Improvement of the prediction of biological effects for Targeted Alpha Therapy

Victor Levrague[1], Mario Alcoler-Avila[2], Lydia Maigne[3], Michaël Beuve[2], Etienne Testa[2] and Rachel Delorme[1]

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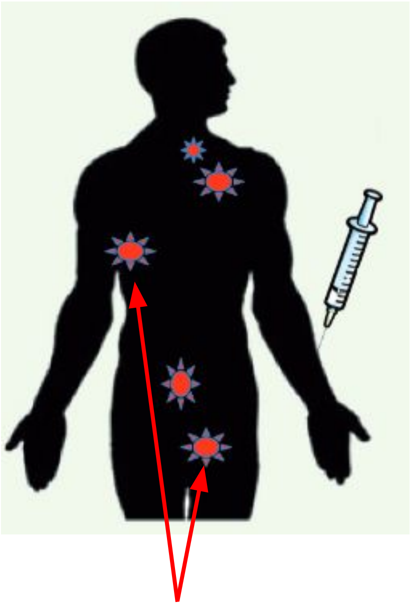
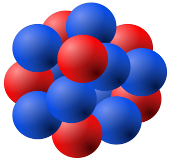
3: LPC, Clermont-Ferrand

Targeted Alpha Therapy : an innovative internal radiotherapy

Radiotherapy: treat a disease, usually **cancer**, using **ionizing** beams

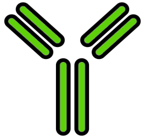


Cancer sites



Alpha-emitter radionuclide

+



Targeting molecule (e.g. antibody)

- ❖ Mean alpha energies : **5-10 MeV**
- ❖ Mean path length : 40-100 µm **(few cells)**

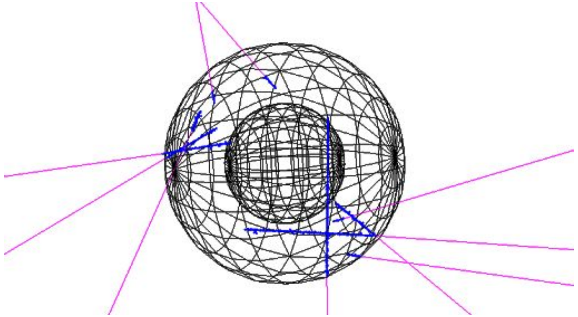
Alpha ionization ⇒ **DNA damage** ⇒ **Cell death**

Micrometric scale *Nanometric scale*

Prediction of biological effects in Targeted Alpha Therapy

Targeted Alpha Therapy : an internal radiotherapy

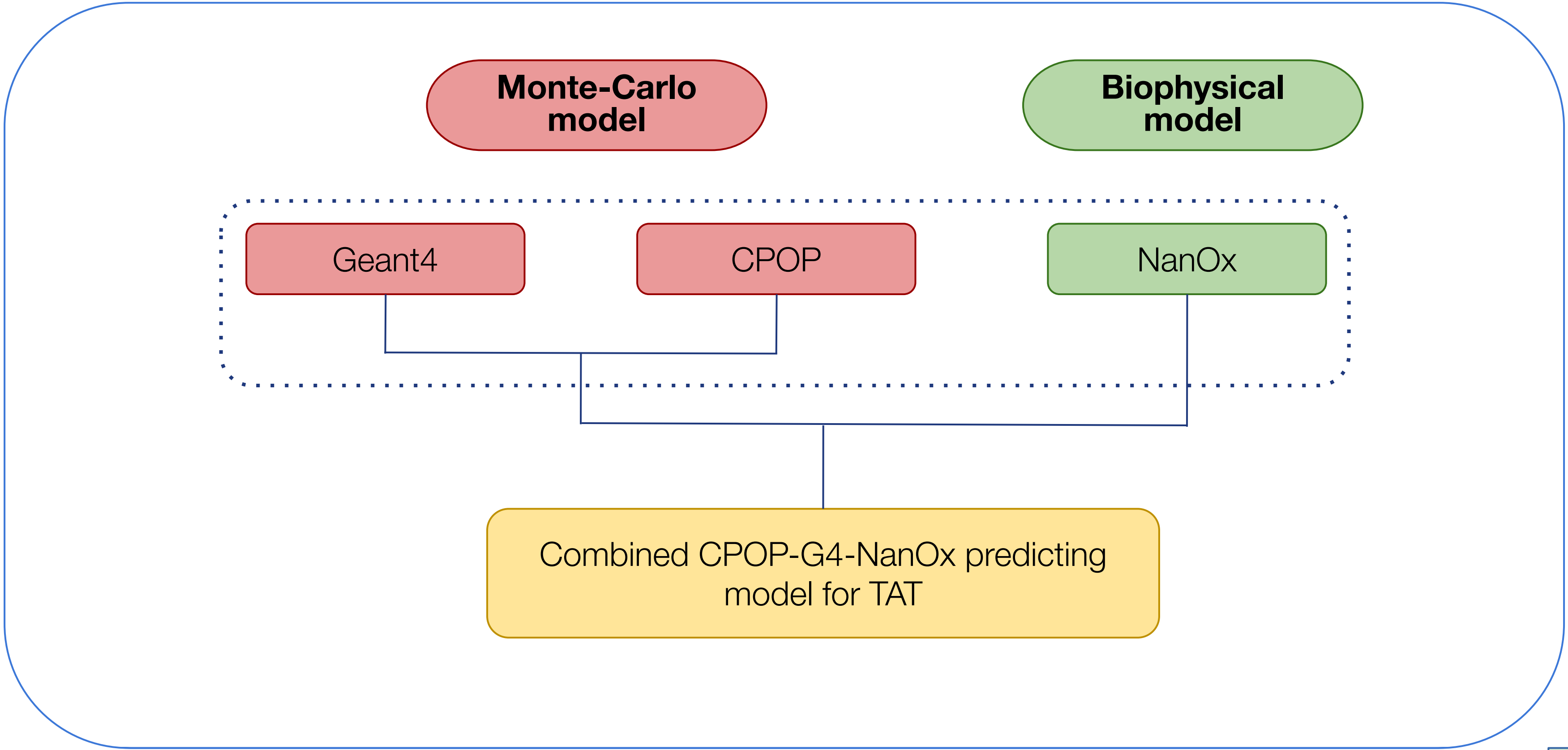
- No direct control of the irradiation
- Heterogeneous tissular dose deposition
- Heterogeneous cellular dose deposition, because of short range of alpha particles (few µm)



Homemade Geant4 simulation on a cell irradiated by alpha particles

Uniform physical dose is not enough to predict biological effects

Prediction model overview



Monte-Carlo model

Biophysical model

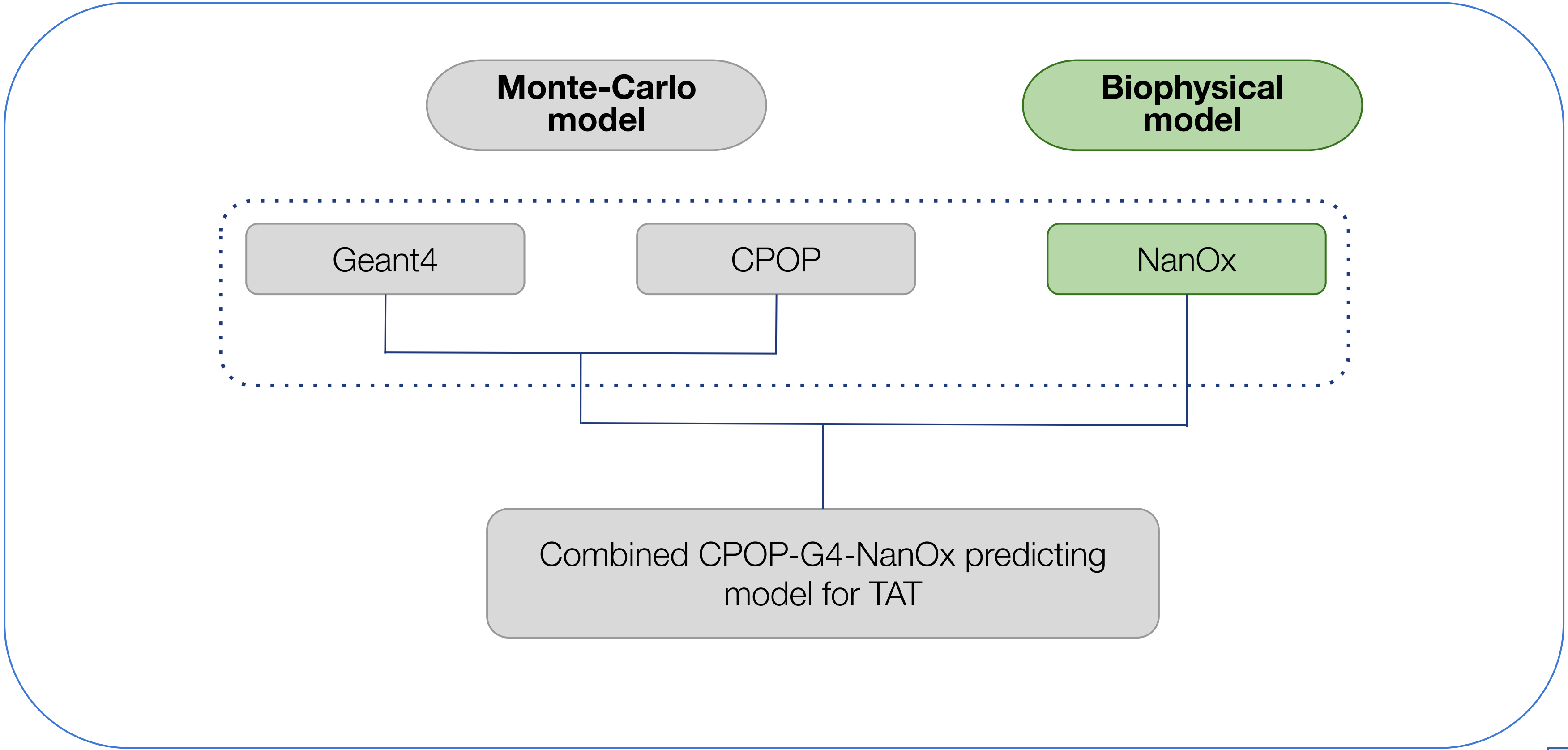
Geant4

CPOP

NanOx

Combined CPOP-G4-NanOx predicting model for TAT

Prediction model overview



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The biophysical model NanOx (1/2)

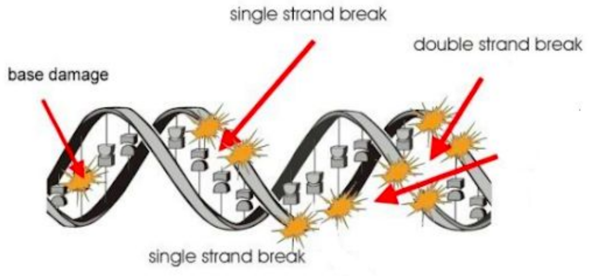
Nanodosimetry: Lethal damage

Microdosimetry: Sublethal damage

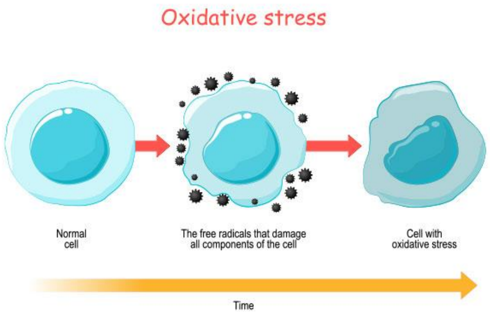
Cell survival prediction

α(E) radiobiological coefficient

β(E) radiobiological coefficient

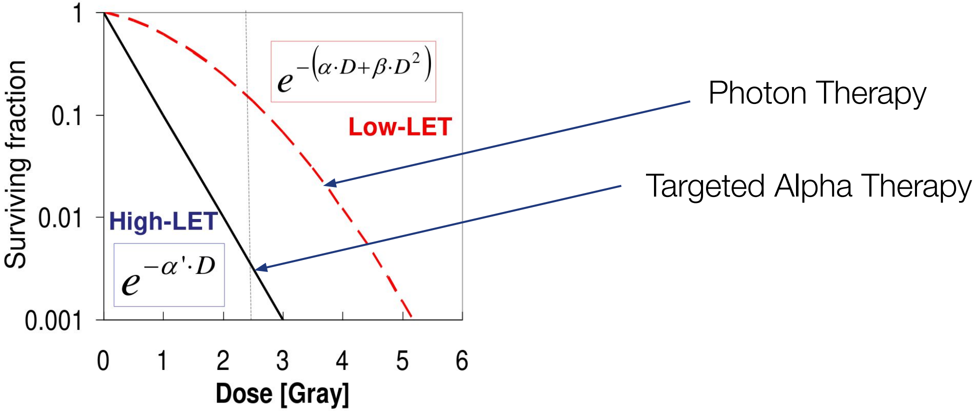


Simple and complex damage that can occur in dna with ionization



From Helvetica Health Care website

The biophysical model NanOx (2/2)



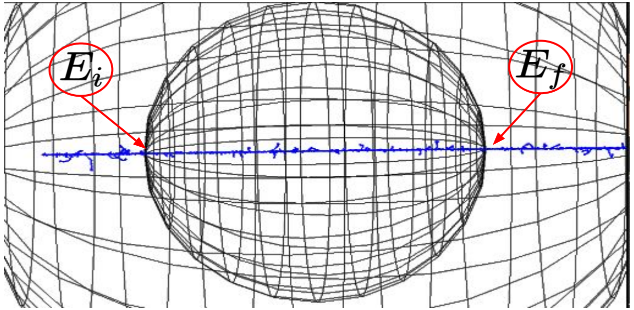
Cell survival curve for low and high LET particles

- Nucleus : only **sensitive volume** = only damage in nucleus induce cell death
- Works for **specific cell lines**, depending on **experimental data**
- **NanOx :** Experimentally calibrated & validated for **hadrontherapy** *(50 - 400 MeV/n)*

NanOx “low energy” formalism

Cell survival to lethal events:

$$S_{lethal} = \exp\left(-\sum_{E_k^i} n(E_k^i)\right)$$



Geant4 simulation of an helium ion crossing a cell nucleus

NanOx “low energy” formalism

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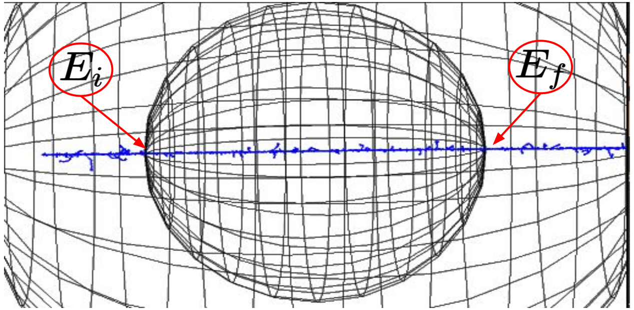
Density of lethal events per energy:

$$\frac{dn}{dE}(E) = -\frac{\ln\left(1 - \alpha(E)\cdot a \cdot LET(E)\right)}{L \cdot LET(E)}$$



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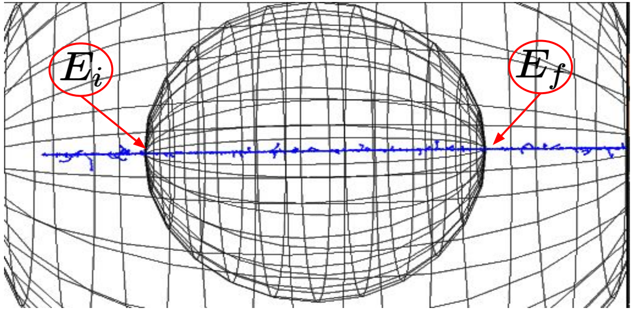

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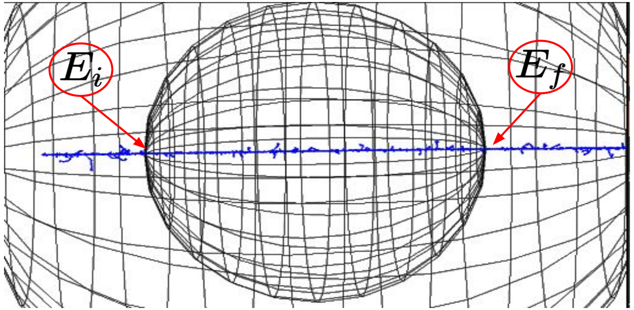
Number of lethal events:

$$n\left(E_k^i,\, E_k^f\right) = \int_{E_k^f}^{E_k^i} \frac{dn}{dE}(E)\cdot dE$$



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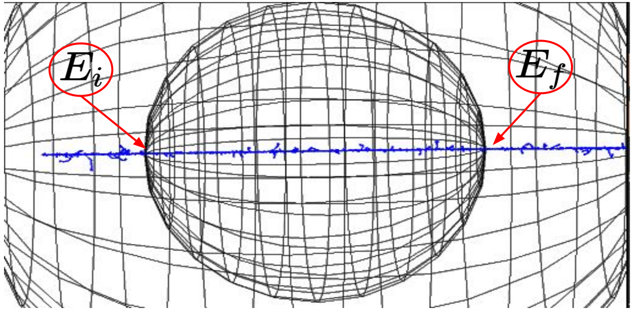
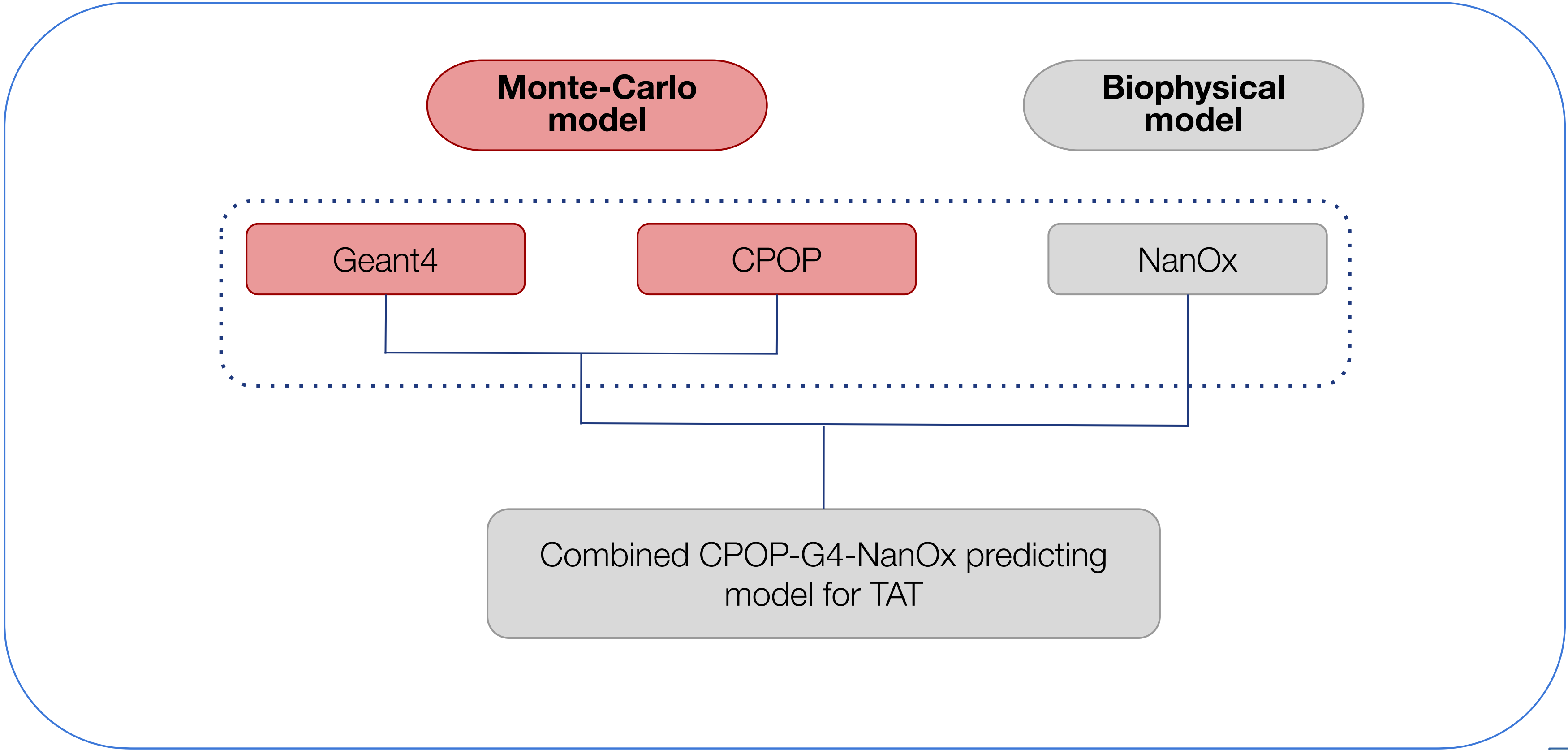


Geant4 simulation of an helium ion crossing a cell nucleus

$$S_{total} = S_{lethal} \cdot S_{global}$$

Python module *nanox_low_energy* available

Prediction model overview


Monte-Carlo model

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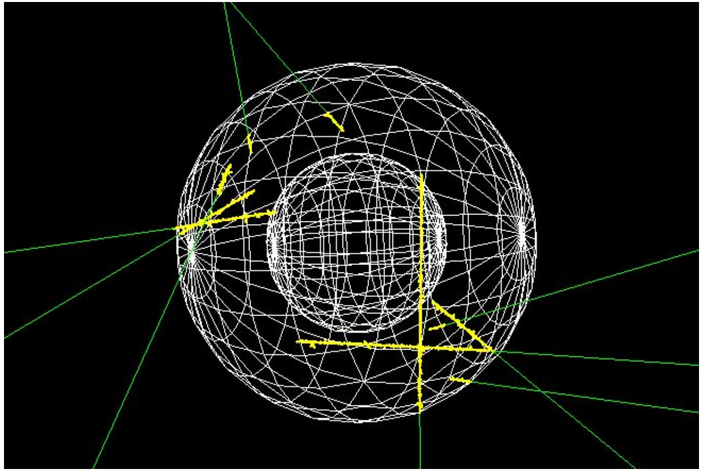
Combined CPOP-G4-NanOx predicting model for TAT

Geant4 simulations

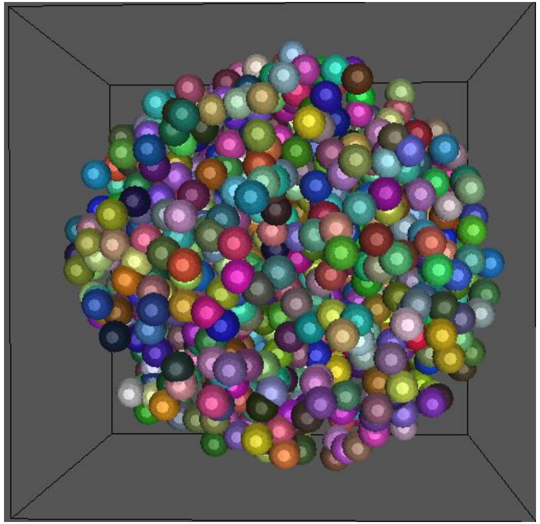
- Open source track-structure Monte-Carlo model
- Tracking of **alpha** particles until 1 keV
- Low energy electromagnetic **physics list**

- **Output :**
  - Physical doses in **nuclei** and cells
  - In **(E^i)** and out **(E^f)** energies of alpha particles in **nuclei**
    - To calculate **cell survivals**



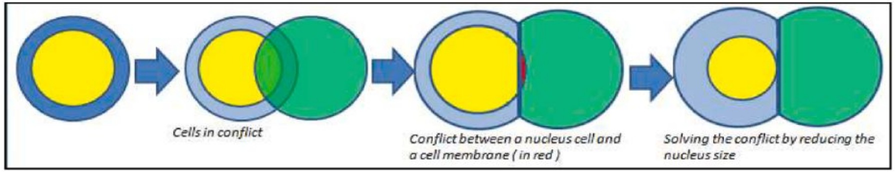
Homemade Monte-Carlo simulation of 10 helium ions emitted in the cytoplasm

Complex geometry generation: CPOP



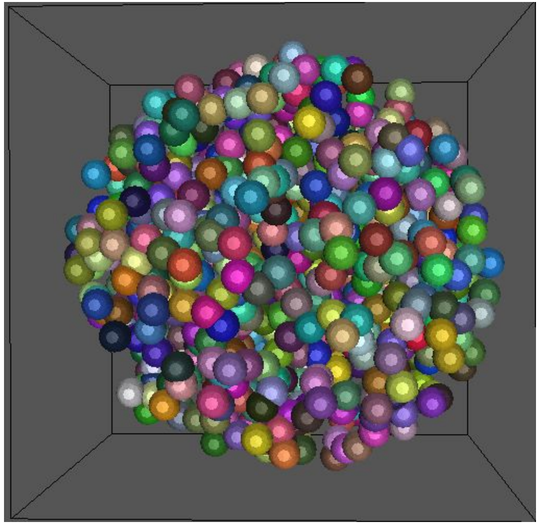
95 µm radius Spheroid generated by CPOP

- Open-source tool that can generate **highly compacted multi-cellular** geometries, with realistic **cell deformation management**
- Based on **Geant4**



Maigne et al. 2021

Complex geometry generation: CPOP



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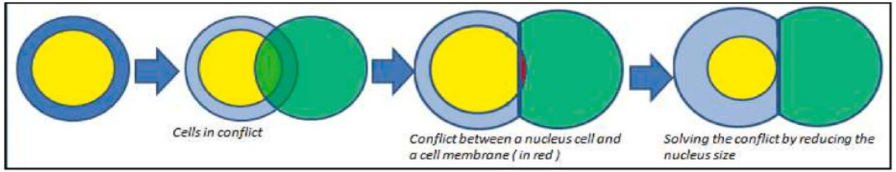
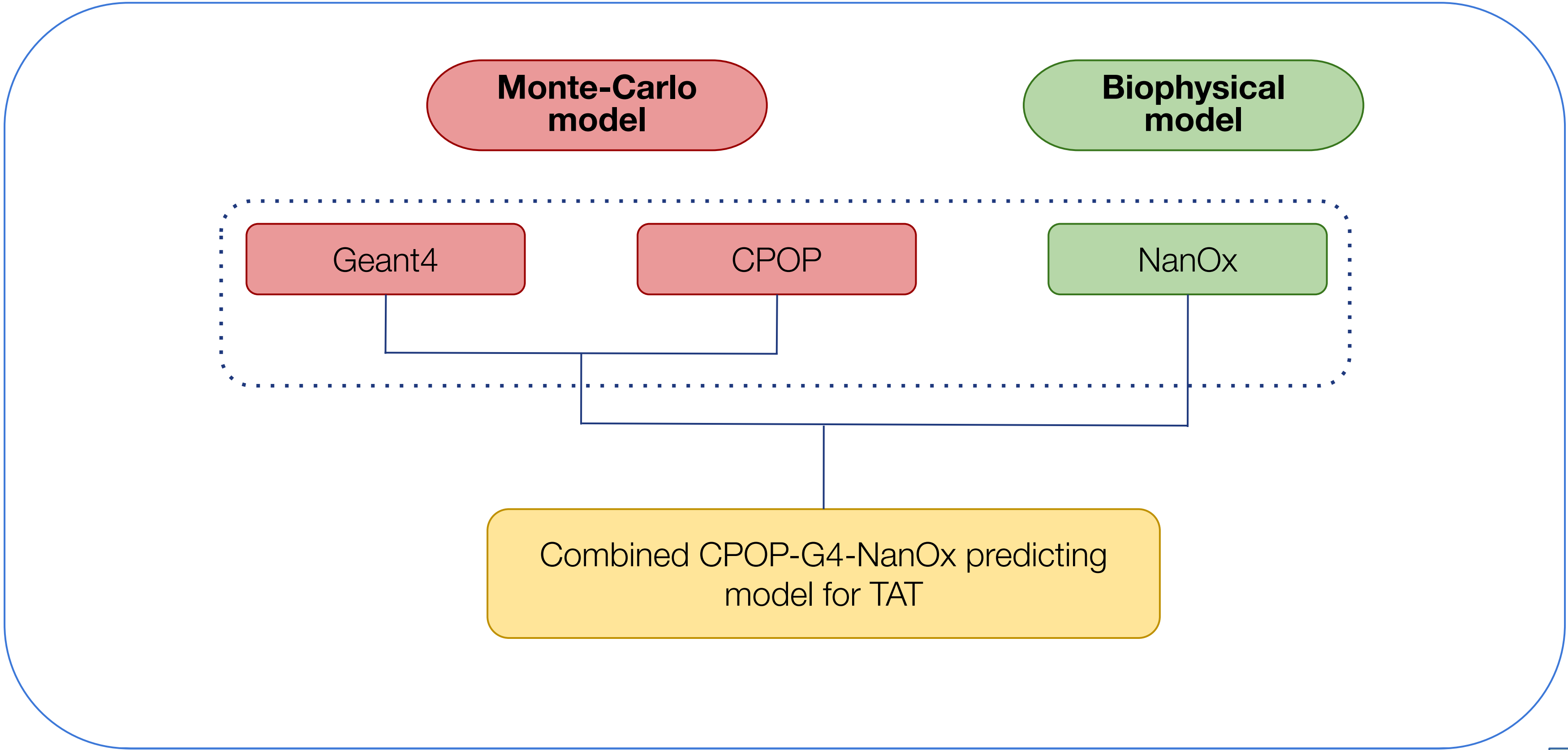


Maigne et al. 2021

- My work: **enhance** CPOP with new functionalities, **updating** the **GitHub** repository and **adapting** the model for **Targeted Alpha Therapy** and the **Geant4 release**
- Collaboration with Lydia Maigne & Alexis Pereda (LPC Clermont)
- **Available** in **GitHub**, and soon in an **official example** of **Geant4**

Prediction model overview



Monte-Carlo model

Biophysical model

Geant4

CPOP

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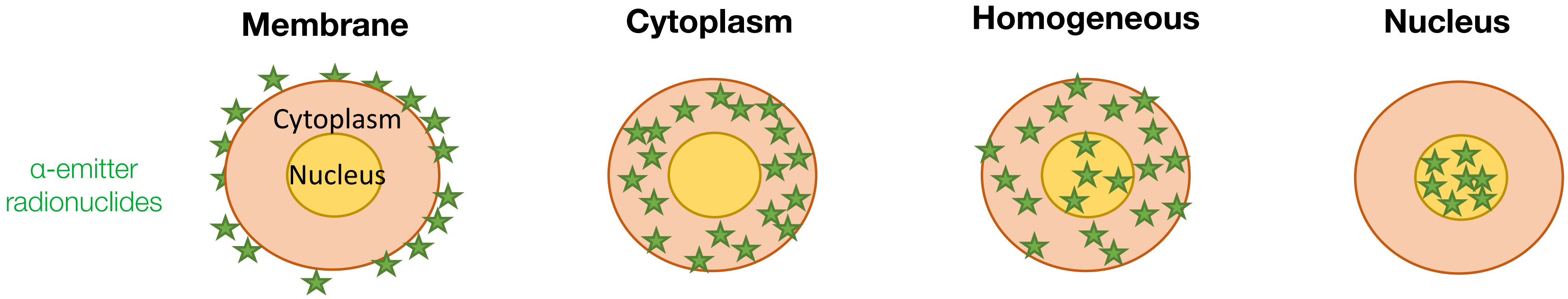
Combined CPOP-G4-NanOx predicting model for TAT

Impact of intracellular radionuclide distribution

In **Targeted Alpha Therapy**,

- Radionuclides can **enter in cells** because of the **chemical vector**
- **Radionuclide distribution cannot** be **known** during treatment

Different distributions studied :



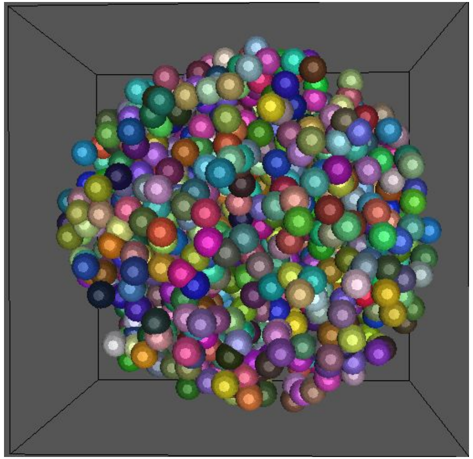
Same number of alpha particles for each distribution

Simulation parameters

Reproduction of the experimental treatment conditions of *Chouin et al. 2012*, murine treatment, 400 kBq injected

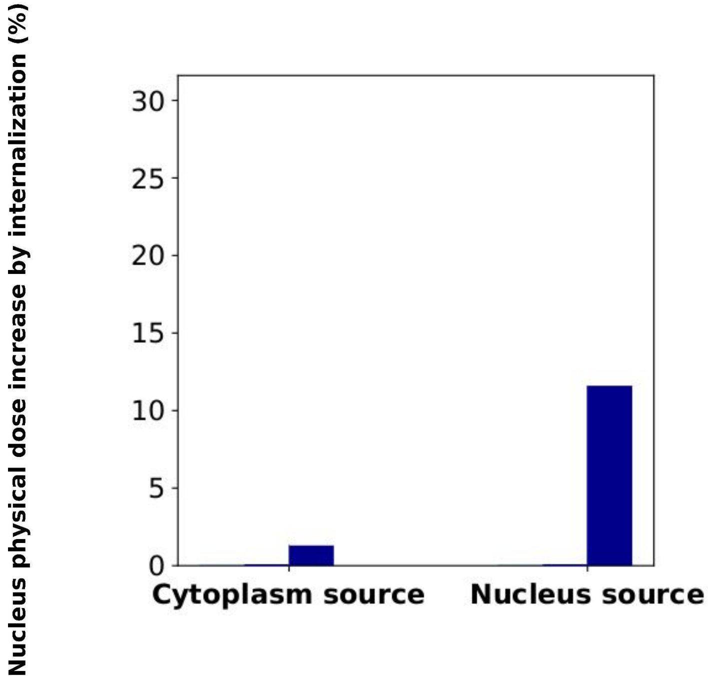
- **Number of alpha particles per cell :** 42 (uniform in spheroid)
- **Studied parameters :**
  - **Spheroid compaction** : 25 - **75 %**
  - **Radionuclide** used : ^{210}Po, **^{211}At** , ^{213}Bi
  - **Spheroid radius** : 30 - **95 µm**

Cell survivals calculated for the HSG cell line



95 µm radius Spheroid generated by CPOP

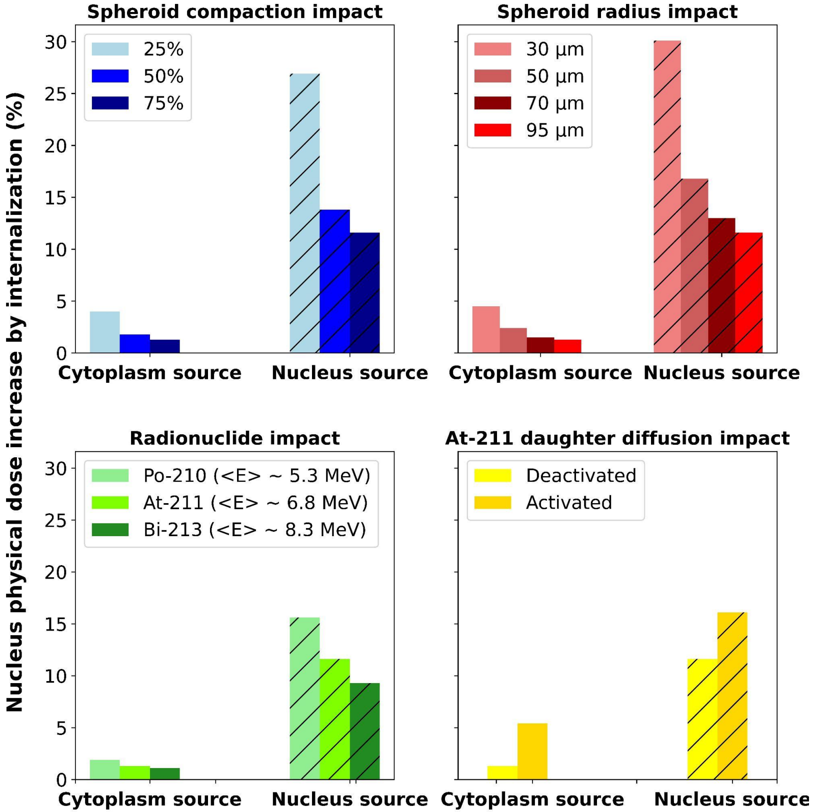
Physical dose increase by internalization



Mean nucleus physical dose increase of cytoplasm and nucleus radionuclide source distribution, compared to membrane source distribution only.

Irradiation conditions : ^{211}At,
95 µm spheroid radius, 75 % compaction

Physical dose increase by internalization



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Constant = activity per cell

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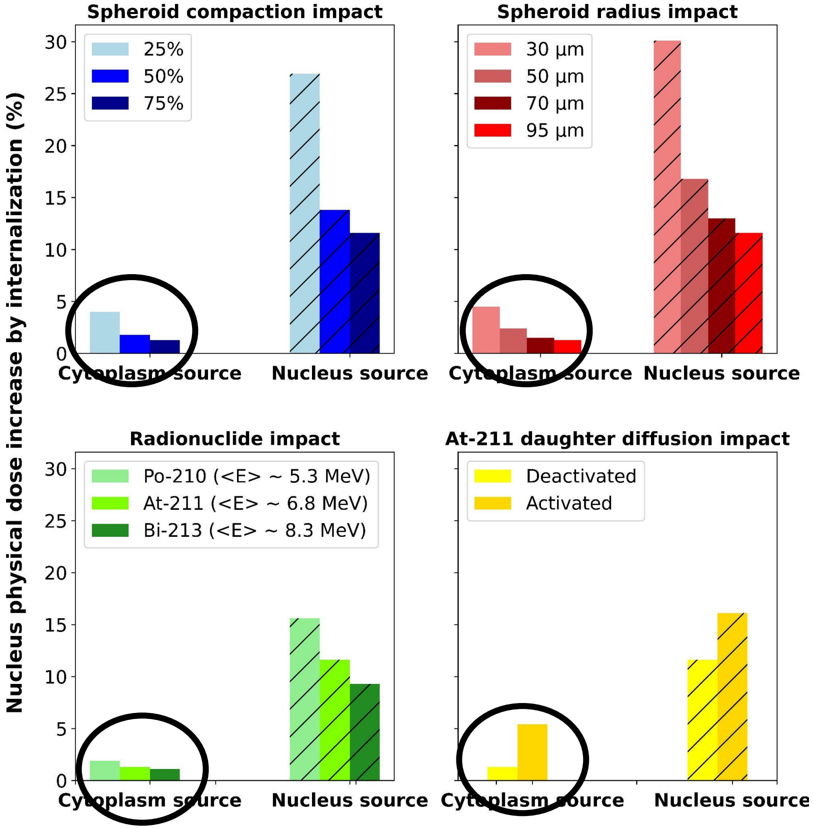

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Constant = activity per cell

❖ With **cytoplasm** only, less than 5% of nucleus dose increase

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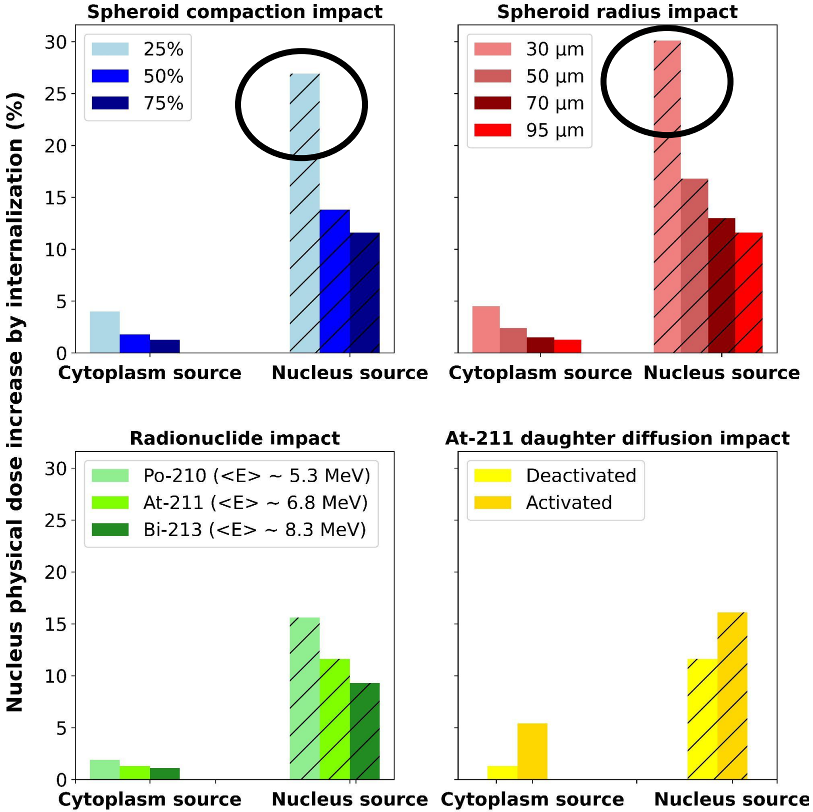


Mean nucleus physical dose increase of cytoplasm and nucleus radionuclide source distribution, compared to membrane source distribution only.

Constant = activity per cell

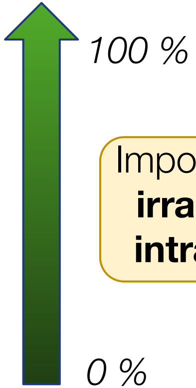
- With **cytoplasm** only, less than 5% of nucleus dose increase

- **Maximum** nucleus dose **increase** of ~**30%**
- **Higher** relative **impact** when **less cells**

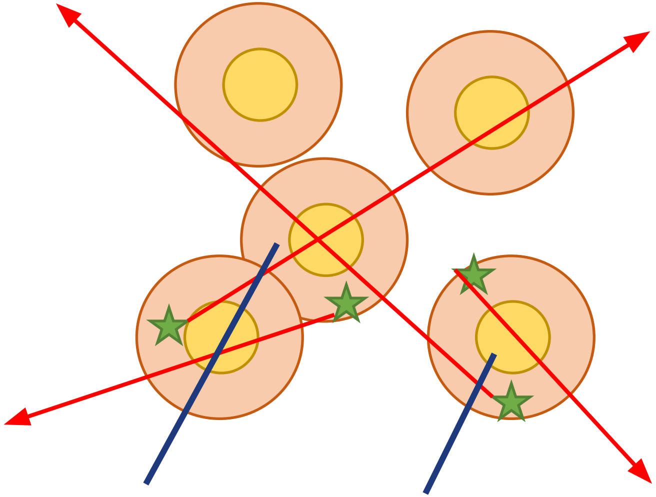
Cross-fire irradiation (1/2)

Cross-fire irradiation to a cell =

Irradiation coming **from radionuclides in the surrounding medium of this cell**



Importance of the **medium irradiation** compared to **intracellular irradiation**

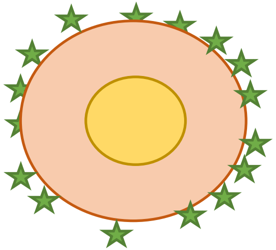


100 % cross-fire

0 % cross-fire

Cross-fire irradiation (2/2)

Membrane radionuclide distribution:



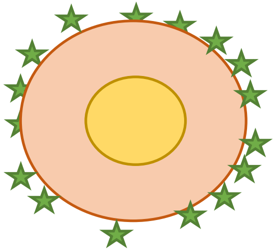
65 to **98%** nucleus **cross-fire** irradiation

Nucleus radionuclide distribution:

86 to **98%** nucleus **cross-fire** irradiation

Cross-fire irradiation (2/2)

Membrane radionuclide distribution:



Nucleus radionuclide distribution:

65 to **98%** nucleus **cross-fire** irradiation

86 to **98%** nucleus **cross-fire** irradiation

For **low compaction** (25%) and **small** (<50 µm) **spheroids**

Impact on biological effect (1/2)

TCP = Tumor Control Probability
(Probability to kill the tumor)

Irradiation conditions : ^{211}*At,*
95 µm spheroid radius, 75 % compaction

$$TCP = \prod_{i=1}^{n} (1 - S_i)$$

Impact on biological effect (1/2)

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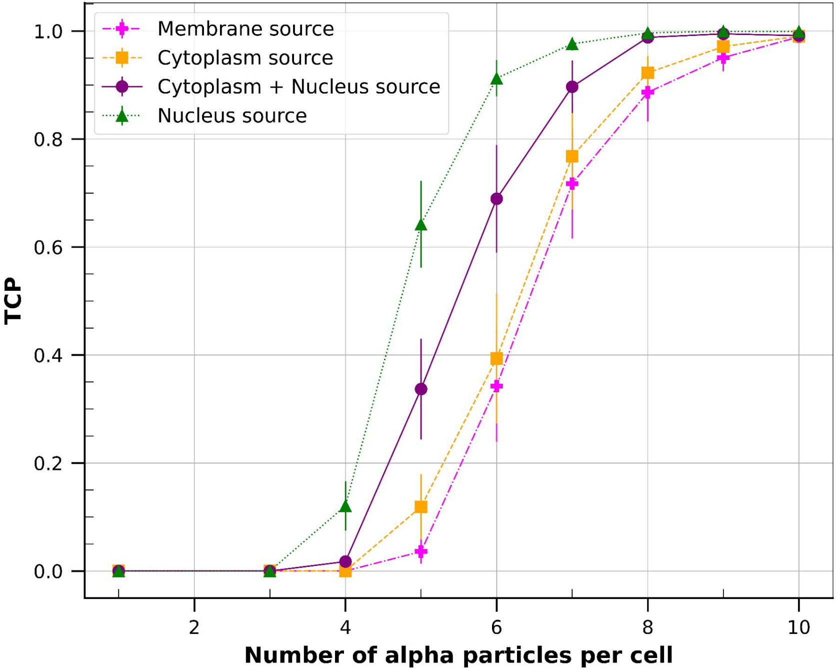

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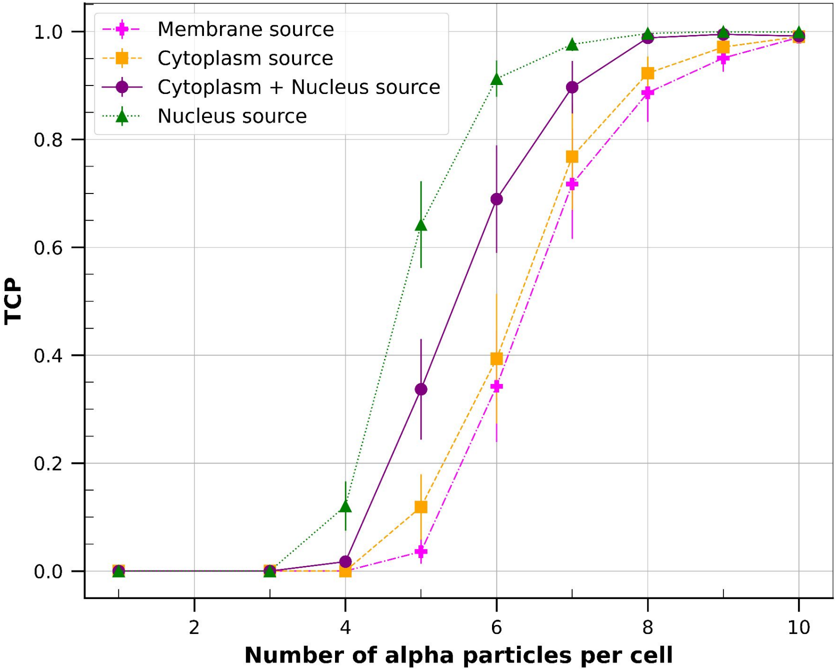

Irradiation conditions : ^{211}At,
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TCP = 1 for particles per cell **> 10**

Impact on biological effect (1/2)

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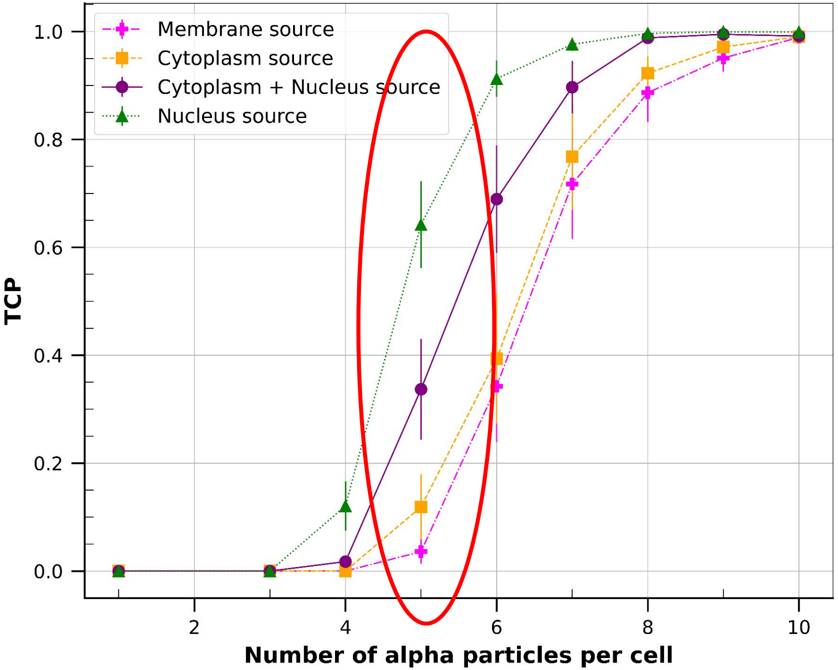

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TCP = 1 for particles per cell **> 10**

Highest differences between distributions at ~ **5 particles per cell** → Threshold effect

18-fold higher TCP between nucleus and membrane source

Impact on biological effect (2/2)

Relative **B**iological **E**ffectiveness = $\dfrac{D_{reference}}{D_{TAT}}$

$$RBE_{\mu} = \frac{-\alpha_{ref} + \sqrt{\alpha_{ref}^2 + 4 \cdot \beta_{ref} \cdot (\alpha \cdot D + \beta \cdot D^2)}}{2 \cdot \beta_{ref} \cdot D}$$

RBEμ at 10% cell survival ≃ **3.5**, compared to external photon irradiation

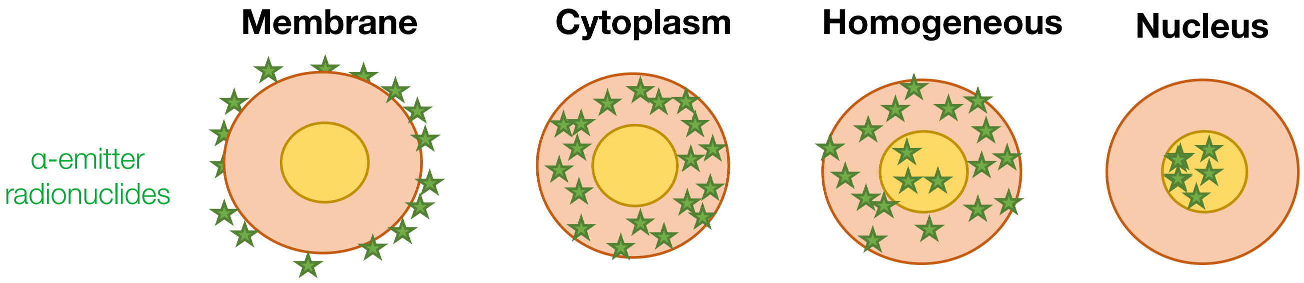
For protons in hadrontherapy,
RBE at 10% cell survival ≈ **1.1**

Take-home messages

- **Cross-fire effect major** in targeted alpha therapy
- Intracellular radionuclide distribution must be **precisely modeled** for **small tumors** (< 50µm radius) and **low compaction** spheroid, especially with **low radionuclide concentration**
- **Biological quantities** are mandatory to take into account in **addition** to **physical ones**

Perspectives and ongoing work

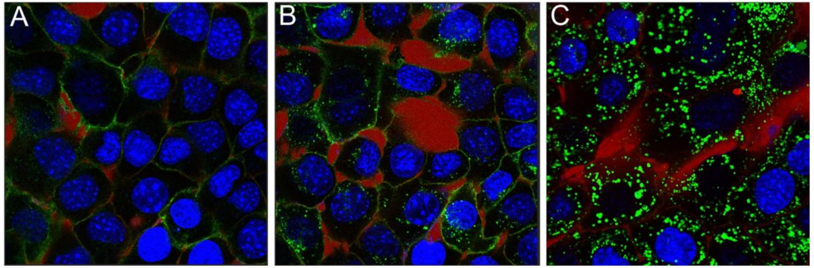
- **Article submission** on intra-cellular radionuclide study, with the remarks of the reviewers from the Green Journal submission



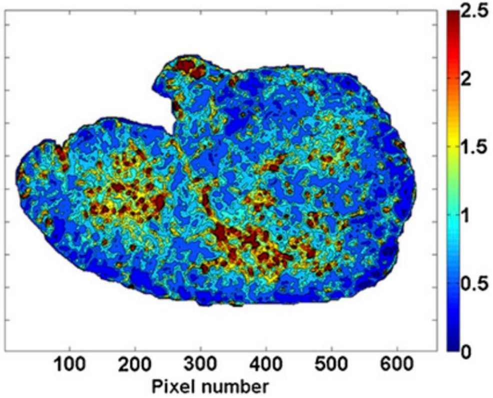
- **Article submission** on NanOx formalism for low energy ion irradiations

Perspectives and ongoing work

- Comparison with **experimental data** of literature (Neti study or others)
- Study on **intra-tumoral** radionuclide **distribution**:
  - Impact of different distribution scenarios
  - Impact of cell labeling %
  - Impact of radionuclide diffusion kinetic



Evolution of antibody kinetics over time. Bastiaannet et al. 2023.



View of an irradiated tumor ***(4*6 cm)*** *with the intra-tumoral activity distribution, Back et al. 2010*

Discussion

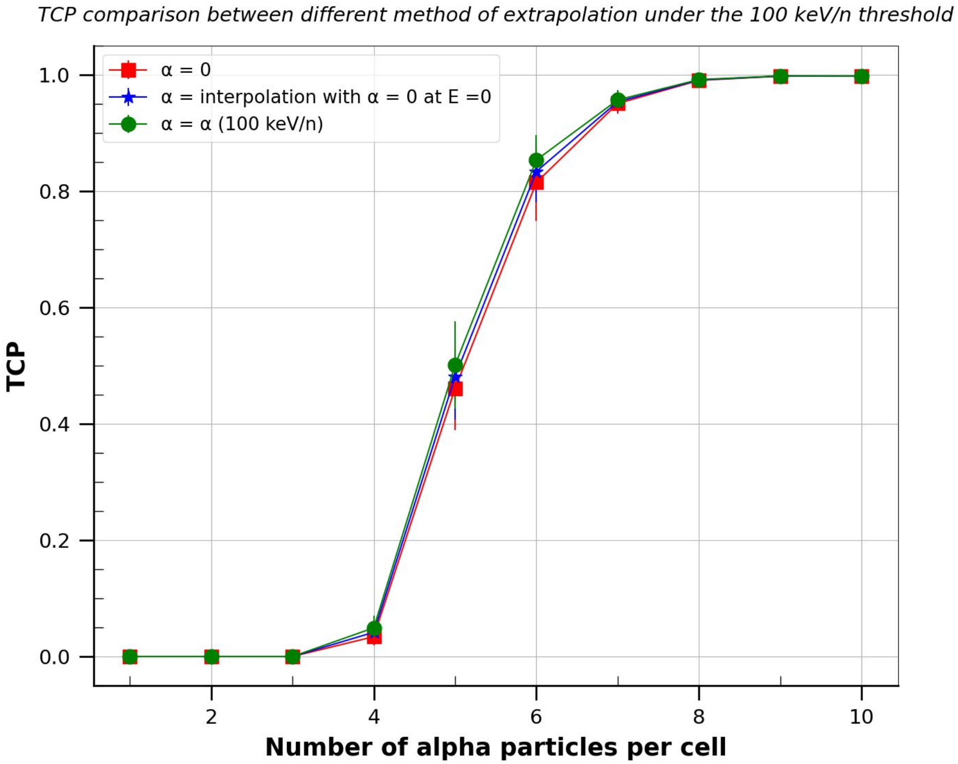
Appendix

Impact of 100 keV/n threshold on TCP: methods

3 hypotheses under 100 keV/n:

- All α are equal to zero under 100 keV/n
- α is assumed = 0 at E = 0. Linear interpolation is done
- All α are equal to α(100 keV/n) under 100 keV/n

Impact of 100 keV/n threshold on TCP: results

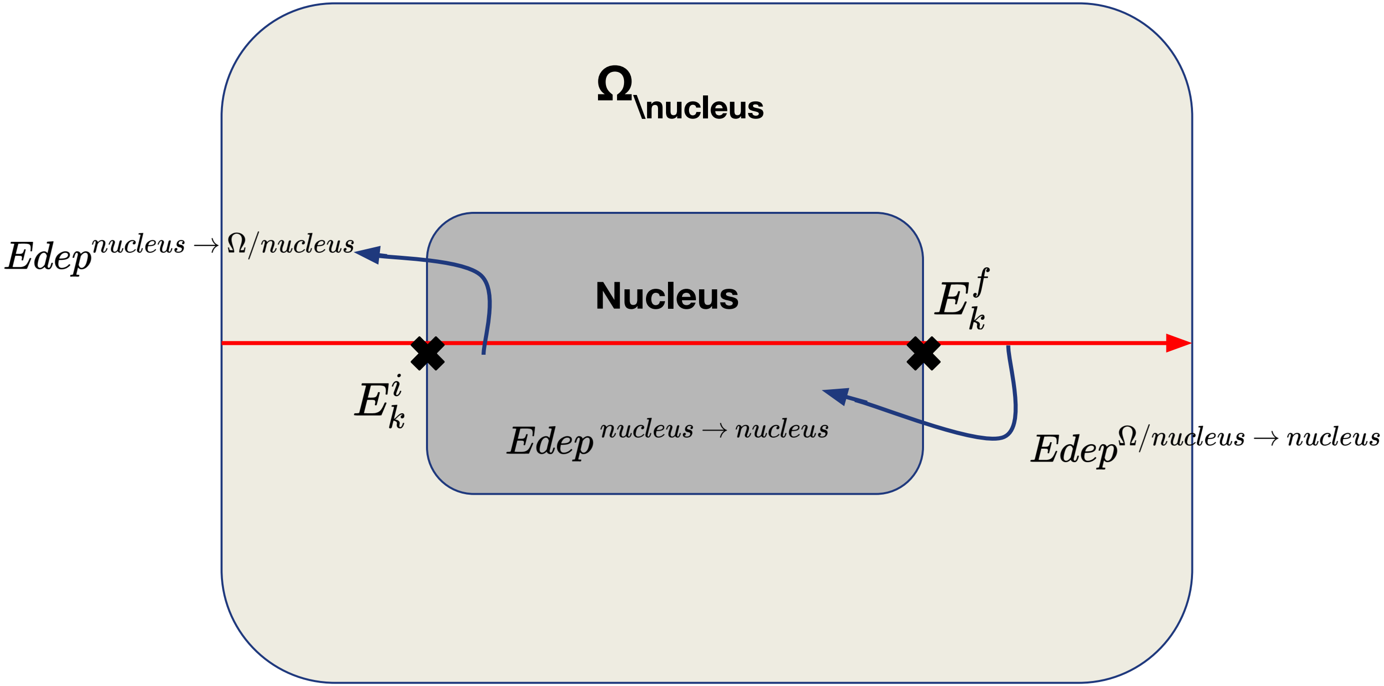


Nucleus radionuclide distribution, At-211, 75% spheroid compaction, HSG

Coherent behaviour

Max absolute difference of TCP ≃ 0.04 → **Low impact of the method**

E_k - E_k = $Edep$ = Edep hypothesis: formalism



$\Omega_{\backslash nucleus}$

Nucleus

$Edep^{nucleus \rightarrow \Omega/nucleus}$

E_k^i

E_k^f

$Edep^{nucleus \rightarrow nucleus}$

$Edep^{\Omega/nucleus \rightarrow nucleus}$

$E_k^{\,i} - E_k^{\,f} = Edep$ hypothesis: formalism

$$Edep^{tot\ in\ nucleus} = E_k^i - E_k^f + Edep^{\Omega/nucleus \rightarrow nucleus} - Edep^{nucleus \rightarrow \Omega/nucleus}$$

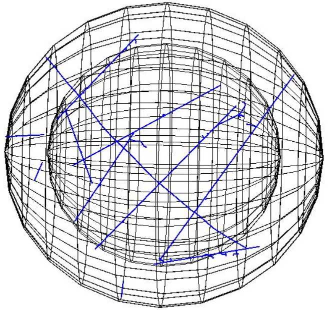
⟺

$$\left(E_k^i - E_k^f\right) - Edep^{tot\ in\ nucleus} = Edep^{nucleus \rightarrow \Omega/nucleus} - Edep^{\Omega/nucleus \rightarrow nucleus}$$

Narrow track hypothesis: Material & Methods

Simulation conditions:

- Mono cellular
- Multi-directional cytoplasm source
- Helium ions from 0.5 to 200 MeV
- Geant4 Monte-Carlo code



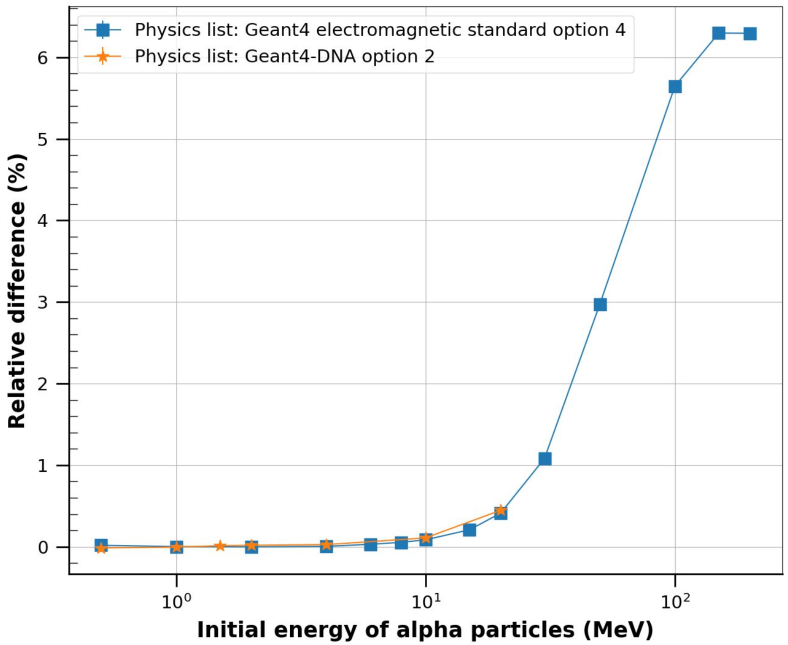
Geant4 simulation of a cell with an helium cytoplasm source

***Physics list*:**

- Low energy **standard** electromagnetic *(emstandard_opt4)*
- **Geant4-DNA** option 2: more precise tracking at low energy for **electron** tracking

Geometry HSG:
r(nucleus) = 5.2 μm
r(cell) = 7.1 μm

Narrow track hypothesis: Results



Relative difference on average:

$$2 \cdot \frac{\left(E_k^i - E_k^f\right) - Edep^{tot\ in\ nucleus}}{E_k^i - E_k^f + Edep^{tot\ in\ nucleus}}$$

Below **10 MeV:** < 0.1% error on the hypothesis

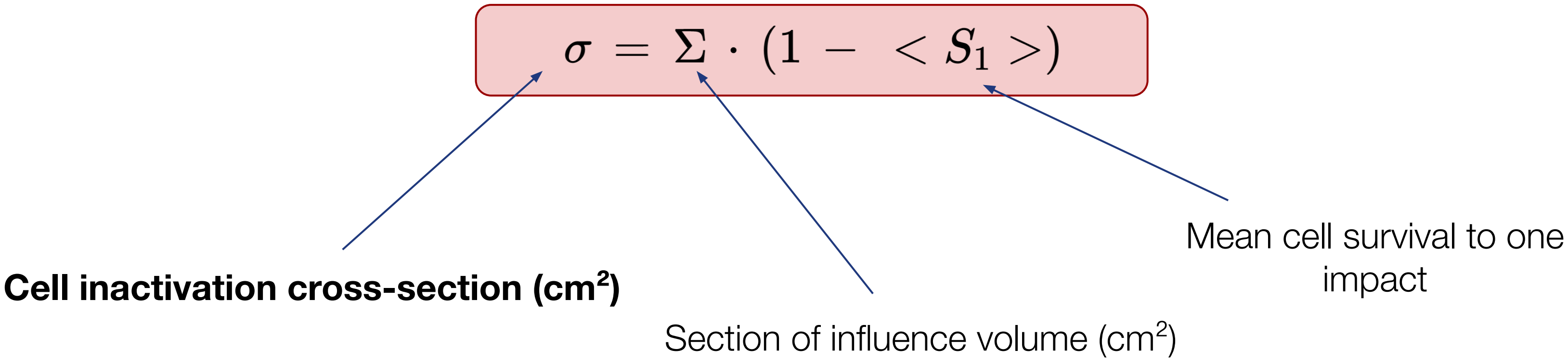
More precise electron tracking doesn't change the results

Formalism comparison

Precision added by this “low energy” formalism ?

High energy limit ?

Comparison with “hadrontherapy” formalism



$$\sigma = \Sigma \cdot (1 - \langle S_1 \rangle)$$

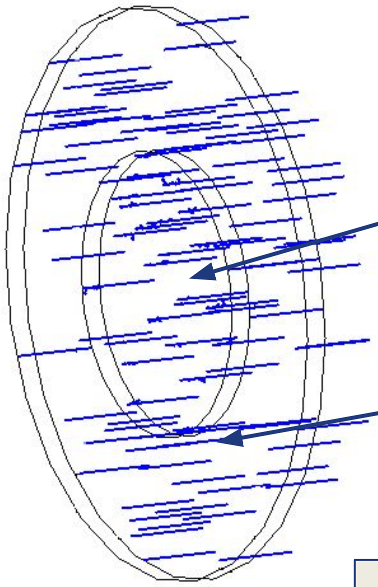
Cell inactivation cross-section (cm²)

Section of influence volume (cm²)

Mean cell survival to one impact

Formalism comparison: Material & Methods

Reproduction of NanOx simulation conditions:



Sensitive volume (R = 7 µm, **L = 1 to 14 µm**)

Influence volume

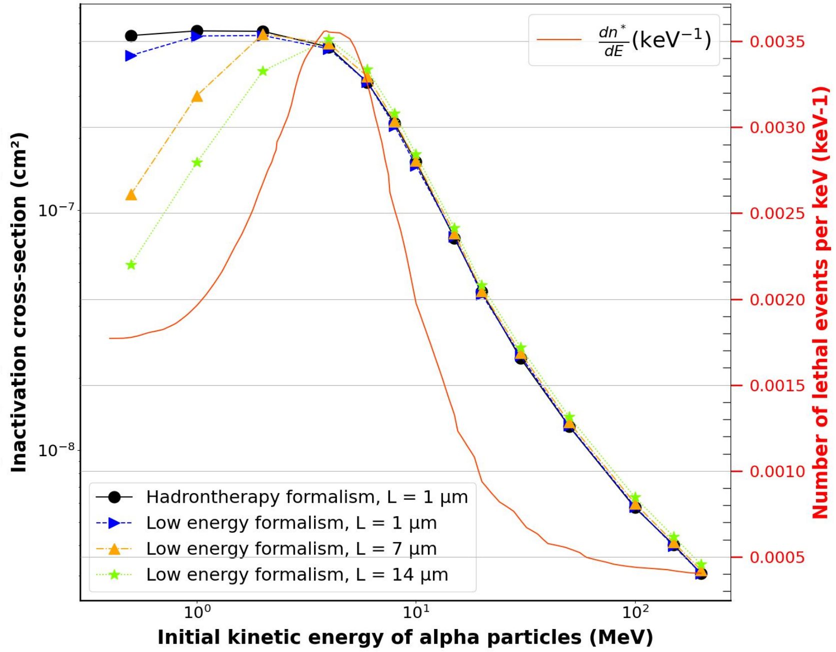
Sensitive volume = nucleus

Influence volume = large enough so an ion can deposit energy in the sensitive volume

HSG cell line considered

Output = *Ei* and *Ef* energies

Formalism comparison: results



Impact of “low energy” formalism appears **under 4 MeV**

Good **agreement** of formalisms between **4 MeV** and **200 MeV**

Cross-section **smaller than** with **hadrontherapy** → due to dn/dE behaviour

Article in writing by Mario Alcoler and me