Impact of intracellular radionuclide distribution in Targeted Alpha Therapy: a Monte Carlo biophysical study in 3D multicellular model

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Impact of intracellular radionuclide distribution in Targeted Alpha Therapy: a Monte Carlo biophysical study in 3D multicellular model

Summary :

- **Problematics**
- **Methods**
- **Mono-cellular**
- **Multi-cellular**

Targeted alpha therapy

Targeted alpha therapy (TAT) :

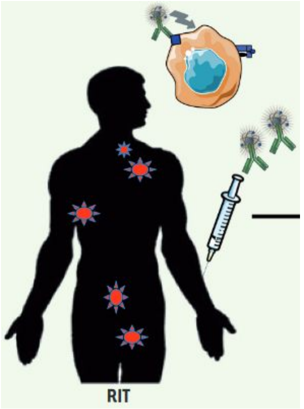
- Mean energies : **5-10 MeV**
- Mean range : **40-100 µm**

How to predict doses and biological effects ?

⟶ **Problematics in Biophysical modeling :**

- **Low ranges** → Need to take into account : - **heterogeneity** of deposited dose
  - energy lost by ions in nuclei
  - cell and tumor **geometry**

- Different scales : **nano**metric (DNA) and **micro**metric (cells)



Antibody + radionuclide

Non-localized cancer sites

Problematics for realistic treatment simulation

1 : Micro-dosimetric biological data, e.g. number of radionuclides per cell, related to an injected activity
→ **rare**

2 : Importance of intra-cellular radionuclide distribution ?

↳ Quantified in **mono-cellular** models *(Guerra Liberal et al. 2021)*

↳ **Objective of this study** to quantify it in a **multi-cellular** model

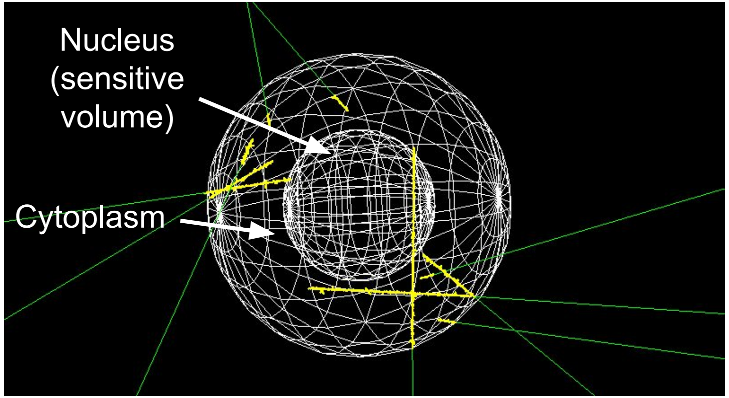
Methods : Simulation and analysis chain

Geometry generation → **Monte-Carlo Simulation (Geant4)**

Biophysical model (NanOx)

Doses and Cell Survivals calculations

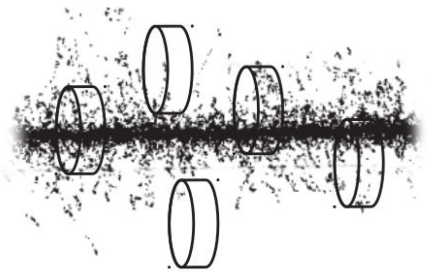
Simulated geometry in Geant4-DNA



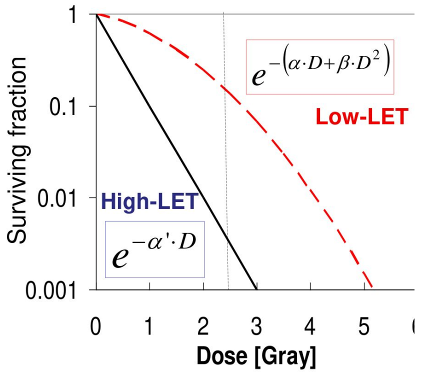
- **Monte-Carlo** code with low energy track of particles
- **Electron cut** applied
- Cells = concentric spheres
- **Output:**
  ° Doses in **nucleus** and cells
  ° In and out energies of alpha in nuclei

Biophysical model : NanOx (1/2)

- **Biophysical model** → calculate DNA damage inflicted by a particle → **cell survival**
- Takes into account **oxidative stress**, **stochastic** aspects of **irradiation**
- Validated for hadrontherapy



Cells irradiated in NanOx, in hadrontherapy
Cunha et al. 2017



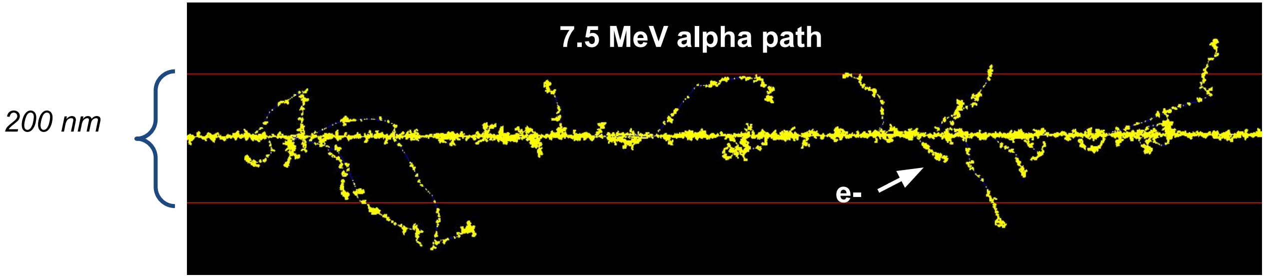
Cell survival curve for low and high LET ions

Biophysical model : NanOx (2/2)

- PICTURE project → objective to adapt **NanOx for low energy ions**
- We validated hypothesis to **use NanOx in our study**

↓

Electron tracks are **concentrated** around the **alpha path**



Internalization study

1 : Mono-cellular model

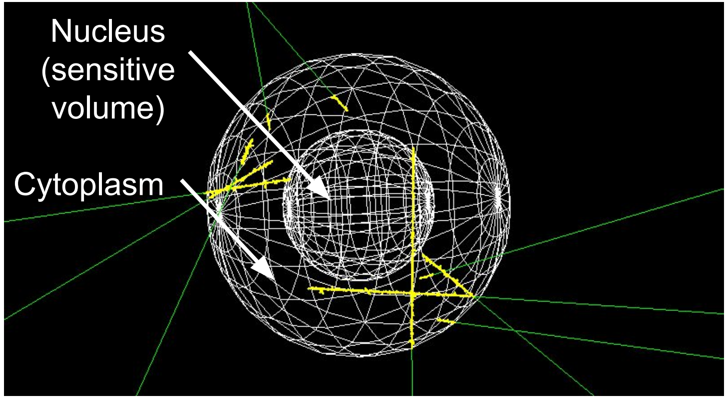
2 : Multi-cellular model

Internalization study : mono-cellular model (1/5)

Irradiations conditions :

- **At-211** irradiation
- 6 MBq = **1700** alpha particles per cell

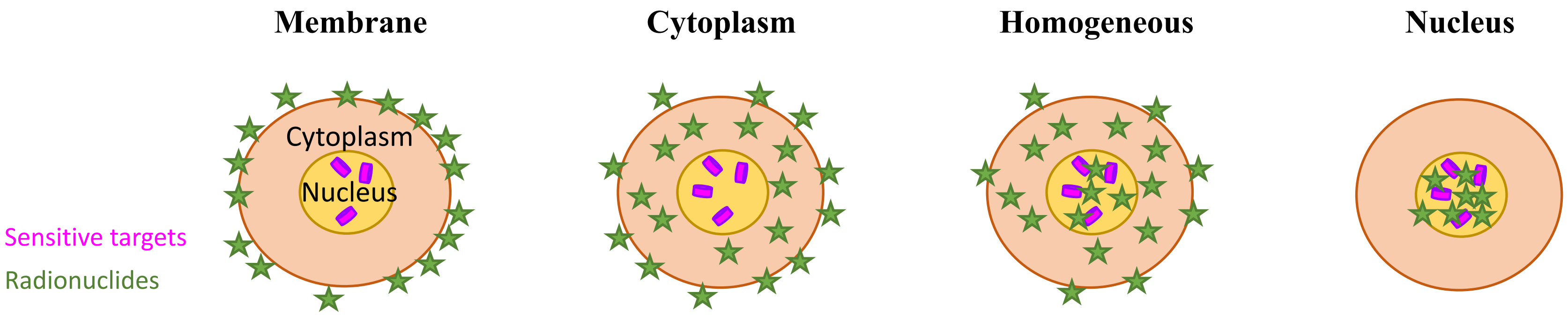
Experimental data from *Chouin et al. 2013*



Nucleus radius = 5 µm
Cell radius = 10 µm

Internalization study : mono-cellular model (2/5)

Different distributions studied :

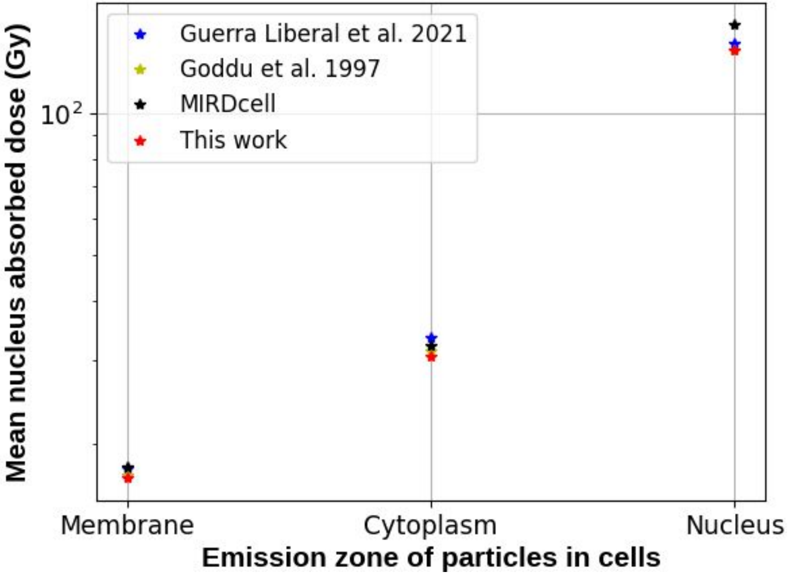


Same number of alpha particles for each distribution

Observables :

Mean **cell and nucleus dose**, mean **energy deposited** by a particle, **probability to hit** the nucleus ⟶ for all distributions

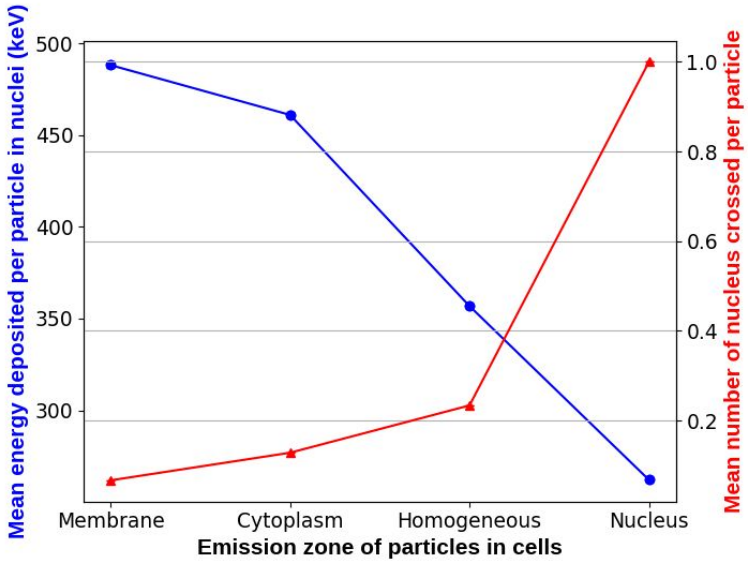
Internalization study : mono-cellular model (3/5)



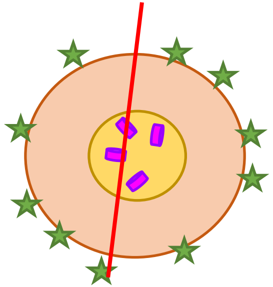
→ Good agreement with other models

Relative deviation with other works			
Emission zone	**Guerra et al.**	**MIRDCELL**	**Goddu et al.**
Membrane	4.7 %	9.4 %	1.8 %
Cytoplasm	9.4 %	5.1 %	2.2 %
Nucleus	3.0 %	12.9 %	0.25 %

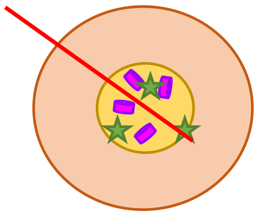
Internalization study : mono-cellular model (4/5)



When nuclei are hit
→ Deposited energy depends on energy of the particle
→ Energy ↘ ~⇒ **L**inear **E**nergy **T**ransfer ↗

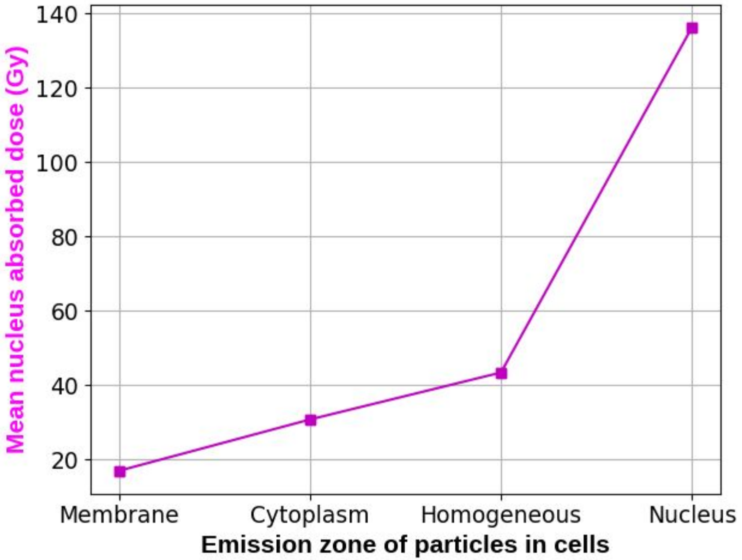


Membrane emission



Nucleus emission

Internalization study : mono-cellular model (5/5)



Two main effects :

- **Edep** per particle (↘ with internalization)
- **Probability** to hit the nucleus (↗ with internalization)

→ *7 between **membrane** and **nucleus** emission

In this study :

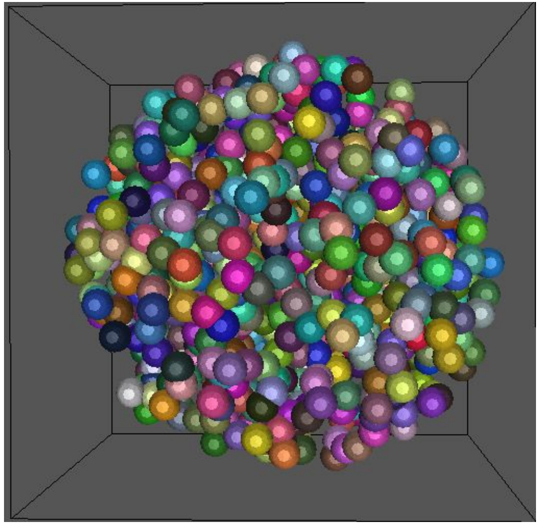
Cell survival always ~ **zero**
→Need a multi-cellular approach

Internalization study

1 : Mono-cellular model

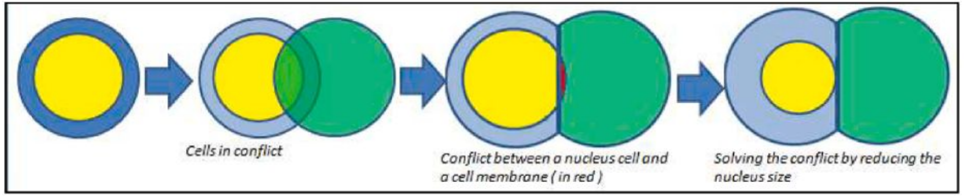
2 : Multi-cellular model

Spheroid generation tool : CPOP



95 µm radius Spheroid generated by CPOP

- Tool to generate **multi-cellular geometries**
- Realistic **cell overlap** management



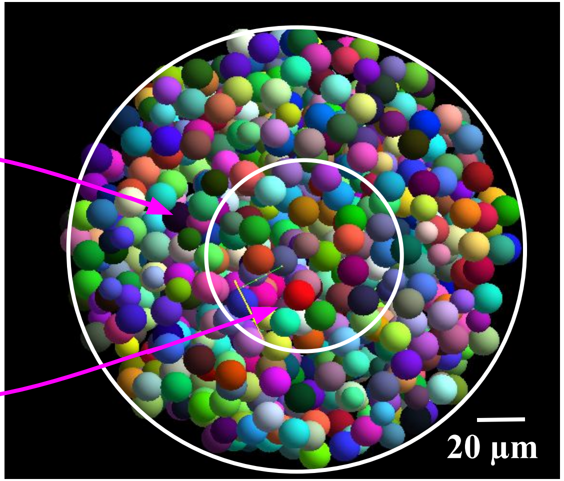
Maigne et al. 2021

Internalization study : multi-cellular model (1/6)

Irradiations conditions :

- **Cell line :** OVCAR-3
- Cell packing ~ **25 %** (681 cells)
- At-211 irradiation
- 400 kBq = **18** alpha particles per cell in **0-50 µm** depth
  9 alpha particles per cell in **50-95 µm** depth
- Particles are all **fixed on all cells**

95 µm radius Spheroid

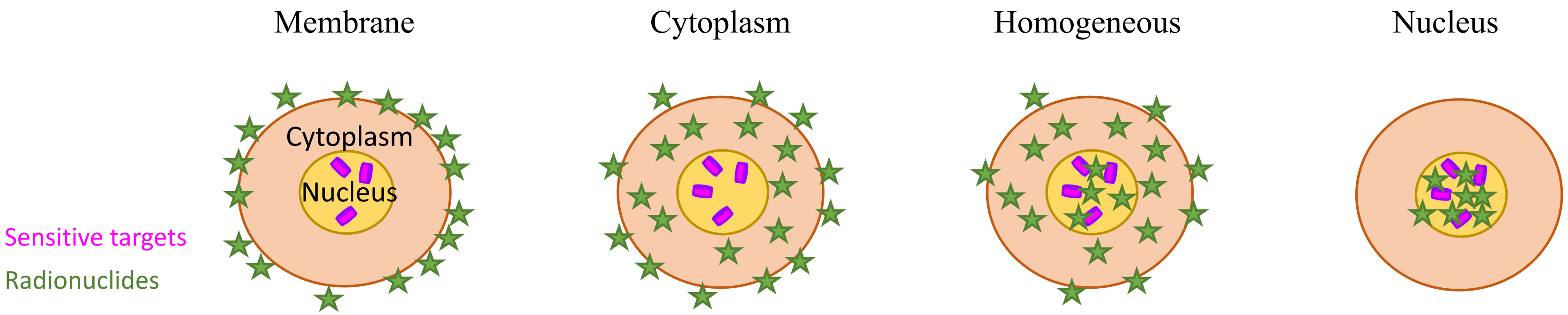


Cell radius ≃ 6.9 µm
Nucleus radius ≃ 5.5 µm

Experimental data *from Chouin et al. 2012*
→ **Murine treatment**

Internalization study : multi-cellular model (2/6)

Different distributions studied :

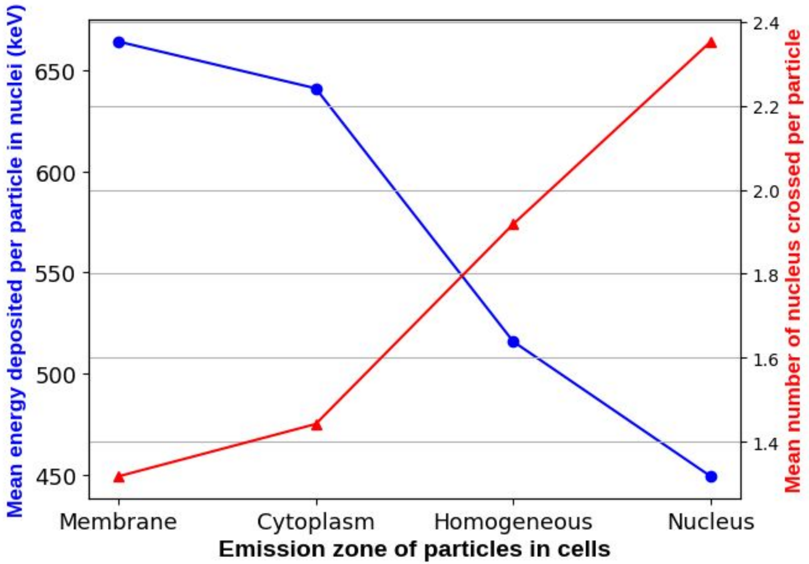


Same number of alpha particles for each distribution

Observables :

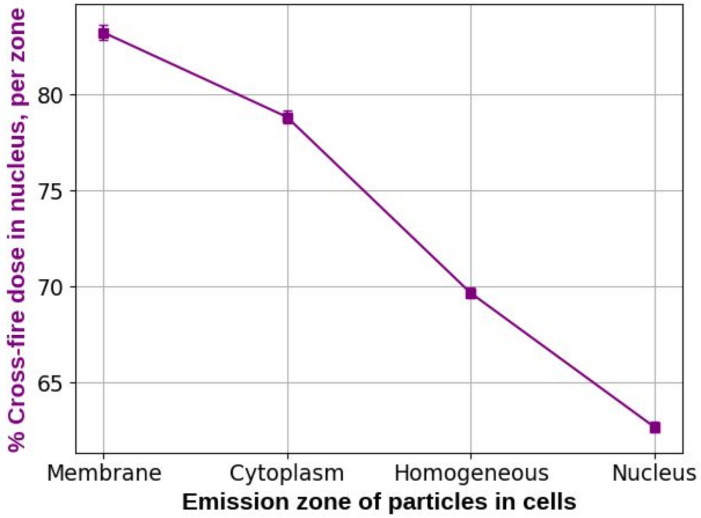
Mean cell and nucleus **dose**, mean **energy deposited** by a particle, **cross-fire** nucleus irradiation, **cell survival**

Internalization study : multi-cellular model (3/6)



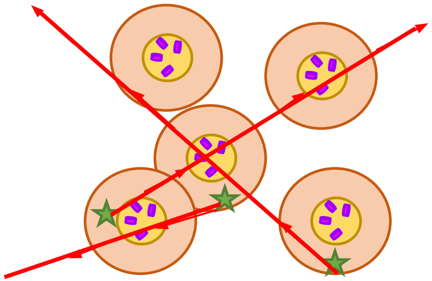
→ Similar behavior with our mono-cellular model

Internalization study : multi-cellular model (4/6)

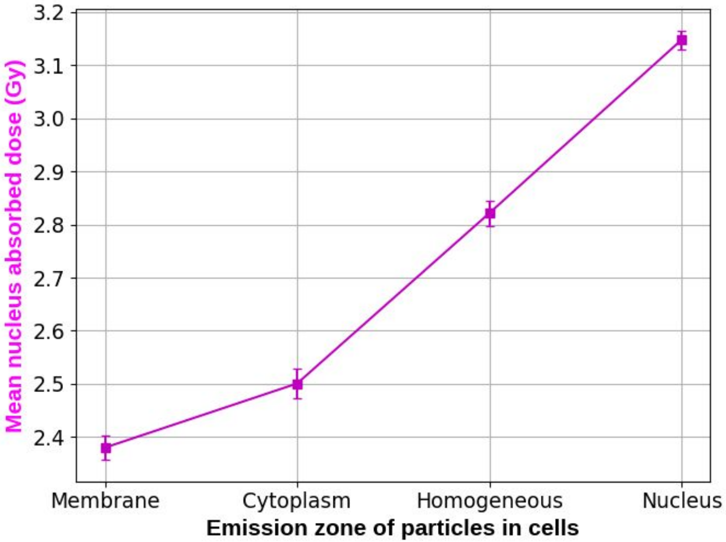


Cross-fire irradiation in nucleus → good quantification of intra-cellular effects importance

With our simulation conditions, at least **higher than 63%**



Internalization study : multi-cellular model (5/6)

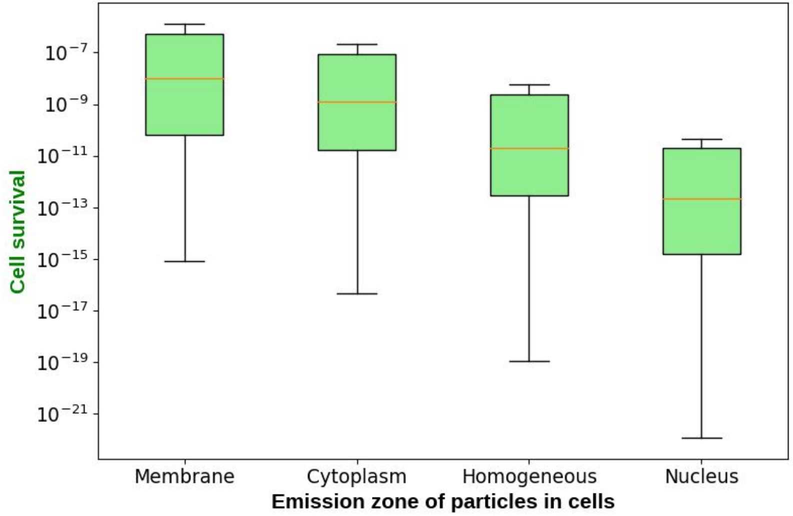


Three effects :

- **Probability** to hit the nucleus (↗ with internalization)
- **Edep** per particle (↘ with internalization)
- **Cross-fire** (↘ with internalization)

⟶ ***1.4** between **membrane** and **nucleus** emission

Internalization study : multi-cellular model (6/6)



→ ***4000** between membrane and nucleus emission

→ Tumor control probability almost always equal to **1**

→ **Reminder :**

- all cells labeled by particles
- curative activity (for mices) used

Conclusion

Conclusion :

- Average **nucleus dose**, from membrane to nucleus emission :
  * 7 on *mono-cellular* model
  * 1.4 on *multi-cellular* model

"Order of magnitude"

- Average **cell survival**, from membrane to nucleus emission :
  *4000 on *multi-cellular* model

- With all cells labeled, **TCP** ≃ 1

To go further

- Consider a model where **cells are not all labeled by particles**, with fixed injected activity
  - With **random labeling** in all the spheroid/tumor
  - With small **unlabeled zones**

- Study **different sizes** of spheroid/tumor

- **Kinetic model** to predict antibody penetration in a tumor

Thanks for your attention

Bibliography

1 : *Maigne, L., et al. 2021. Physica Medica 89: 41-50.*

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3 : *Chouin N et al. 2013. J Nucl Med. Aug;54(8):1347-53*

4 : Chouin, N., et al. 2012. *The Quarterly Journal of Nuclear Medicine and Molecular Imaging.* 56.6 : 487-495.