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

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## 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)

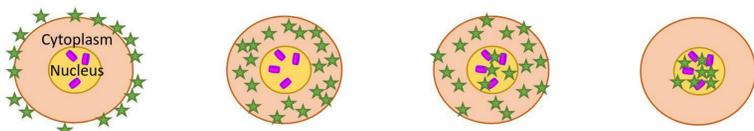
**Proposed method to predict biological effects:**

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)

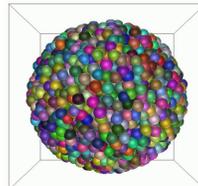
## Materials & Methods

**CPOP** [1]

**GEANT4** [2]

**NanOx** [3]

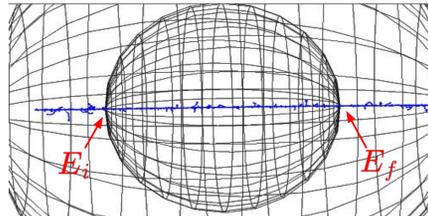
- **Generation of high cellular density 3D spheroid**, with **CPOP**



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

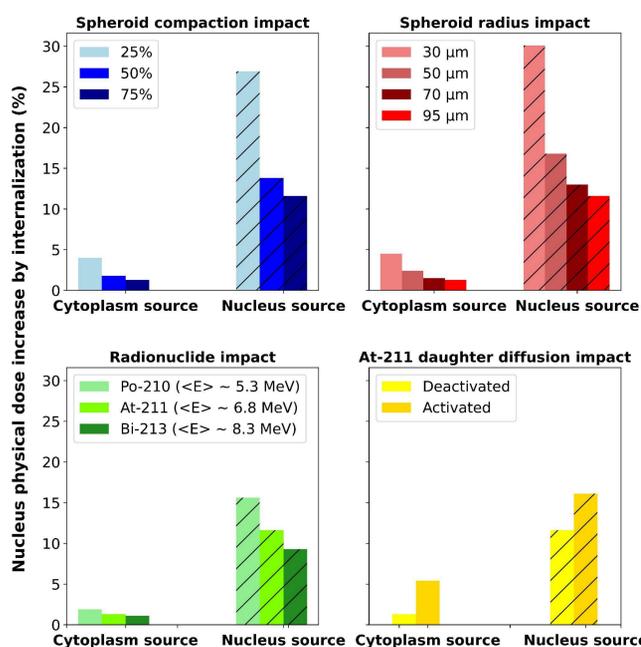
Combined calculations of **cell survivals S** and **TCP** :

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

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

## Results and Discussion

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

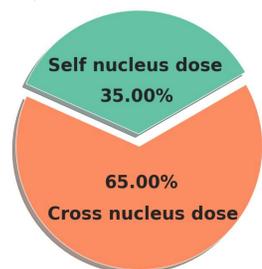


**Mean nucleus physical dose increase of cytoplasm and nucleus radionuclide source distribution compared to membrane source distribution only.**

*Default parameters:*  
95 μm 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



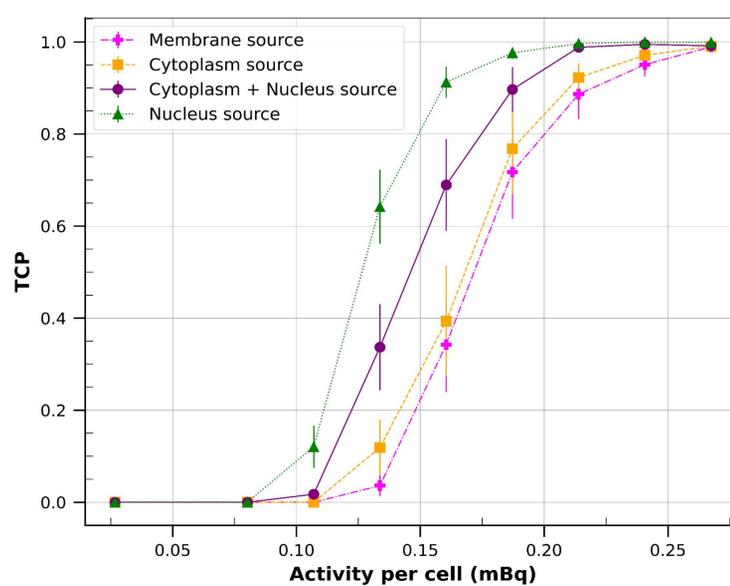
**Cross nucleus dose:** dose to cell nucleus due to radionuclide **not fixed** to this cell

- 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 %: 30 μm 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 95 μm 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** (< 50 μm 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.