



**HAL**  
open science

## Parametric study of the impact of intracellular radionuclide distribution in Targeted Alpha Therapy, with multi-scale modeling

Victor Levrague, Mario Alcocer-Avila, Sarah Otmani, Lydia Maigne, Etienne Testa, Michaël Beuve, Rachel Delorme

### ► To cite this version:

Victor Levrague, Mario Alcocer-Avila, Sarah Otmani, Lydia Maigne, Etienne Testa, et al.. Parametric study of the impact of intracellular radionuclide distribution in Targeted Alpha Therapy, with multi-scale modeling. 17th International Congress for Radiation Research (ICRR), Aug 2023, Montréal, Canada. . hal-04305468

**HAL Id: hal-04305468**

**<https://hal.science/hal-04305468>**

Submitted on 24 Nov 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



## Context

**Targeted Alpha Therapy:** Vectorization of an **α-emitter** radionuclide in **tumors** thanks to **targeting** pharmaceutical **agent**

**Heterogeneous** dose deposition at the **micro-metric** scale:

Two identical macroscopic doses  
≠ two identical biological effects

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

**Proposed method to predict biological effects:**

Combination of biophysical modeling and Monte-Carlo simulations at the micrometric scale

## Objectives

Study the **impact** of **intracellular radionuclide distribution** on the **efficiency** of TAT as a function of **influence parameters**

Membrane      Cytoplasm      Homogeneous      Nucleus



Intracellular radionuclide distribution scenarios considered in this study

**Observables:** Physical dose (also called specific energy, at the microscopic scale), cell survival, tumor control probability (cell line: Human Salivary Gland)

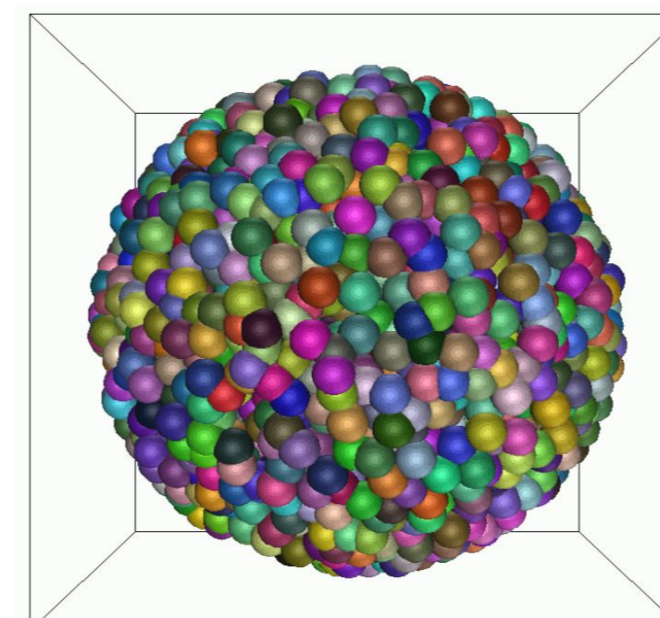
## Materials & Methods

**CPOP** [1]

**GEANT4** [2]

**NanOx** [3]

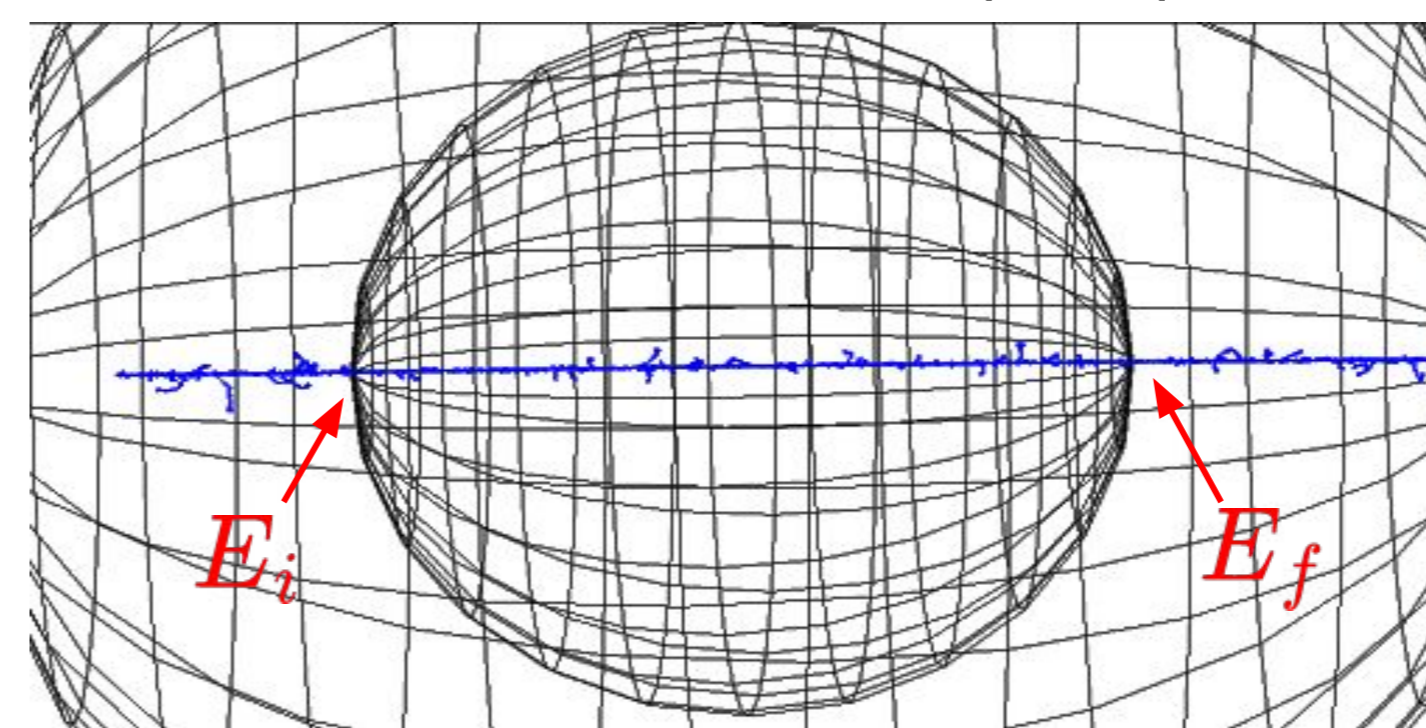
- **Generation of high cellular density 3D spheroid**, with **CPOP**



Spheroid with 75% compaction and 3069 cells

- **Monte-Carlo simulations of alpha particles** in cells, with **Geant4 - CPOP**

- **Output:** physical doses, entrance  $E_i$  and exit  $E_f$  kinetic energies for each nucleus traversal of an alpha particle



Geant4 simulation of an alpha particle crossing a cell nucleus

- **Cell survival prediction model**
- **Nucleus = sensitive volume**

Nanodosimetry

Microdosimetry

Lethal local damage

Sublethal global damage

- Takes into account **variation of damage density** with the ion's **energy**

- **Output:**  $(\alpha, \beta)$  radiobiological coefficients

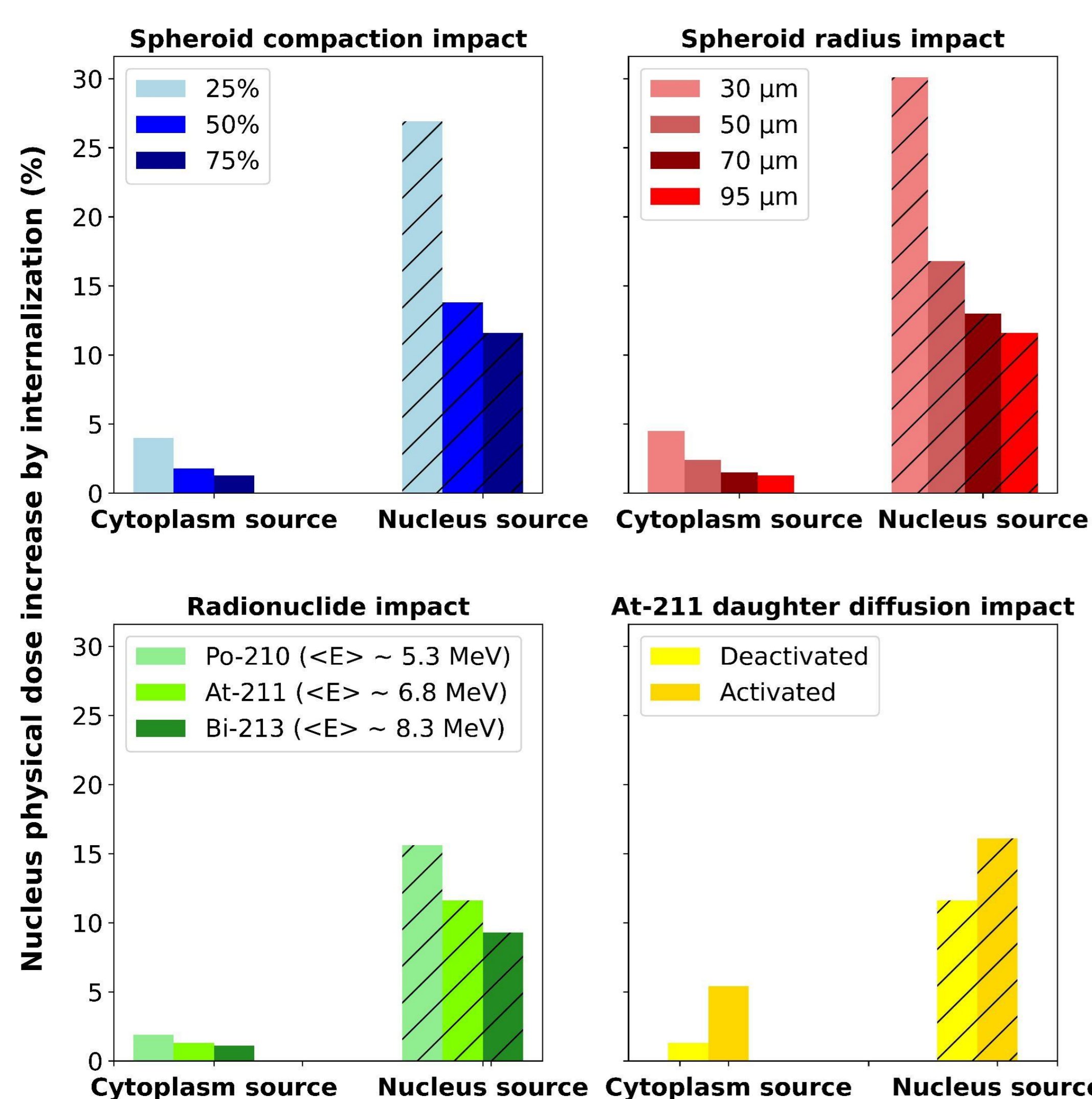
Combined calculations of **cell survivals S** and **TCP** :

$$S = f((\alpha, \beta), (E_i, E_f))$$

$$TCP = \prod_{k=1}^{n_{cell}} S_k$$

## Results and Discussion

### A-1: Impact of geometry and irradiation parameters on nucleus physical dose, according to radionuclide internalization

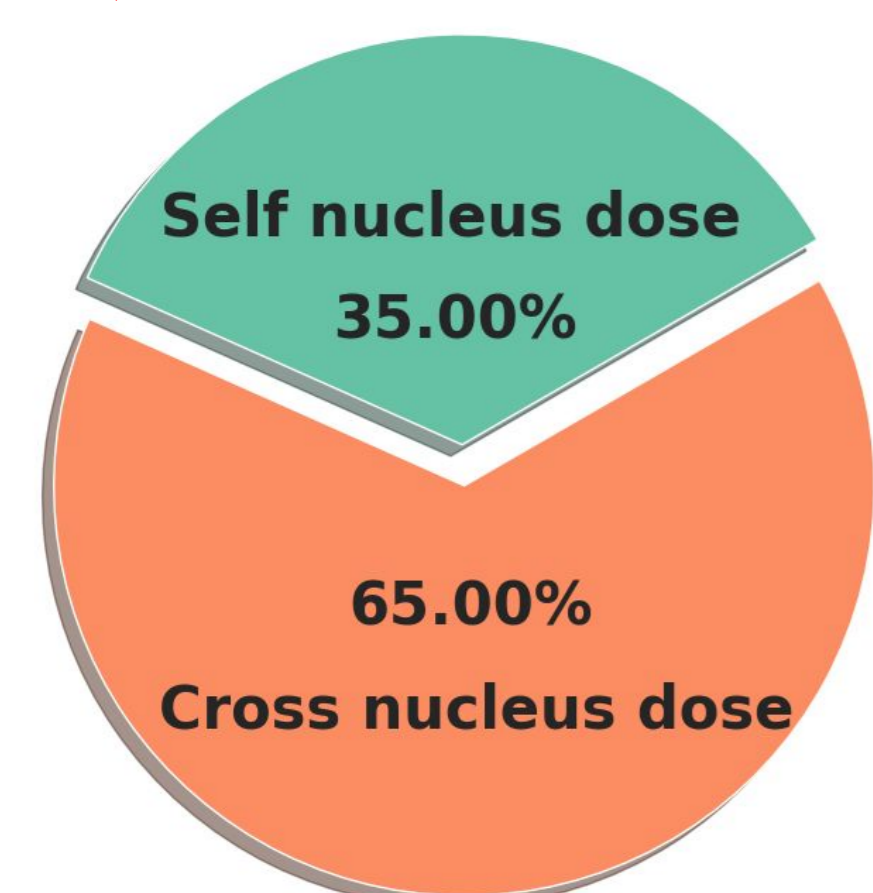


**Mean nucleus physical dose increase of cytoplasm and nucleus radionuclide source distribution compared to membrane source distribution only.**

*Default parameters:*  
95μm radius spheroid,  
75% compaction,  
irradiated by At-211. In each plot, one parameter was changed at a time.

- **Low impact** of **cytoplasm** only internalization
- **Moderate impact** of **nucleus** only internalization
- **High impact** of **small and low compaction** spheroid

### A-2: Quantification of cross-fire irradiation



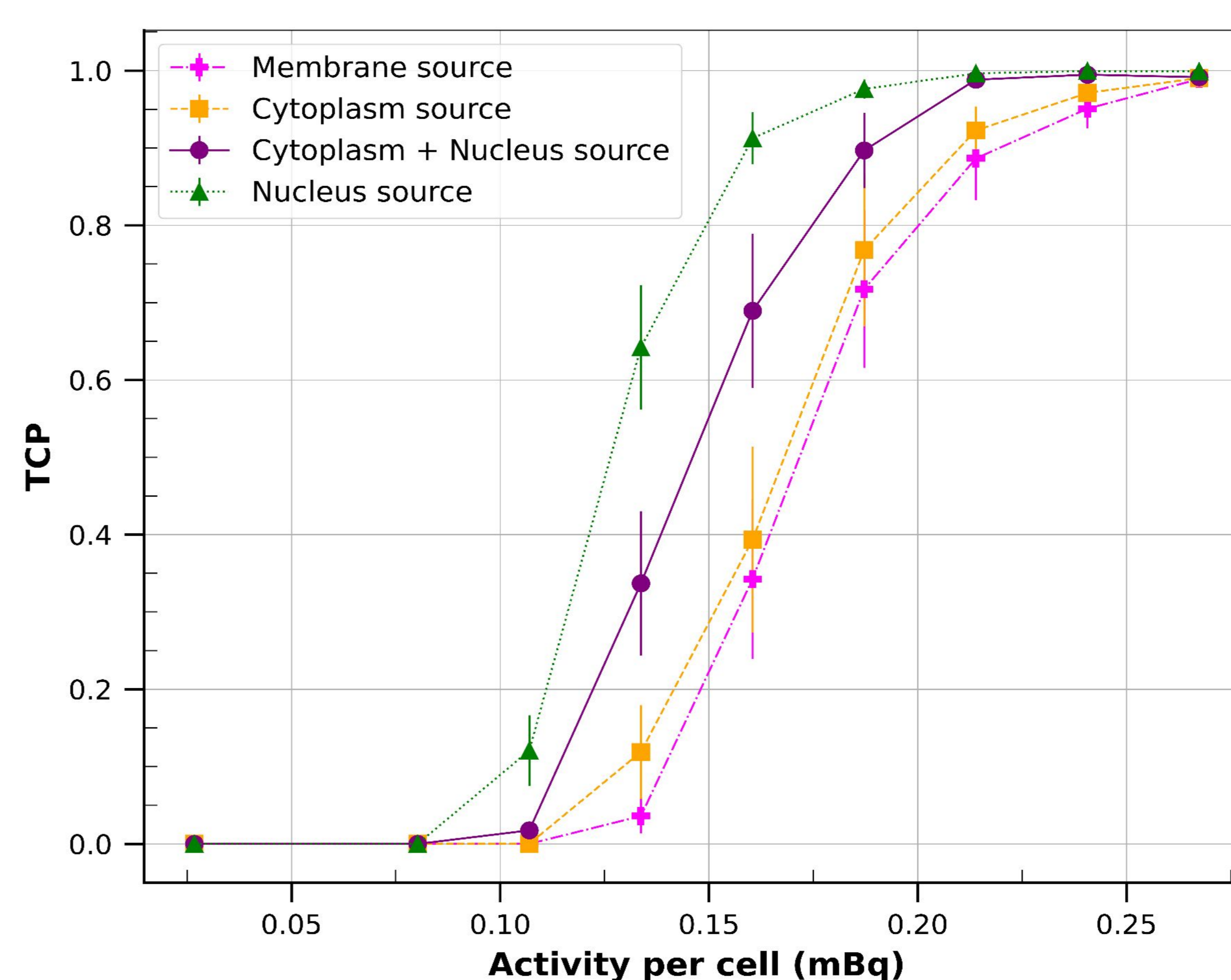
**Cross nucleus dose:** dose to cell nucleus due to radionuclide **not fixed** to this cell

- In this study = 65 to 98% of total irradiation

→ **Cross-fire effect more important than intracellular distribution** due to **high range of alpha particles**

Minimum observed cross-fire nucleus dose %: 30μm radius spheroid

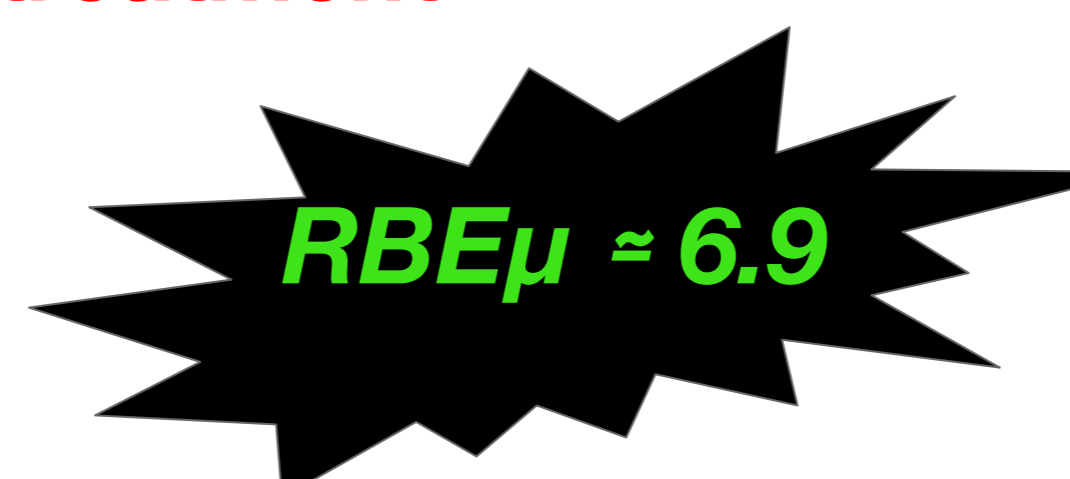
### B-1: Tumor Control Probability as a function of activity per cell



Tumor control probability as a function of the activity per cell (mBq). The simulations were performed in a 95μm radius spheroid, with 75% compaction, irradiated by At-211.

- **Threshold effect** around 0.15 mBq per cell
- At 0.15 mBq per cell: ~ **18 fold higher TCP** between **nucleus** and **membrane source distribution**

### B-2: RBEμ of alpha particles in the condition of an <sup>211</sup>At TAT treatment



RBEμ value found at 10% cell survival, for a membrane source distribution

**RBEμ:** Relative biological effectiveness at the micrometric scale, compared to a reference photon irradiation.

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

→ **High biological impact** of **alpha particle**, confirmed by literature [4].

## Conclusions

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

## Perspectives

- Modeling of **intratumoral** heterogeneity of radionuclide **distribution**
- Validation against **experimental data**
- Modeling radionuclide **diffusion kinetic**

## References

[1] Maigne, L., et al. *Physica Medica* 89 (2021): 41-50  
[2] Agostinelli, Sea, et al. *Nucl. Instrum. Methods. Phys. Res. B NUCL INSTRUM METH A* 506.3 (2003): 250-303.Z

[3] Cunha, Micaela, et al. *Physics in Medicine & Biology* 62.4 (2017): 1248.  
[4] Loucas, Bradford D., et al. *Radiation research* 179.1 (2013): 9-20.