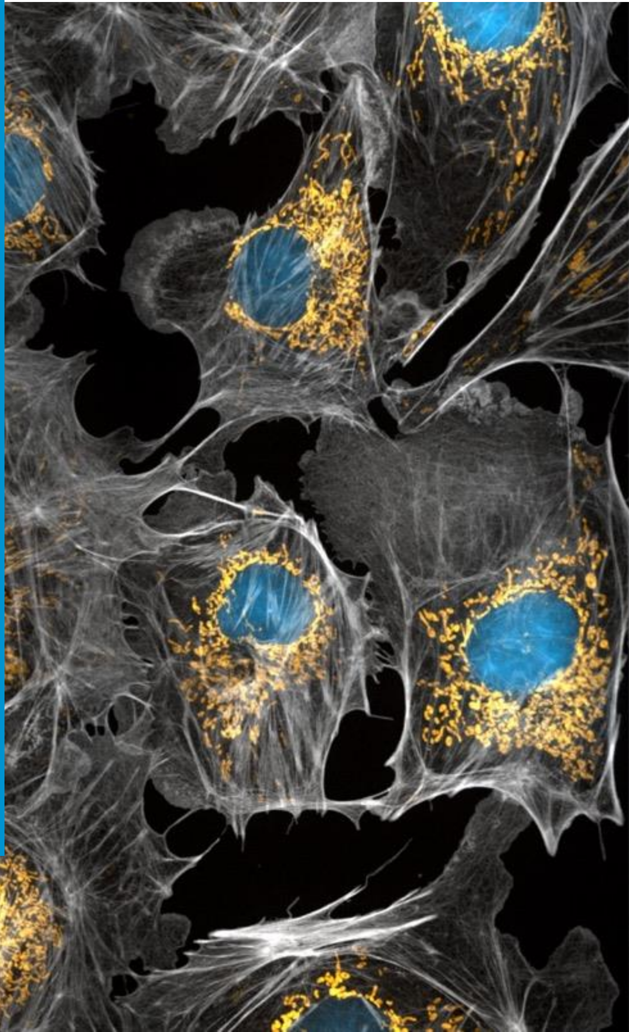

Multiscale Monte Carlo simulations for radiotherapy.

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Collaborators

ID-Collaboration

(NIH/NCI R01CA266467)

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Loma Linda University

dkfz. German Cancer Research Center in the Helmholtz Association

Berkeley Lab
Lawrence Berkeley National Laboratory

1. Background.
2. Monte Carlo track-structure, nanodosimetry and its link with radiobiology.
3. A formalism for computing nanodosimetric quantities in macroscale.
4. Take aways.

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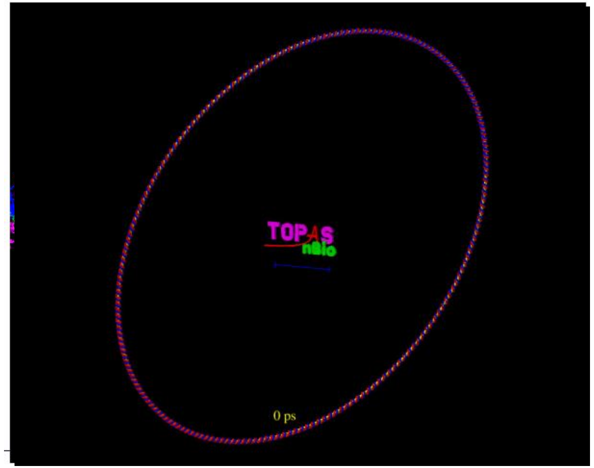
Multiscale stochastic modeling

- Condensed-history Monte Carlo
- Monte Carlo Track-structure

NIH/ITCR U24CA215123



$OH\bullet$
e^-_{aq}
H_3O^+
H, H_2
H_2O_2
proton
e^-

NIH R01CA187003

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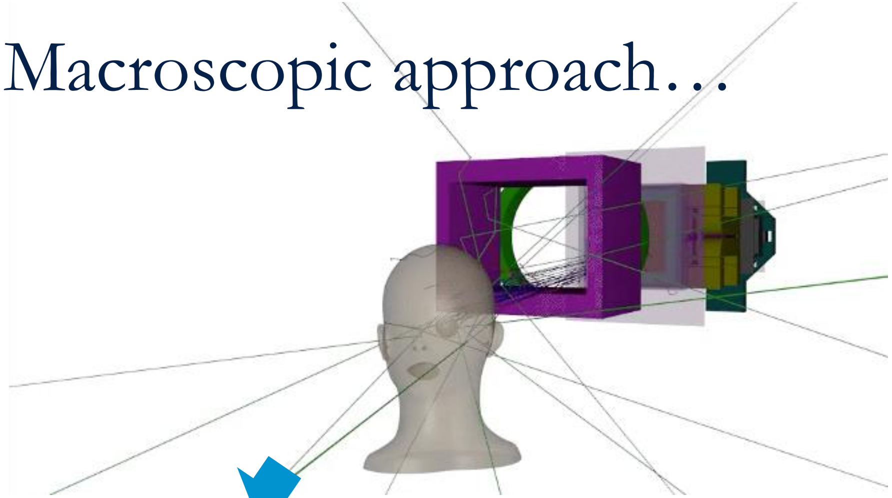
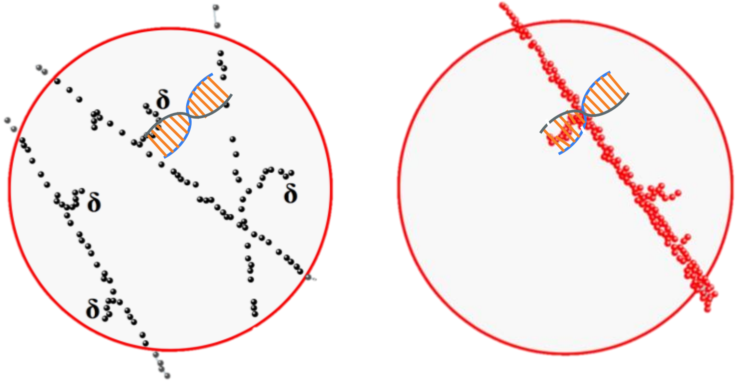
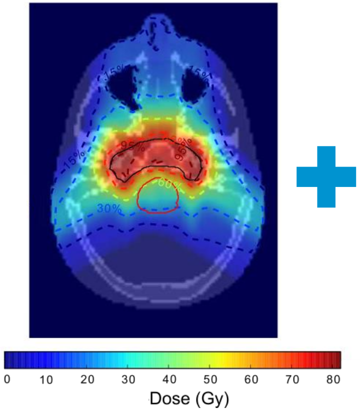
Macroscopic approach…

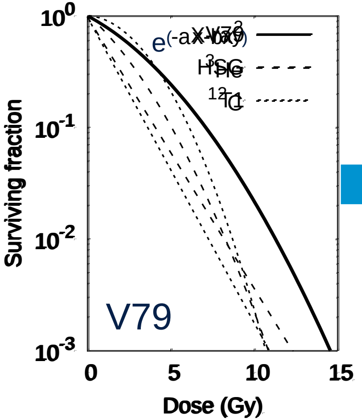


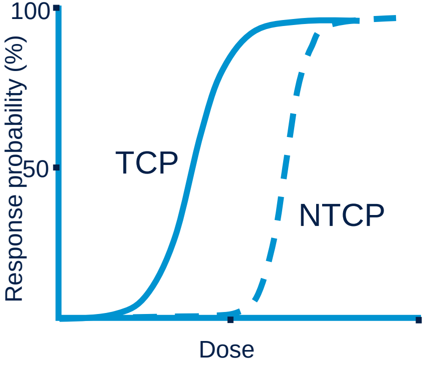


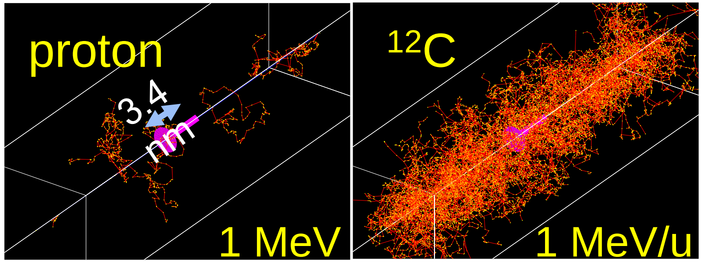
Same absorbed dose, different quality beams

Adapted from: H. Rabus. Course "Monte Carlo Simulations for micro-and-nanodosimetry, KIT, Karlsruhe, 2011









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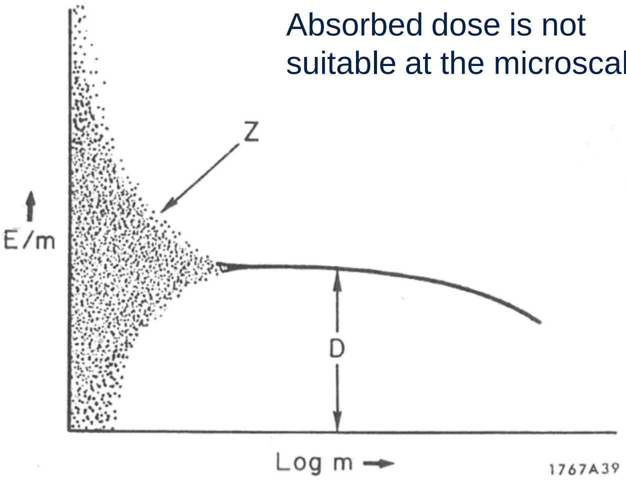
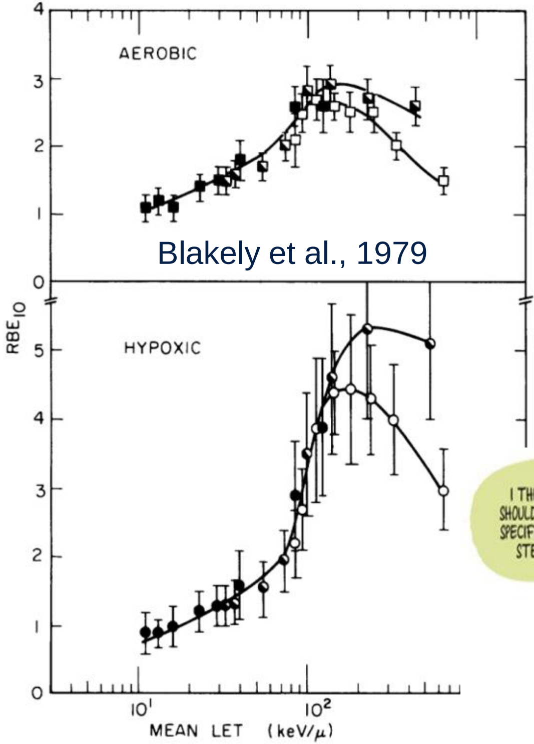
Justification.
A macroscopic approach…

Absorbed dose is not suitable at the microscale.

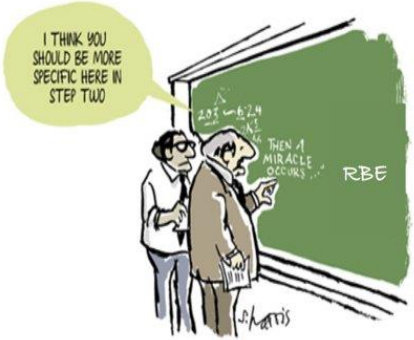


Rossi (1996)



Blakely et al., 1979

LET is sensitive to the type of radiation.



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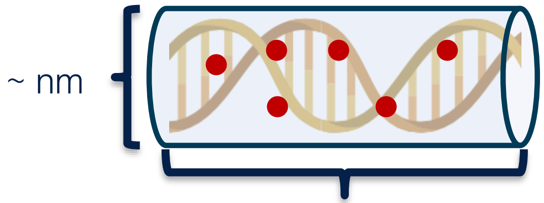
Nanodosimetry.

It is concerned with measuring ionization track structure down to nanometric resolution, a scale comparable to the dimension of DNA base pairs.

Track segment (250 nm) of 0.5 MeV/u alpha particle,

- Postulate 1. The probability to produce a SSB in a short segment of DNA is expected to be proportional to the probability of obtaining an ionization cluster size of one.
- Postulate 2. As each relevant interaction is expected to occur with a probability proportional to that for an ionization, the overall probability for at least two relevant interactions (DSB) should also be proportional to the cumulative probability F2 for having ionization cluster sizes of two or more. (Grosswendt 2005, Rabus & Nettelbeck 2011)

Nanodosimetry concepts



Register the number of individual ionizations in nanoscopic target volume.

(Charlton *et al,* 1989) (Brenner and Ward 1992) (Goodhead 1994)

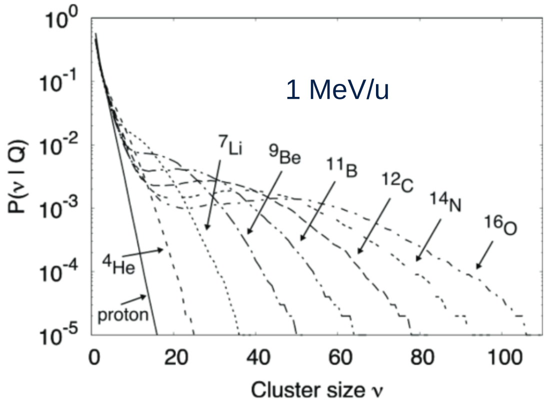
- **The size of ionization clusters (ν)**: the number of ionizations produced in a nanoscopic target volume.

- Ionization cluster size distribution (ICSD):

  * probability, $P_\nu(Q,V)$

  * frequency, $f_\nu(Q,V)$

  Distribution of ionization cluster sizes ν in a target volume V and radiation quality (type and energy) Q.



Ramos-Méndez *et al,* 2018

Nanodosimetry concepts

- **Ionization clusters** of size ν, where ν is the number of ionizations produced in a nanoscopic target volume.

- Ionization cluster size distribution (ICSD):

  probability, $P_\upsilon(Q,V)$
  frequency, $f_\upsilon(Q,V)$

  distribution of ionization cluster sizes ν in a target volume V and radiation quality (type and energy) Q.

- **Mean cluster size** (M_1): first statistical moment of the ICSD.

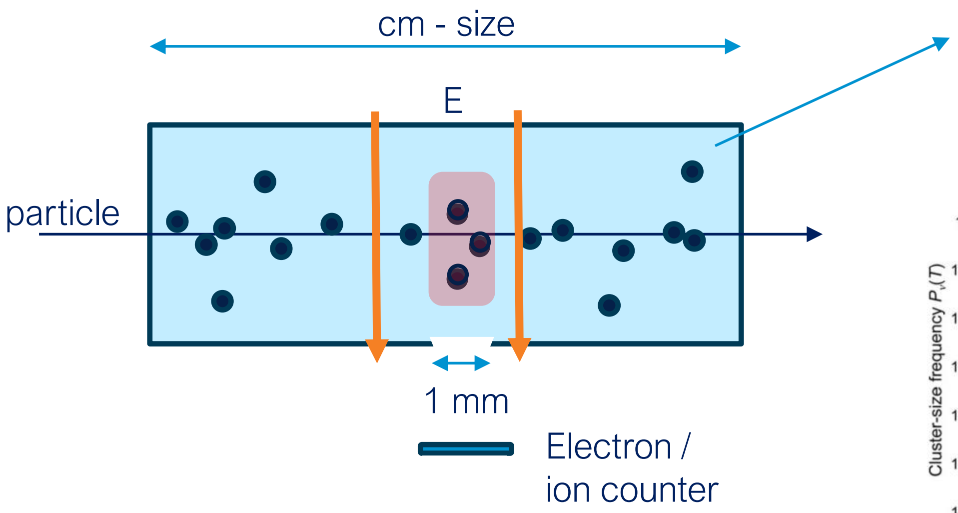
- **Cumulative probabilities** (F_k): the probability of k or more ionizations in the target volume.

Grosswendt's track-structure approach to link with biological effectiveness.

- **Conditional ICSD**: conditional probability distribution of cluster sizes given a minimum cluster size, e.g., $P_\upsilon^{C_2}$. (Hilgers, 2017)

(Conte 2012,2014,2017,2018,2020,2023) (Bueno *et al,* 2015) (Alexander *et al,* 2015) (Ramos-Méndez *et al,* 2018), (Rabus *et al,* 2020), etc

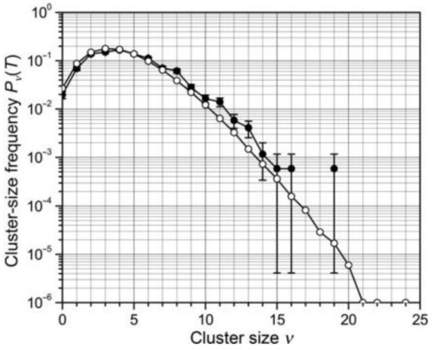
Experimental nanodosimetry



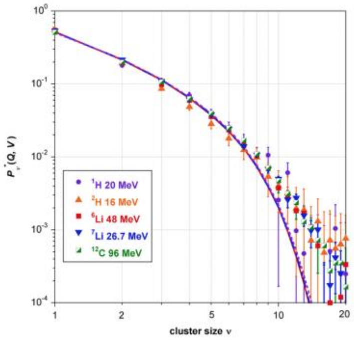
Low pressure gas (e.g., propane or nitrogen)

at 2.1 x 10^{-6} g/cm^3 of propane gas:

1 mm in gas ≡ 2.1 nm in water



Grosswendt *et al,* 2007



Conte *et al,* 2012

Jet Counter (JC)

NCNJ (Poland)

Ion-counter

α, low E e-, Auger e-, C-ions

Ion Counting (IC)

WIS (Israel),PTB (Germany), LLU and UCSD (USA)

Ion-counter

e-, p+, α, C-ions

Startrack Counter (SC)

INFN LNL (Italy)

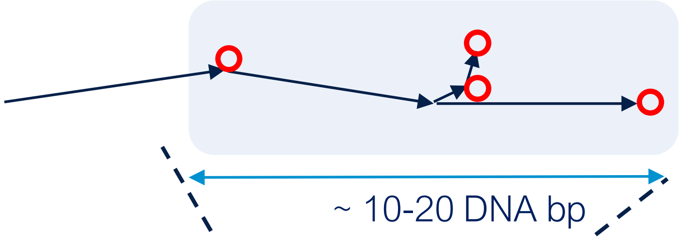
electron-counter

p+, α, Li- and C-ions

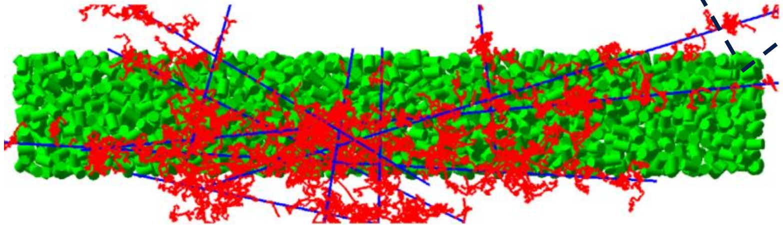
Monte Carlo track structure (MCTS) simulations

MCTS allows the simulation of interactions of individual charged particle tracks on an event-by-event basis at nanometer scale.

PARTRAC

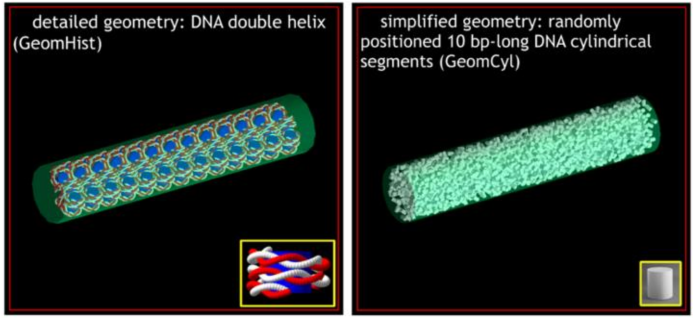


TOPAS-nBio



Ramos-Méndez *et al,* 2018

Geant4-DNA

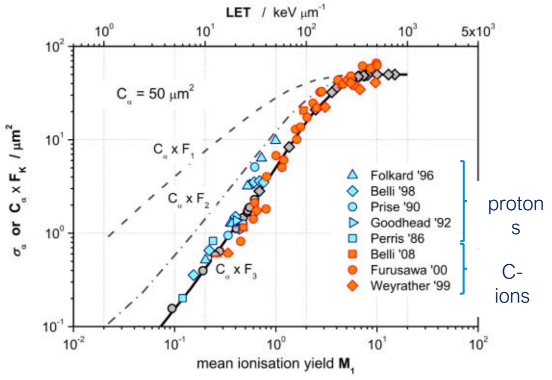


Bueno *et al,* 2015

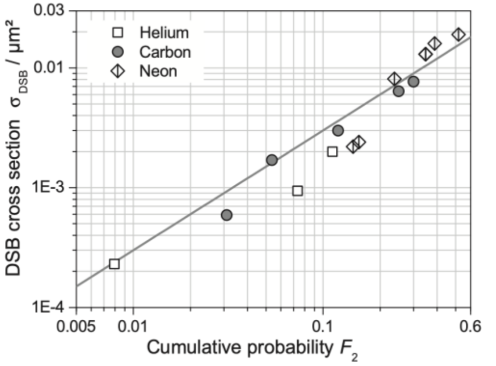
(Conte *et al,* 2017, 2018) (Ramos-Méndez *et al,* 2018), (Bueno *et al,* 2015), (Villegas *et al,* 2016), (Nettelbeck and Rabus, 2011), etc.

The link with radiobiology

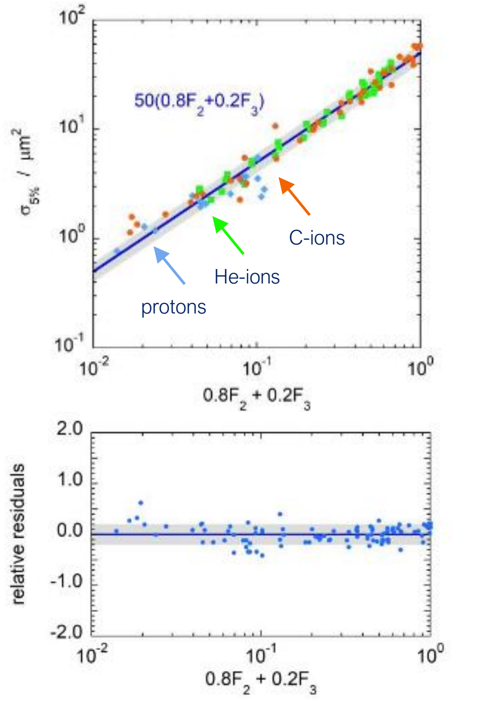
Cell inactivation cross sections (Conte *et al*, 2017, 2018)



DSB cross sections (Nettelbeck and Rabus, 2011)



Cell inactivation cross sections and respective relative residuals (Conte *et al*, 2023)



- Nanodosimetric parameters correlate with biological effects.

Nanodosimetric quantities provide an opportunity for improving the biologically optimized charge particle treatment planning

Nanodosimetry-based treatment planning

- Hypothesis. ID can predict, better than approaches based on LET and current RBE models, the biological effects associated with high ionization density radiation.
- Implications. ID will provide a practical means of planning mixed beam radiotherapy with potentially compelling evidence for its application in the clinic

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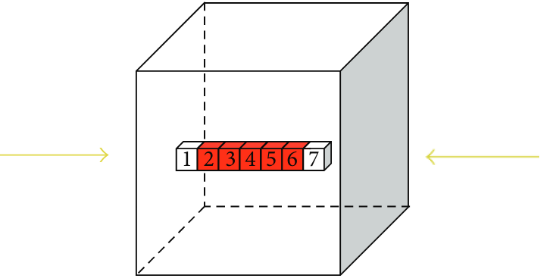
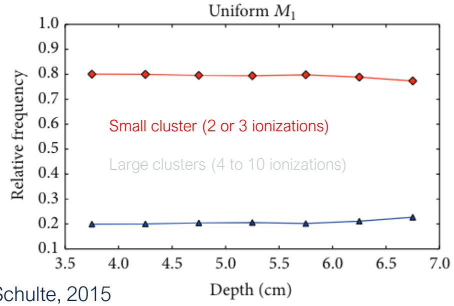
Nanodosimetry-based treatment planning

Previous work.

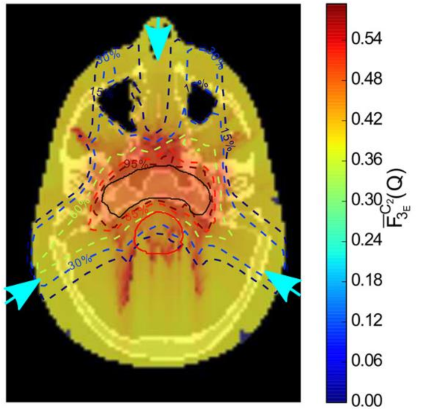


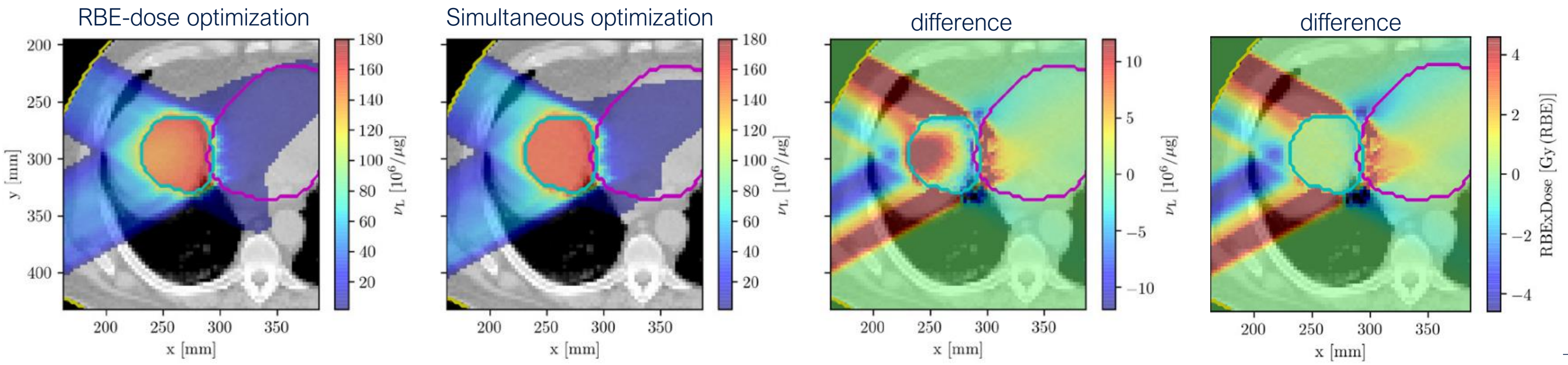


Adapted from Casiraghi and Schulte, 2015

$$\overline{\text{ID}}_E\,(Q) = \frac{\sum_{j,p} q_j^p\,(E_j)\,\Delta E_j}{\sum_j \Delta E_j},$$

Adapted from Ramos-Méndez *et al*, 2018





Adapted from Burigo *et al*, 2019

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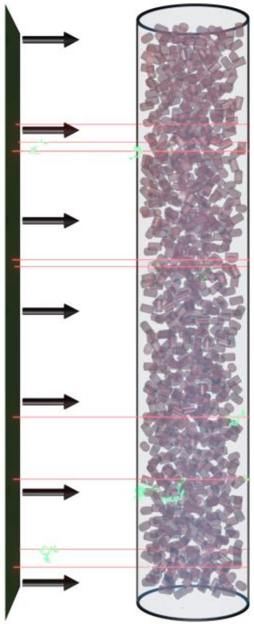
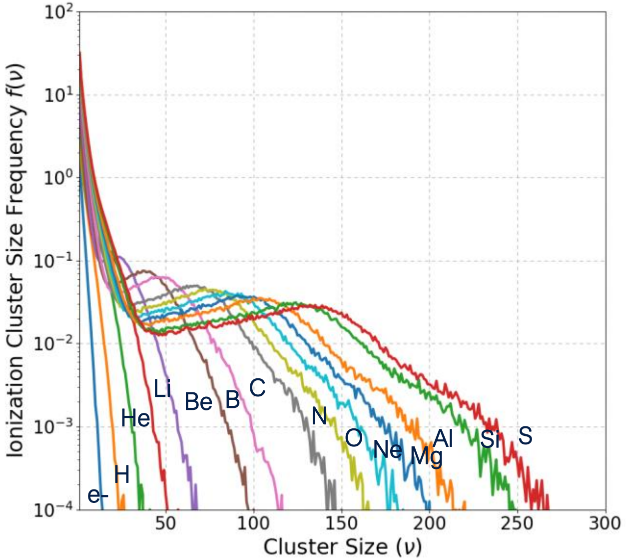


Electrons	10 keV – 100 MeV
Protons	0.5 MeV – 100 MeV
Helium	1 MeV/u – 100 MeV/u
	. . .
Oxygen	1 MeV/u – 100 MeV/u
	. . .
Argon	1 MeV/u – 1000 MeV/u



Courtesy of Dr D-Kondo

frequency distribution of cluster size ν for particle class (particle and energy) c → $f^{c}(\nu)$ $\left[{}^{1}/_{length}\right]$

- per particle, thus, can scale with the particle fluence.
- per average track length through the sampling volume.

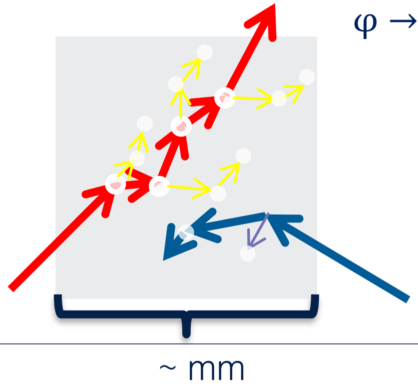
ID formalism – definition of I_p

Ionization detail parameter → $I_p \coloneqq G_p\,[f^c(\nu)]$

$$N_k = \sum_{\nu=k}^{\nu_{max}} \nu\, f(\nu)$$ number of ionizations in clusters of k or more ionizations. $[per\ unit\ length]$

$$F_k = \sum_{\nu=k}^{\nu_{max}} f(\nu)$$ number of clusters of k or more ionizations. $[per\ unit\ length]$

ID formalism – Macroscale



φ → set of particle classes (type and energy) interacting within the voxel *j*

$$I_p^{\varphi_j} = \frac{\sum_{c\epsilon\varphi_j} t_j^c I_p^c}{\sum_{c\epsilon\varphi_j} t_j^c}$$

$[per\ unit\ length]$

$$f^{\varphi_j}(\nu) = \frac{\sum_{c\epsilon\varphi_j} t_j^c f^c(\nu)}{\sum_{c\epsilon\varphi_j} t_j^c}$$

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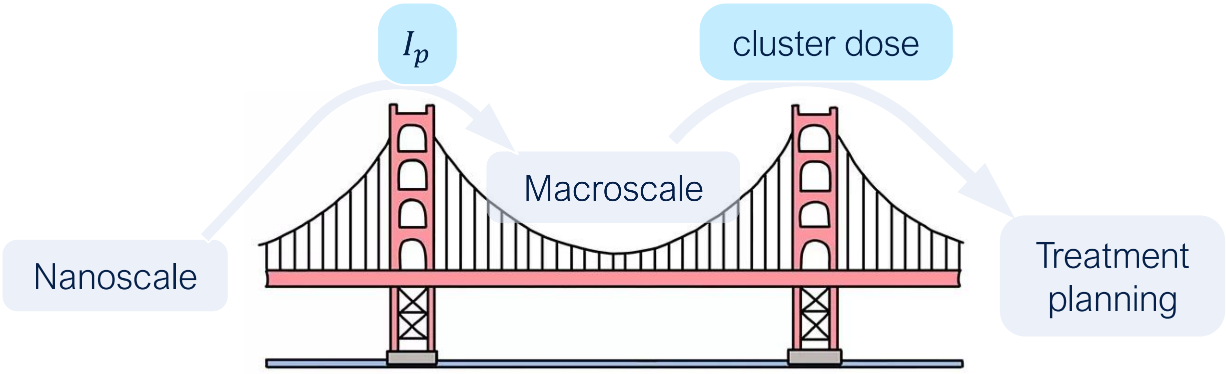
ID formalism – Cluster dose

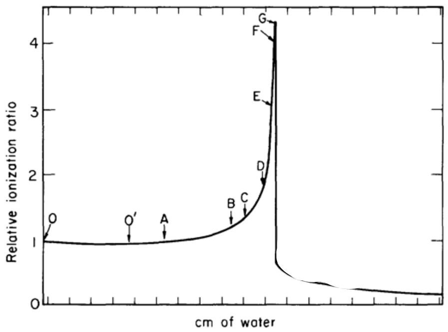
Generalized ionization cluster size dose (***cluster dose***) → $g^{(I_p)}$

$$g_j^{(I_p)} := \phi_j \; F_2^{\varphi_j} / \rho_0 \qquad [per\ unit\ mass] \qquad D = \phi \, S/\rho_0$$

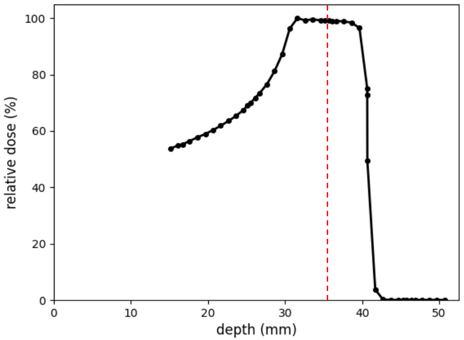


- Different particle classes having the same I_p are expected to lead to the same biological effect.
- Different source ion beams with the same local fluence and I_p will have the same biological effect.

ID formalism – Association with biological endpoints



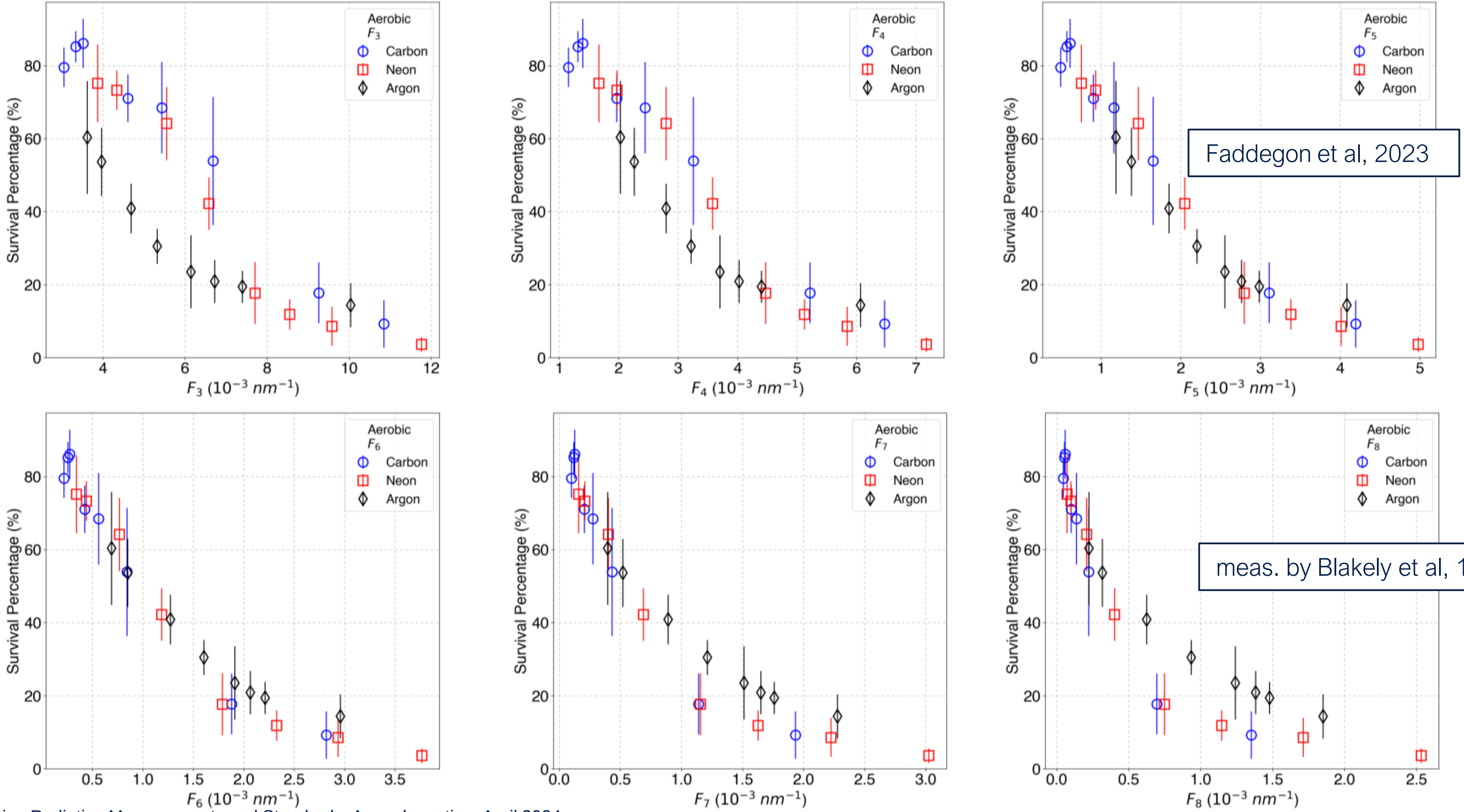
- Human kidney T-1 cells in aerobic and hypoxic conditions. (Blakely *et al*, 1979)
- Monoenergetic beams:
  - Carbon - 400 MeV/u
  - Neon - 425 MeV/u
  - Argon - 570 MeV/u



- Human alveolar carcinoma cells in aerobic conditions. (Dokic *et al*, 2016)
- 1 cm SOBP:
  - Proton - 70 MeV
  - Helium - 70 MeV/u
  - Carbon - 130 MeV/u
  - Oxygen - 150 MeV/u

ID formalism – Association with biological endpoints

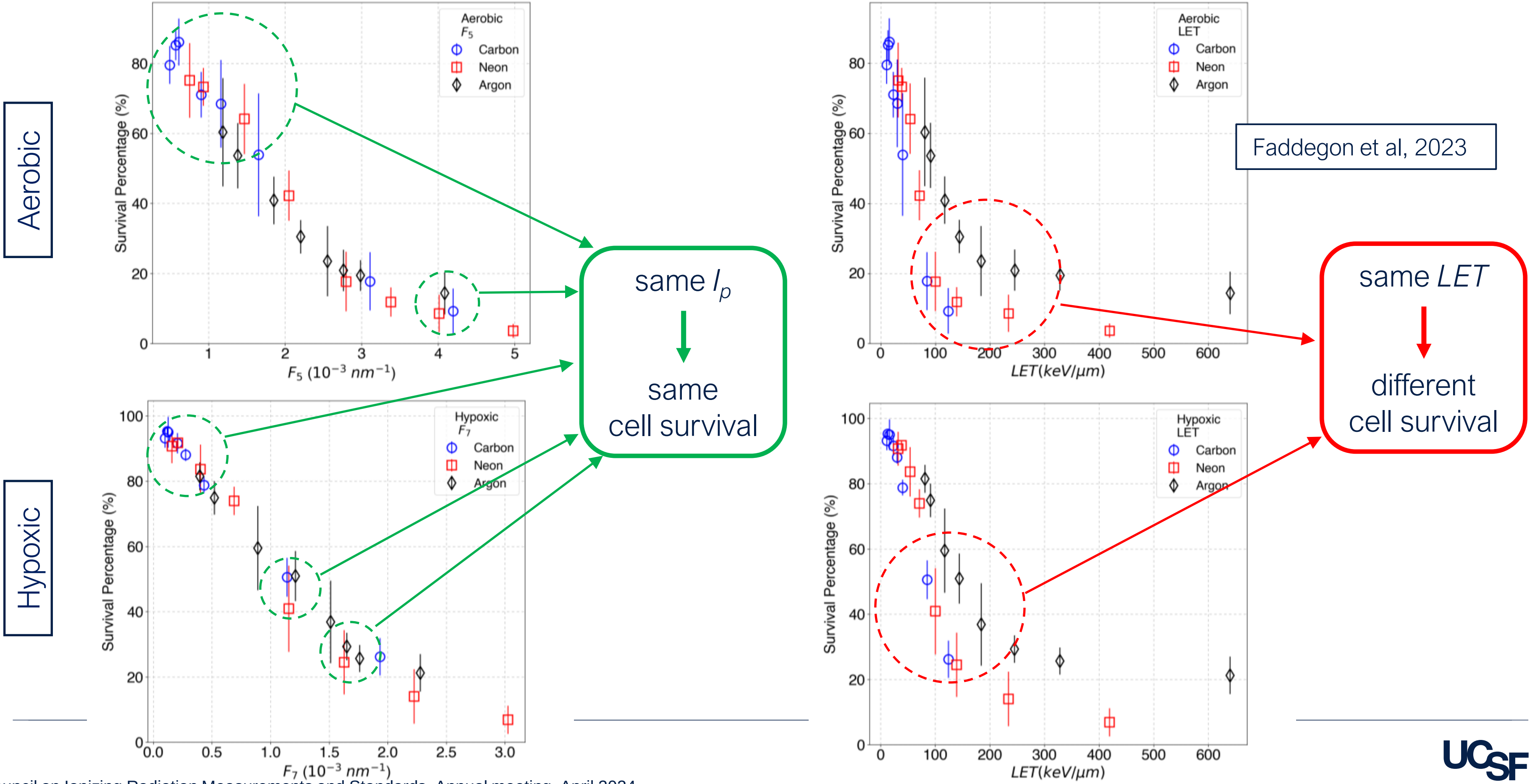
Constant fluence



Faddegon et al, 2023

meas. by Blakely et al, 1979

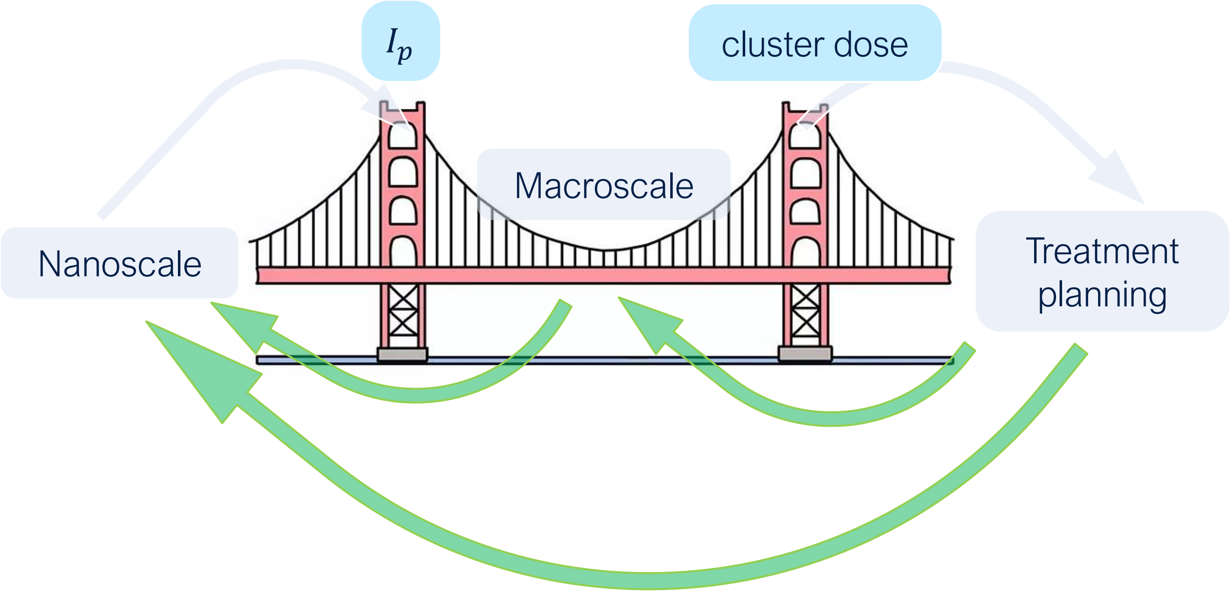
ID formalism – Association with biological endpoints



ID formalism – Outcome and Outlook

There exists a preferred ionization-detail parameter (I_p) that results in comparable biological effects.

- identification of other definitions of I_p with a larger set of data and biological endpoints.



ID formalism – Outcome and Outlook

There exists a preferred ionization-detail parameter (I_p) that results in comparable biological effects.

- identification of other definitions of I_p with a larger set of data and biological endpoints.

We defined the quantity *cluster dose* which closely associates with cell survival and has potential for its practical application in treatment planning

- study its potential for use in particle beam treatment planning.

$$\vec{w}^* = \arg\min \chi(\vec{w}) := \sum_{n=1}^{N} (p_{n,D} f_{n,D}(\vec{w}) + p_{n,I_p^{\mathscr{C}}} f_{n,I_p^{\mathscr{C}}}(\vec{w}) + p_{n,g} f_{n,g}(\vec{w}))$$

Burigo *et al.*, Simultaneous optimization of RBE-weighted dose and nanodosimetric ionization distributions in treatment planning with carbon ions, *Physics in Medicine and Biology*, 2018, 64:015015.
Faddegon *et al*. Ionization detail parameters and cluster dose: a mathematical model for selection of nanodosimetric quantities for use in treatment planning in charged particle radiotherapy, *Phys Med Biol*, 2023, 68(17):175013.

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Take aways.

Summary

- Extensive work has been performed during decades in the field of nanodosimetry to reveal the potential of this field and to determine the more appropriate approach to calculate, interpret and associate nanodosimetric quantities with biological endpoints.

- It seems reasonable to assert that ionization detail parameters present and opportunity to advance the understanding of radiation therapy and provide the means to apply nanodosimetric quantities in clinical treatment planning.

- We provided a means to compute nanodosimetric quantities in macroscopic volumes, compatible for treatment planning optimization.

- Further analysis of existing experimental data as well as sensitivity analysis with MCTS simulations are required to select a suitable Ip

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