PhD day 2026

Linking ion interaction processes to biological effects in hadrontherapy with the NanOx biophysical model

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- Outline

1. **Context & motivation**
   - Hadrontherapy vs. conventional radiotherapy
   - Relative Biological Effectiveness
   - Objectives

2. **From ion interactions to chemical stage**
   - Ion interactions with matter
   - Stopping power and range
   - Water radiolysis

3. **NanOx biophysical model**
   - Local and global events
   - Influence of physical processes on α
   - Role of Auger electrons

4. **Toward a simplified NanOx model**

5. **General conclusions & future steps**

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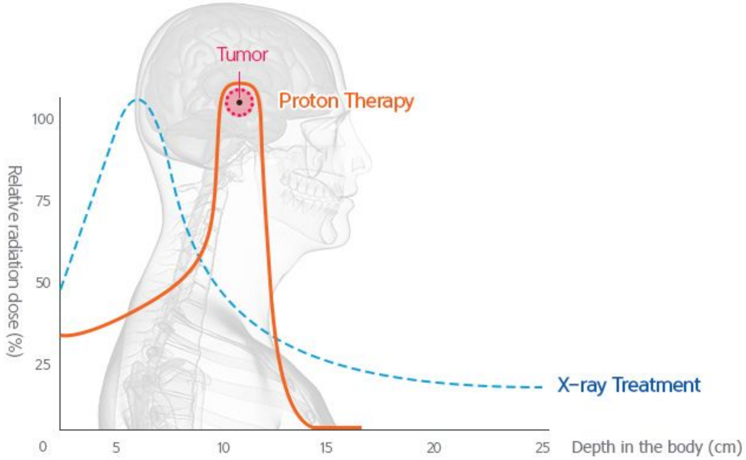
- Hadrontherapy vs. conventional radiotherapy

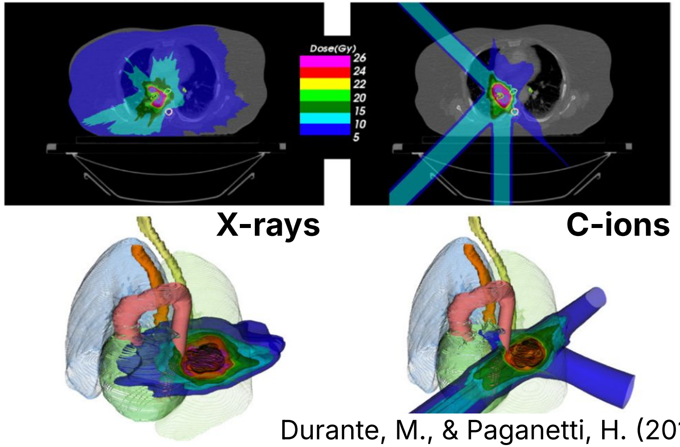
What is hadrontherapy?

Advanced form of radiation therapy that utilizes proton and heavy-ion beams to treat cancer. It represents a significant evolution in cancer treatment, offering enhanced precision and efficacy.

Superior Ballistic Accuracy



Targets Tumors Near Critical Organs and Treats Radioresistant Tumors



Durante, M., & Paganetti, H. (2016)

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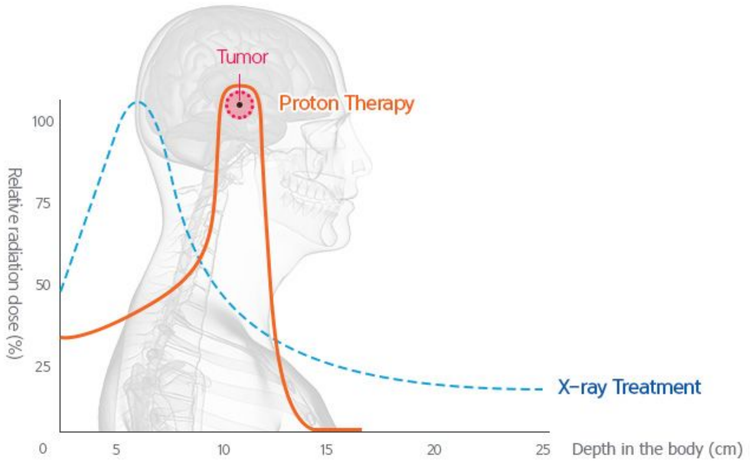

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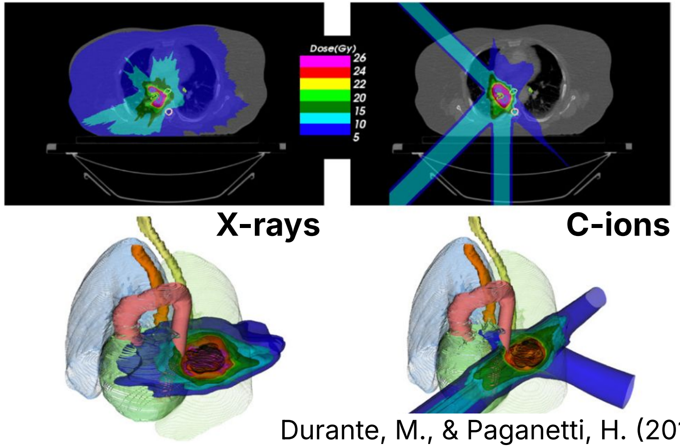

Durante, M., & Paganetti, H. (2016)

$$D_{bio} = D_{phy} \times RBE$$

Biological dose calculation is key for treatment planning

- Relative Biological Effectiveness (RBE)

$$RBE = \frac{D_r}{D_{ion}}\Big|_{isoeffect}$$

⇨ complex function which depends on physical and biological parameters

in clinical practice, RBE is either taken as a fixed value: 1.1 for proton therapy

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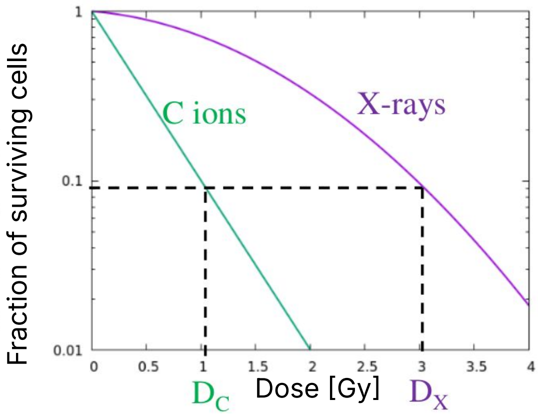
Empirical approaches → cell survival experiments



linear-quadratic fit → $S(D) = e^{-(\alpha D + \beta D^2)}$

limitations

- Purely phenomenological
- Fails for high-LET clustering

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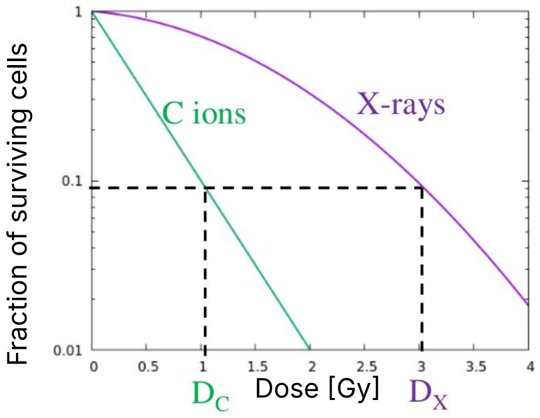

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Theoretical methods → biophysical models

Mathematical formalism used to predict the biological effects of ionizing radiation.

- LEM I
- mMKM

} currently implemented in Treatment Planning System (TPS) of hadrontherapy facilities

- **NanOx** → developed in IP2I - PRISME group

Biological endpoints: probability of cell survival

- Objectives

Main goal:

Establish a closer link between ion interaction processes and NanOx predictions to enable a simplified model suitable for clinical TPS.

To achieve this I have to:

1. Model the interaction physics

ion cross sections on targets of biological interest

2. Derive macroscopic dosimetric quantities

- stopping power
- range

3. Assess the impact on:

- chemical yields
- cell survival parameters

4. Bridge to NanOx

- correlations
- model simplification

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- Ion interactions with matter

Inelastic processes in the physical stage (<10^{-16} s):

Ionization (single & multiple)	ejection of one or more electrons, produces secondary δ-electrons
Electronic excitation	target molecule promoted to excited state without ionization
Electron capture	projectile captures a target electron
Electron loss	projectile loses an electron

cross sections

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cross sections

↓

calculated with semi-empirical models

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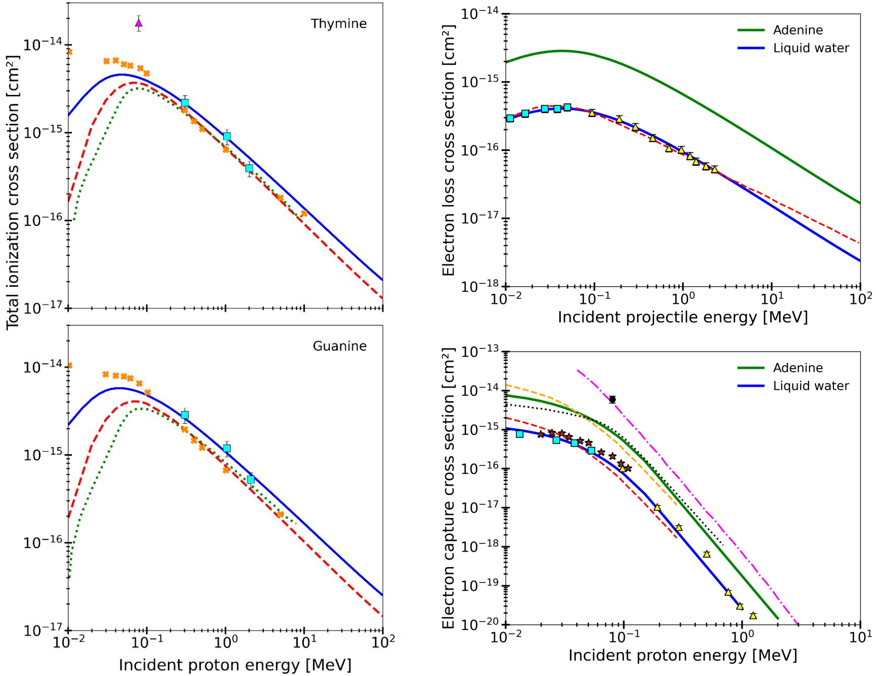
for liquid water, and DNA/RNA nucleobases

For protons:

Strubbia Mangiarelli et al. (2025)



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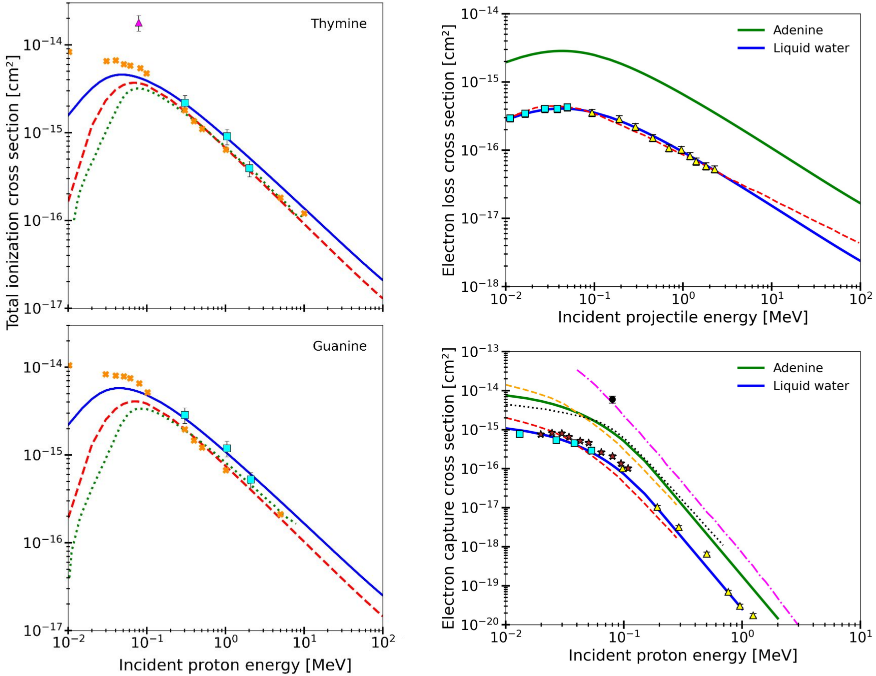

→ Cross sections are the fundamental input to Monte Carlo simulations and determine all subsequent biological predictions

- Stopping power and range

$$S(E) = -\frac{dE}{dx}$$ → mean energy loss per unit path length

$$R_{CSDA} = -\int_{E_i}^{0} \frac{dE}{S(E)}$$ → depth at which the ion stops → location of the Bragg peak

the Bragg peak position must be predicted to within ~1 mm for treatment planning, errors here directly misplace the dose

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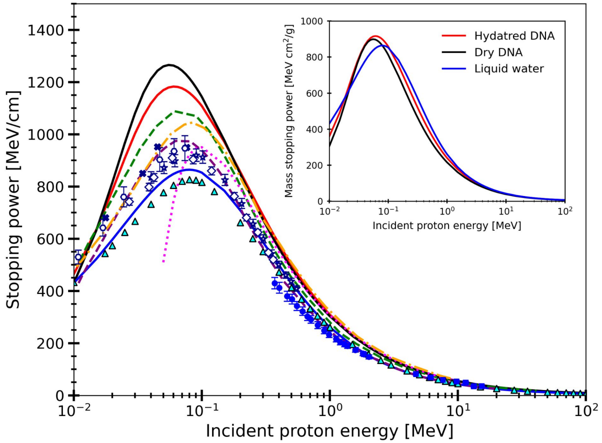

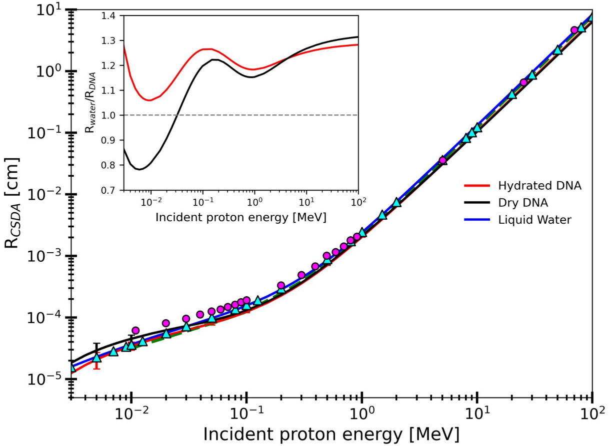

Strubbia Mangiarelli et al. (2025)

- Stopping power differences with liquid water: up to 60% (dry DNA), 40% (hydrated DNA)
- Even after density normalization → 25–30% shift in position of the maximum (for S)
- Water as surrogate ≠ DNA → risk of misrepresenting damage
- Explicit DNA modeling is a good way to improve accurate hadrontherapy predictions

- Water radiolysis

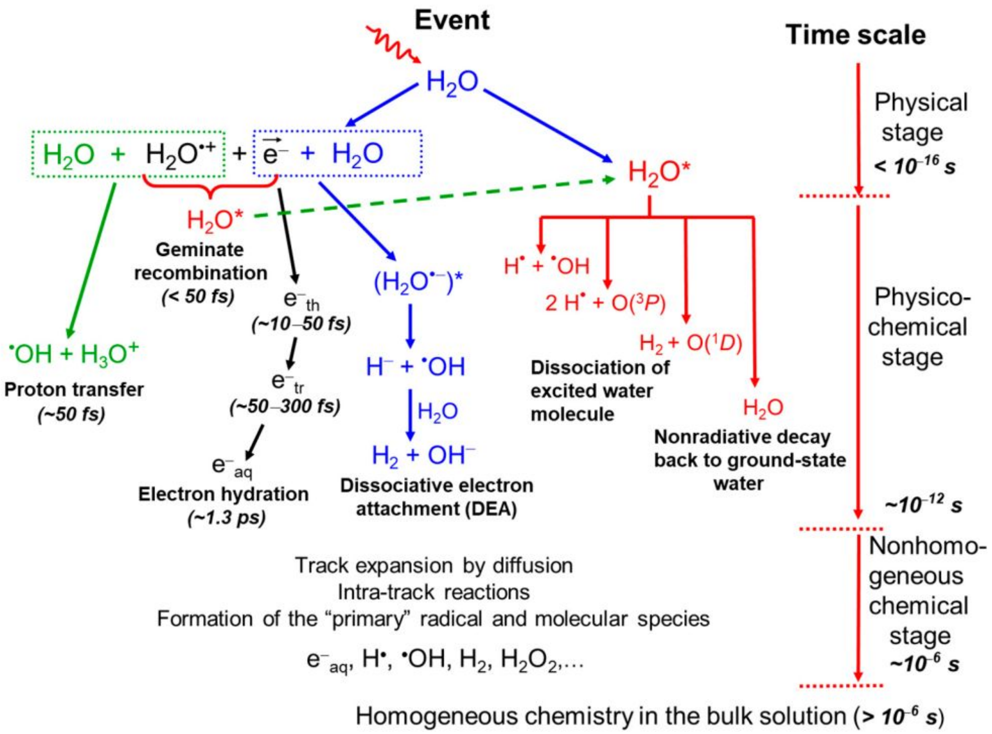

Diagram: The time scale of events in the water radiolysis at low LET. The figure is divided into three distinct consecutive stages: physical, physicochemical, and chemical.

Jay-Gerin, J.-P. (2025)

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- NanOx biophysical model

NanOx → Nanodosimetry and Oxidative stress

→ Predicts cell survival to ionizing radiation
→ Considers:

- The stochastic nature of energy deposition (micro- and nano-scales)
- Sublethal damage and oxidative stress induced by free radicals (e.g., $^{\bullet}OH$)

→ Has two types of biological events:

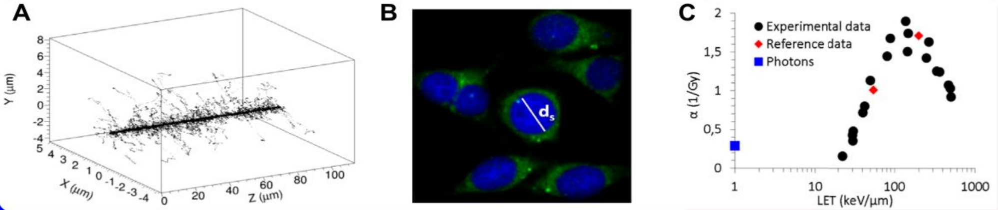
- Local lethal events (LLE)
- Global events (GB)

→ Outputs: cell survival parameters (α,β)

The NanOx model (hadrontherapy implementation)

INPUT

	Data (MC simulations and biological measures)	NanOx Scale	Input	Main param.
Physico-chemical	- Spatial distribution of energy transfer points and radical species ⇒ configuration c_k - c_K: combination of K configurations c_k	Nano	${}^{ck}z$	
		Micro	${}^{tk}RCE$, ${}^{ck}Z$	
		Macro	D, K	
Biological	- Cell geometry from microscopy images	Micro	d_s	
	- Experimental α and β coefficients	Macro	(α_r, β_r) α_{int}, α_{high}	(α_G, β_G) σ, h, z_0



MEAN CELL SURVIVAL FRACTION AT DOSE *D*

$\overline{S(D)} = \sum_{k=0}^{\infty} P(K,D) \cdot \langle {}^{c_K}S \rangle_{c_K}$ where ${}^{c_K}S = {}^{c_K}S_{\mathrm{L}} \times {}^{c_K}S_{\mathrm{G}}$ and $\langle {}^{c_K}S \rangle_{c_K}$ is the survival fraction ${}^{c_K}S$ averaged over **all radiation configurations C_K generated with MC simulations**

Alcocer-Ávila et al. (2022)

- Local and global events

LOCAL LETHAL EVENTS

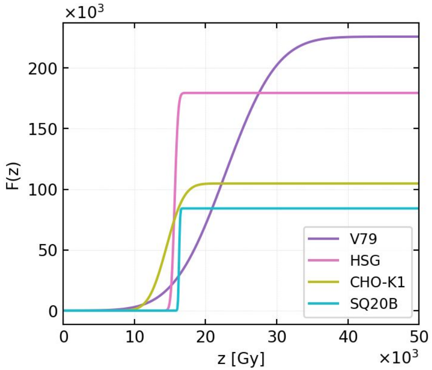
Example: irreparable DNA damage
Modeling: inactivation of 1 among *N* nanometric targets. The cell survival S_L is expressed via an effective function *F* characterizing the response of each cell line to the restricted specific energy deposited in targets (^{ck}z):

$$^{c_K}S_L = \prod_{k=1}^{K} \exp(-F(^{c_k}z))$$

EFFECTIVE LOCAL LETHAL FUNCTION (ELLF) →

$$F(z) = \frac{h}{2}\left[1 + erf\left(\frac{z - z_0}{\sigma}\right)\right]$$

(z_0, σ, h) determined from a fit of experimental values of the linear parameter α (Monini et al. (2020))
z_0: threshold energy,
σ: width of the transition region,
h: saturation level



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GLOBAL EVENTS

Example: oxidative stress due to accumulation of reactive chemical species
Modeling: cell survival S_G computed from the chemical specific energy:

$$^{c_K}\tilde{Z} = {}^{c_K}\mathrm{RCE} \cdot {}^{c_K}Z$$

$$^{c_K}S_G = \exp\left(-\alpha_G {}^{c_K}\tilde{Z} - \beta_G {}^{c_K}\tilde{Z}^2\right)$$

EFFECTIVE LOCAL LETHAL FUNCTION (ELLF) →

$$F(z) = \frac{h}{2}\left[1 + erf\left(\frac{z - z_0}{\sigma}\right)\right]$$

relative chemical effectiveness → $^{c_K}RCE = \frac{^{c_K}G}{G_r}$

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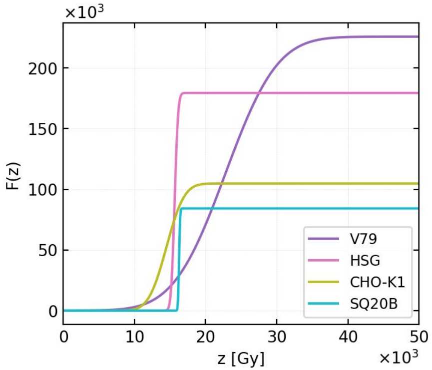
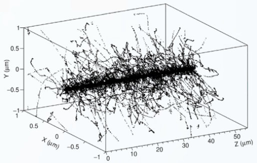


- **Chemical yield G**: number of reactive chemical species generated per 100 eV.
- Currently, only primary hydroxyl radicals (•OH) produced at time $T_{RCE}=10^{-11}$ s are considered for calculation of cell survival fraction.

- First study: Influence of core ionization processes on cell survival calculated with NanOx

MC simulations
LPChem code
(Gervais et al. (2006)



Physical and physico-chemical stages of ion impact on water molecules

Modifications to consider different physical scenarios:

- Without 1s ionization
- Without Auger emission: all energy deposited locally
- Without tracking Auger electrons: energy considered lost

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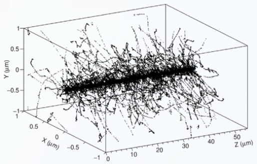

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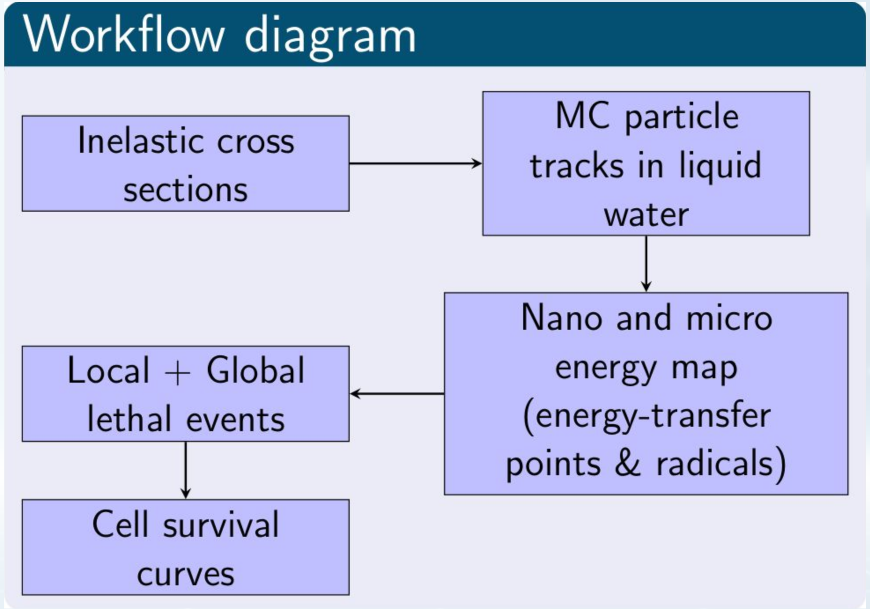
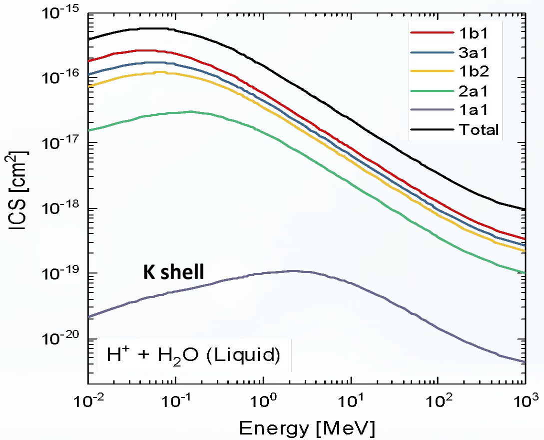


- Post-collisional Auger e⁻ emission: why does it matter?

The significance of this effect does not stem from its low probability of occurrence (less than 1%), but rather from the kinetic energy of the emitted Auger electron.

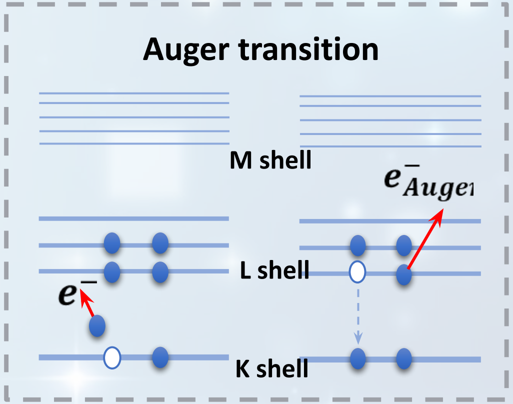


- The probability of ionizing the innermost shell of the molecule is very low

$$\langle E \rangle = \frac{\sum_{j=1}^{5} \int \epsilon \ d\sigma_j / d\epsilon \ d\epsilon}{\sigma_{Total}} \cong 40\ eV$$

Average kinetic energy of electrons emitted

$$E_{Auger} = |B_{2a1} - B_{1a1}| - B_{2a1} \cong 470\ eV$$



$E_{Auger} > \langle E \rangle$ thus can produce further ionizations

H_2O

Mol. orbital	
$1a_1$	540.0
$2a_1$	33.30
$1b_2$	16.60
$3a_1$	14.70
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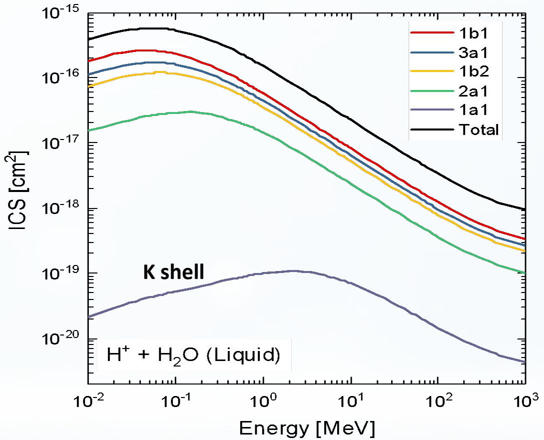

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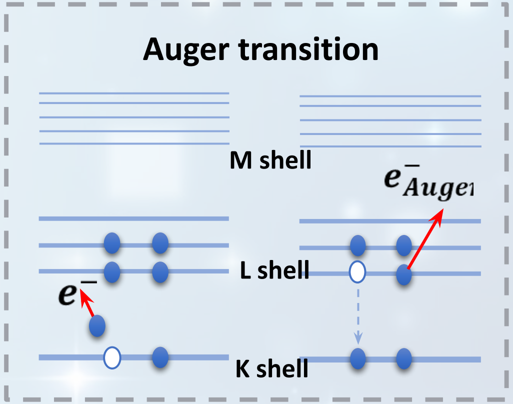

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Moreover, since the Auger process occurs after the collision, it does not involve energy loss from the projectile itself and this is why it doesn't impact on the stopping power

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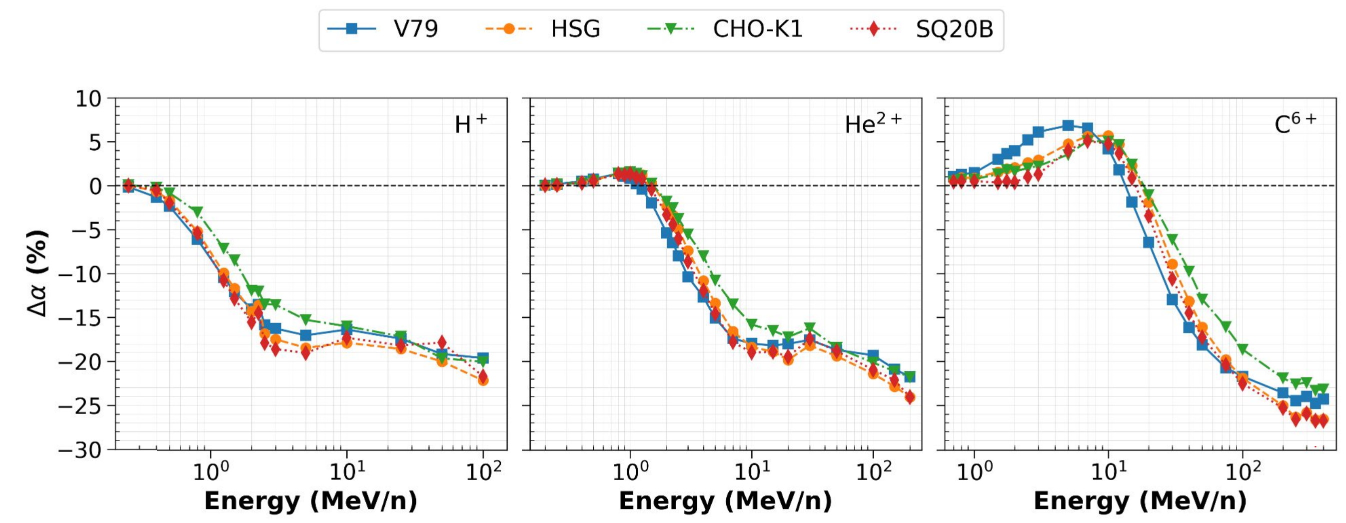
- Results: effect of physical processes on α value

Suppressing 1s ionization



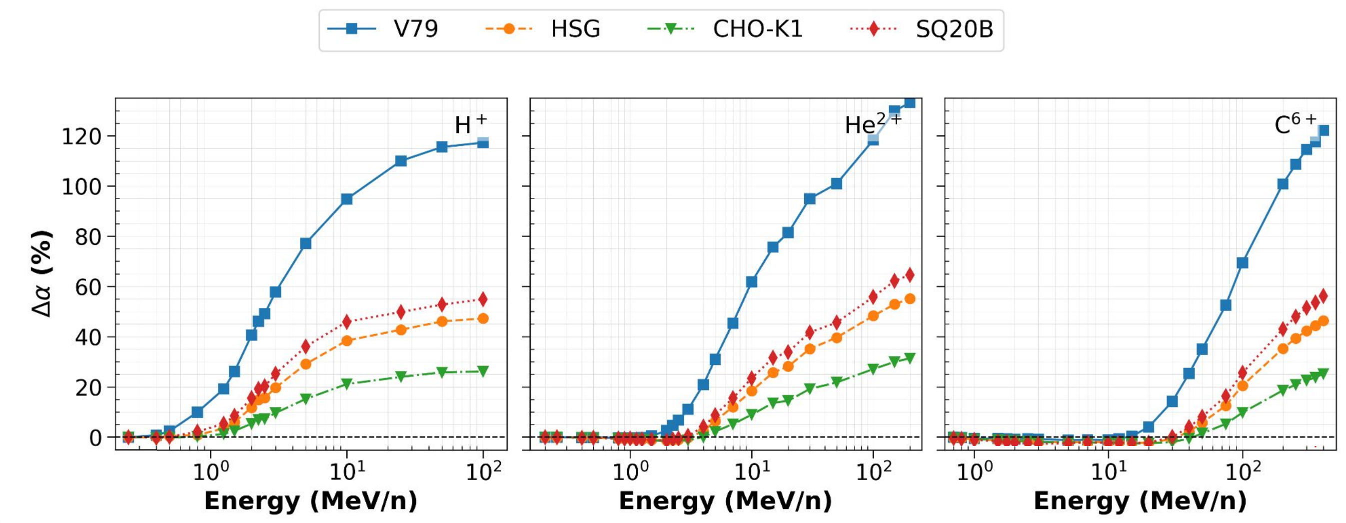
* 1s ionization contributes up to 26.6% to α, effect grows with energy as LET decreases and localized deposits become more critical

$\Delta\alpha = (\alpha_{mod} - \alpha_{full})/\alpha_{full} \times 100$. Statistical uncertainty below 2% in all cases.

Lower LET → sparse energy deposits → highly localized 1s electrons matter more → suppressing them reduces z → fewer LLE → lower α

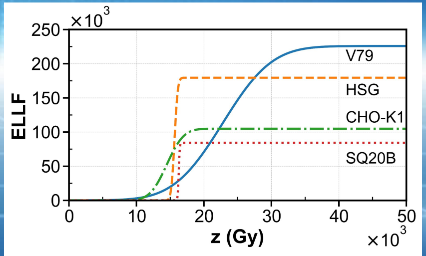
- Results: effect of physical processes on α value

Suppressing Auger emission



$\Delta\alpha = (\alpha_{mod} - \alpha_{full})/\alpha_{full} \times 100$. Statistical uncertainty below 2% in all cases.

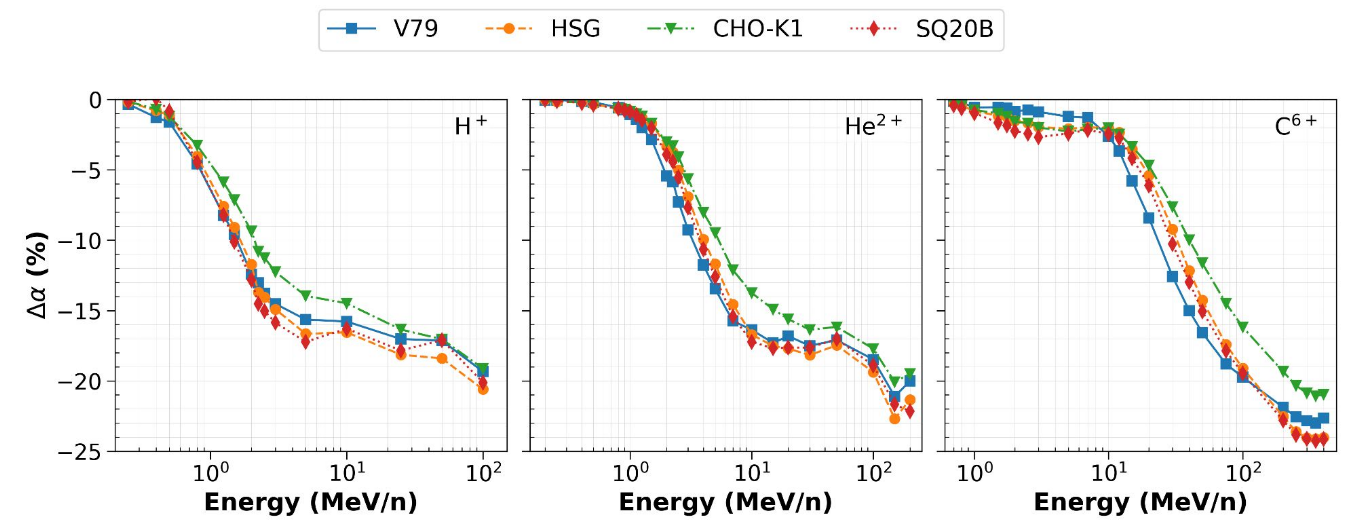
* Largest effect: up to 133% increase in α (He^{2+}, V79); strongly correlated with z_o threshold of each cell line



Auger emission suppressed → relaxation energy stays local → z overestimated → ELLF activated more → α artificially increased. Effect largest in V79 (highest z_o)

- Results: effect of physical processes on α value

No tracking Auger electrons



* ~15–20% reduction in α — Auger energy escapes nanometric volume, reducing z and LLE probability

$\Delta\alpha = (\alpha_{mod} - \alpha_{full})/\alpha_{full} \times 100$. Statistical uncertainty below 2% in all cases.

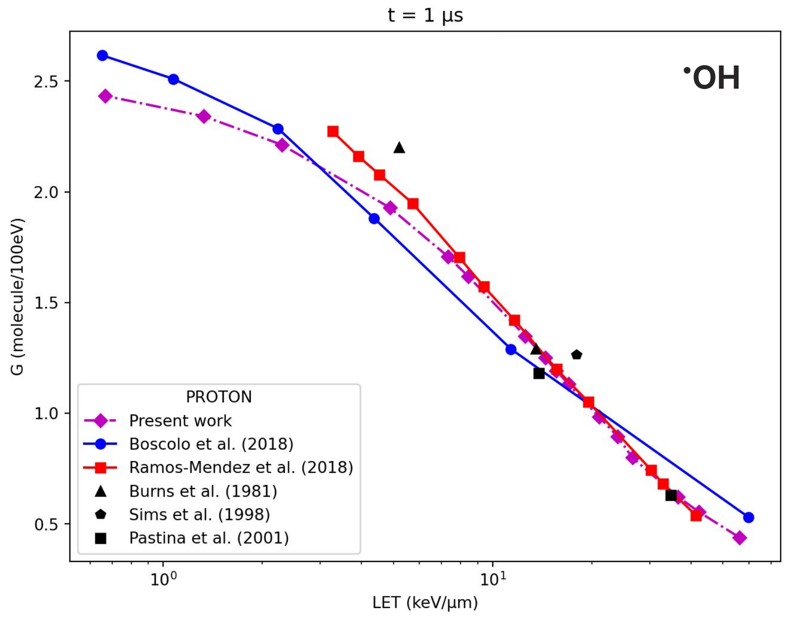
Auger electrons emitted but not tracked → energy carried away from nanometric volume → z reduced → fewer targets reach lethal threshold → lower α

- Results: effect of physical processes on G-value

Work in progress !

- **Preliminary baseline results:** G(•OH) decreasing with increasing LET, is consistent with experimental data, which validates our simulation framework.

- The **next step** is to apply the same physical modifications — suppressing 1s ionization, Auger emission, and Auger tracking — and quantify how each one affects G.



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- Correlation between physical parameters and NanOx

Work in progress !

- NanOx requires Monte Carlo simulations at micro/nano scales.
- These simulations are computationally expensive and time-consuming.
- Our goal: build a “fast version” of NanOx.
- Idea: **replace part of the MC workflow** with an **AI-based predictive model**.

Introducing α_{core}

- NanOx splits an ion track in two regions:
  - **core** → high-density energy-deposit
  - **penumbra** → low-density δ-ray

- In the core region ⇒ the linear coefficient α_{core} quantifies:
  - the number of LLE per unit of restricted energy deposited
  - how efficiently core-region energy deposition produces lethal nanometric damage (e.g., irreparable DNA lesions)

$$ {}^{t_N,t_k}\alpha_{core} = \int_0^{+\infty} \underbrace{\frac{1}{{}^{t_i}z_c^{hit}}\;{}^{t_i,c_k}\left[\frac{dP}{dz}\right]_c^{hit}}_{\text{MC simulation}} \underbrace{{}^{t_N}F(z)}_{\text{ELLF}}\; dz $$

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↓

$$ \alpha_{core} = a\sigma + bS_{res} + \dots $$

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- Conclusions & future steps

✓ **Conclusions:**

- **Cross sections** → calculated and validated for protons on H_2O and DNA/RNA bases; good agreement with experiment (Strubbia Mangiarelli et al. 2025)
- **Stopping power** → differs up to 60% from liquid water; water-as-surrogate introduces real dosimetric error
- **Cell survival (α)** → 1s ionization: up to 26.6% effect; Auger emission: up to 133%, correlated with z_0 threshold

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→ Next steps:

1. Integrate proton cross sections in DNA into Geant4-DNA
2. Complete G(•OH) sensitivity study across all physical scenarios and ion species
3. Establish α_{core} ↔ correlations → simplified NanOx
4. Train AI/ML surrogate → fast NanOx for clinical TPS

Thanks for your attention

Questions?

Appendix

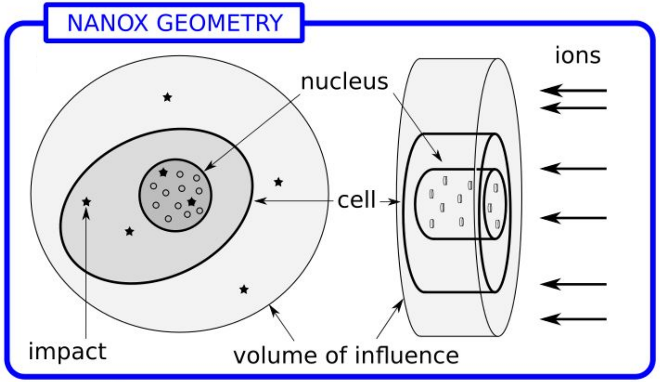
- NanOx for hadrontherapy

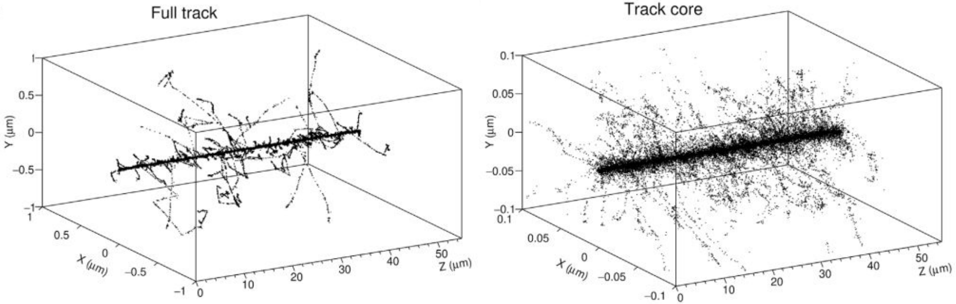
Premises:

- One sensitive volume (SV): cell nucleus
- SV with cylindrical geometry and incident beam parallel to the SV axis
- Irradiation under 'track segment' conditions
- Core and penumbra at the ion track

Input parameters:

- SV diameter
- Coefficients α_r and β_r, for reference radiation (e.g., γ photons of ^{60}CO)
- Parameters (z_0, σ, h) of the effective local lethal function (ELLF), used to calculate S_L





Alcocer-Ávila et al. (2023): 2.6 MeV proton track and a zoom of its core

- Cell lines considered

Alcocer-Ávila et al. 10.3389/fphy.2022.1011063

TABLE 1 Values of the parameters used to model the cell lines V79, CHO-K1 and HSG with NanOx. d_s and L_s represent the sensitive volume diameter and length, respectively. Similarly, d_t and L_t are the local targets' diameter and length, respectively. T_{RCE} is the time at which the concentration of $^{\bullet}OH$ radicals is considered.

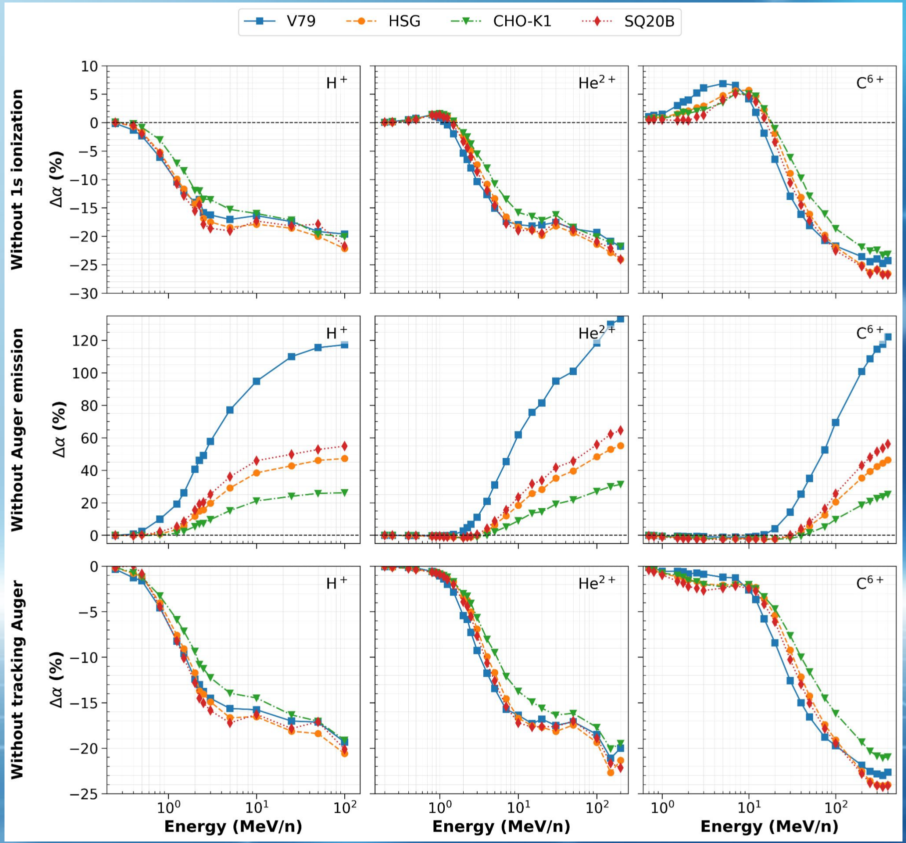
Event class	Parameters	V79 cells Chinese-hamster lung fibroblast	CHO-K1 cells Chinese-hamster ovary	HSG cells human salivary-gland
Local/Global	d_s (μm)	9.8	11.8	14
	L_s (μm)	1.0	1.0	1.0
Local	z_0 (Gy)	22,789	14,507	15,654
	σ (Gy)	8117	2781	549
	h	225,841	104,810	179,439
	d_t (nm)	20	20	20
	L_t (nm)	10	10	10
Global	β_G (Gy^{-2})	0.0405	0.0625	0.0961
	α_G (Gy^{-1})	0	0	0
	T_{RCE} (s)	10^{-11}	10^{-11}	10^{-11}

SQ20B (human squamous cell carcinoma, head-and-neck radioresistant cell)

Appendix

- Results: effect of physical processes on α value

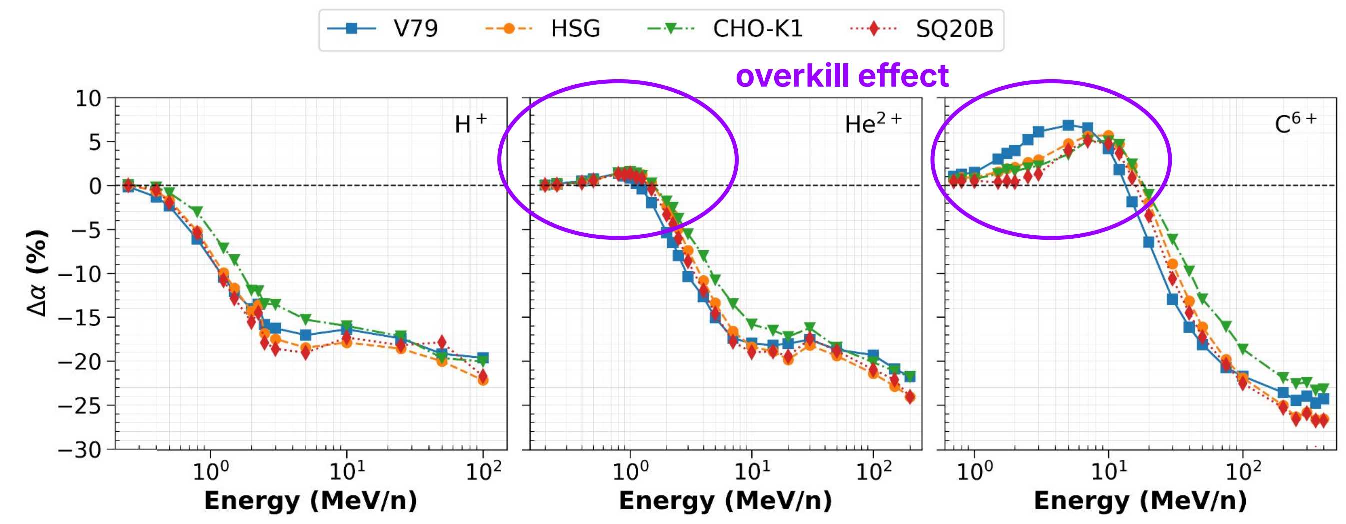
Relative percentage difference in the α parameter with respect to the full model, defined as $\Delta\alpha = (\alpha_{mod} - \alpha_{full})/\alpha_{full} \times 100$, for protons, helium, and carbon ions as a function of projectile energy. Results are shown for the four analyzed cell lines: V79, HSG, CHO-K1, and SQ20B. Symbols represent the calculated values, and lines are included only to guide the eye. Statistical uncertainties in Δα are below 2% in all cases.



Appendix

- Results: effect of physical processes on α value

Suppressing 1s ionization



* 1s ionization contributes up to 26.6% to α, effect grows with energy as LET decreases and localized deposits become more critical

$\Delta\alpha = (\alpha_{mod} - \alpha_{full})/\alpha_{full} \times 100$. Statistical uncertainty below 2% in all cases.

Lower LET → sparse energy deposits → highly localized 1s electrons matter more → suppressing them reduces z → fewer LLE → lower α

Appendix

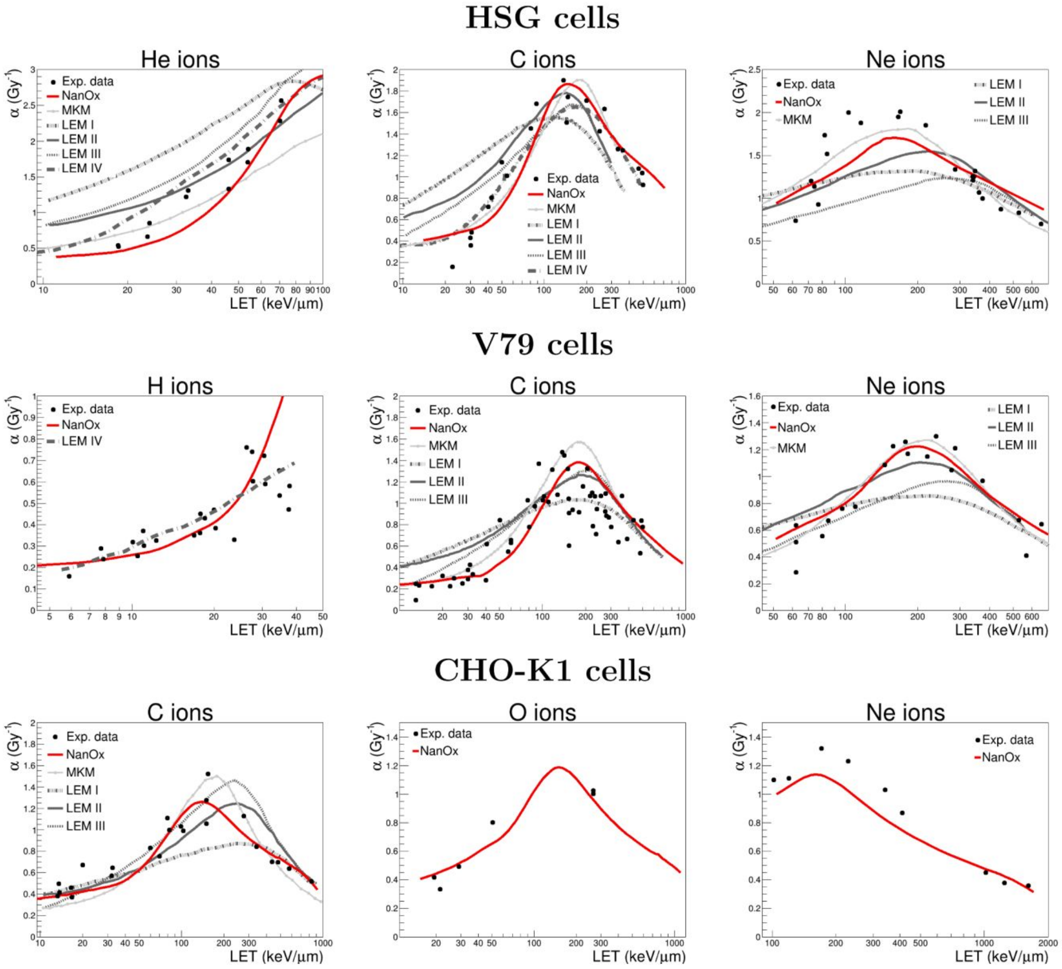
- Why NanOx? Limitations of existing models

Limitations of existing models (LEM, MKM, BIANCA...)	How NanOx closes the gaps
Single scale Operate at microscopic dose or domain level, ignore nanometric clustering of ionizations critical for high-LET damage	**Multi-scale track-structure** Full stochastic track-structure (core + penumbra) down to 10 nm targets, explicit nanometric energy clustering
Implicit chemistry Treat indirect effects ($^{\bullet}OH$ radicals) without any quantitative link to actual radical chemistry or track-dependent G-values	**Explicit radical chemistry** Computes chemical yield $G(^{\bullet}OH)$ from MC simulations, direct quantitative link between radical production and cell survival
Poisson statistics Assume Poisson distribution for lethal events, valid for sparse photon deposits, but breaks down for densely ionizing ion tracks	**Two-component stochastic model** Separates local lethal events (nanometric inactivation) from global events (oxidative stress), no Poisson assumption needed
Ad-hoc corrections Cannot predict RBE across different particles without empirical re-fitting for each new condition	**Mechanistic RBE prediction** Predicts RBE across diverse radiation qualities and cell lines without ad-hoc corrections, using the ELLF and LQ global component

NanOx provides a multiscale, physics-based description that predicts RBE for diverse radiation qualities, something earlier models cannot achieve without ad-hoc corrections.

Appendix

- Comparison of biophysical models with experimental data



Monini et al. (2019)