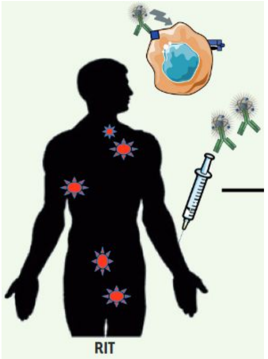
Impact of intra-cellular radionuclide distribution in Targeted Alpha Therapy : a Monte-Carlo biophysical study in 3D multicellular model

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

1: LPSC, Grenoble
2: IP2I, Lyon
3: LPC, Clermont-Ferrand

Targeted alpha therapy context



Targeting molecule + radionuclide

Non-localized cancer sites

Targeted alpha therapy (TAT) :

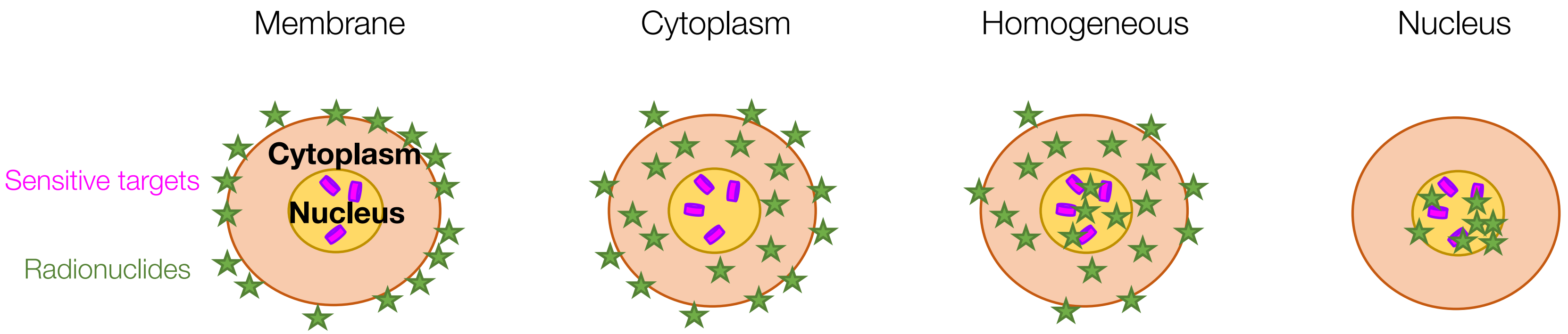
- Mean energies : **5-10 MeV**
- Mean range : 40-100 µm **(few cells)**

Biophysical Monte-Carlo predictions :

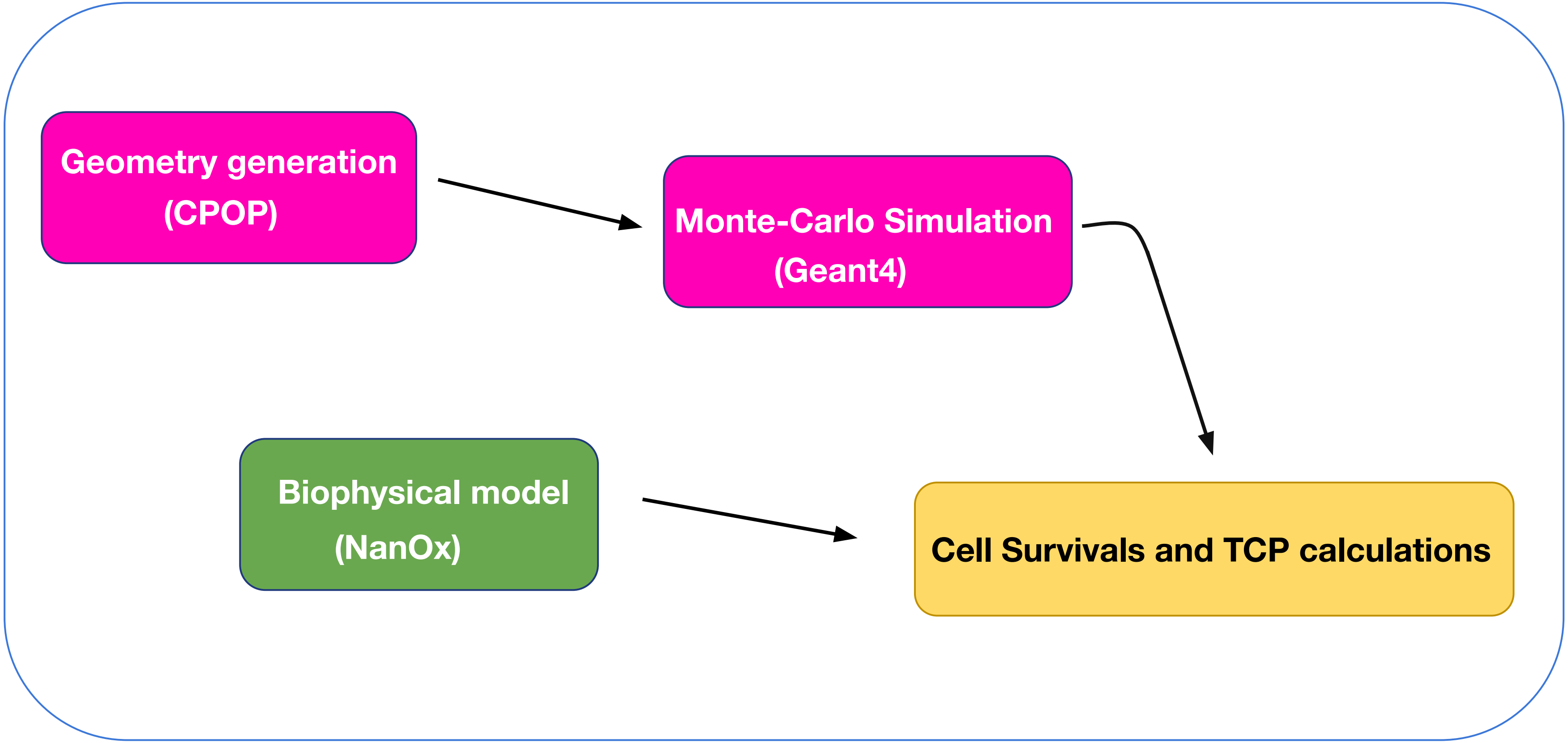
- **Low ranges** : Need to take into account :
  - **heterogeneity** of deposited energy
  - cell and tumor **geometry**
- **Different scales** : **nano**metric (DNA) and **micro**metric (cells)

Impact of intra-cellular radionuclide distribution

- **Few studies** on the topic
- **This work :** Parametric study in multi-cellular model, with physical and biological indexes calculations



Simulation and analysis chain



Biophysical model : NanOx (1/2)

- Biophysical model

  → **cell survival probability** prediction, with **nano**- and **micro**-dosimetry

  Lethal damage : **DNA Double Strand Breaks**

  Sub-lethal damage : **oxidative stress**

- Takes into account **stochastic** aspect of **irradiation**

- Nucleus : only **sensitive volume** (perspective : **whole cell** as sensitive volume)

Biophysical model : NanOx (2/2)

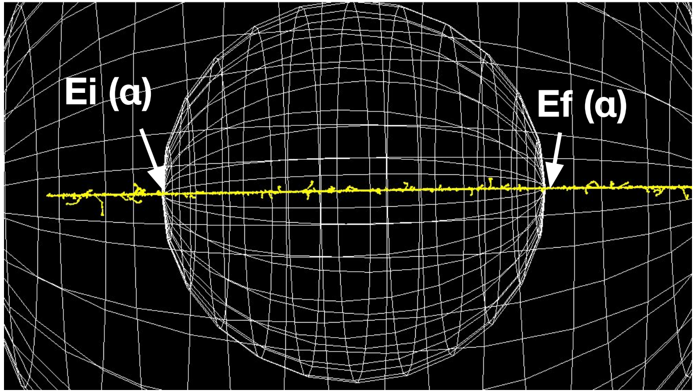
- **NanOx :** Experimentally calibrated & validated for **hadrontherapy**
- **Formalism adapted** to consider energy loss by ions in nuclei

Cell Survival = f (α, β, Ei, Ef)

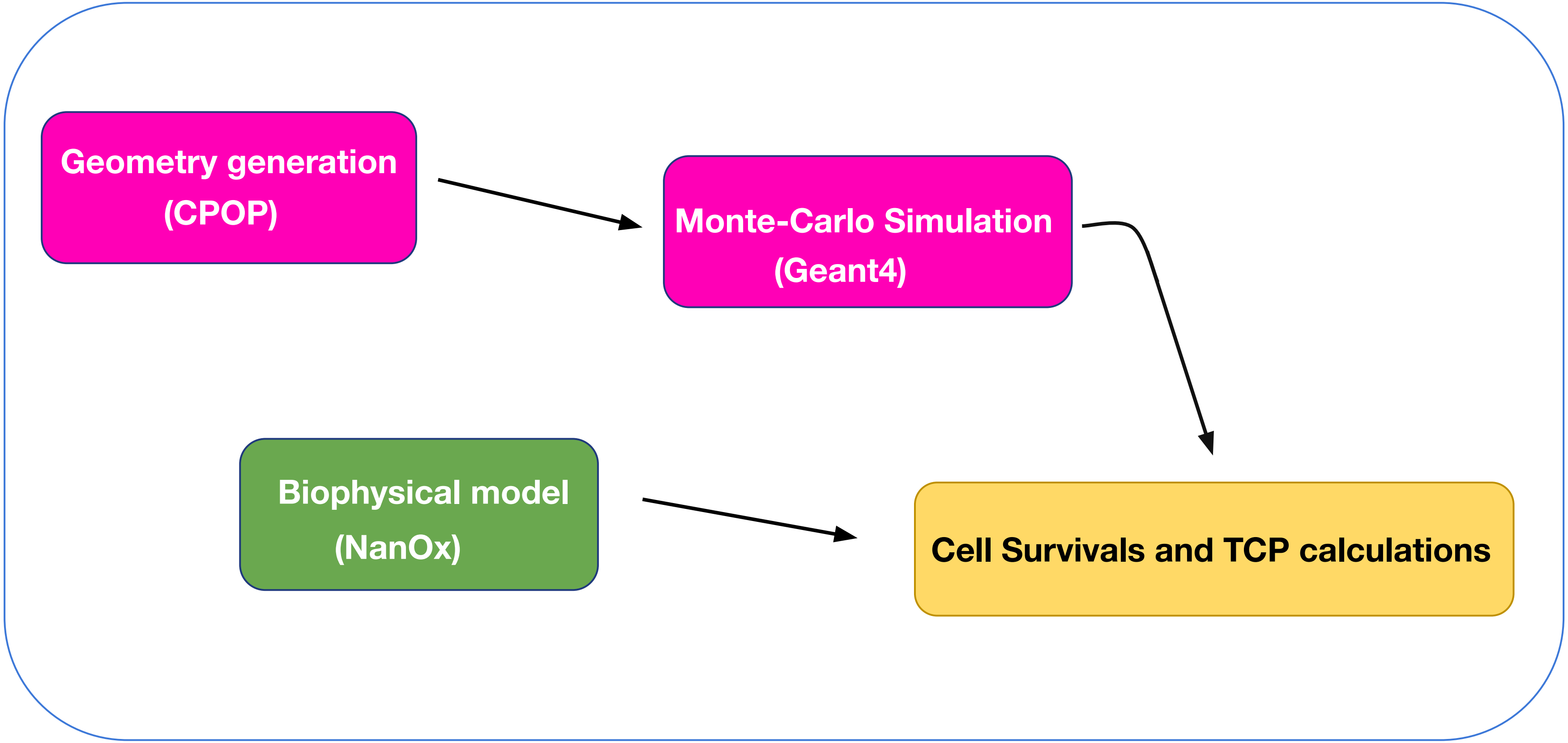
$\underbrace{\alpha, \beta}_{\text{NanOx output}}$, $\underbrace{Ei, Ef}_{\text{Geant4 output}}$

NanOx output

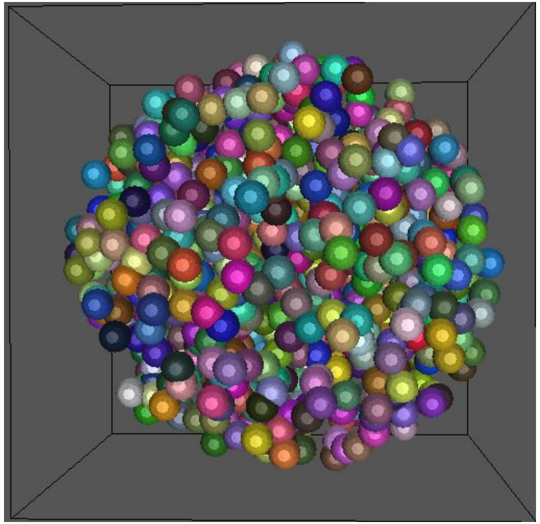
Geant4 output



Simulation and analysis chain

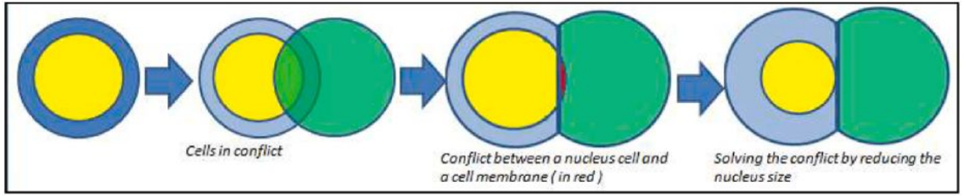


Geometry generation : CPOP



95 µm radius Spheroid generated by CPOP

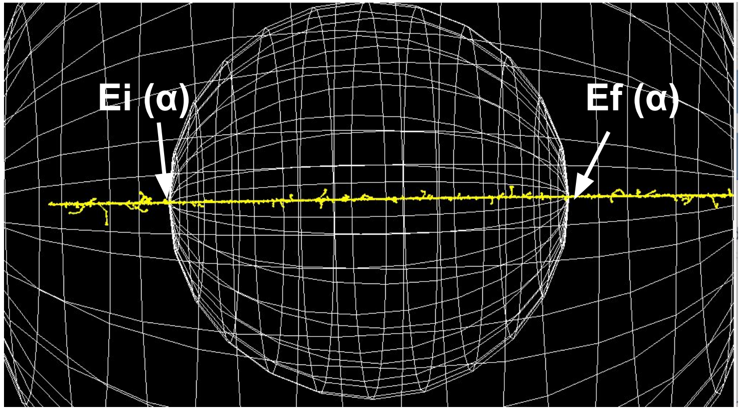
- Open-source tool that can generate **highly compacted multi-cellular** geometries
- Based on **Geant4**
- Realistic **cell overlap management**
- Example coming soon in official G4 release



Maigne et al. 2021

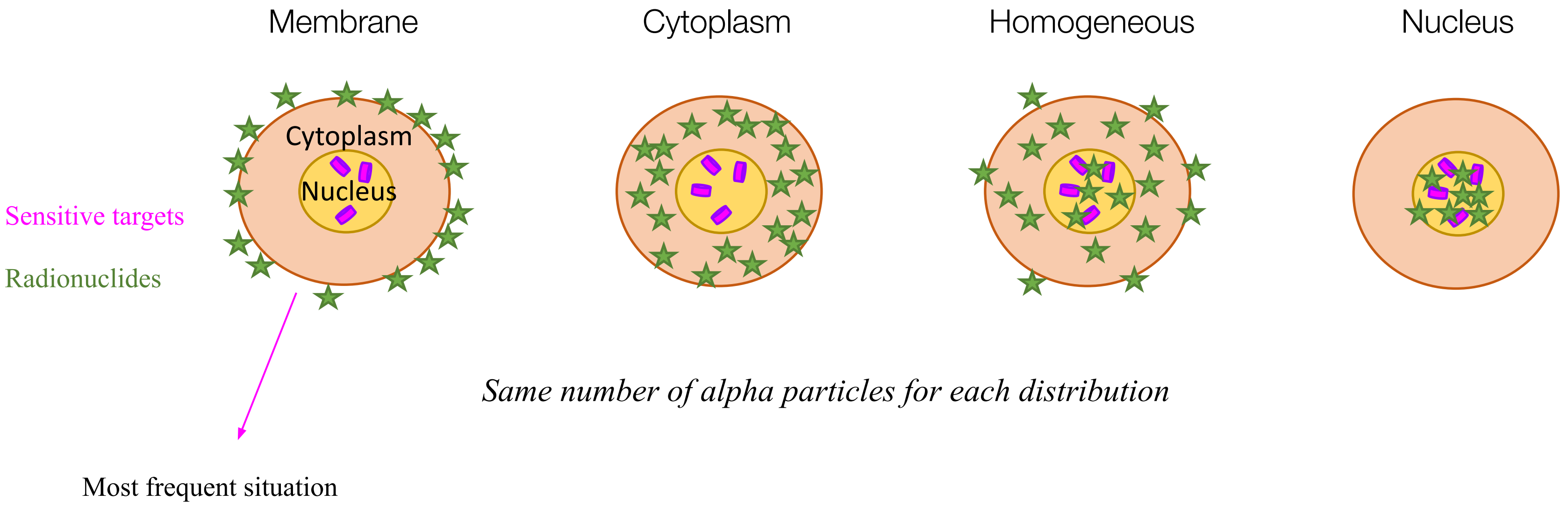
Monte-Carlo simulation : Geant4

- **Alpha particles** < 10 MeV, with **electron cut**
- G4EmStandardPhysics_option4 **physics list**
- **Output :**
  - Physical doses in **nuclei** and cells
  - **In (Ei)** and **out (Ef)** energies of alpha particles in **nuclei**



Intra-cellular radionuclide distribution study

Different distributions studied :

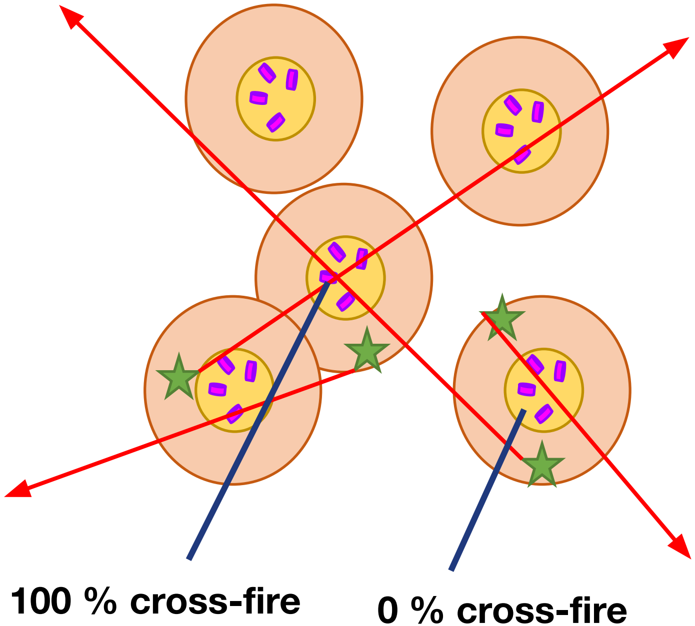


Same number of alpha particles for each distribution

G4 - NanOx coupling calculations

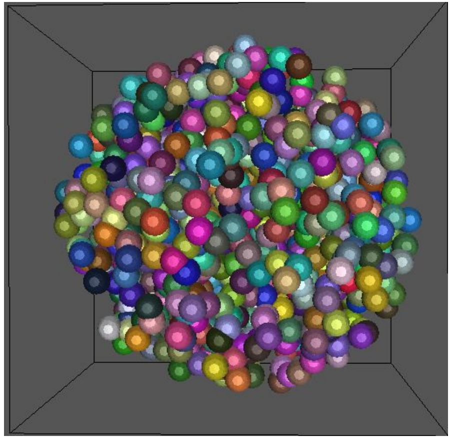
Observables:

- **Cell survival** probabilities (HSG cell line)
- **Tumor Control Probability**
- Physical doses in nuclei and cells
- **Cross-fire** nucleus dose %

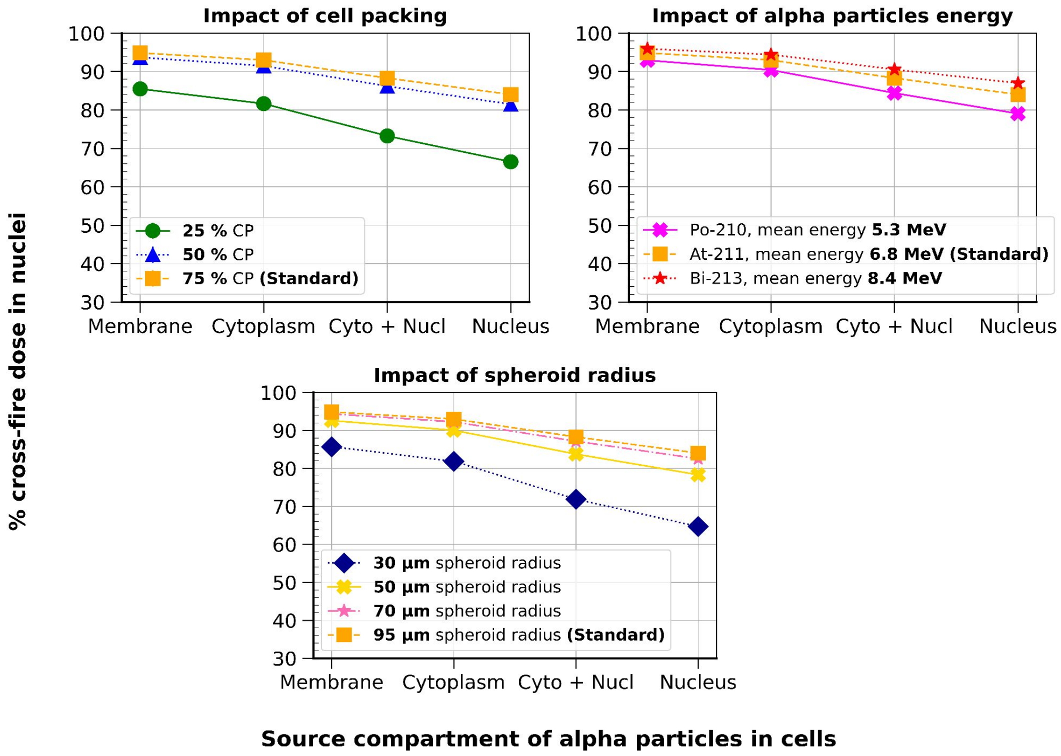


Simulation parameters

- **Number of particles per cell :** 42 *(Chouin et al. 2012, murine treatment)*
- **Hypothesis :** 100 % labeling
- **Cell size :** nucleus radius = 5.5 µm, cell radius = 6.9 µm
- **Cell packing** : 25 - **75 %**
- **Radionuclide** used : ^{210}Po, ^{211}**At** , ^{213}Bi
- **Spheroid radius** : 30 - **95 µm**



Results : effects on cross-fire

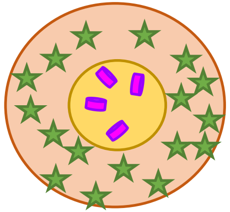


Strong **cross-fire effect**, between 65 and 98 % nucleus cross-fire dose

Less % cross-fire when particles are **closer to nucleus**

Small parameters impact, except for low compaction and small spheroids

Results : effects on nucleus physical dose

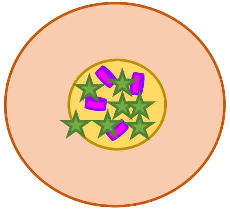


Cytoplasm only distribution :

< 3 % mean **nucleus physical dose** increase compared to **no internalization**

→ **No influence** of cytoplasm internalization

Nucleus only distribution :



+ ~ **15 %** mean **nucleus physical dose** compared to no internalization, **in most cases**

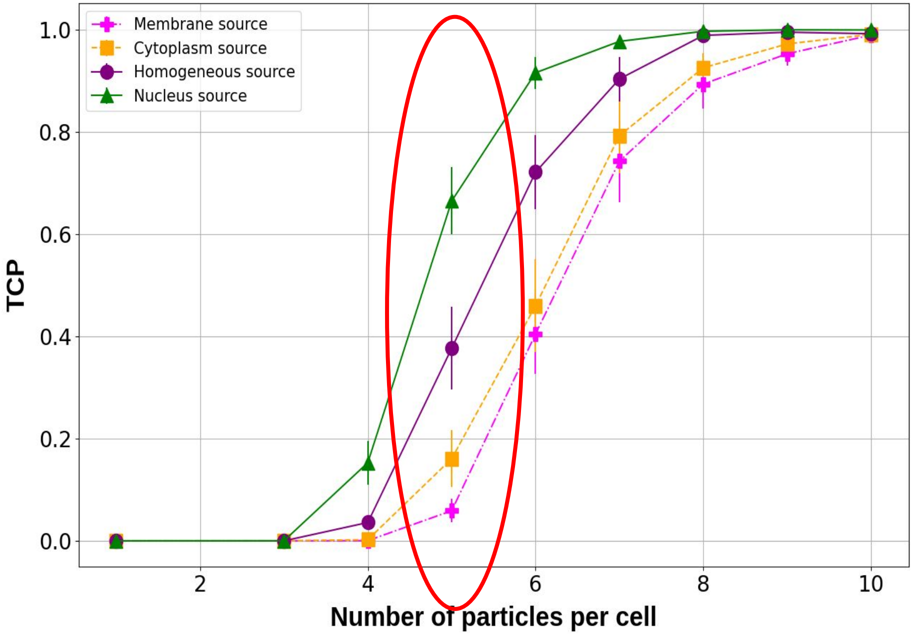
+ ~ **30 %** mean nucleus physical dose for 25 % compaction spheroid and 30 µm spheroid radius

Significant effect of nucleus internalization, especially for low compaction and small spheroids.

Results : biological effect

Tumor **C**ontrol **P**robability always **equal to 1**, with 42 particles per cell

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



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

Highest differences at ~ **5 particles per cell**

18-fold higher TCP between nucleus and membrane source

Study's conclusion

Low impact of **cytoplasm internalization**

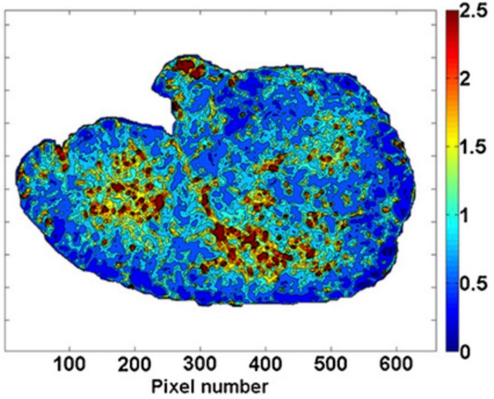
High impact of **nucleus internalization** for **low compaction** spheroids and **small** (<50 μm radius) **tumors**, and when **few radionuclides** are **labeled per cell**

Article in progress

Perspectives

- Influence of **cell line** on our calculations

- **Intra-tumoral** radionuclide distribution study
  → variation of **labeled cell %**
  → **cold regions of cells** protected by fibroblasts



Intra-tumoral activity distribution, Back et al. 2010

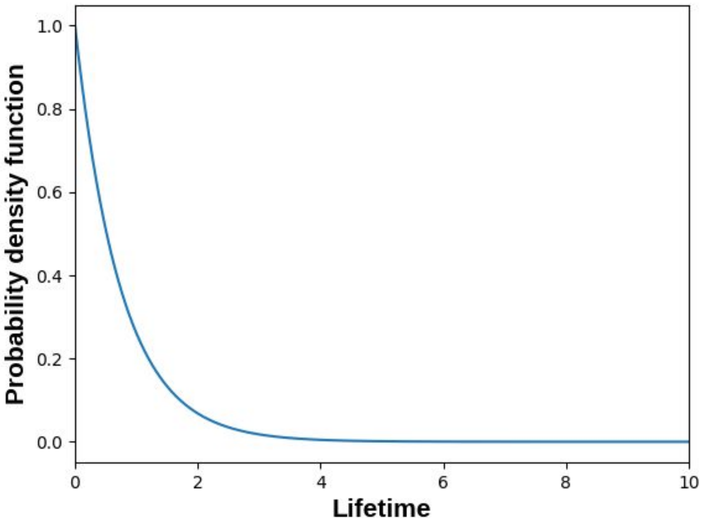
- Work with **biologist teams** that can achieve **TAT experiments**

Thank you for your attention

Grenoble, France

Diffusion of Po-211

Probability density function for lifetime :



Thermal diffusion equation in 1D :

$$\frac{d\langle x^2\rangle}{dt} = 2\ \mathrm{D_t}$$

$$x = f(t)$$

Distance between emission site and new location

Inspired from *Palm et al. 2004* → Mono-cellular