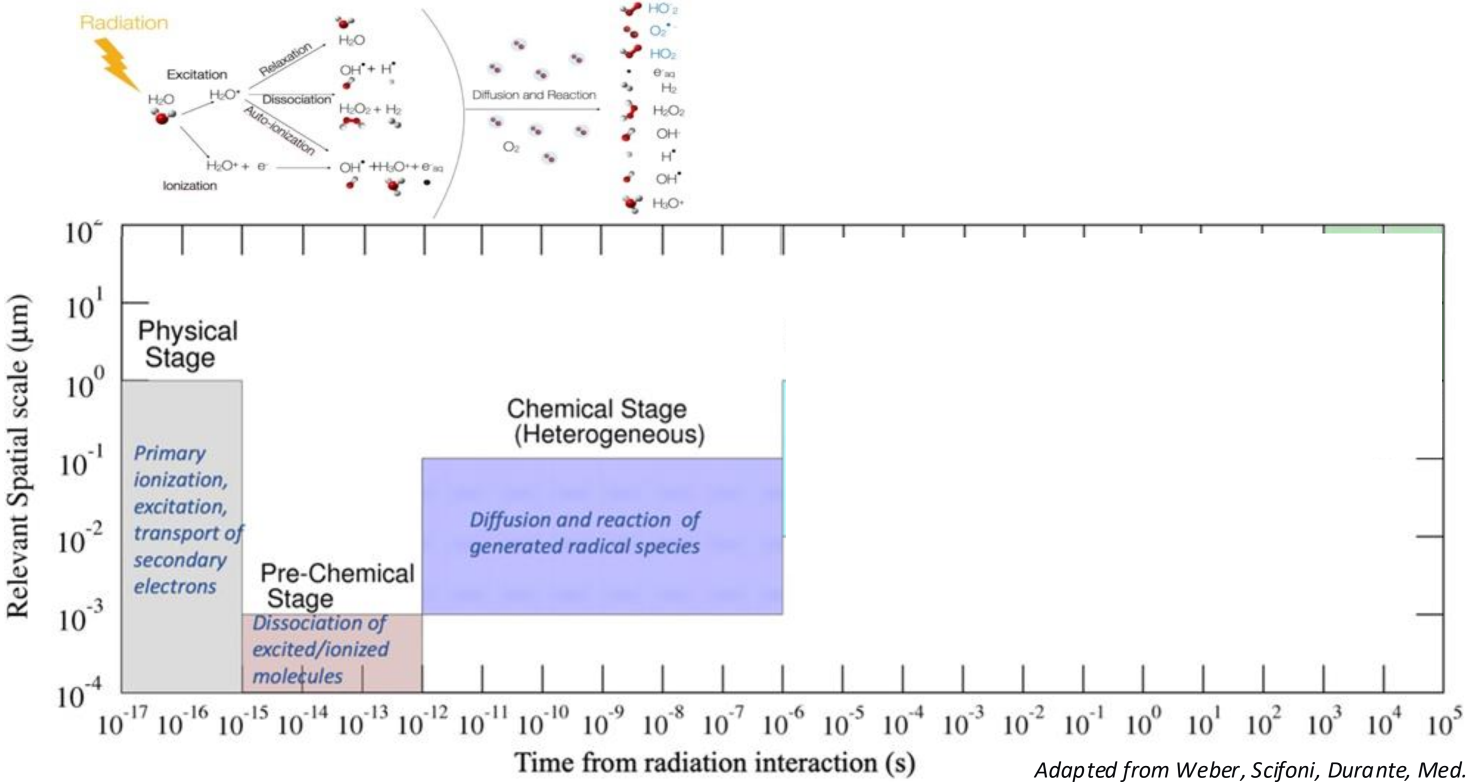

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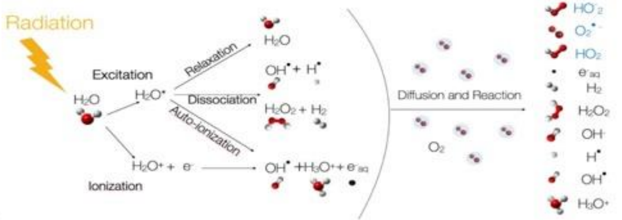
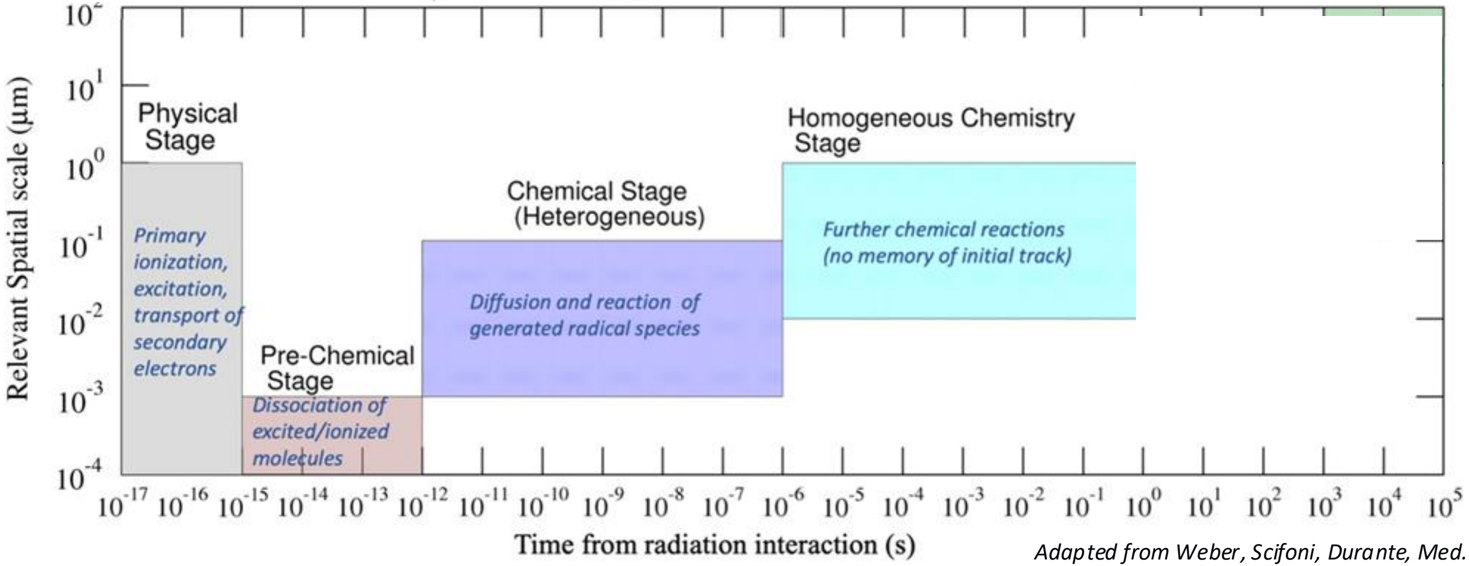


Reactions with
intra-cellular oxygen O_2

Reactions with
organic molecules
(after direct ionization of
RH)



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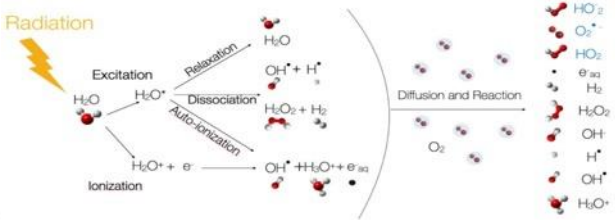
Spatiotemporal scales of radiation damage



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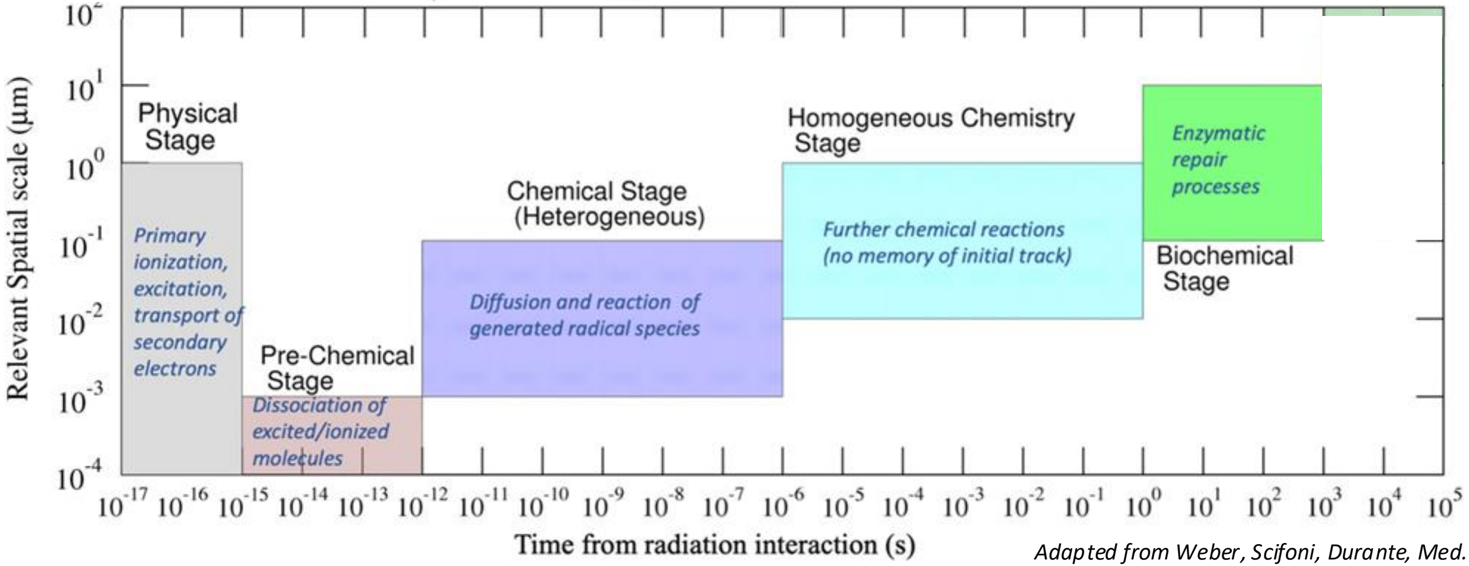

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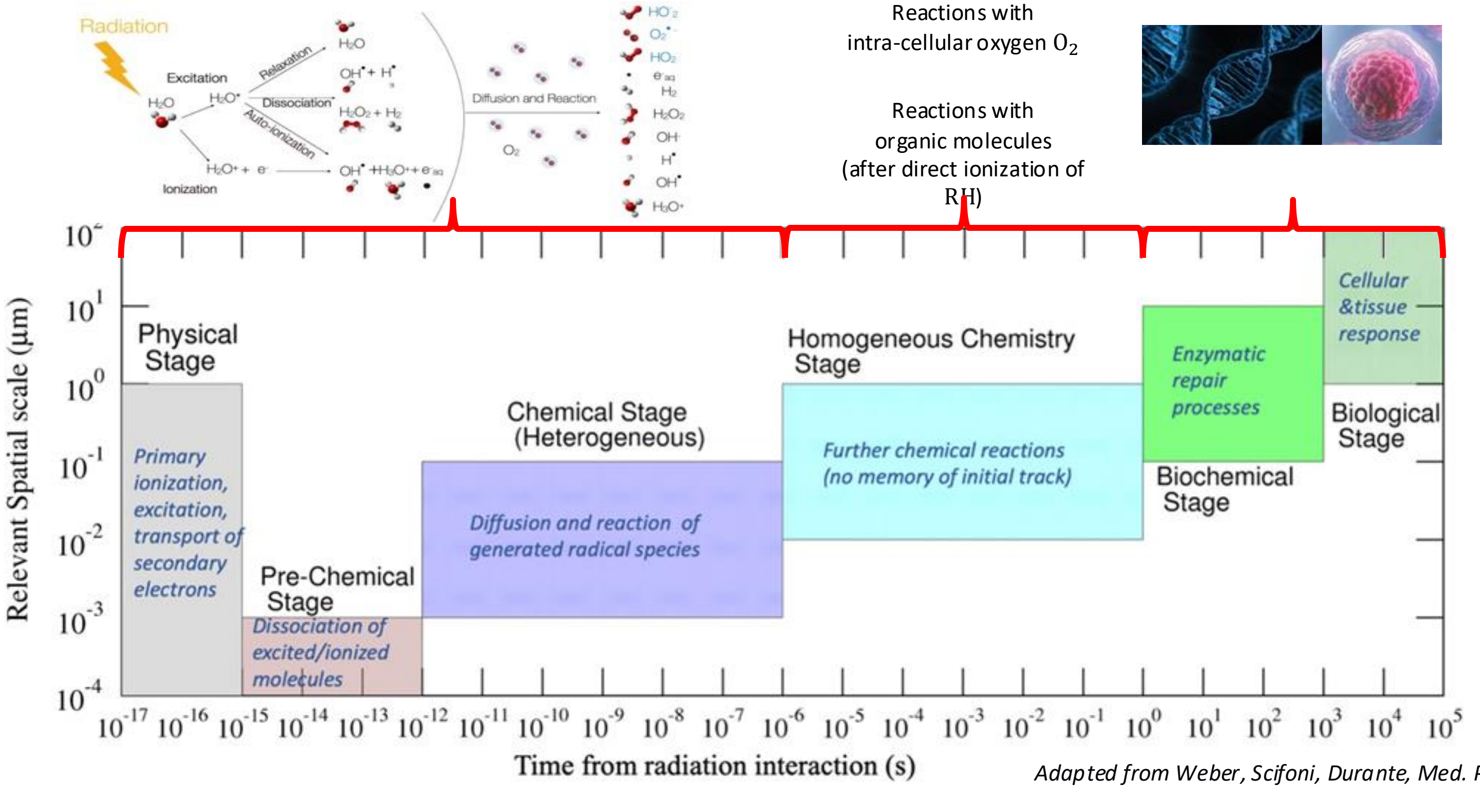
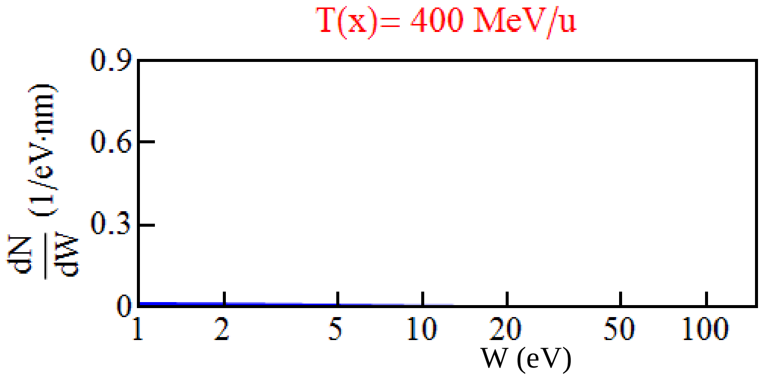


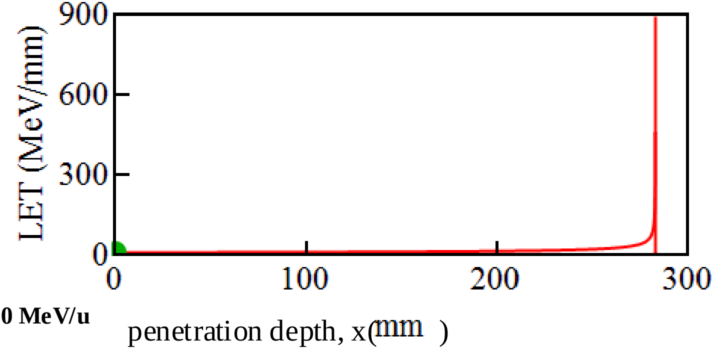
Reactions with intra-cellular oxygen O_2

Reactions with organic molecules (after direct ionization of RH)

Adapted from Weber, Scifoni, Durante, Med. Phys. (2022)

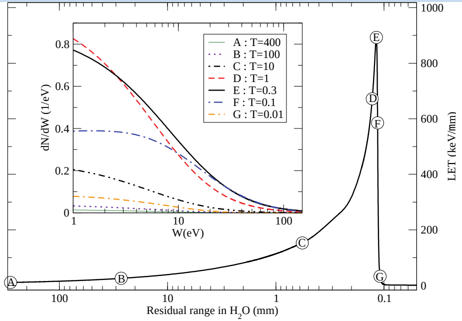
Secondary Electrons produced by an ion along a Bragg Peak



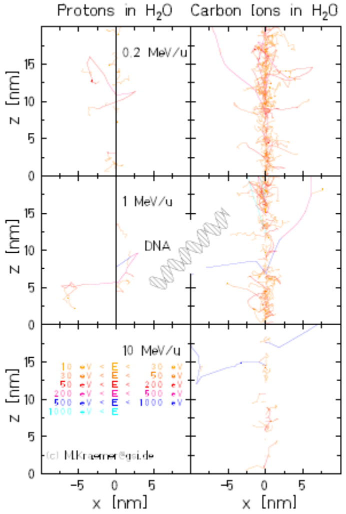


T_0=400 MeV/u

Scifoni,et al., PRE 2010



Scifoni,et Mod Phys Lett. 2015

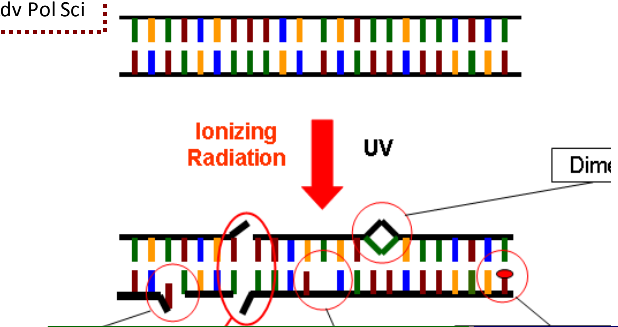


Kraemer et al JPCS 2012

Track Structure simulation

Differential DNA Damage

Scholz 2006
Adv Pol Sci

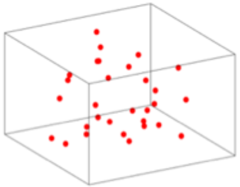


- The DNA **Double Strand Break (DSB)** is considered the type of lesion most directly related to cell killing
- Different radiation qualities produce the same spectrum of DNA lesions
- **BUT** the distribution of lesions inside the target can be very different

Photons

x-rays

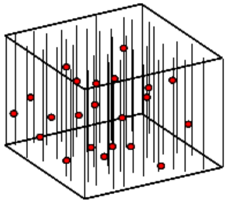
Random
DSB distribution



^{12}C Low LET

200 MeV/u, ≈ 16 keV/μm

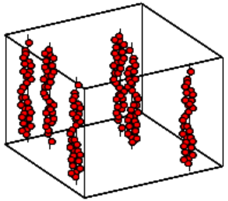
Random
DSB distribution
(photon-like)



^{12}C High LET

1 MeV/u, ≈ 690 keV/μm

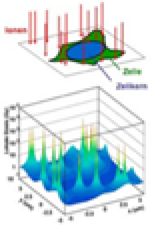
Non-random
DSB distribution
(RBE>>1)



Courtesy of F. Tommasino

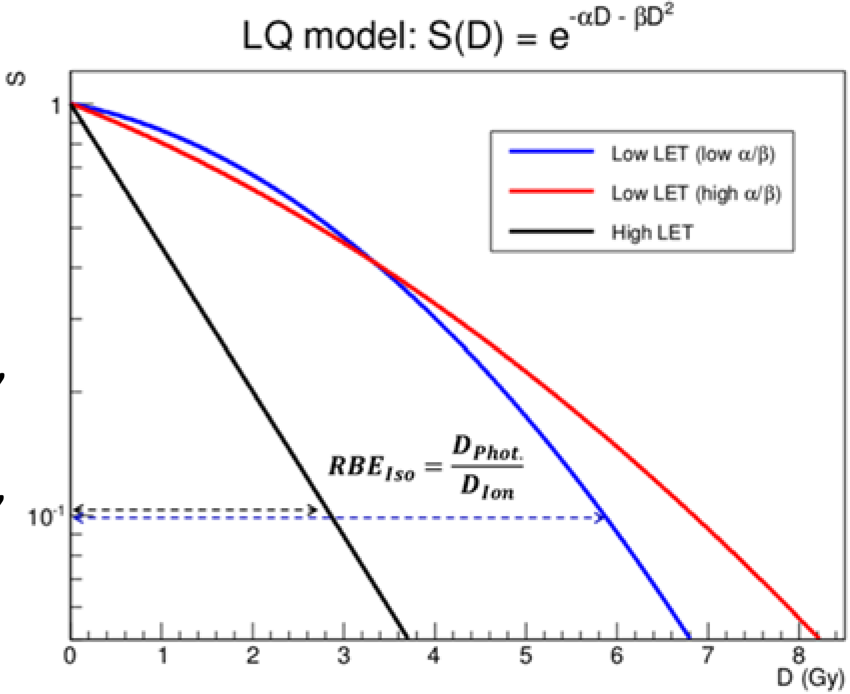
Relative Biological Effectiveness (RBE):

$$RBE = \frac{D_{\gamma}}{D_{Ion}}\bigg|_{Isoeffect}$$



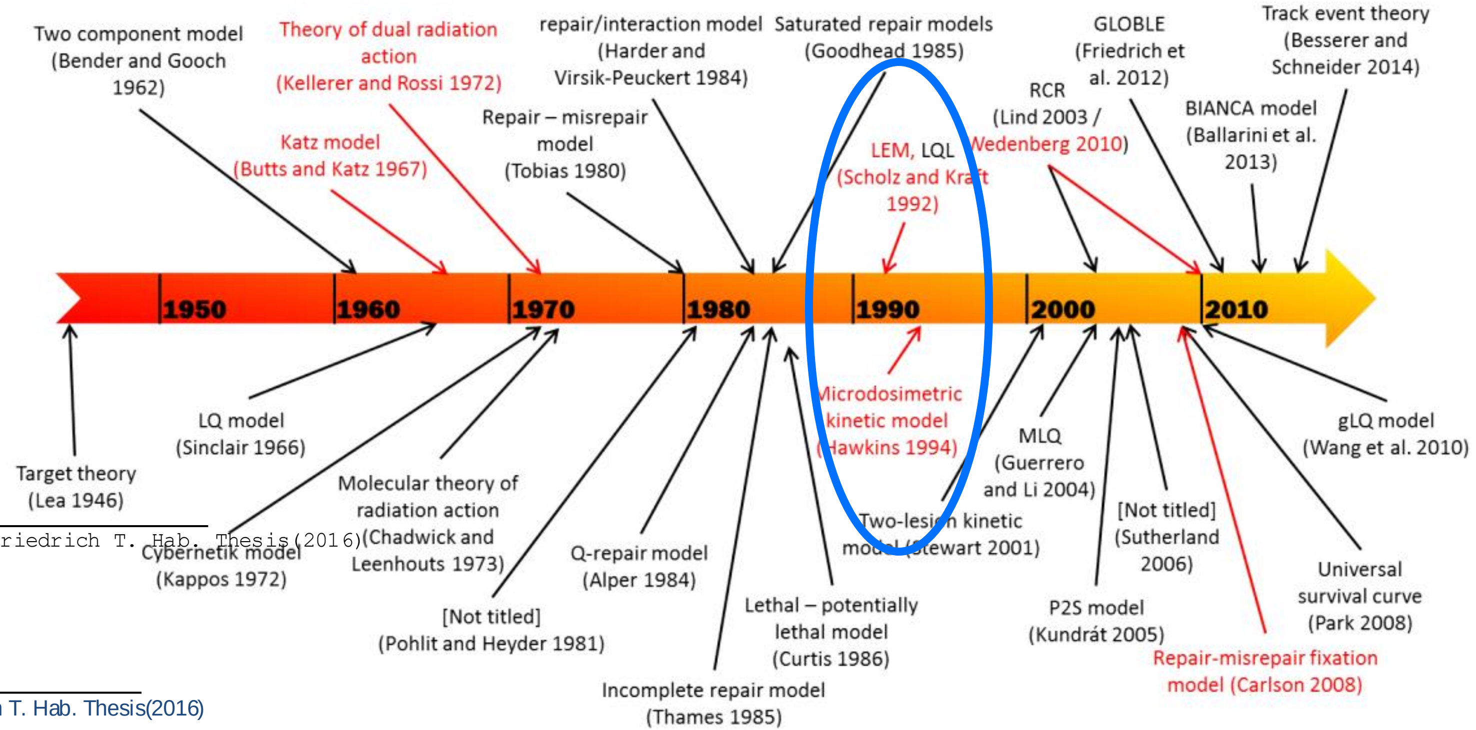
RBE depends on:

- Physical parameters (dose, LET, fractionation).
- Biological parameters (cell cycle, oxygenation, end-point).



Courtesy of F. Tommasino

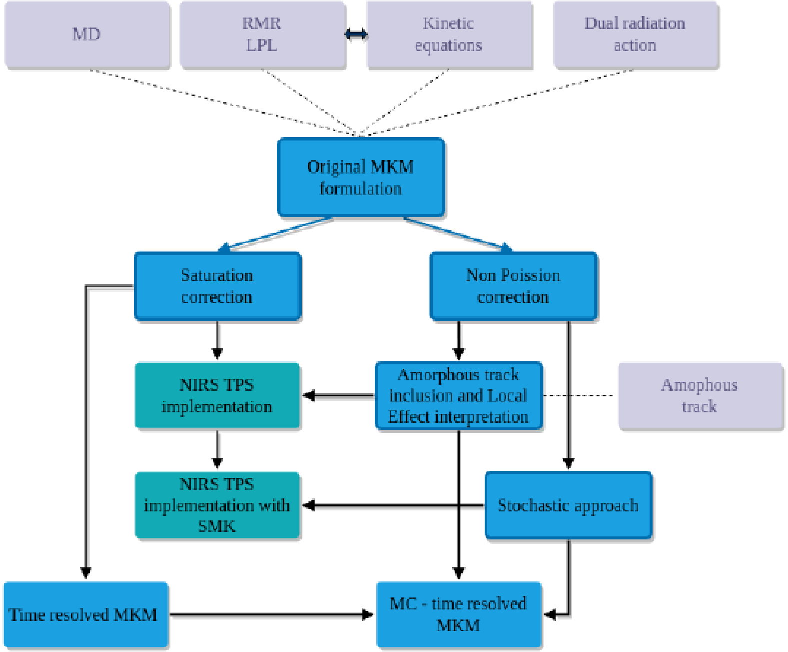
Mechanistic RBE models



Friedrich T. Hab. Thesis(2016)

Friedrich T. Hab. Thesis(2016)

Microdosimetry based modeling



Bellinzona et.al. Linking Microdosimetric Measurements to Biological E.ectiveness in Ion Beam Therapy: A review of theoretical aspects of MKM and other models. Frontiers in Physics (2021): 623

The Generalized Stochastic Microdosimetric Model (GSM^2)

GOAL:

- To develop a general probabilistic model that accounts for all of levels of stochasticity in the formation and temporal evolution of DNA damages induced by radiation:

1. temporal stochasticity of DNA damage;

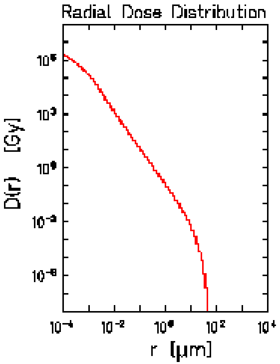
2. spatial stochasticity of DNA damage:
    -intra-cellular level
    -inter-cellular level

3. ionizing radiation stochasticity:
    -physical level energy deposition stochasticity
    (microdosimetric distributions)
    -biological level DNA damage formation stochasticity

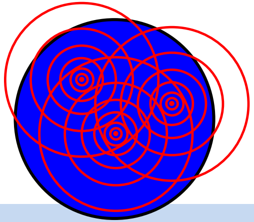
Francesco G. Cordoni

An example (LEM IV)

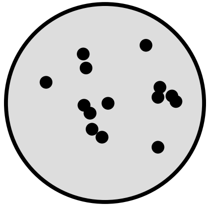
Courtesy of T.Friedrich



Amorphous track structure



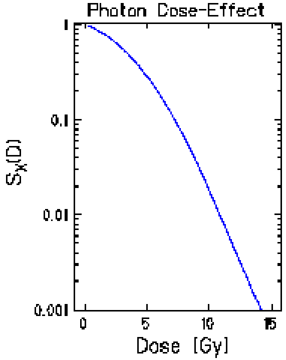
Local dose distribution



Local lesion distribution

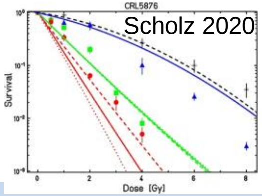
Lesion statistics

:	7
:	3



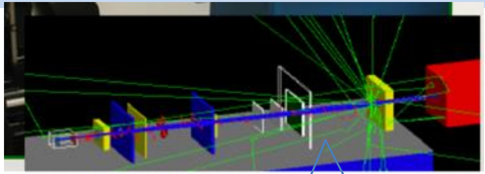
Photon equivalent situation

RBE



Scholz 2020

Monte Carlo Methods for Radiation Research



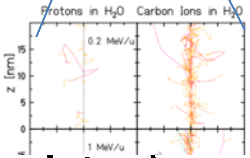
- **MC radiation transport codes**

  =Condensed history codes.

(GEANT4(*), FLUKA, PHITS, SHIELD-HIT, EGS4, MCNPX, ..)

\+ possibility to describe entire irradiation geometry

\- Imposition of thresholds (i.e. G4: e->~900eV)



- **MC Track Structure codes**

  =Event by Event. Stochastic (physics+chemistry)

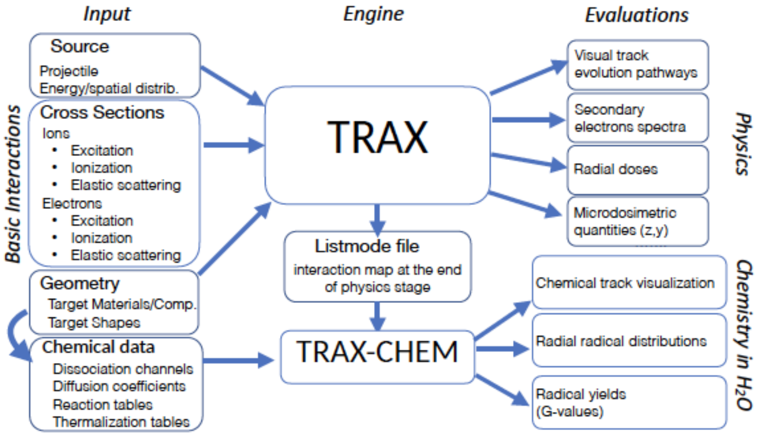
(PARTRAC, TRAX, GEANT4DNA, TOPASnBIO, RITRACKS…)

\+ no, or negligible (~1eV) energy/space threshold

\- Limited portion of track describable (normally “track segment”)

(*) with its wrappers TOPAS, GATE, MCHIT

TRAX and TRAX-CHEM



Input

Engine

Evaluations

Basic Interactions

Source
Projectile
Energy/spatial distrib.

Cross Sections
Ions
- Excitation
- Ionization
- Elastic scattering

Electrons
- Excitation
- Ionization
- Elastic scattering

Geometry
Target Materials/Comp.
Target Shapes

Chemical data
Dissociation channels
Diffusion coefficients
Reaction tables
Thermalization tables

TRAX

Listmode file
interaction map at the end of physics stage

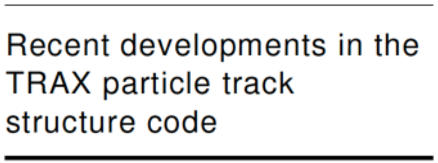
TRAX-CHEM

Physics

- Visual track evolution pathways
- Secondary electrons spectra
- Radial doses
- Microdosimetric quantities (z,y)

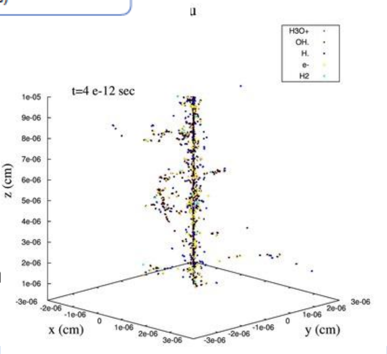
Chemistry in H2O

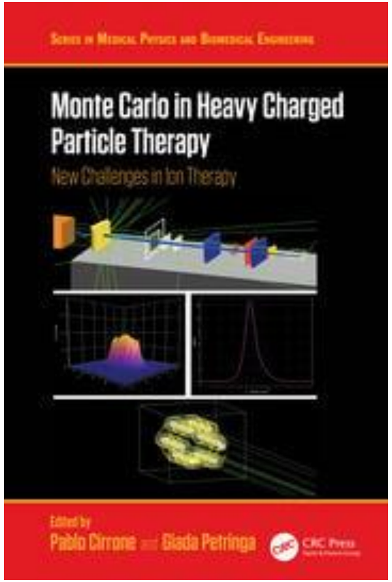
- Chemical track visualization
- Radial radical distributions
- Radical yields (G-values)



Recent developments in the TRAX particle track structure code

M. Kraemer, D. Boscolo, M. Fuss & E. Scifoni
(chapter in print on T&F Book)





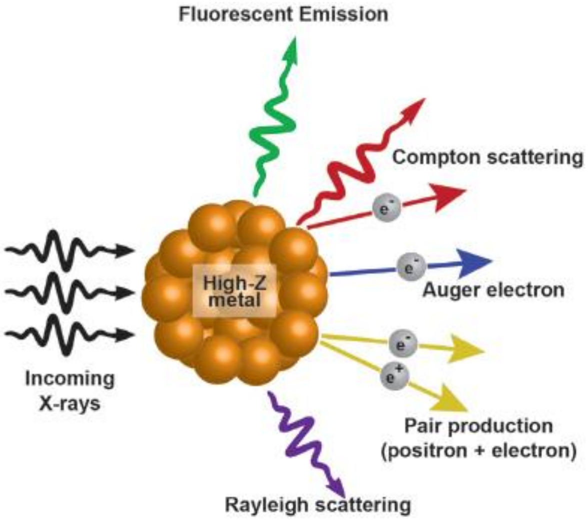
Series in Medical Physics and Biomedical Engineering

Monte Carlo in Heavy Charged Particle Therapy
New Challenges in Ion Therapy

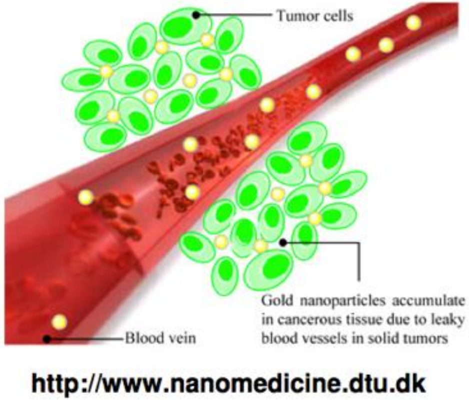
Edited by
Pablo Cirrone and Giada Petringa

CRC Press

High Z Nanoparticle radiosensitization



Kwatra et al. Transl. Cancer Res. 2013



NP: high cellular uptake in tumours

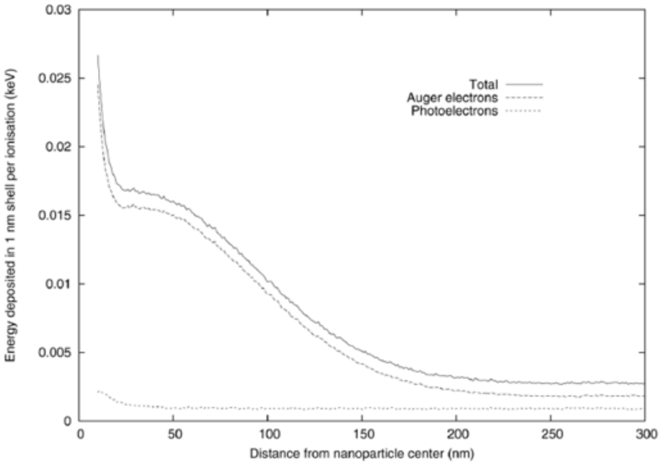
well known adavantage for photons;
high Z ➔ high e^- emission vs. high absorption

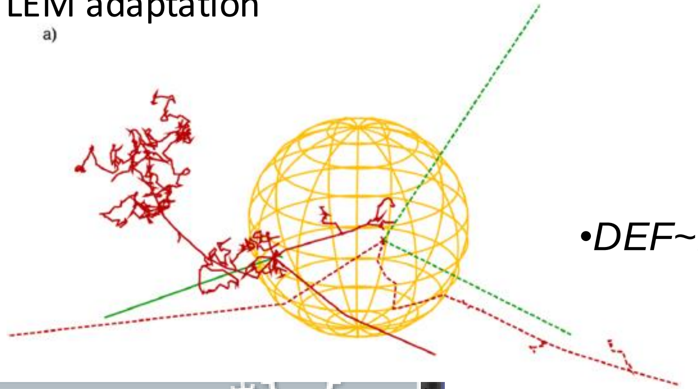
advantage with ion irradiation?

Au NP with photons – Mechanistic insight

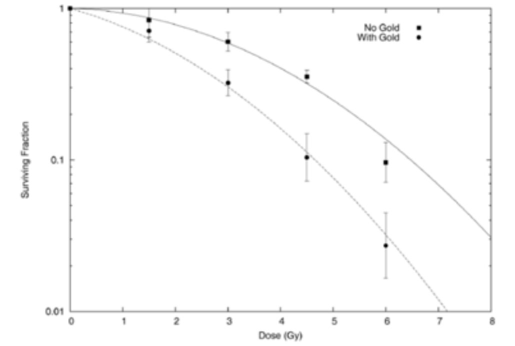
- Auger electrons play a crucial role for photons
- local dose enhancement

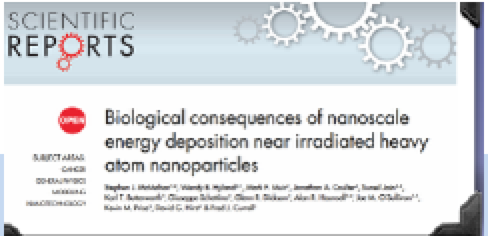
analysis based on track structure and LEM adaptation





•*DEF~1.5*




SCIENTIFIC REPORTS

Biological consequences of nanoscale energy deposition near irradiated heavy atom nanoparticles

Mc Mahon et al. Sci. Rep. 2011

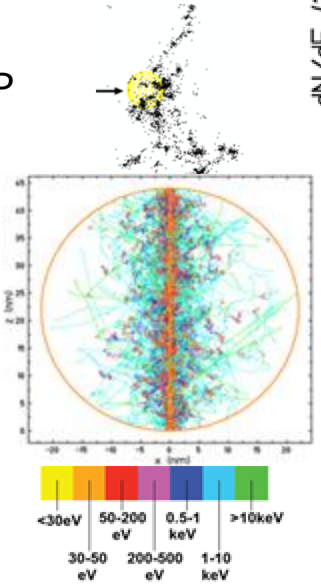
High Z NP+ion local dose enhancement

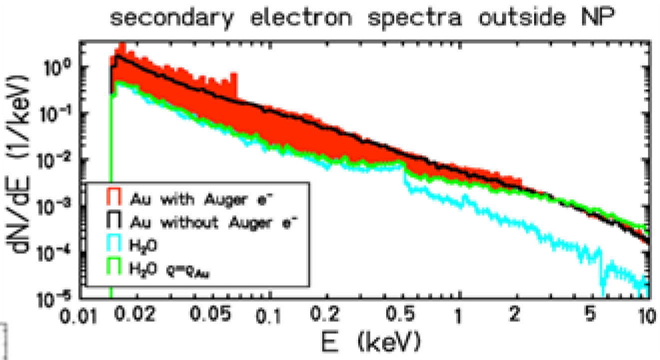
- Extensive Cross sections implementation for several High Z materials
- Au, Pt, Gd, Fe,Including Auger Cascades

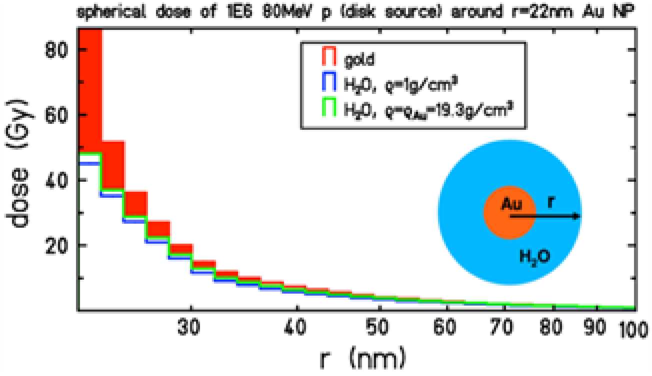
1st track structure study of ion+NP (2014)

Since NP traversal very improbable event at typical fluences

Observed dose enhancement not enough to justify relevant sensitization



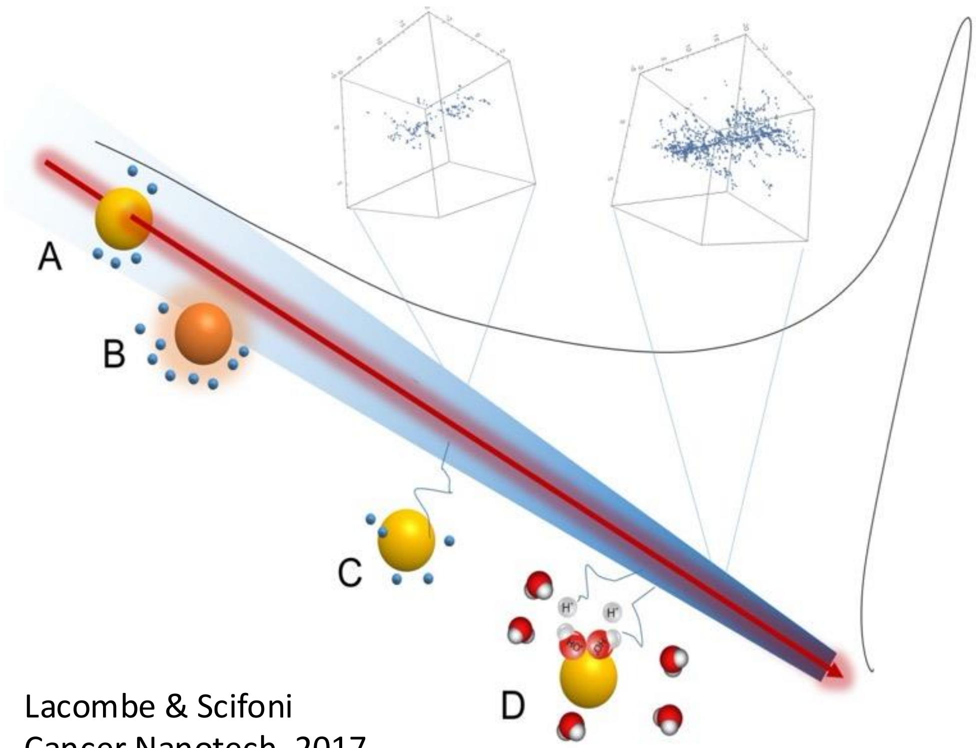




Waelzlein, Scifoni, Kramer, Durante PMB 2014

Similar conclusions in *Lin 2015, Martinez 2016*

Possible sensitization mechanisms



Lacombe & Scifoni
Cancer Nanotech. 2017

A) Direct traversal: enhanced electron production from Auger processes

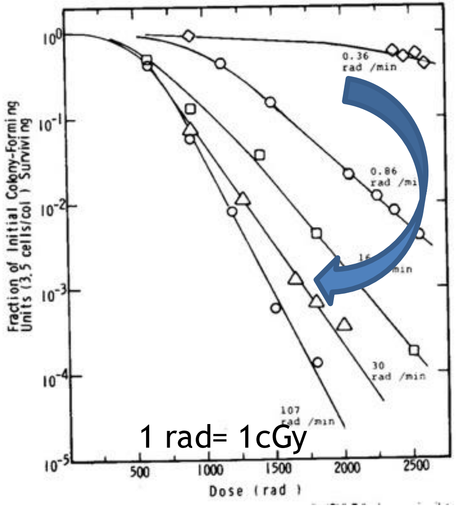
B) Plasmon excitation coupling with strong electron production.

C) Secondary electrons on the NP, produces additional electron emission

D) Catalytic effect on radiolytic species

Dose Rate effect
in conventional Radiobiology

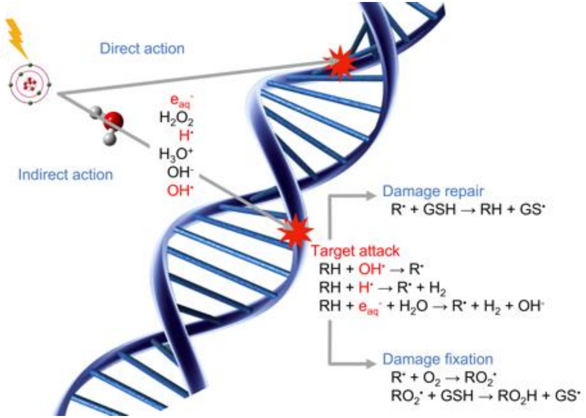
Clonogenic Survival



1 rad= 1cGy

$$DREF = \frac{D(\dot{D})}{D(\dot{D}_{ref})}\Bigg|_{same\ effect}$$

Dose-Rate Effectiveness Factor



It is observed a sparing effect at **decreasing** dose rate (at very low dose rate – “protracted” irradiation)

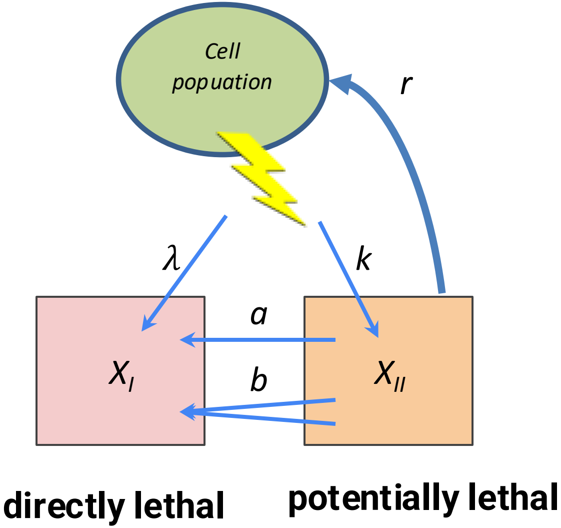
Mechanistic Explanation easy: **Potentially Letal Damage** allowed to be repaired

Modeling dose rate effects

Kinetic equations (c: cell, d: domain in cell)

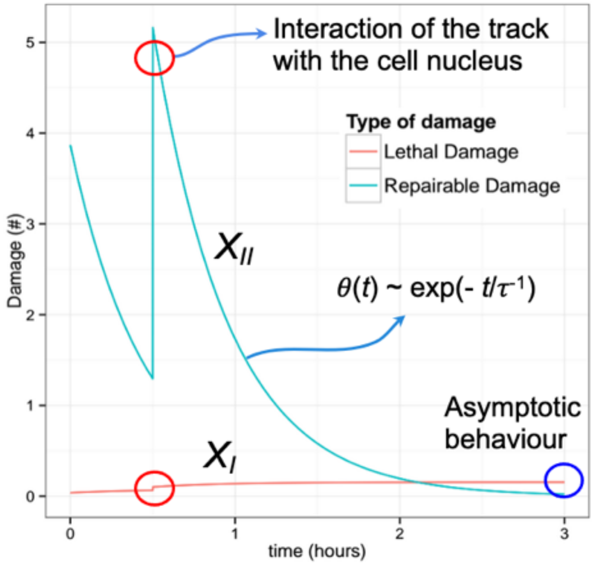
$$\begin{cases} \dot{x}_I^{(cd)} = \lambda \dot{z}^{(cd)} + a x_{II}^{(cd)} + b (x_{II}^{(cd)})^2 \\ \dot{x}_{II}^{(cd)} = k \dot{z}^{(cd)} - (a + r) x_{II}^{(cd)} - 2b (x_{II}^{(cd)})^2 \end{cases}$$

- z → microscopical absorbed dose
- x_I → type-I lesions: associated with clustered DNA damages which are **directly lethal** for the cell
- x_{II} → type-II lesions: non-directly lethal damages that may be **repaired** (r), spontaneously **converted to irreparable damages** (a) or undergo **pairwise combination** (b).



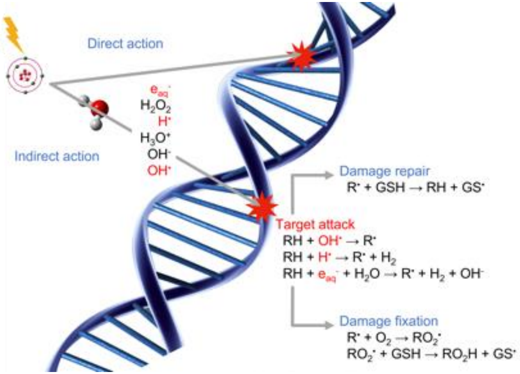
Courtesy from A.Attili

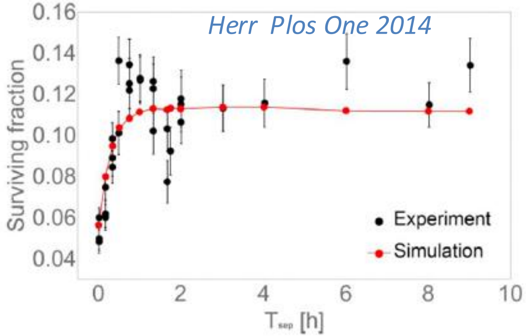
Modeling dose rate effects



Courtesy from A.Attili

D. Boscolo PhD Thesis





Herr Plos One 2014

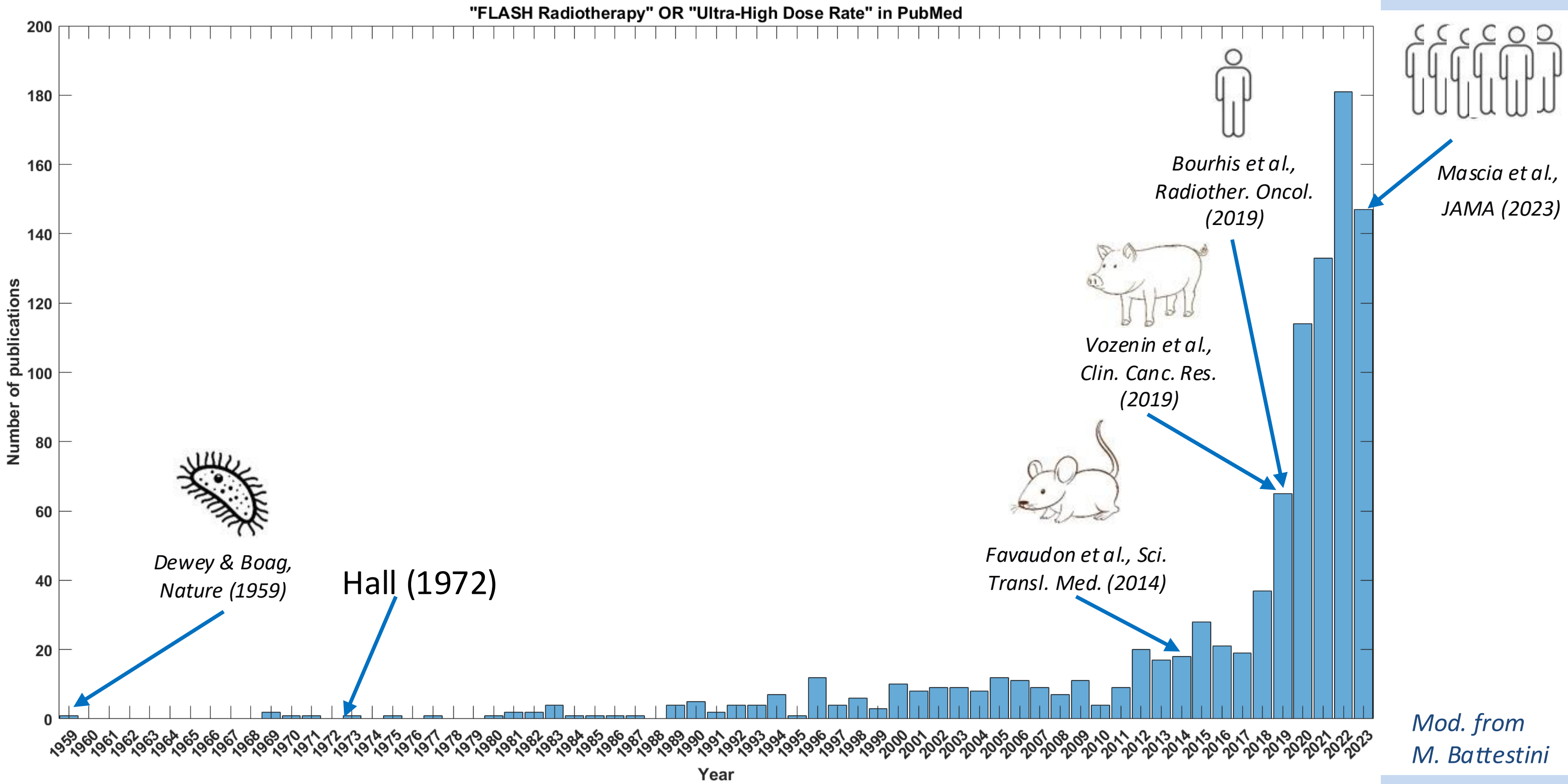
Dose rate effect (Hall 1972):

- A wide range of dose-rates has been used in radiobiology or radiotherapy, extending from a few rads per day to thousands of rads in a fraction of a second.

- At ultra-high dose-rates (pulses of micro or nanoseconds) a clear dose-rate effect has been demonstrated for bacteria, but is less certain for mammalian cells; these doserates **have no certain application in radiotherapy** at the present time.

- The principal dose-rate effect is observed between 100 rads/minute and 10 rads/hour; the cell-killing effect of X or γ rays decreases continuously as the dose-rate decreases throughout this range, and may be explained readily **in terms of the repair of sub-lethal damage taking place during the irradiation**.

UHDR exploitable for RT?



Dewey & Boag, Nature (1959)

Hall (1972)

Favaudon et al., Sci. Transl. Med. (2014)

Vozenin et al., Clin. Canc. Res. (2019)

Bourhis et al., Radiother. Oncol. (2019)

Mascia et al., JAMA (2023)

Mod. from M. Battestini

FLASH Radiotherapy: what’s that

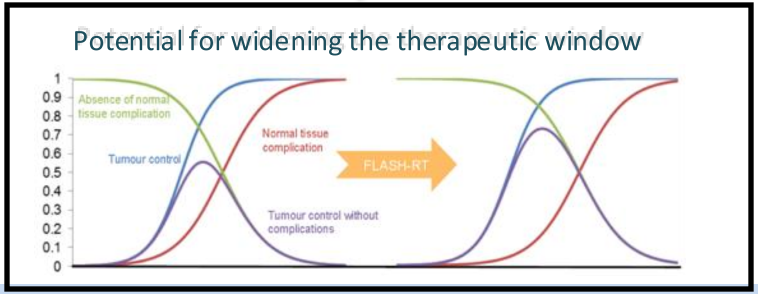
FLASH Radiotherapy, is a novel approach of RT using ultra-high dose rate

(>40 Gy/s overall dose rate, for a total irradiation time <100 ms

but much higher rates (up to 10^9 Gy/s) during each pulse)

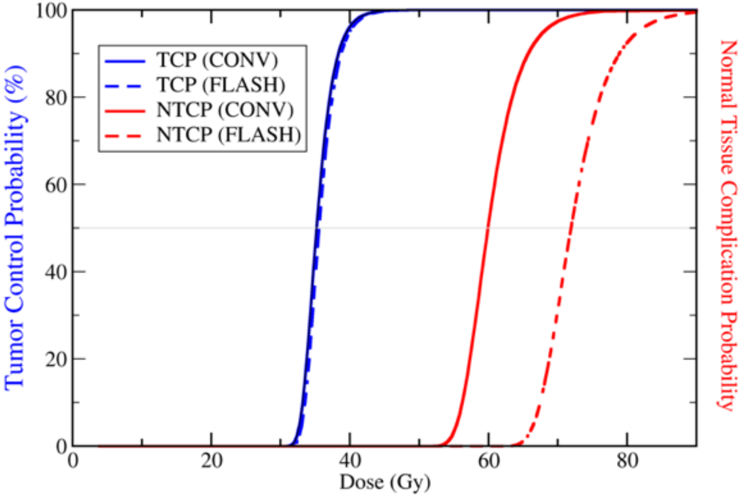
aiming to get **unchanged tumor control** and **protection in the normal tissue.**

TCPWC=TCP(1-NTCP)



Conventional Irradiation

~0.03 Gy/s



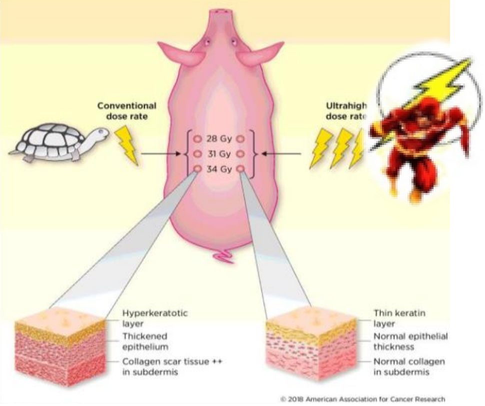
Ultrafast (FLASH) Irradiation

>40 Gy/s

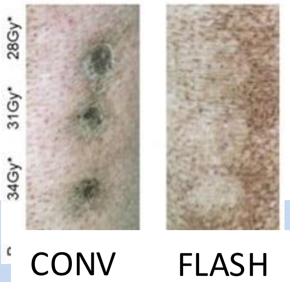
The FLASH Effect

Irradiation with **ultra-high dose rate**

- Decreasing of the normal tissue response

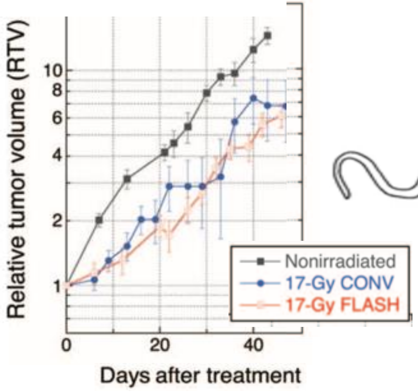


Vozenin et al. 2019, Clin. Canc. Res.



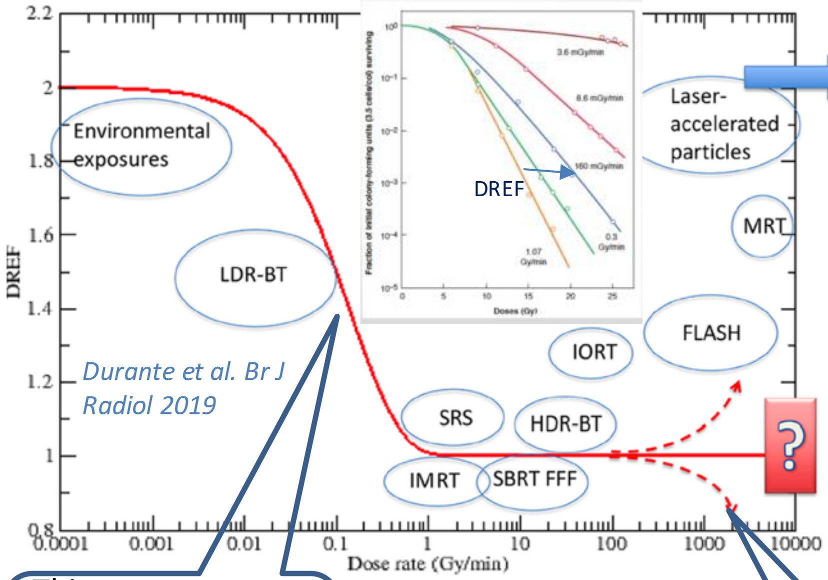
SAME BIOLOGY
DIFFERENT PHYSICS

- Preservation of the tumor responses



V. Favaudon et al. 2014, Sci. Transl. Med.

Ultrahigh Dose Rate Response and FLASH

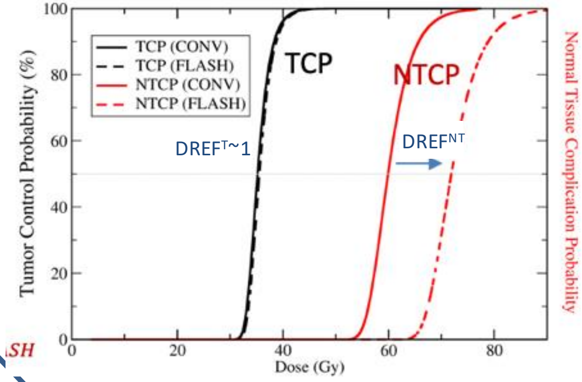


Durante et al. Br J Radiol 2019

This we understand (sublethal damage repair etc..) e.g.:

$$DREF = \left.\frac{D(\dot{D})}{D(\dot{D}_{ref})}\right|_{same\ effect}$$

Dose-Rate Effectiveness Factor



This we presently **DON'T** understand

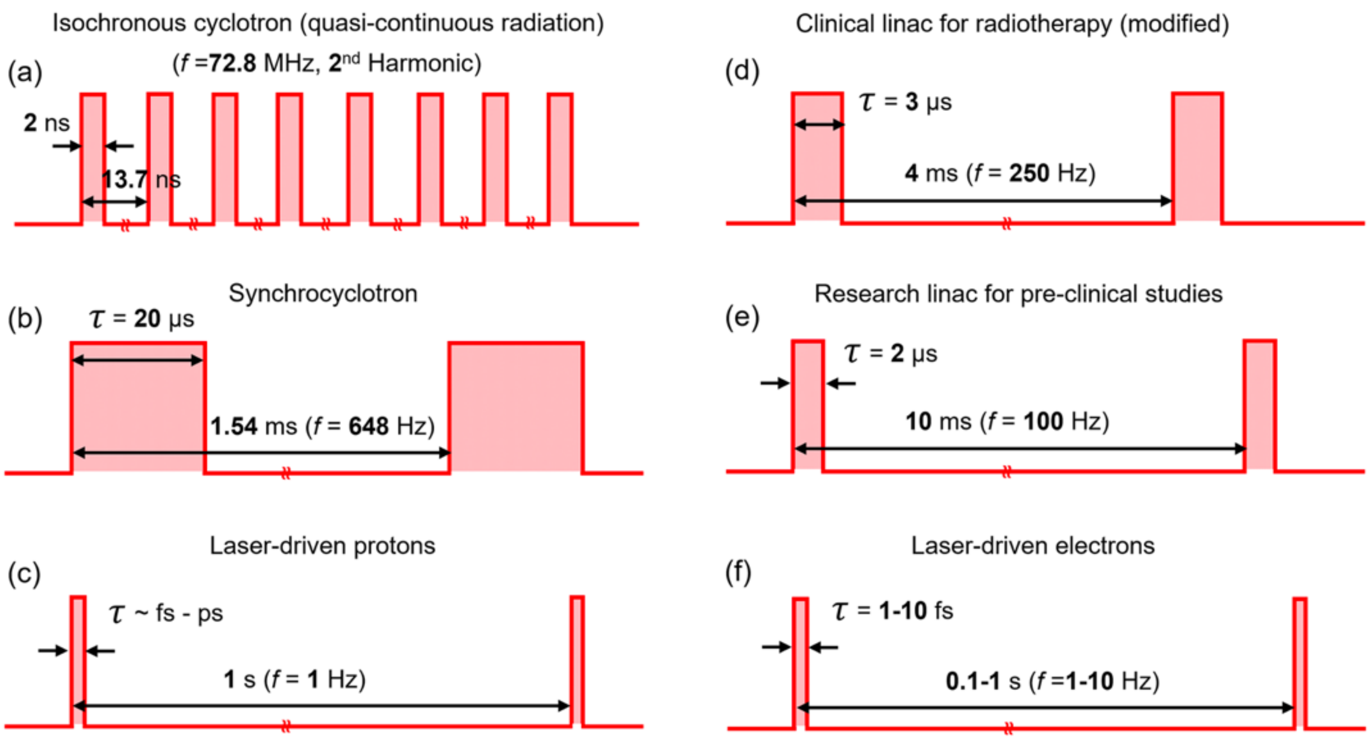
Despite plenty of accumulating exp evidence….

Time structure for different particles

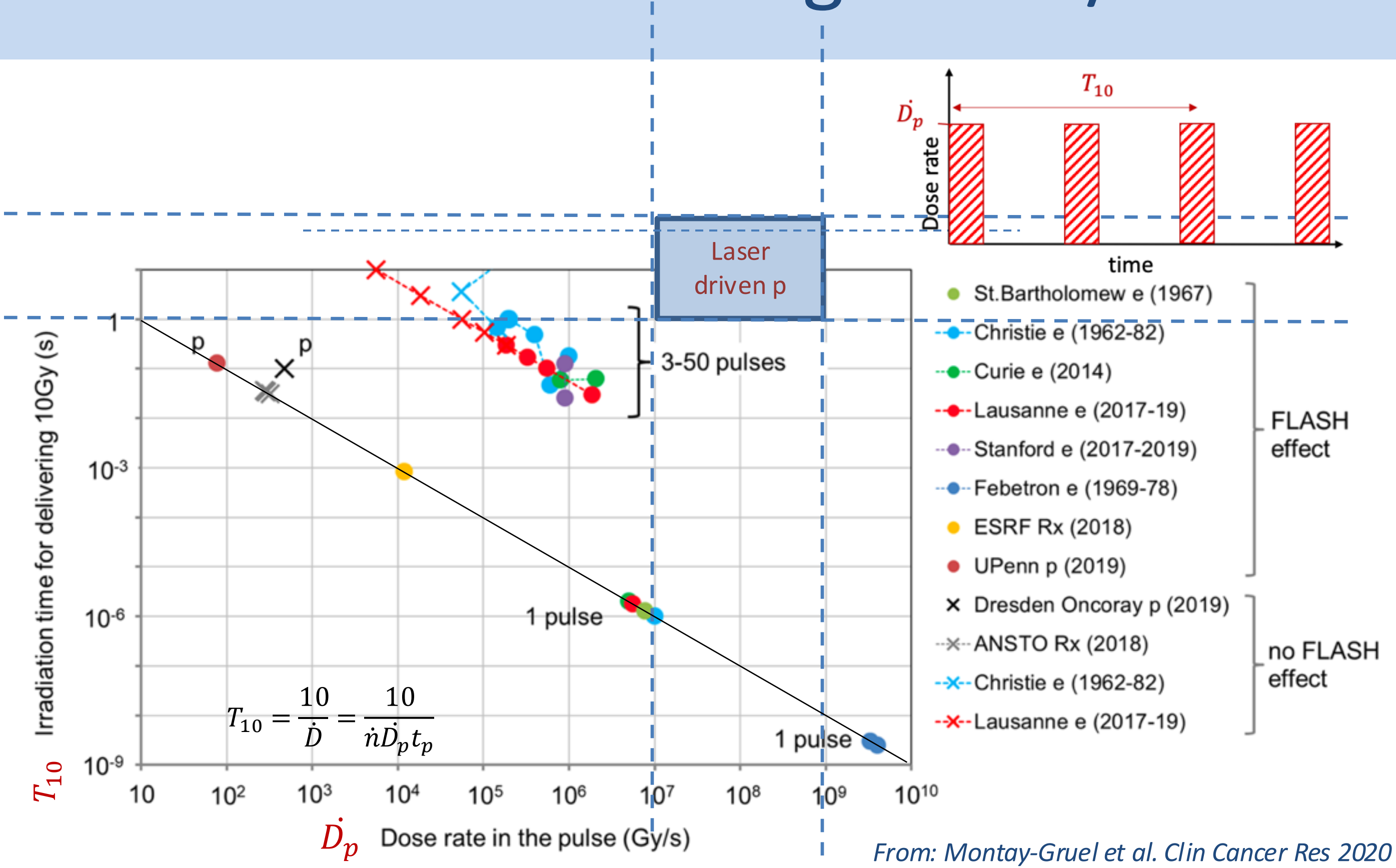
PROTONS

Romano et al. MP 20220

ELECTRONS



Parameters for observing FLASH/noFLASH

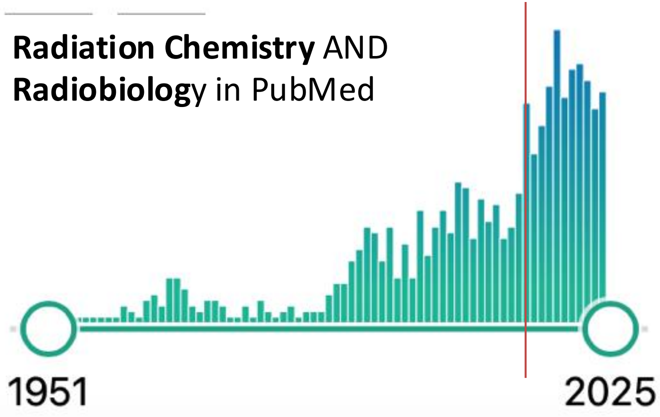


$$T_{10} = \frac{10}{\dot{D}} = \frac{10}{\dot{n}\dot{D}_p t_p}$$

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

Why Radiation Chemistry

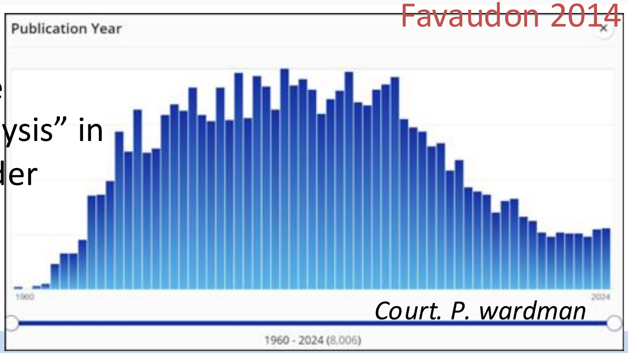
Radiation Chemistry AND **Radiobiology** in PubMed



Favaudon 2014

Radiation Chemistry AND (**FLASH Radiotherapy** OR **Ultraihigh dose rate**) in PubMed

“Pulse Radiolysis” in Scifinder

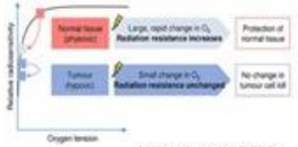


Court. P. wardman

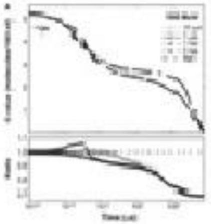
- A strong Reprise of an old Discipline in connection to the discovery of new radiotherapies, Including FLASH and SFRT

Which are difficult to explain without it

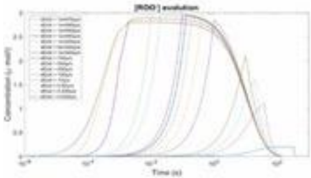
Main FLASH mechanistic hypotheses



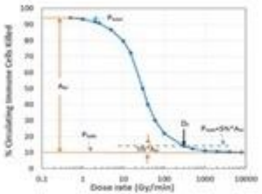
Wilson et al 2020



Ramos et al 2020



Labarbe et al 2020



Zhou et al 2020

Transient hypoxia

Intertrack effects

Organic radical recombination

Immune system driven

- irradiation and its effect on the oxygen enhancement ratio, PMB (2019)
- K. Petersson, et al. A quantitative analysis of the role of oxygen tension in FLASH radiotherapy, IJROBP (2020)
- G. Adrian, et al., The FLASH effect depends on oxygen concentration, Brit. J. Radiol. (2020)
- R. Abolfath, et al, "Oxygen depletion in FLASH ultra-high-dose-rate radiotherapy: A molecular dynamics simulation." *Med. Phys.* (2020).
- S. Zhou, et al. "Minimum dose rate estimation for pulsed FLASH radiotherapy: A dimensional analysis." *Med. Phys.* (2020).
- A. Hu,, et al. "A computational model for oxygen depletion hypothesis in FLASH Effect." Radiation Research 197.2 (2022): 175-183. Zakaria, A. et al.. (2021). Transient hypoxia in water irradiated by swift carbon ions at ultra-high dose rates: implication for FLASH carbon-ion therapy. Canadian Journal of Chemistry,
- Zhu, H, et al. "Modeling of cellular response after FLASH irradiation: a quantitative analysis based on the radiolytic oxygen depletion hypothesis." arXiv subm.(2021).

- .M. Zakaria, et al. "Ultra-High Dose-Rate, Pulsed (FLASH) Radiotherapy with Carbon Ions: Generation of Early, Transient, Highly Oxygenated Conditions in the Tumor Environment." *Rad. Res.* (2020).
- J. Ramos-Méndez, et al. "LET-Dependent Intertrack Yields in Proton Irradiation at Ultra-High Dose Rates Relevant for FLASH Therapy." *Rad. Res.* (2020).
- Alanazi, A., et al.. (2021). A computer modeling study of water radiolysis at high dose rates. Relevance to FLASH radiotherapy. Radiation research, 195(2), 149-162.

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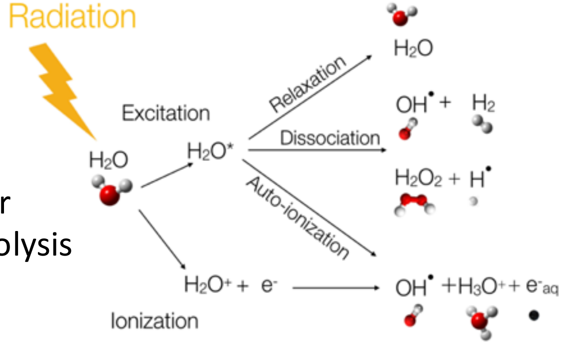
- Jin, Jian-Yue, et al. "Ultra-high dose rate effect on circulating immune cells: A

(2-fold) Oxygen and radiation interplay

Nanoscale

Water Radiolysis



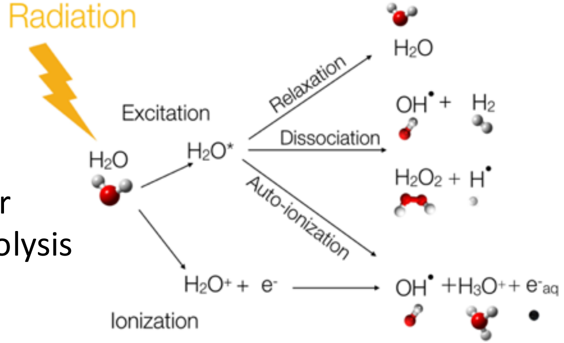
- irradiation generates free radicals which react with the dissolved **molecular oxygen** in the target:

$$e_{aq}^{-} + O_2 \rightarrow O_2^{\bullet -}$$
$$H^{\bullet} + O_2 \rightarrow HO_2^{\bullet}$$

- high doses of radiation gradually remove the O_2 to produce toxic superoxide or perhydroxyl
- shown already in historical experiments (*Weiss et al. 1974*)

(2-fold) Oxygen and radiation interplay

Nanoscale



Water Radiolysis

- irradiation generates free radicals which react with the dissolved **molecular oxygen** in the target:

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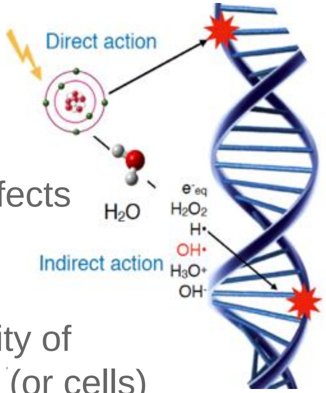
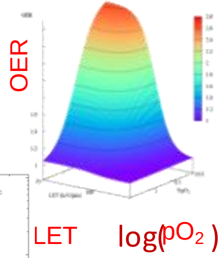
Macroscale

Radiobiological oxygen enhancement

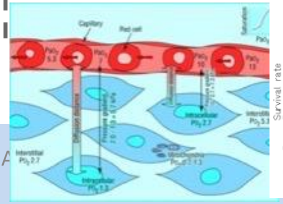


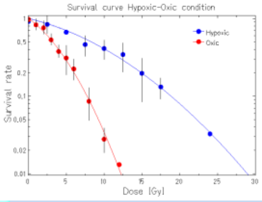
- oxygen is a strong **sensitizer** towards indirect radiation effects
- increase in sensitivity of oxygenated tissues (or cells) compared to hypoxic ones is described by **OER**

$$\mathrm{OER}(pO_2) = \frac{D_{\text{anoxia}}}{D_{pO2}}\Big|_{\text{same effect}}$$

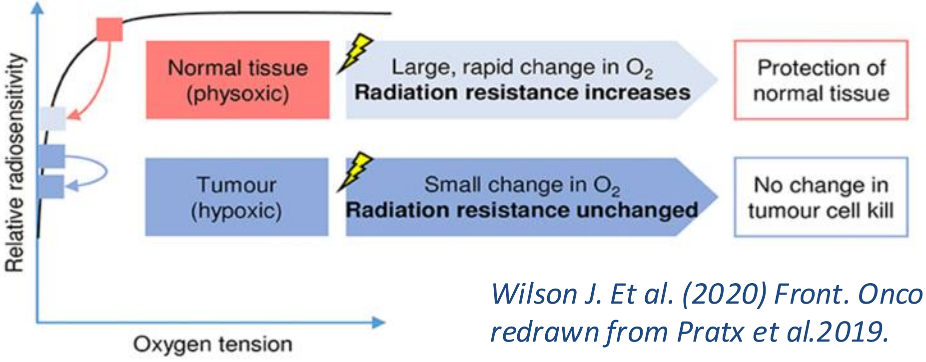


Scifoni et al. 2013





The Oxygen Depletion Hypothesis (ROD)



Normal tissue (physoxic)

Large, rapid change in O_2
Radiation resistance increases

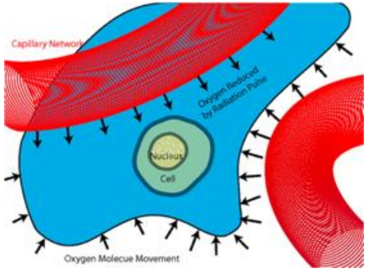
Protection of normal tissue

Tumour (hypoxic)

Small change in O_2
Radiation resistance unchanged

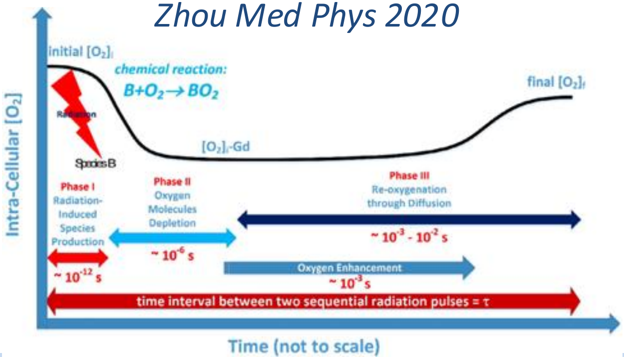
No change in tumour cell kill

Wilson J. Et al. (2020) Front. Oncol redrawn from Pratx et al.2019.

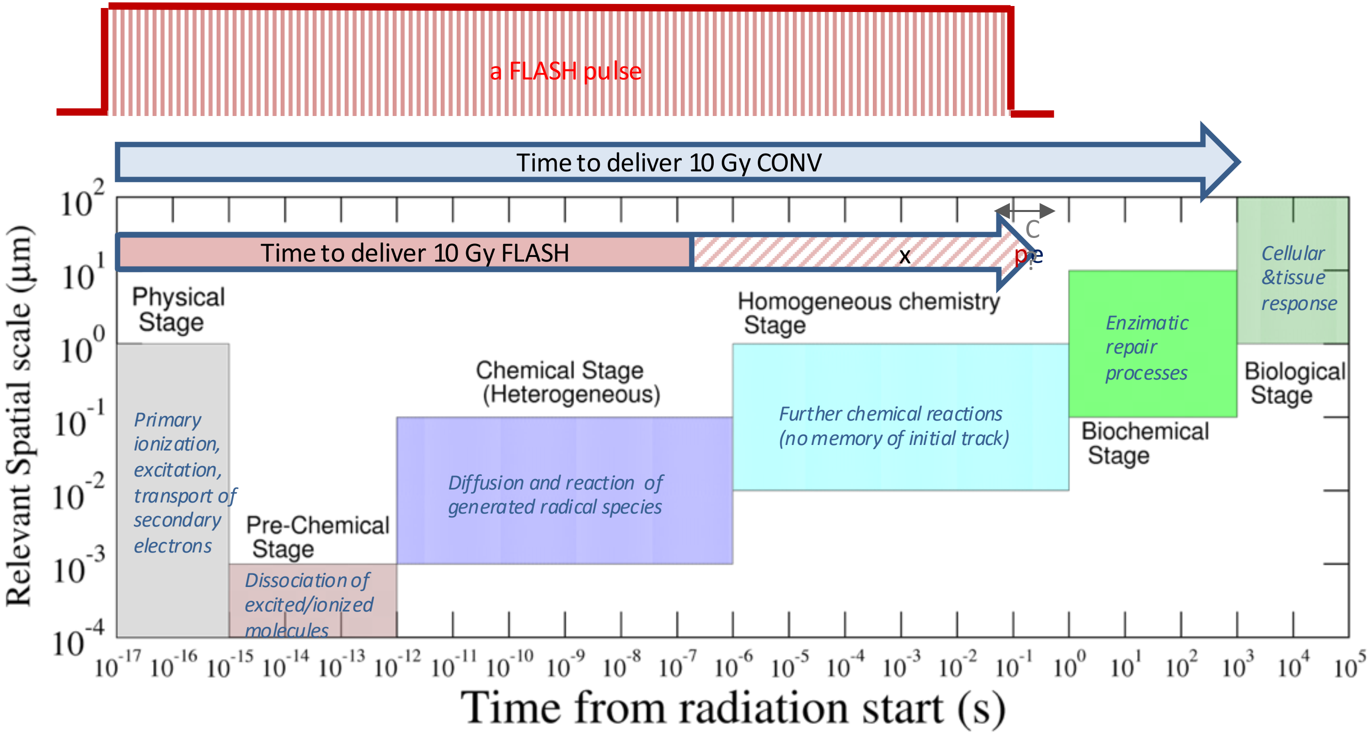


- Ultrahigh dose rate:
  Oxygen consuption too quick for redifussion to restore initial levels
- Transient hypoxia generated -> induced radioresistabce
- Already suggested in Hall&Brenner 1991

Zhou Med Phys 2020

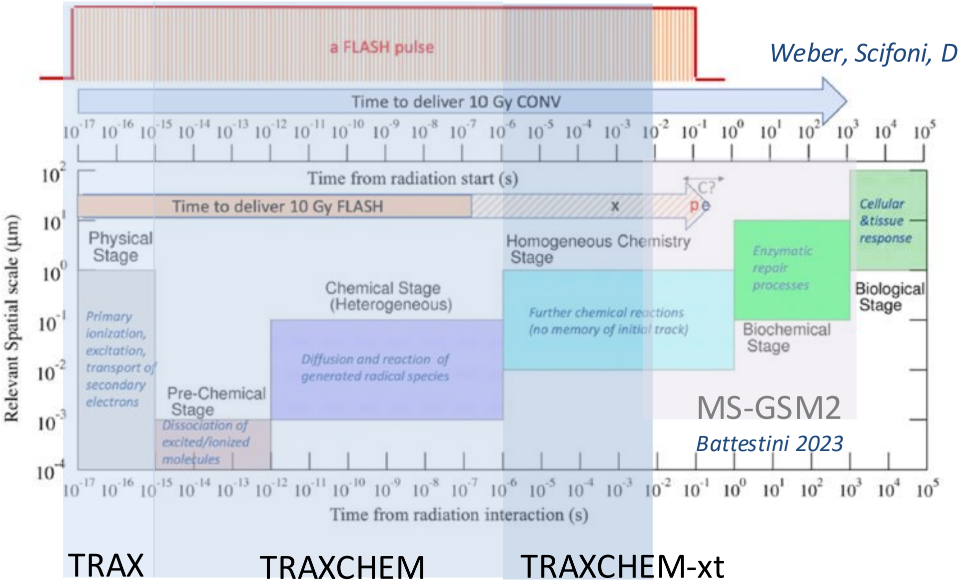


FLASH and Spatio-temporal Scales of Radiation Damage



Weber, Scifoni, Durante 2021

FLASH and Spatio-temporal Scales of Radiation Damage



Weber, Scifoni, Durante 2021

MS-GSM2
Battestini 2023

TRAX
Kraemer 1994

TRAXCHEM
Boscolo 2018-2022

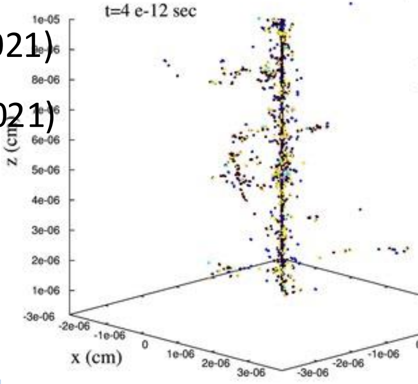
TRAXCHEM-xt
Camazzola 2023

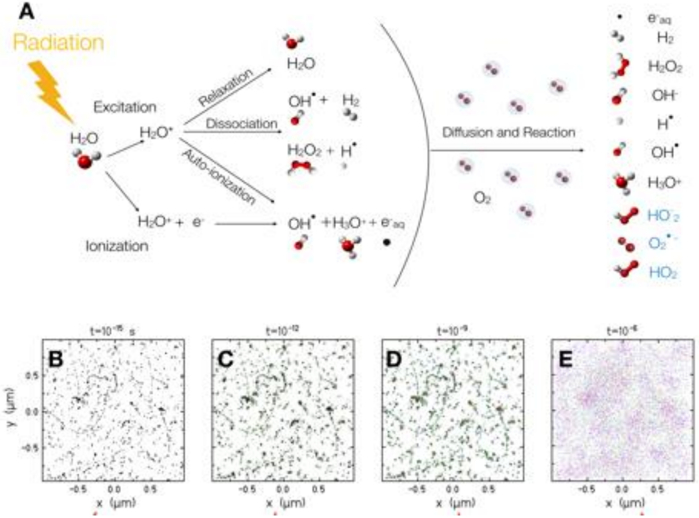
Monte Carlo Track structure Codes for exploring FLASH Chemistry

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)

Carbon 3MeV/u





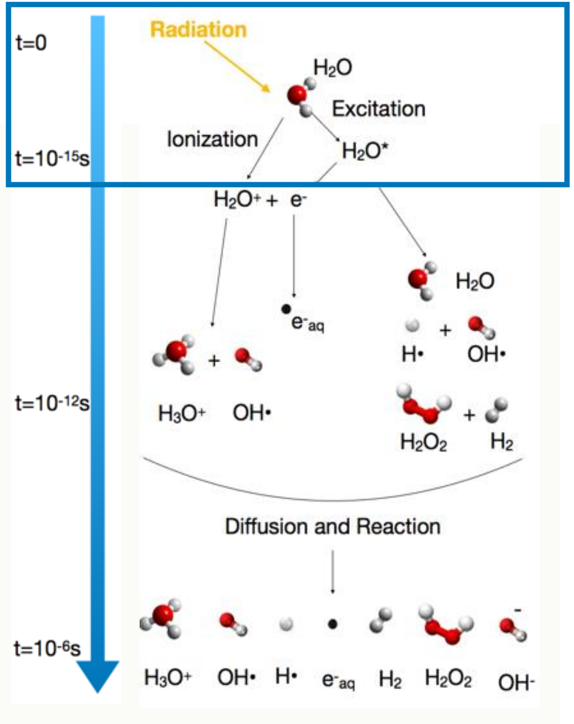
Boscolo et al. 2021 u.r.

From TRAX to TRAX CHEM:

1)Physical stage

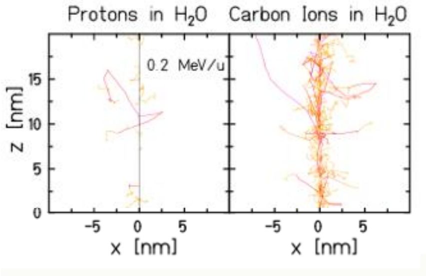
2)Pre-chemical stage

3)Chemical stage



Classical version TRAX

Ionization sand excitations
of ion and electron tracks

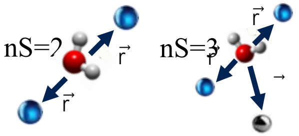


- *Wälzlein et al. 2014*
- *Kraemer et al.1994*

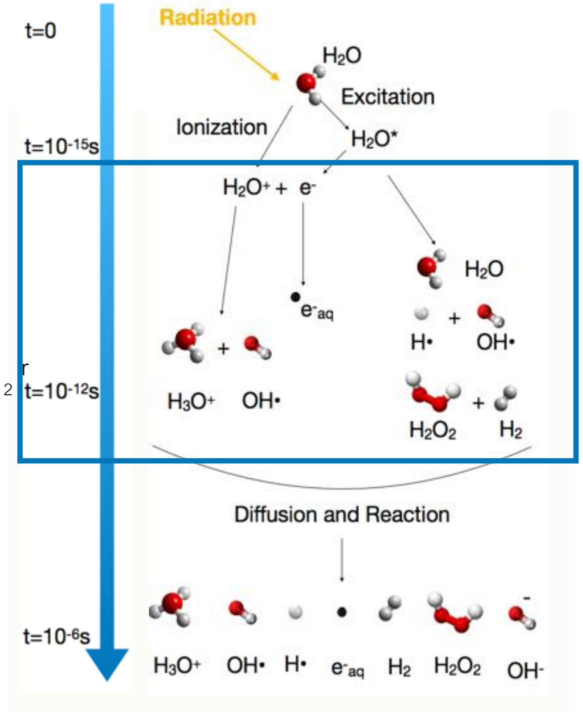
Pre-chemical stage

1)Physical stage

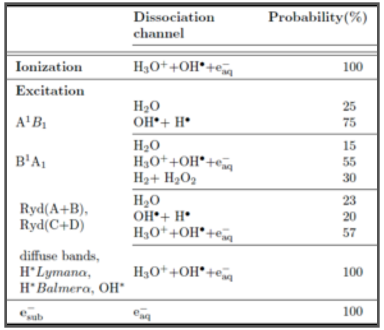
2)Pre-chemical stage



3)Chemical stage



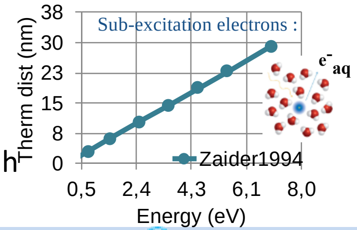
- **Molecular dissociation:**
  Excited and ionized water molecules **dissociate or relax to the ground state**.



	Dissociation channel	Probability(%)
Ionization	$H_3O^+ + OH^\bullet + e^-_{aq}$	100
Excitation		
A^1B_1	H_2O	25
	$OH^\bullet + H^\bullet$	75
B^1A_1	H_2O	15
	$H_3O^+ + OH^\bullet + e^-_{aq}$	55
	$H_2 + H_2O_2$	30
Ryd(A+B), Ryd(C+D)	H_2O	23
	$OH^\bullet + H^\bullet$	20
	$H_3O^+ + OH^\bullet + e^-_{aq}$	57
diffuse bands, H^* *Lymanα*, H^* *Balmerα*, OH^*	$H_3O^+ + OH^\bullet + e^-_{aq}$	100
e^-_{sub}	e^-_{aq}	100

- **Thermalisation model:**

Products of molecular dissociation thermalise with the solvent



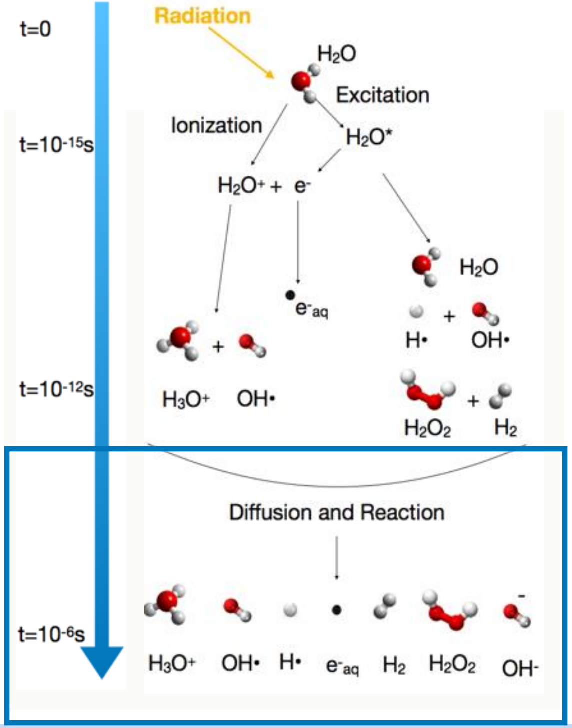
Chemical stage

1) Physical stage

2) Pre-chemical stage

3) Chemical stage

- a_{AB} reaction radius



- **Diffusion:**

Jump in a **random direction**
Einstein Smoluchowski eq.:

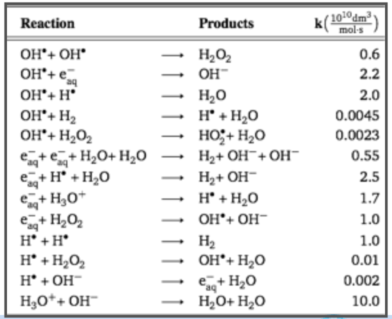
$$\lambda = \sqrt{6D\Delta t}$$

D the diffusion coefficient
Δt the time step

- **Reaction:**

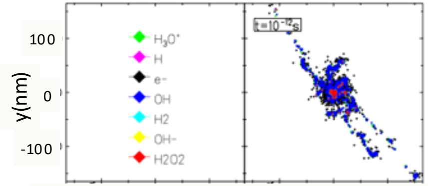
$$a_{AB} = \frac{k_{AB}}{4\pi(D_A + D_B)}$$

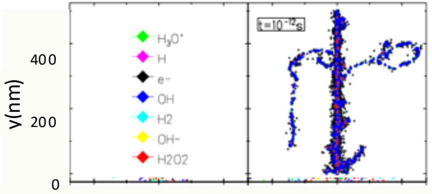
Described with a proximity parameter



Reaction		Products	$k\left(\frac{10^{10}\,dm^3}{mol \cdot s}\right)$
$OH^\bullet + OH^\bullet$	$\longrightarrow$	H_2O_2	0.6
$OH^\bullet + e^-_{aq}$	$\longrightarrow$	OH^-	2.2
$OH^\bullet + H^\bullet$	$\longrightarrow$	H_2O	2.0
$OH^\bullet + H_2$	$\longrightarrow$	$H^\bullet + H_2O$	0.0045
$OH^\bullet + H_2O_2$	$\longrightarrow$	$HO_2^\bullet + H_2O$	0.0023
$e^-_{aq} + e^-_{aq} + H_2O + H_2O$	$\longrightarrow$	$H_2 + OH^- + OH^-$	0.55
$e^-_{aq} + H^\bullet + H_2O$	$\longrightarrow$	$H_2 + OH^-$	2.5
$e^-_{aq} + H_3O^+$	$\longrightarrow$	$H^\bullet + H_2O$	1.7
$e^-_{aq} + H_2O_2$	$\longrightarrow$	$OH^\bullet + OH^-$	1.0
$H^\bullet + H^\bullet$	$\longrightarrow$	H_2	1.0
$H^\bullet + H_2O_2$	$\longrightarrow$	$OH^\bullet + H_2O$	0.01
$H^\bullet + OH^-$	$\longrightarrow$	$e^-_{aq} + H_2O$	0.002
$H_3O^+ + OH^-$	$\longrightarrow$	$H_2O + H_2O$	10.0

TRAX-CHEM: Simulation results

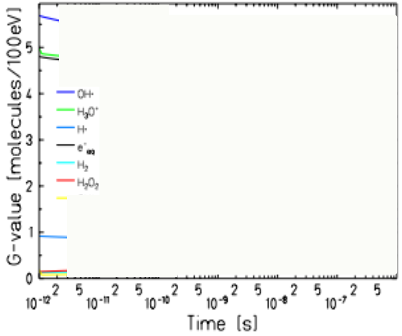




Carbon 8MeV/u

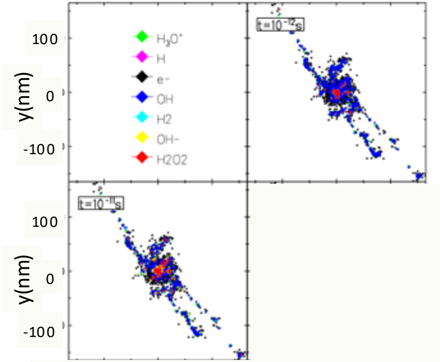
$t=10^{-12}$s

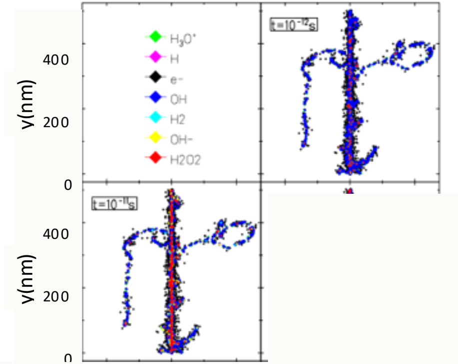
Pre-Chemical stage



Boscolo, Krämer, Fuss, Durante & Scifoni, Chem Phys Lett 2018

TRAX-CHEM: Simulation results

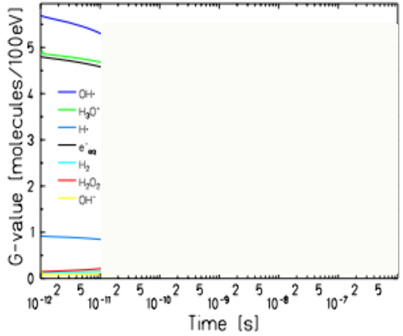




Carbon 8MeV/u

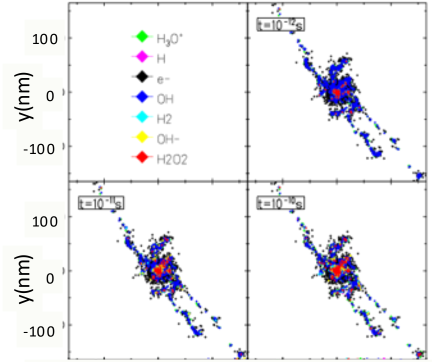
$t=10^{-11}s$

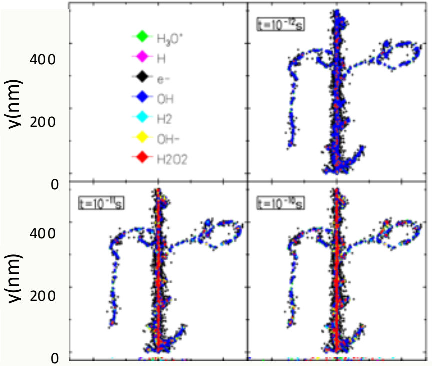
Chemical stage



Boscolo, Krämer, Fuss, Durante & Scifoni, Chem Phys Lett 2018

TRAX-CHEM: Simulation results

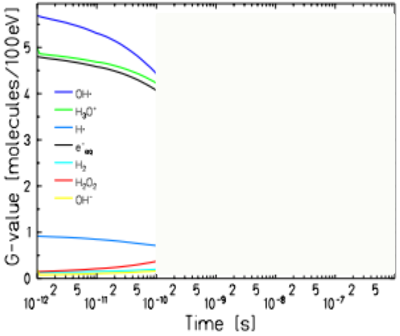




Carbon 8MeV/u

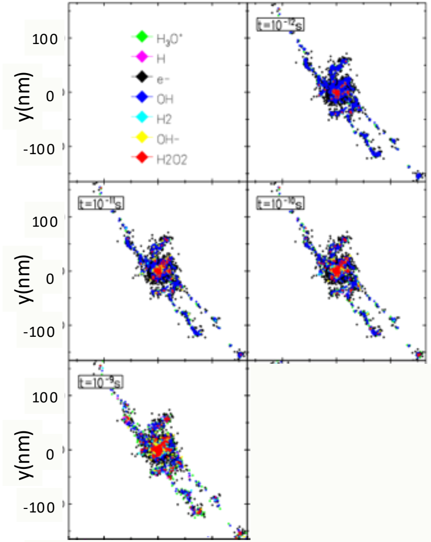
t=10^{-10}

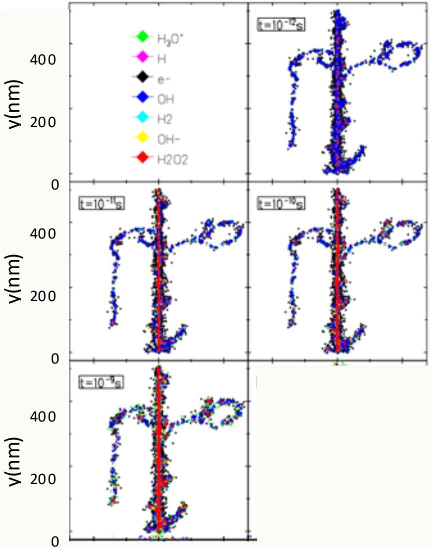
Chemical stage



Boscolo, Krämer, Fuss, Durante & Scifoni, Chem Phys Lett 2018

TRAX-CHEM: Simulation results

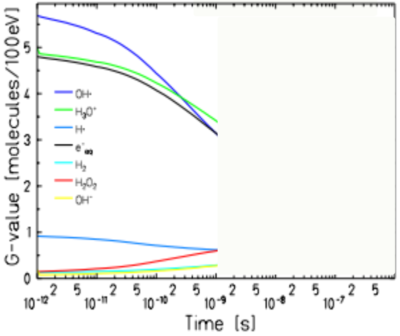




Carbon 8MeV/u

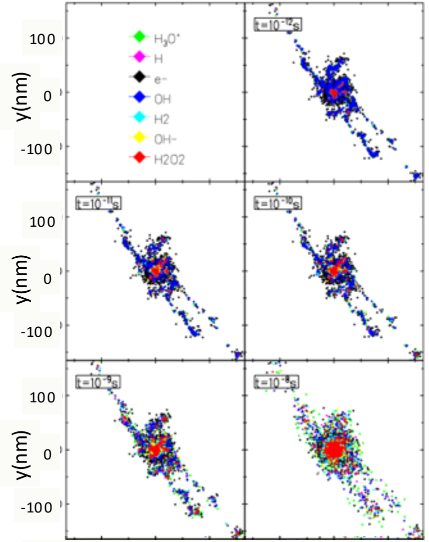
t=10^{-9}s

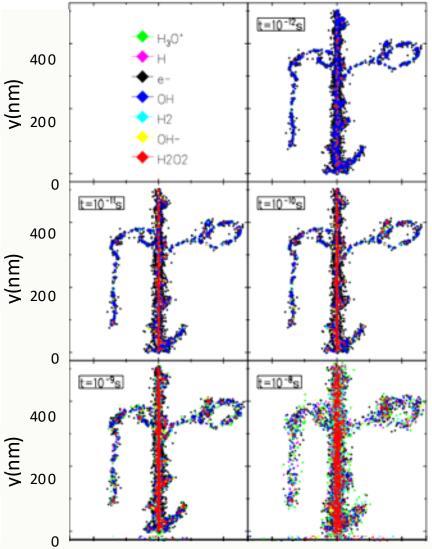
Chemical stage



Boscolo, Krämer, Fuss, Durante & Scifoni, Chem Phys Lett 2018

TRAX-CHEM: Simulation results

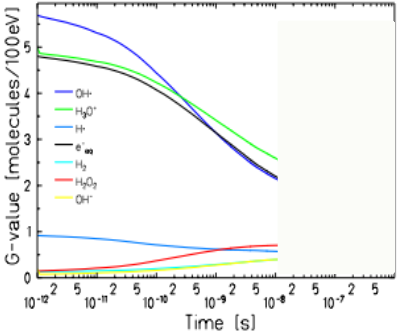




Carbon 8MeV/u

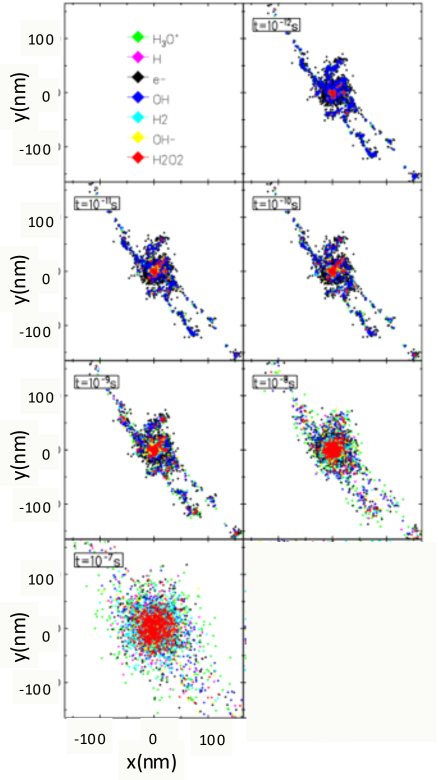
t=10^{-8}s

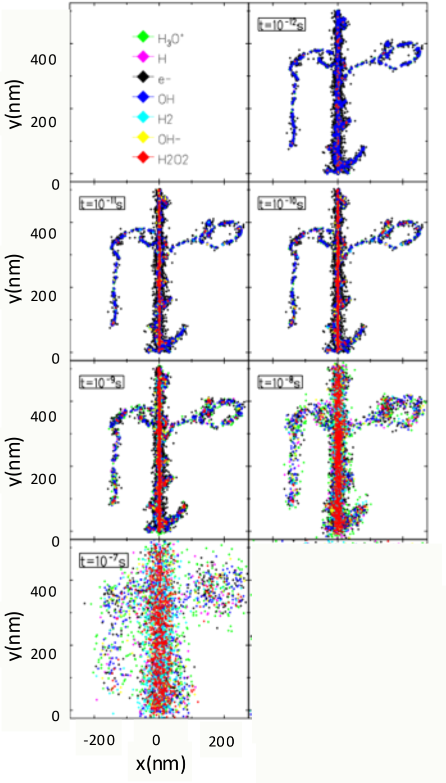
Chemical stage



Boscolo, Krämer, Fuss, Durante & Scifoni, Chem Phys Lett 2018

TRAX-CHEM: Simulation results

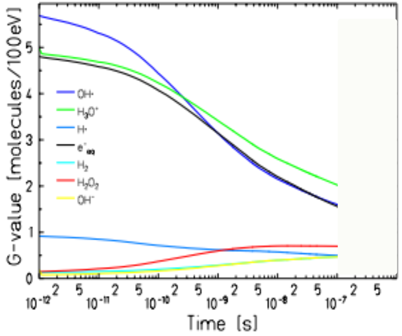




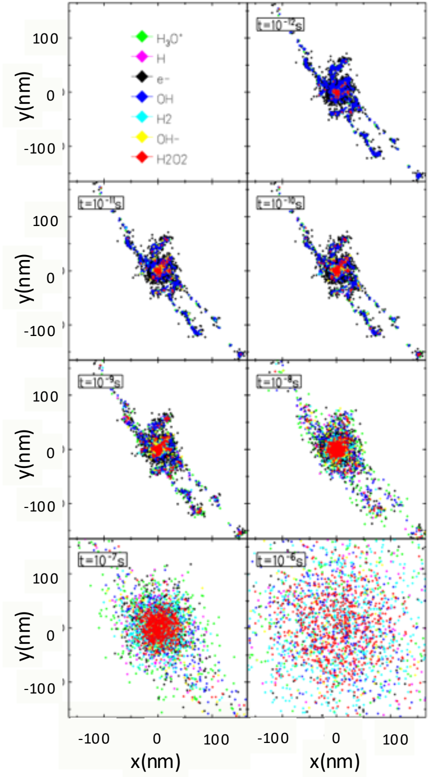
Carbon 8MeV/u

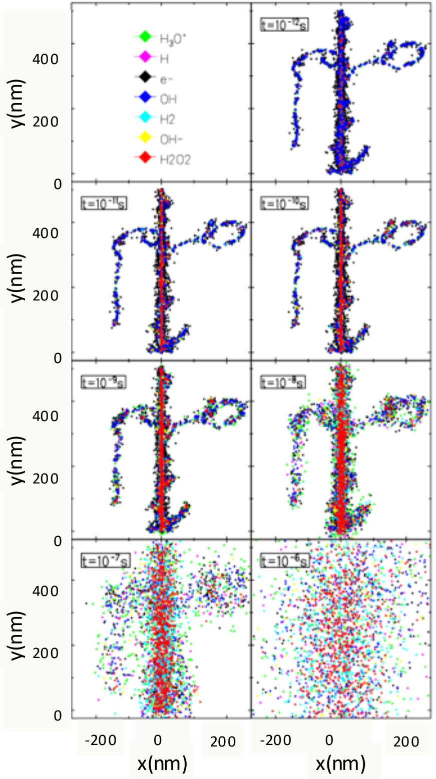
t=10^{-7}s

Chemical stage



TRAX-CHEM: Simulation results

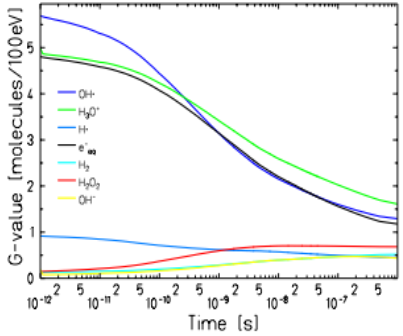




Carbon 8MeV/u

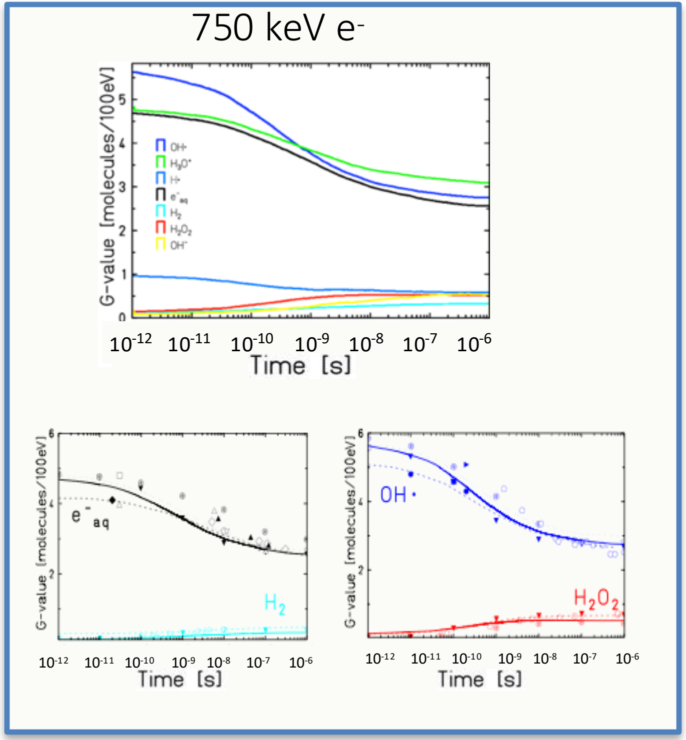
t=10^{-6} s

End of the
Chemical stage

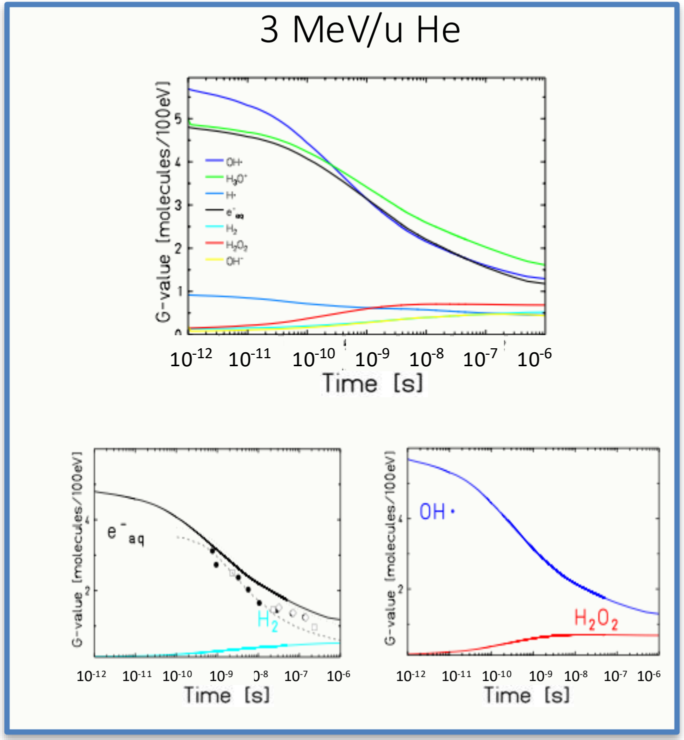


Boscolo, Krämer, Fuss, Durante & Scifoni, Chem Phys Lett 2018

Radiolytic yields time dependence



750 keV e^-



3 MeV/u He

Boscolo, Krämer, Fuss, Durante & Scifoni, Chem Phys Lett 2018

Exp: Shirashi 1988, Omar et al.2011

Dissolved oxygen in the target

- Dissolved oxygen implemented as a **continuum**
- Probability of not interacting with oxygen

$$\frac{d\Omega}{dt} = -k(t)c_s\Omega(t)$$

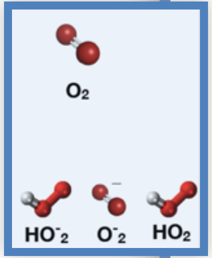
- Probability of interact with oxygen in a time

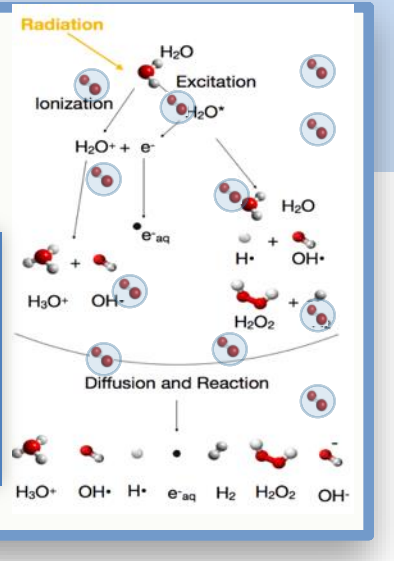
$$W(t) = 1 - e^{-4\pi D' R_{reac} c_s \left(t + 2R_{reac}\sqrt{\frac{t}{\pi D' t}}\right)}$$

c_s oxygen concentration [molecule/ liter]

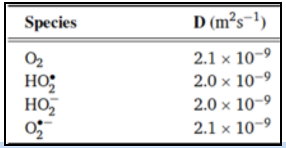
$$c_s = K_H * p_{gas}$$

$$K_{H oxygen} = 1{,}3\text{x}10^{-3}\,\frac{\text{M}}{\text{atm}}$$

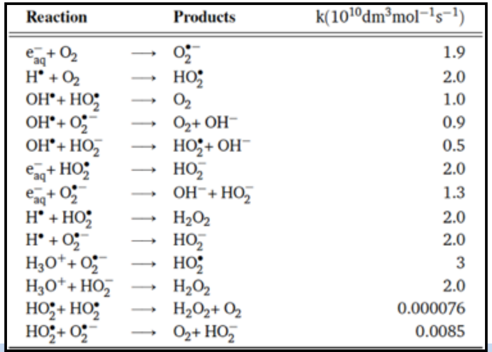




Boscolo et al. IJMS 2020;

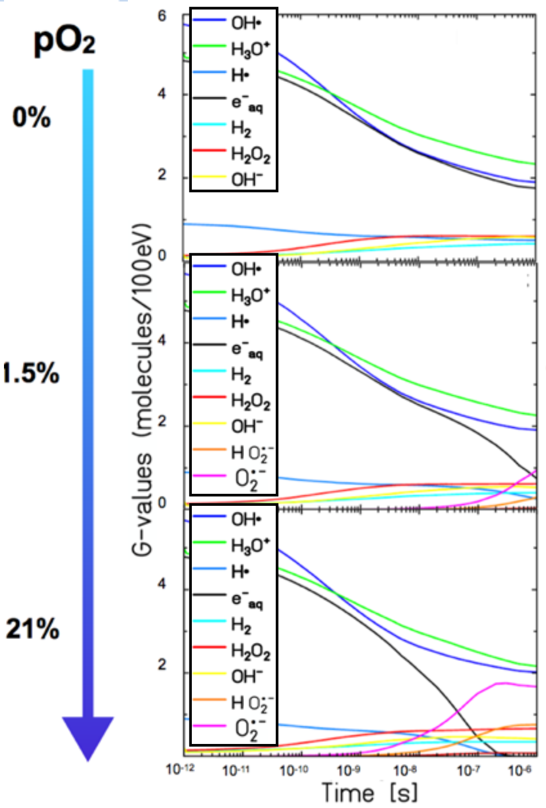


Species	D (m^2s^{-1})
O_2	2.1×10^{-9}
$HO_2^\bullet$	2.0×10^{-9}
HO_2^-	2.0×10^{-9}
$O_2^{\bullet-}$	2.1×10^{-9}



Reaction		Products	k($10^{10}dm^3mol^{-1}s^{-1}$)
$e^-_{aq} + O_2$	⟶	$O_2^{\bullet-}$	1.9
$H^\bullet + O_2$	⟶	$HO_2^\bullet$	2.0
$OH^\bullet + HO_2^\bullet$	⟶	O_2	1.0
$OH^\bullet + O_2^{\bullet-}$	⟶	$O_2 + OH^-$	0.9
$OH^\bullet + HO_2^-$	⟶	$HO_2^\bullet + OH^-$	0.5
$e^-_{aq} + HO_2^\bullet$	⟶	HO_2^-	2.0
$e^-_{aq} + O_2^{\bullet-}$	⟶	$OH^- + HO_2^-$	1.3
$H^\bullet + HO_2^\bullet$	⟶	H_2O_2	2.0
$H^\bullet + O_2^{\bullet-}$	⟶	HO_2^-	2.0
$H_3O^+ + O_2^{\bullet-}$	⟶	$HO_2^\bullet$	3
$H_3O^+ + HO_2^-$	⟶	H_2O_2	2.0
$HO_2^\bullet + HO_2^\bullet$	⟶	$H_2O_2 + O_2$	0.000076
$HO_2^\bullet + O_2^{\bullet-}$	⟶	$O_2 + HO_2^-$	0.0085

O_2 impact on the nanoscale

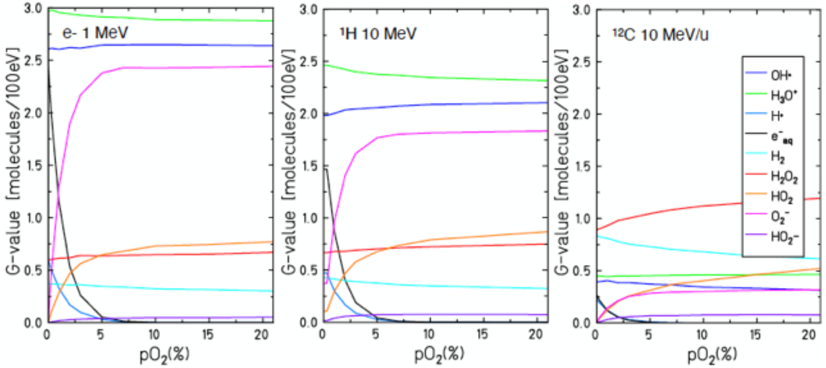


International Journal of
Molecular Sciences

Article

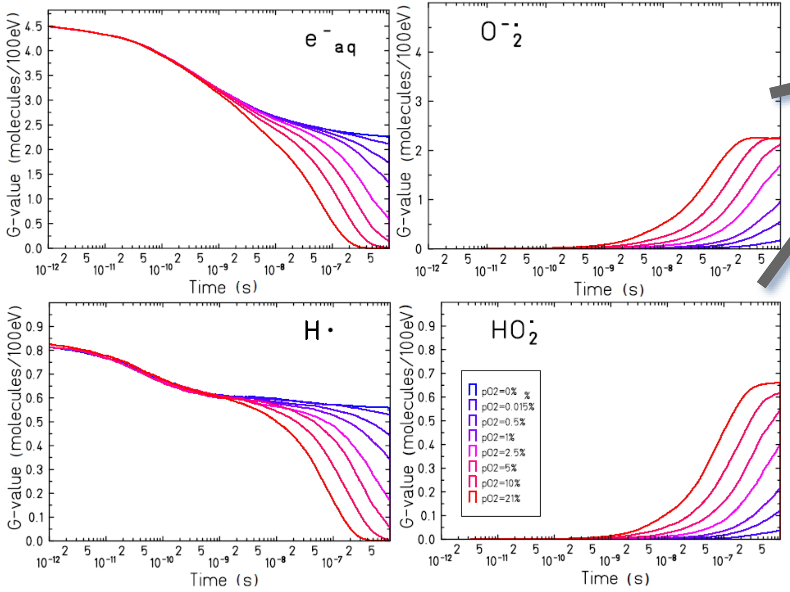
Impact of Target Oxygenation on the Chemical Track Evolution of Ion and Electron Radiation

Daria Boscolo [1,*], Michael Krämer [1], Martina C. Fuss [1] and Marco Durante [1,2,3] and Emanuele Scifoni [3]

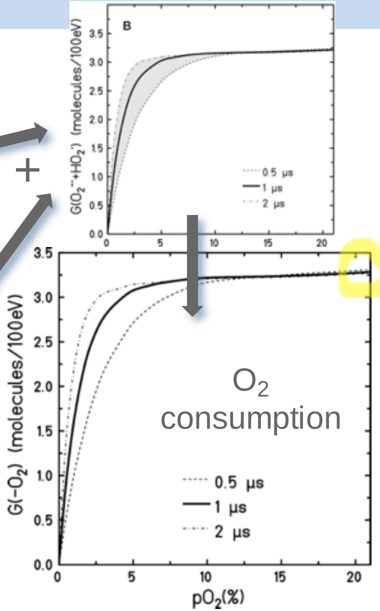


TRAX-CHEM predicted oxygen depletion in water

low-LET electrons



Boscolo et al. 2020



O_2 consumption

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

Boscolo et alIJMS 2020; RO 2021

ELSEVIER

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

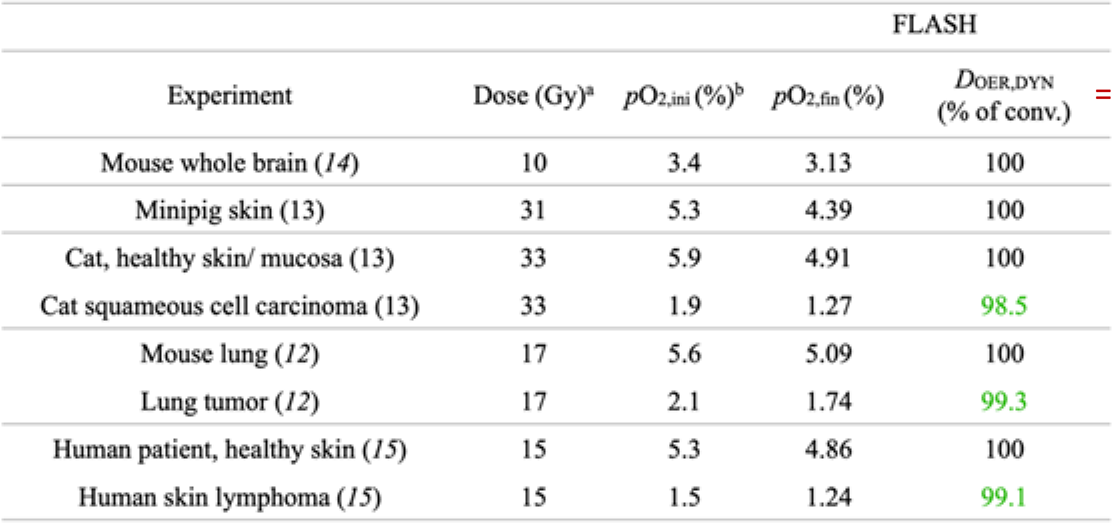
May oxygen depletion explain the FLASH effect? A chemical track structure analysis

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

Expected ROD effect on DMF

Boscolo et al Radiother Oncol 2021

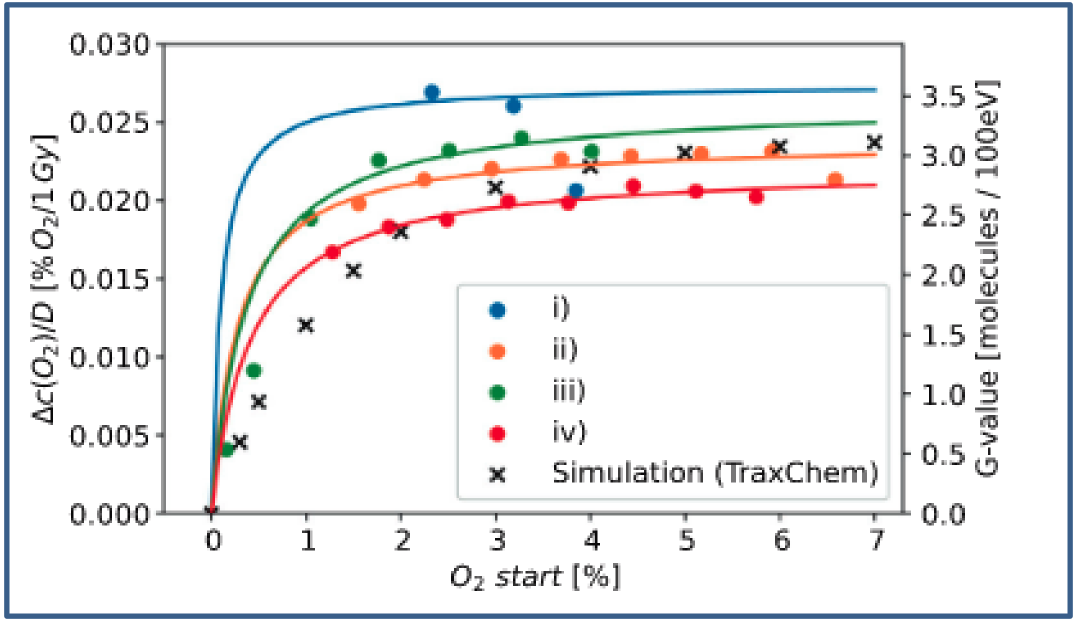
OER impact for the published in vivo results



			FLASH	
Experiment	Dose (Gy)^a	$pO_{2,\mathrm{ini}}$ (%)^b	$pO_{2,\mathrm{fin}}$ (%)	$D_{\mathrm{OER,DYN}}$ (% of conv.)
Mouse whole brain (*14*)	10	3.4	3.13	100
Minipig skin (13)	31	5.3	4.39	100
Cat, healthy skin/ mucosa (13)	33	5.9	4.91	100
Cat squameous cell carcinoma (13)	33	1.9	1.27	98.5
Mouse lung (*12*)	17	5.6	5.09	100
Lung tumor (*12*)	17	2.1	1.74	99.3
Human patient, healthy skin (*15*)	15	5.3	4.86	100
Human skin lymphoma (*15*)	15	1.5	1.24	99.1

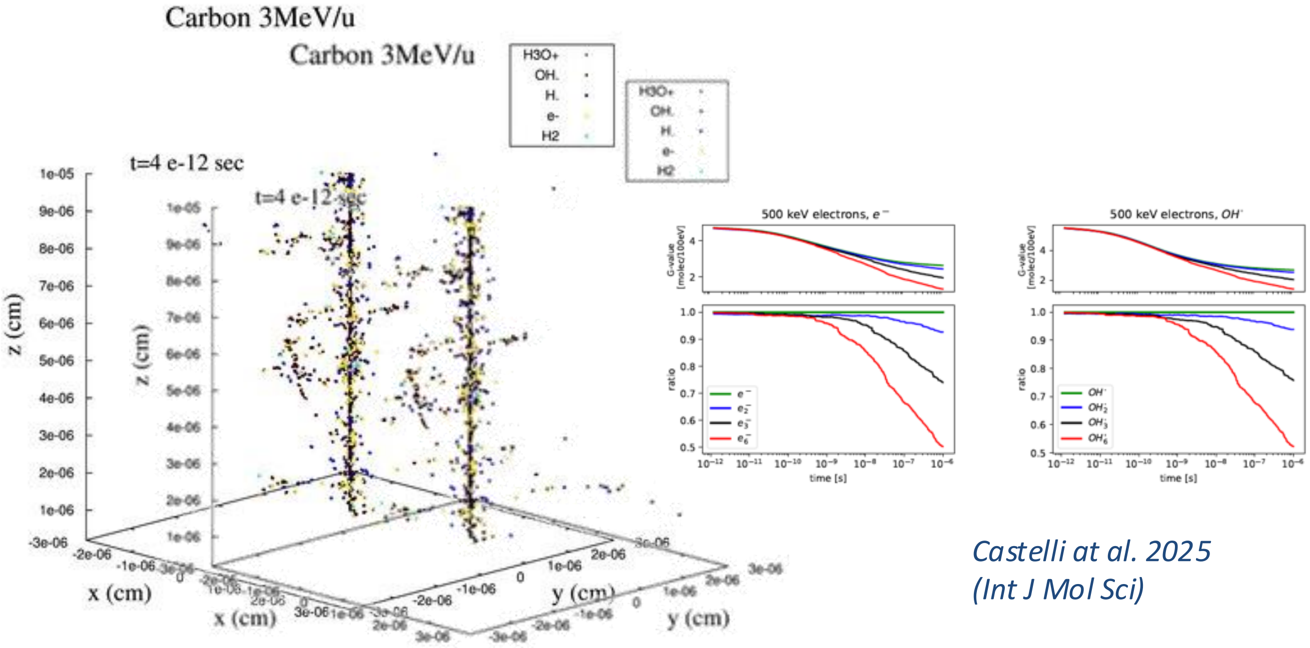
=DMF(%)

Experimental validation



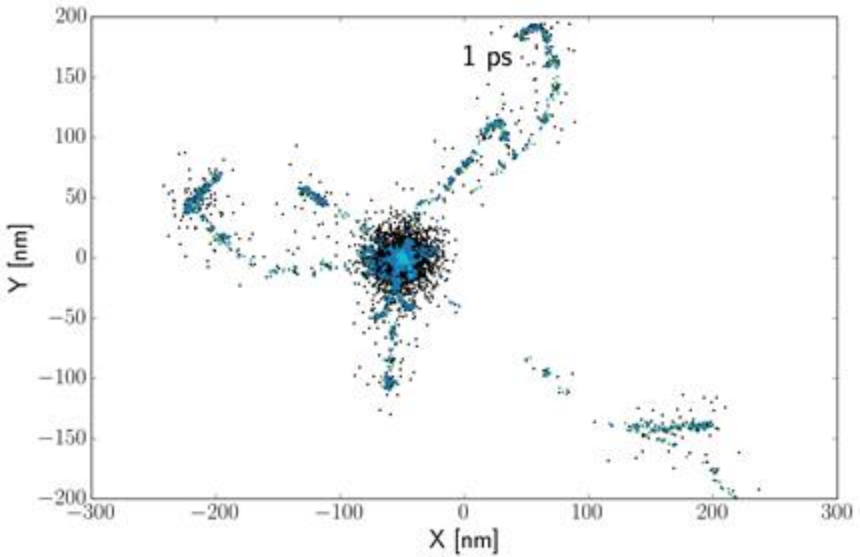
Jansen et al RO 2022

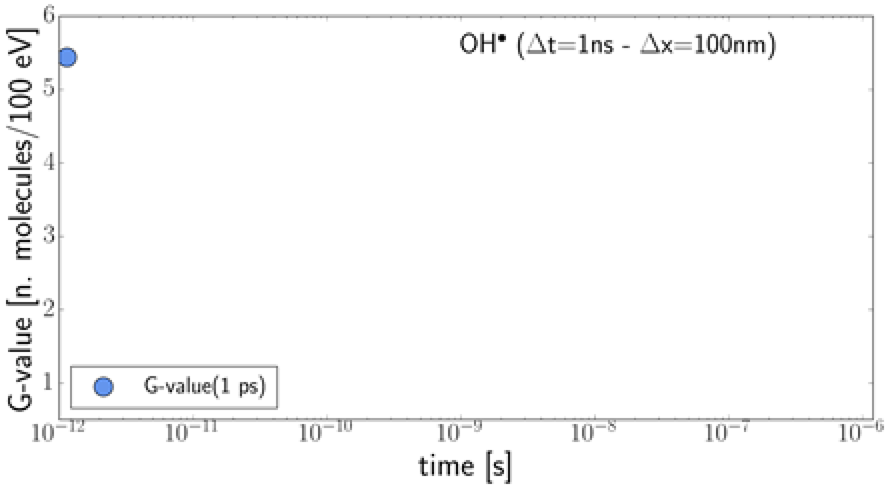
Intertrack effects

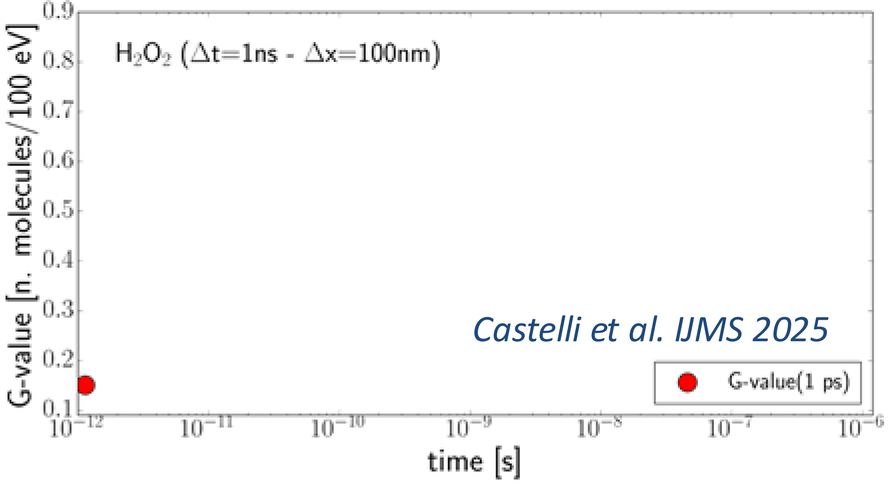


Castelli at al. 2025
(Int J Mol Sci)

INTERTRACK: Quantities and their time evolution





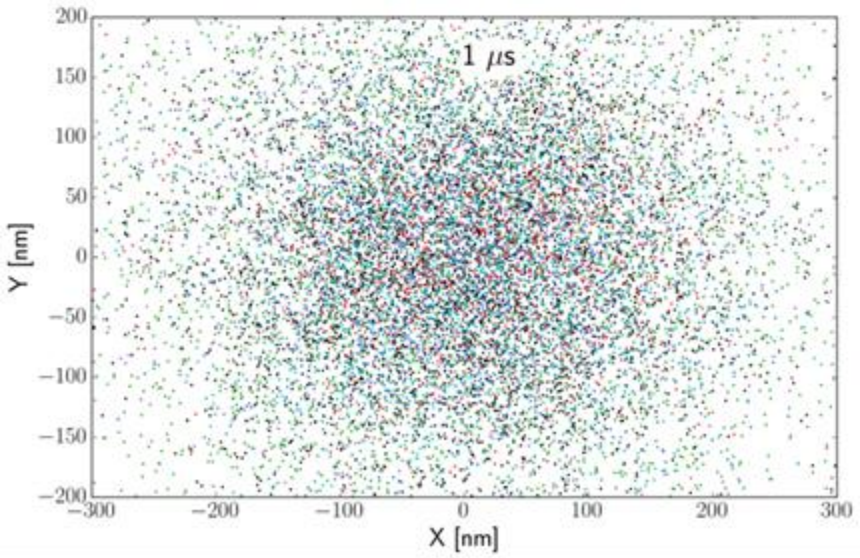


Castelli et al. IJMS 2025

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

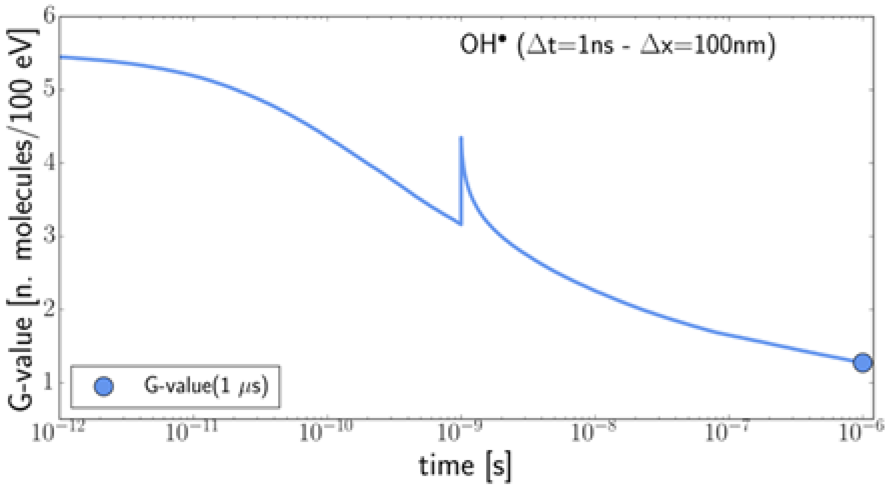
$$\text{G-value} = \frac{N_1 + N_2}{E_1 + E_2}$$

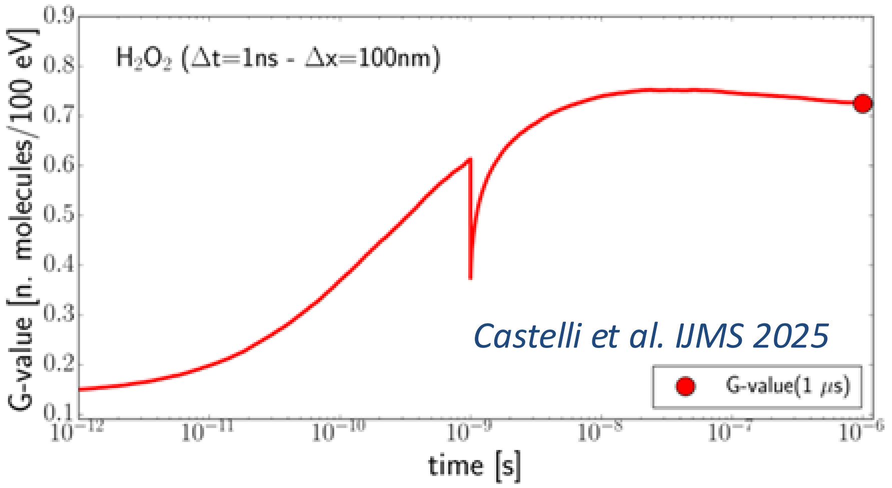
INTERTRACK: Quantities and their time evolution



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

$$\text{G-value} = \frac{N_1 + N_2}{E_1 + E_2}$$

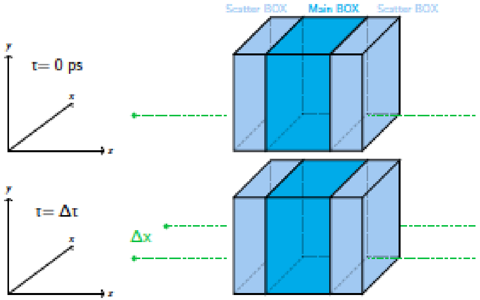


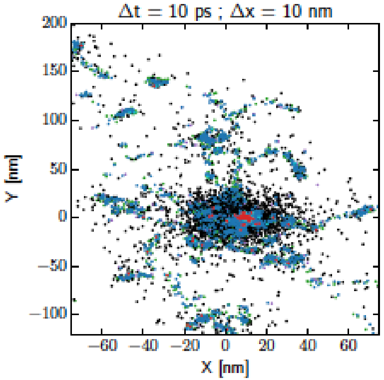


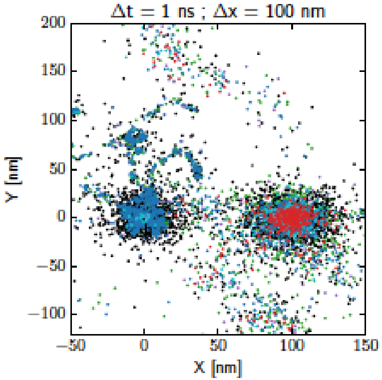
Castelli et al. IJMS 2025

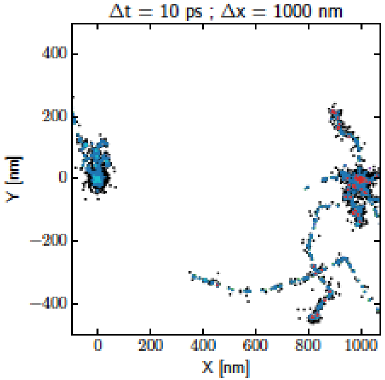
Spatiotemporal shifts

- **Point-like Source:**
  - 20 MeV protons (LET = 2.25 keV/μm)
  - 20 MeV/u helium ions (LET = 33.5 keV/μm).
- **Main Target:** Square face (25 μm^2) and depth 2.5 μm (H^+) and 1.5 μm (He^{2+}).
- **Δx [nm]:** 0, 1, 10, 10^2, 10^3
- **Δt [ps]:** 0, 1, 10, 10^2, 10^3, 10^4, 10^5



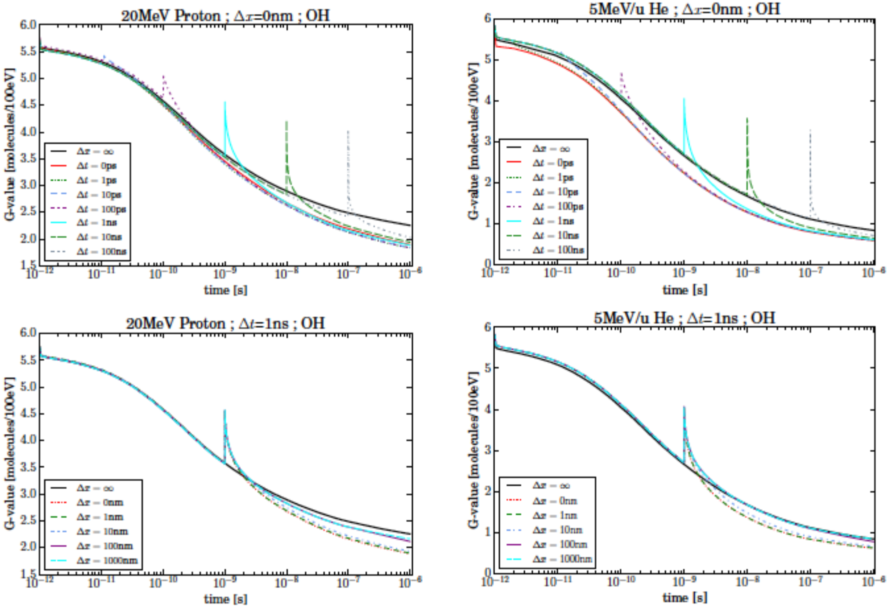




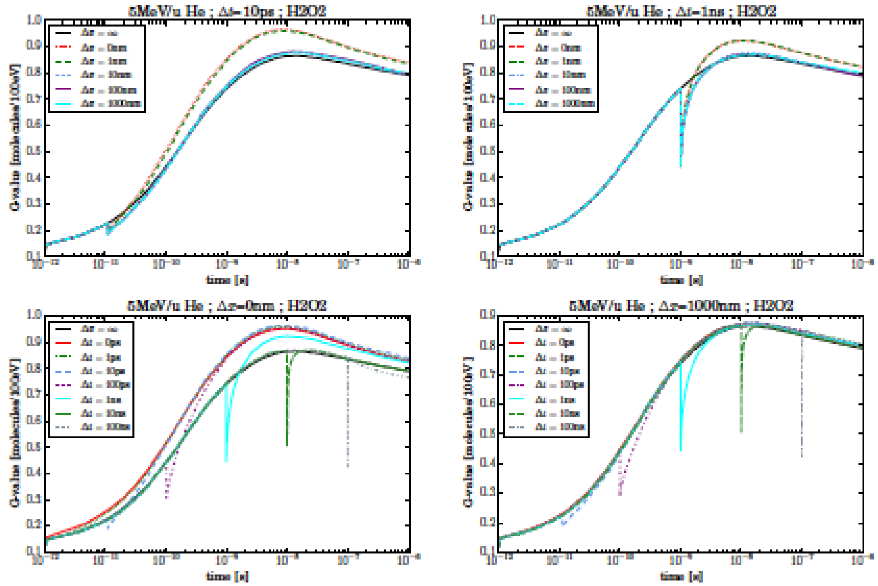


Overall yields for tracks at different Δx and Δt

OH.

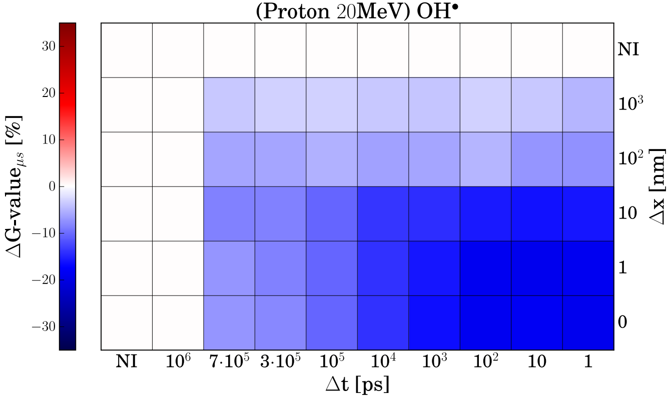


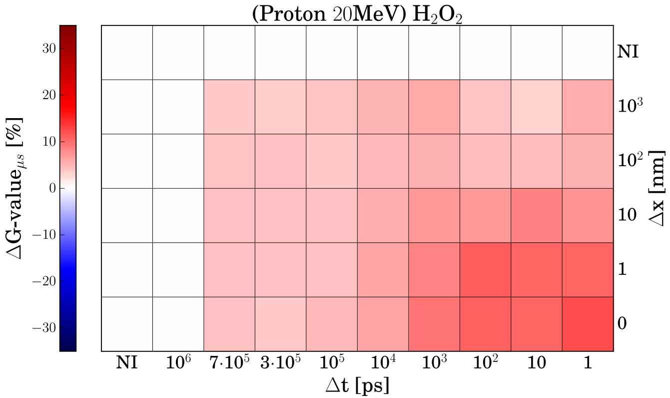
H_2O_2

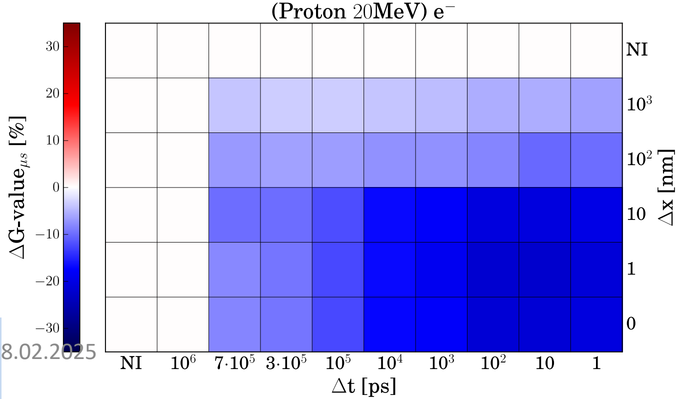


Proton ΔGs for given s/t separation

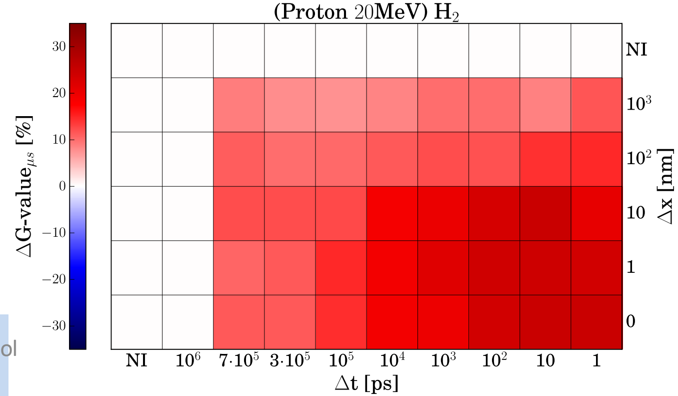
$$\Delta\text{G-value}_{\mu s} = (\text{G-value}_{\mu s}(\Delta x, \Delta t) - \text{G-value}_{\mu s}(\text{NI}))/\text{G-value}_{\mu s}(\text{NI})$$


(Proton 20MeV) $OH^\bullet$

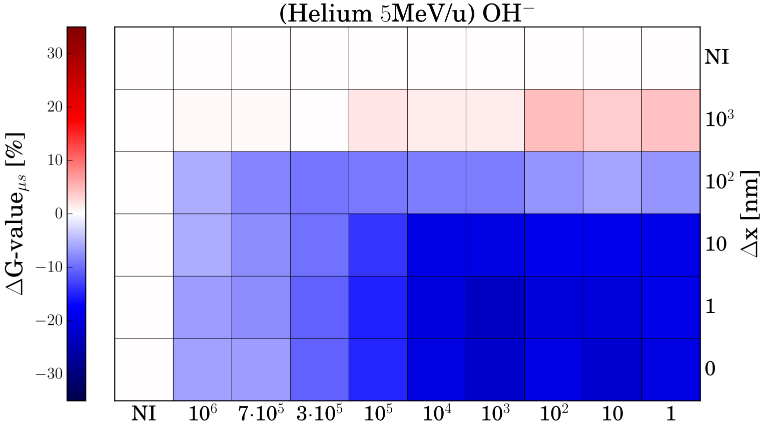

(Proton 20MeV) H_2O_2

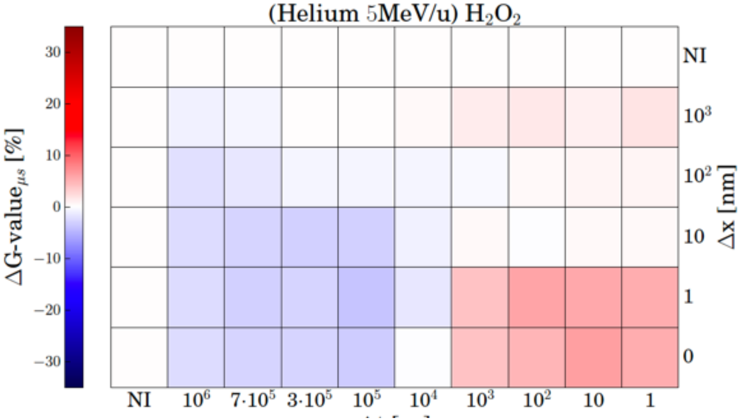

(Proton 20MeV) e^-

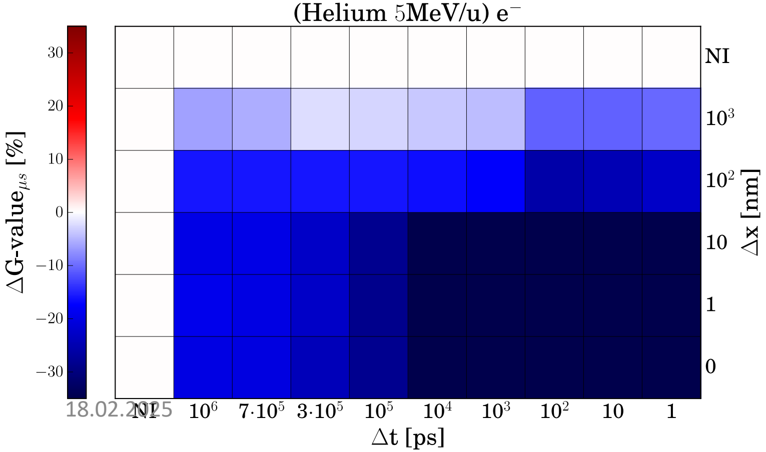
Castelli at al. 2025 (Int J Mol Sci)

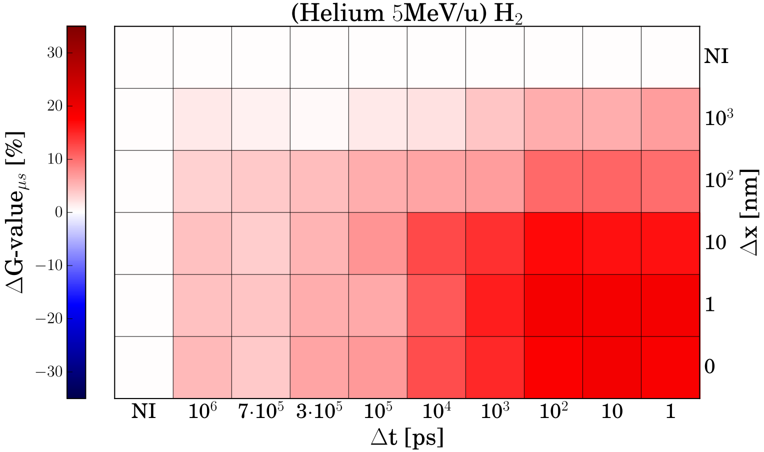

(Proton 20MeV) H_2

Helium ΔGs for given s/t separation









Castelli at al. 2025
(Int J Mol Sci)

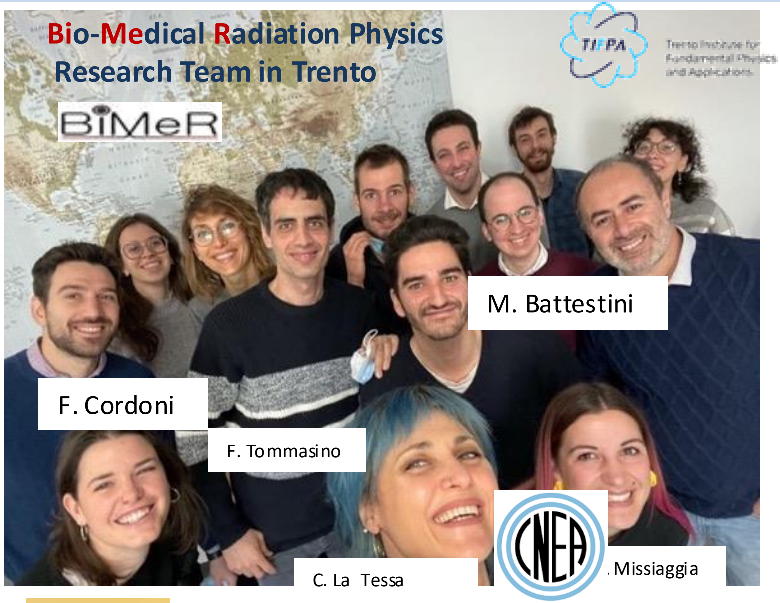
Conclusions

- The radiotherapy effectiveness depend on the different types of energy deposition at the molecular level

- FLASH radiotherapy exploits the dose rate effect in ultrahigh regime and its mechanism remain not understood, while Is object of intense investigation

- Multiscale modeling allows to provide insights in the mechanism,
- The heterogeneous stage is accurately described by TRAXCHEM, depicting the chemical evolution of tracks at different conditions allowing to explore impact of oxygenation and LET up to ms time scale. The mulltitrack feature evidences a clear range in time and space where intertrack may occur, which is extremely limited in typical FLASH experiments

Acknowledgments



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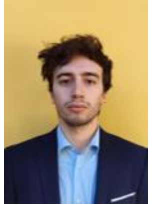

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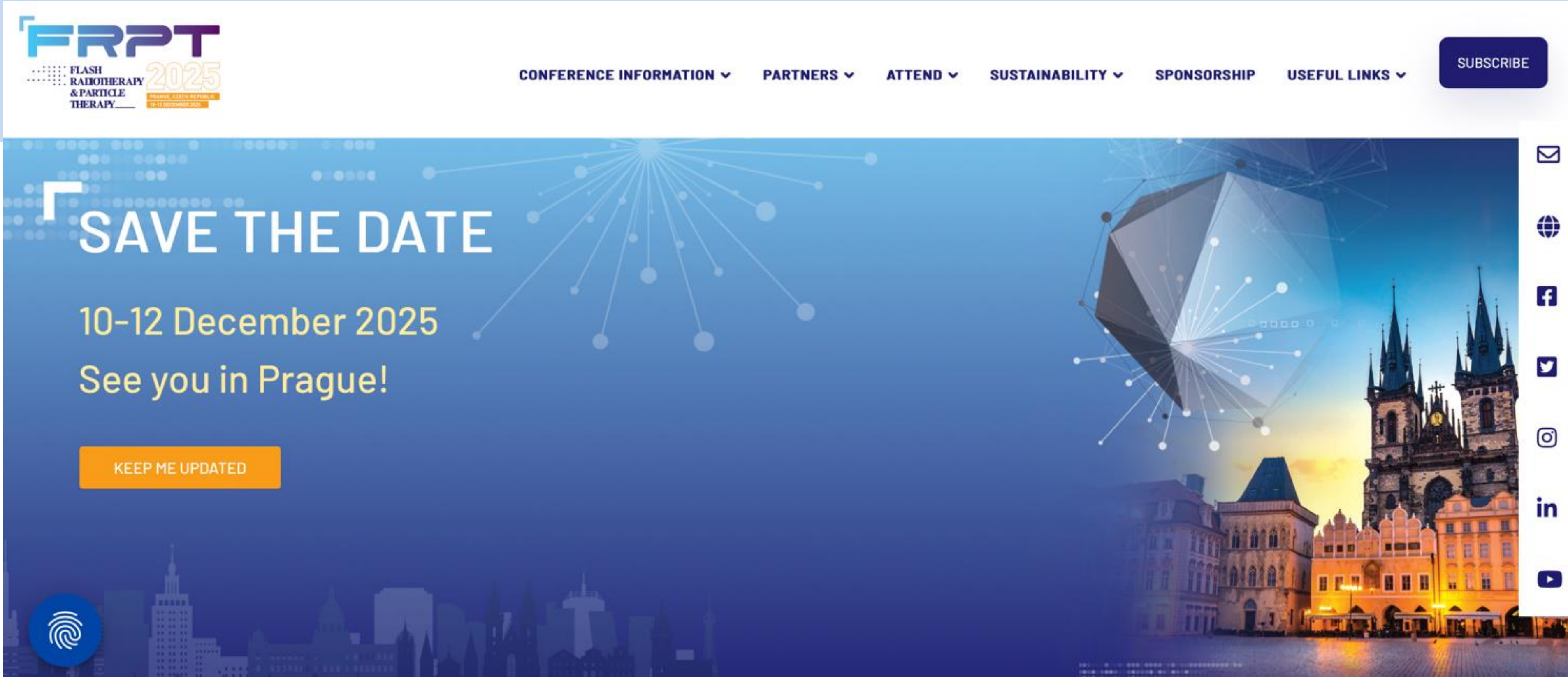

SAVE THE DATE

10-12 December 2025

See you in Prague!

OC:

- Pavel Vitek,
- Petra Trnkova
- Anna Jelinek Michaelidesova
- Pavel Blaha
- Marie-Catherine Vozenin
- Emanuele Scifoni
- Francesco Romano

FLASH WORKSHOP 2025

THE ROLE OF OXYGEN IN FLASH RADIATION THERAPY

HEIDELBERG (GERMANY), JULY 1ST – JULY 3RD, 2025

MORE INFORMATION ON: WWW.DKFZ.DE/FLASH_WORKSHOP2025

dkfz.
GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

SCIENTIFIC COMMITTEE

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Iuliana Toma-Dasu (Stockholm, Sweden)

Marie-Catherine Vozenin (Geneva, Switzerland)

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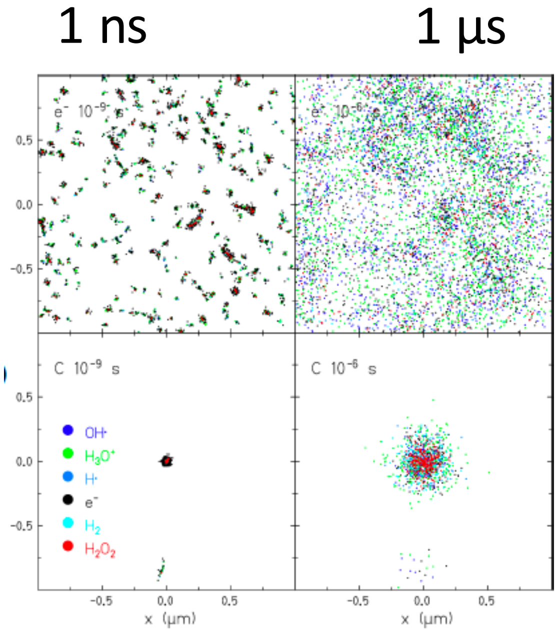
PRECISION
X-RAY IRRADIATION

Thanks for your attention!

Discussion Slides

Hetero/Homogeneous stage transition



- Higher LET homogeneizes later
- Track remains denser at later stage
- Diffusion may still play a relevant role

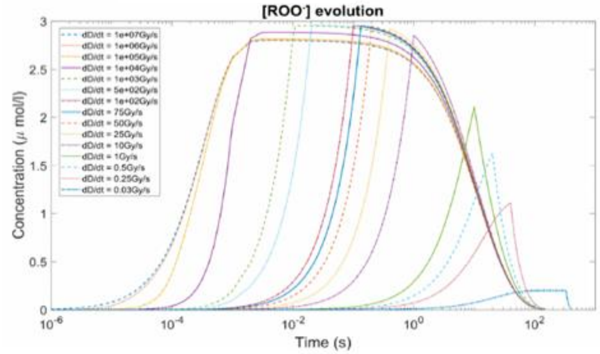
Camazzola et al. 2023

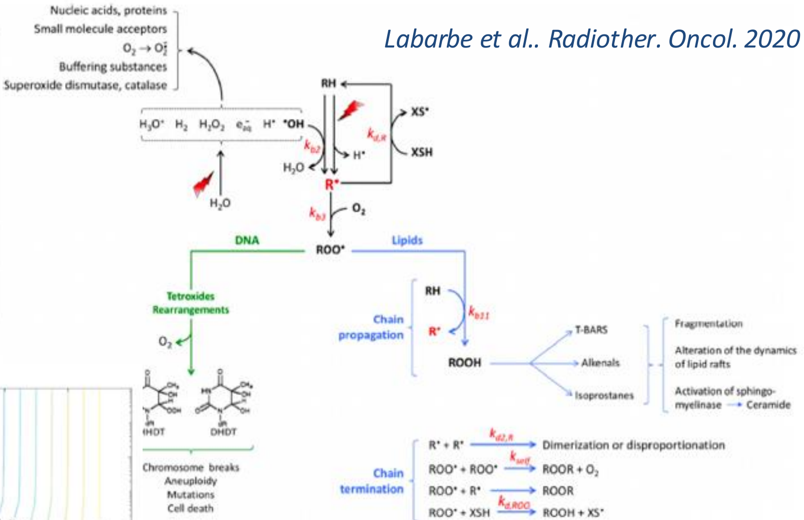
Radical recombination hypothesis

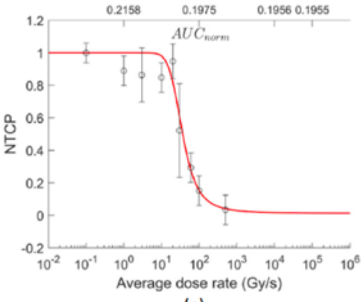
$$AUC_{ROO} = \int_0^{T_{sim}} [ROO\cdot](t) \cdot dt$$

Pure Homogeneous stage based study

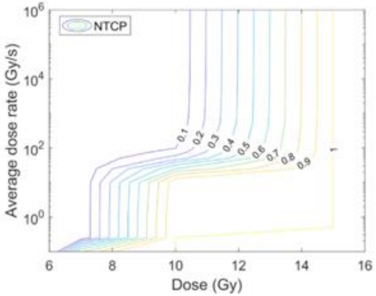
Labarbe et al.. Radiother. Oncol. 2020







(c)



$$NTCP_{model}\left(D,\frac{dD}{dt}\right) = 1/\left(1+exp\left(-\gamma\cdot\left(AUC_{norm}\left(D,\frac{dD}{dt}\right)-AUC_{50}\right)\right)\right)$$

The MultiScale-Generalized Stochastic Microdosimetric Model

Battestini et al. Front. Phys. 2023 .

MS-GSM²: a multi-stage tool

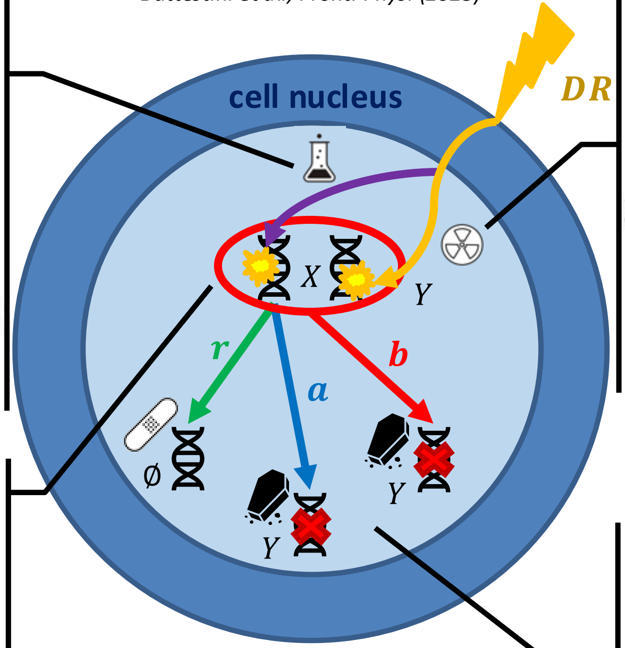
Battestini et al., Front. Phys. (2023)

Fast chemical reaction kinetics

$$\begin{aligned}
\frac{d}{dt}\left[e^-_{aq}\right](t) &= f_{e^-_{aq}}(\xi(s)) + G_e\rho\dot{z}\,,\\
\frac{d}{dt}[O_2](t) &= f_{O_2}(\xi(s))\,,\\
\frac{d}{dt}C_{H_2O_2}(t) &= f_{H_2O_2}(\xi(s)) + G_{H_2O_2}\rho\dot{z}\,,\\
\frac{d}{dt}C_{OH\bullet}(t) &= f_{OH\bullet}(\xi(s)) + G_{OH\bullet}\rho\dot{z}\,,\\
\frac{d}{dt}[H^\bullet](t) &= f_{e^-_{aq}}(\xi(s)) + G_{H\bullet}\rho\dot{z}\,,\\
\frac{d}{dt}[H_2](t) &= f_{e^-_{aq}}(\xi(s)) + G_{H_2}\rho\dot{z}\,,\\
\frac{d}{dt}C_{O_2^\bullet-}(t) &= f_{O_2^\bullet-}(\xi(s))\,,\\
\frac{d}{dt}[R^\bullet](t) &= f_{R\bullet}(\xi(s)) + G_{R\bullet}\rho\dot{z}\,,\\
\frac{d}{dt}[ROO^\bullet](t) &= f_{ROO\bullet}(\xi(s))\,,\\
\xi &= \left(\left[e^-_{aq}\right], [O_2], C_{H_2O_2}, C_{OH\bullet}, [H^\bullet], [H_2], C_{O_2^\bullet-}, [R^\bullet], [ROO^\bullet]\right)
\end{aligned}$$

Mod. From Labarbe 2020

system of ordinary differential equations resolution in each domain

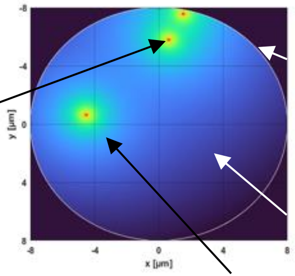


X: **sub-lethal lesions**

Y: **lethal lesions**

Spatial and temporal dose deposition

single particle track hitting
+
energy deposition
+
elapsed time



cell nucleus

domain

track dose distribution

Damage formation

DNA damage yield k

direct term

k_d

LET

indirect term

$k_i([ROO^\cdot](t))$

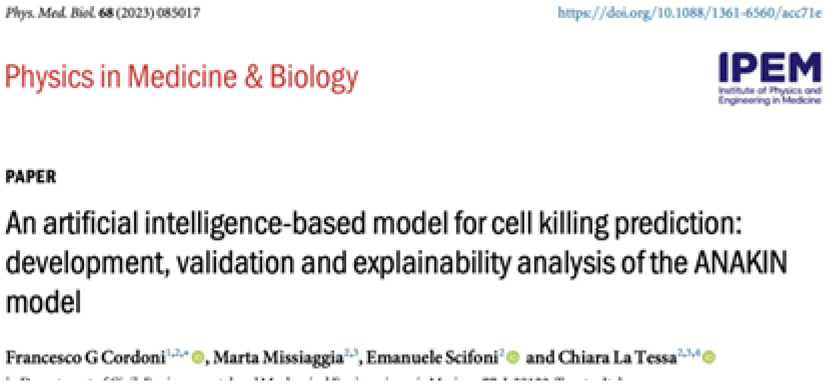
conventionally considered constant

Damage evolution and cell survival

$$\begin{aligned}
Y(t) &= Y_0 + \mathcal{P}^a\left(\int_0^t aX(s)ds\right) + \mathcal{P}^b\left(\int_0^t bX(s)(X(s)-1)ds\right) +\\
&\quad \boxed{+Z_Y(\xi(t))\mathcal{P}^d\left(\int_0^t \dot{d}\,ds\right)}\\
X(t) &= X_0 - \mathcal{P}^a\left(\int_0^t aX(s)ds\right) - \mathcal{P}^r\left(\int_0^t rX(s)ds\right) +\\
&\quad -2\mathcal{P}^b\left(\int_0^t bX(s)(X(s)-1)ds\right)\boxed{+Z_X(\xi(t))\mathcal{P}^d\left(\int_0^t \dot{d}\,ds\right)}\,.
\end{aligned}$$

$$S_n(z_n) := (S_d(z_n))^{N_d} = \left(\mathbb{P}\left(\lim_{t\to\infty} Y(t) = 0\right)\right)^{N_d}$$

Combining AI with particle beam radiobiology



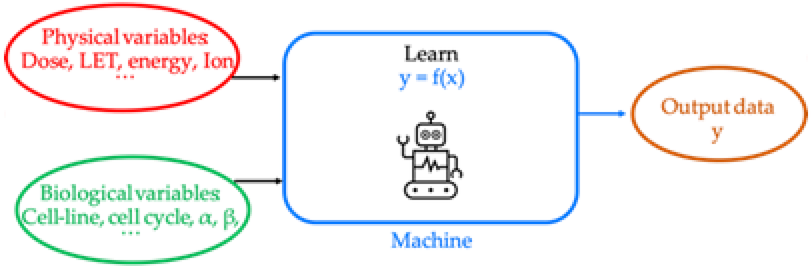
Phys. Med. Biol. **68** (2023) 085017 https://doi.org/10.1088/1361-6560/acc71e

Physics in Medicine & Biology

PAPER

An artificial intelligence-based model for cell killing prediction: development, validation and explainability analysis of the ANAKIN model

Francesco G Cordoni[1,2,*], **Marta Missiaggia**[2,3], **Emanuele Scifoni**[2] and **Chiara La Tessa**[2,3,4]



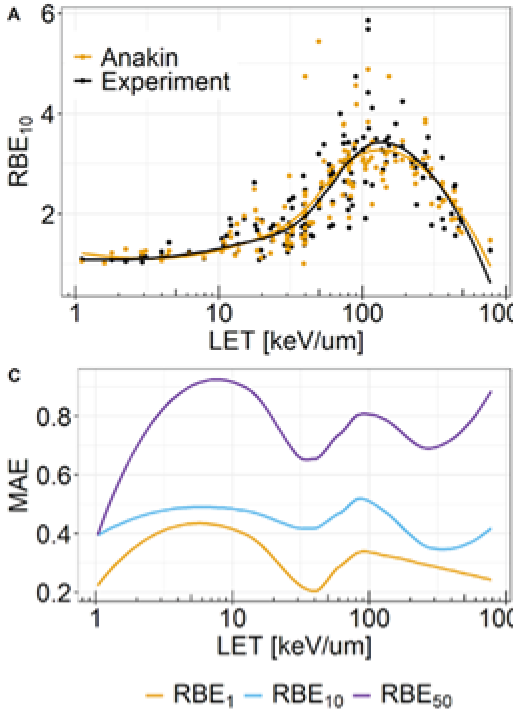
Physical variables
Dose, LET, energy, Ion
...

Biological variables
Cell-line, cell cycle, α, β,
...

Learn
y = f(x)

Machine

Output data
y



Biological-based treatment planning

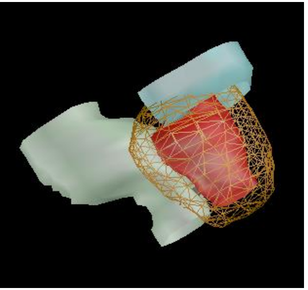
- Bio-TPS for ion beams aims to include as much as possible biological effect information in the planning strategy.

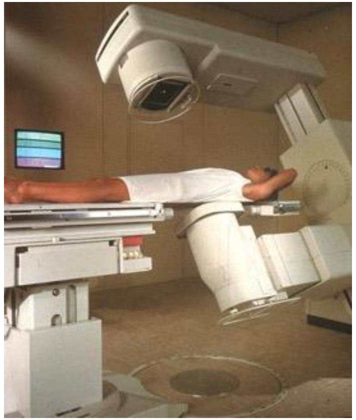
- Relevant for plan recalculation but ideally needed for **inverse** planning.

- Substantial e.g., for assessing differential benefits of different irradiation modalities and selecting the most suitable choice for a given patient case.

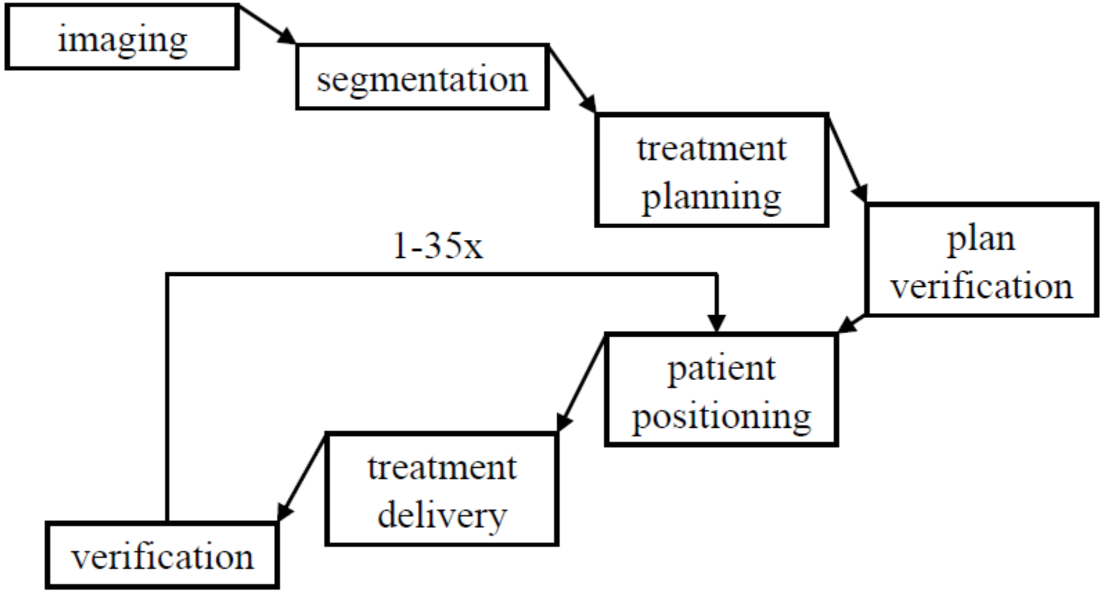
- **Additional physics data** needed, since the different components (E,Z) of the mixed field in a beam should be properly accounted in order to get a proper overall biological effect.

TPS in the Radiation therapy workflow





Radiotherapy chain



imaging

segmentation

treatment planning

plan verification

patient positioning

treatment delivery

verification

1-35x

Dose modifying factors

- in general a „dose modifying factor“ (DMF) is defined as a ratio of doses compared to normal conditions (n.c.) giving **a Same biological effect**

-more properly called `Dose effectiveness factor (DEF)-

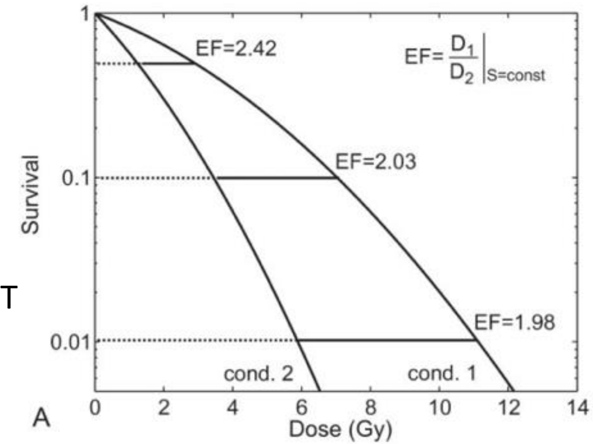
$$DEF = \left.\frac{D_{specialconditions}}{D_{n.c.}}\right|_{sameeffect(S)} \quad ; \qquad DEF([C]) = \left.\frac{D([C])}{D_{n.c.}}\right|_{sameeffect(S)}$$

- Can be a radiation quality related feature like **RBE**, or a more target related property (like e.g. **OER**)

- it is called properly a „dose modifying factor“ if independent on S (or D)

Depending on several parameters, in particular LET

$$DEF(LET,[C]) = \left.\frac{D(LET,[C])}{D_{n.c.}}\right|_{sameeffect(S)}$$



Wenzl&Wilkens 2011

The Optimization problem

Optimal particle numbers $\vec{N}_{opt}$ **for all rasterpoints in order to obtain a 3D dose distribution that respects the constraints imposed.**

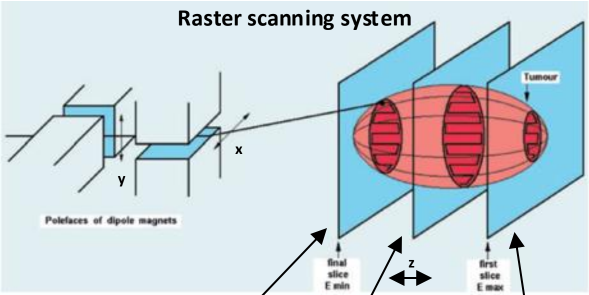
TRiP98 cost function ⟶ formalizes the treatment goals:

$$\chi^2(\vec{N}) = (w_t)^2 \sum_{i=1}^{N_T} \frac{\left(D_{pre} - D_i(\vec{N})\right)^2}{\Delta D_{pre}^2}$$

Target (uniform dose)

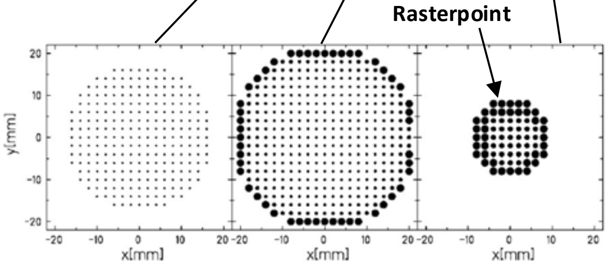
OAR (maximum dose)

$$+\left(w_{OAR}^{Dmax}\right)^2 \sum_{i=1}^{N_{OAR}^{Dmax}} \frac{\left(D_{max} - D_i(\vec{N})\right)^2}{\Delta D_{max}^2} \cdot \theta\left(D_i(\vec{N}) - D_{max}\right)$$



Krämer et al. (2000)

Where in order to account for bio effects, the "bio" dose is obtained through scaling the physical dose by the specific DMF



Krämer et al. (2000)

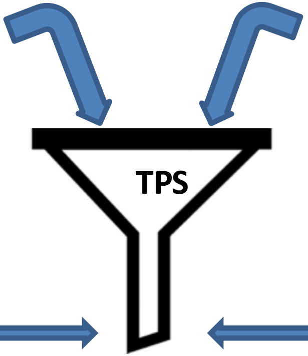
Aim: searching the **minimum** of $\chi^2(\vec{N})$ for **all fields simultaneously (multiple field optimization)**.

MoVe IT

Modeling and Verification for Ion beam Treatment planning

A Graphycal summary

Physics



Radiobiology

(= Biological effects + micro/nanoscale physics)

- Depth dose distributions
- Nuclear fragment spectra (including target)
- Stopping power data

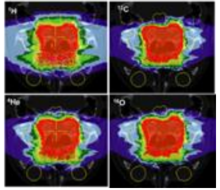
- RBE (eg. LEMx, MKM)
- OER
- any other DMF…

Beamline specifics

Patient Imaging data

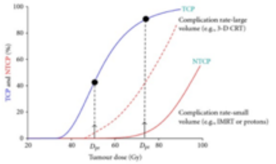
Including intratumor heterogeneity

Effective Dose profile



Verification

Clinical Impact



TCP/NTCP

advanced beam monitoring

“Bio”-dosimetry