PhD Seminar 2023/03/27 : Victor Levrague

Improvement of the prediction of biological effects for targeted innovative radiotherapies involving short-range ions, using a biophysical approach

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2: IP2I, Lyon

Team : Nuclear Physics and Medical Applications

Summary

Introduction

- Targeted Alpha Therapy context
- Problematics in predicting biological effects

Materials & Methods

- Biophysical model : NanOx
- Monte-Carlo model & Complex geometries : Geant4 & CPOP

Results

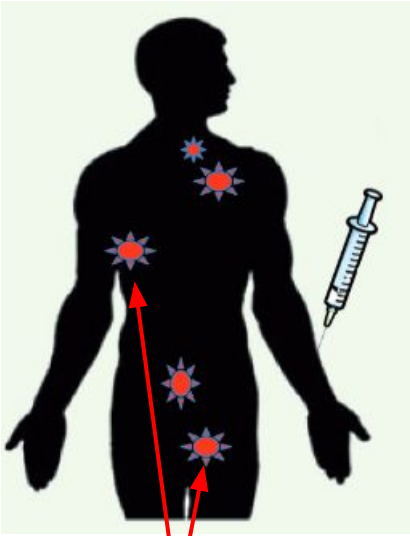
- Parametric study of the impact of intracellular radionuclide distribution

Conclusions

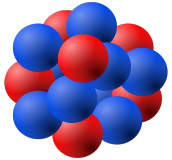
Perspectives

Targeted Alpha Therapy : an innovative internal radiotherapy

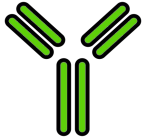
Radiotherapy: treat a disease, usually **cancer**, using **ionizing** beams



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*

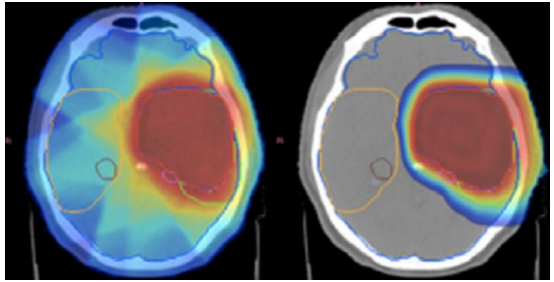
Prediction of biological effect (1/2)

External radiotherapies

- Control of the irradiation beam
- Homogeneous macroscopic dose deposition
- Physical dose prescription

X-rays radiotherapy
(Photons)

- **Reference** radiotherapy



X-rays *Protons*

Treatment plans of central nervous system with photons and protons beams. Durante et al. 2019

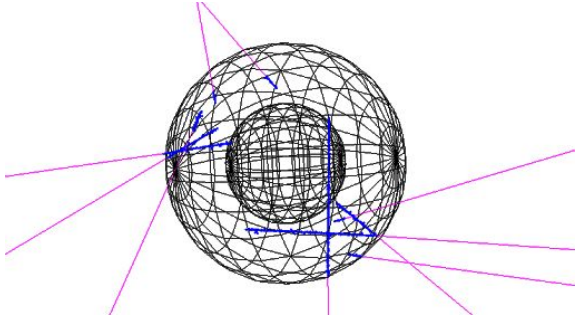
Hadrontherapy
(hadrons: e.g. protons or carbons)

- Benefit from the **biological effect** of **ions** to create **complex dna damage**

Prediction of biological effect (2/2)

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

- Biological effects are complex to predict
  ⇒ Treatments are complex to planify

Materials & Methods

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The biophysical model NanOx (1/2)

❖ **Biophysical model**

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

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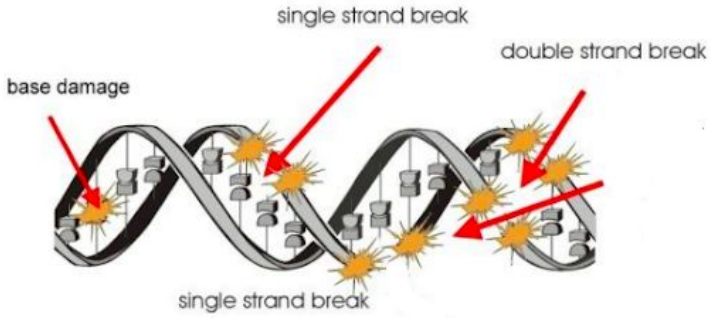
Lethal damage : **DNA Double Strand Breaks**

α radiobiological coefficient



Simple and complex damage that can occur in dna with ionization

The biophysical model NanOx (1/2)

❖ **Biophysical model**

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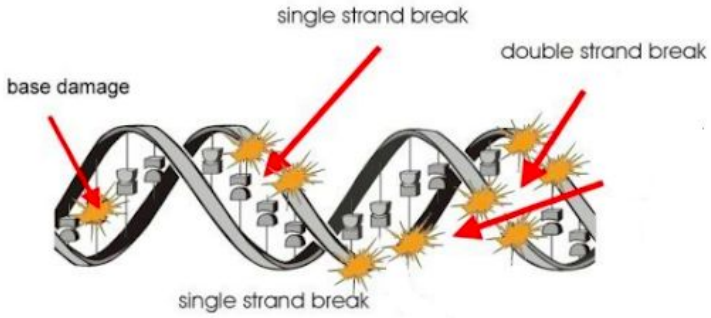
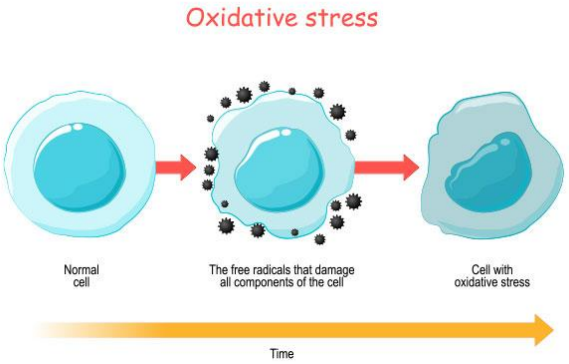


Simple and complex damage that can occur in dna with ionization

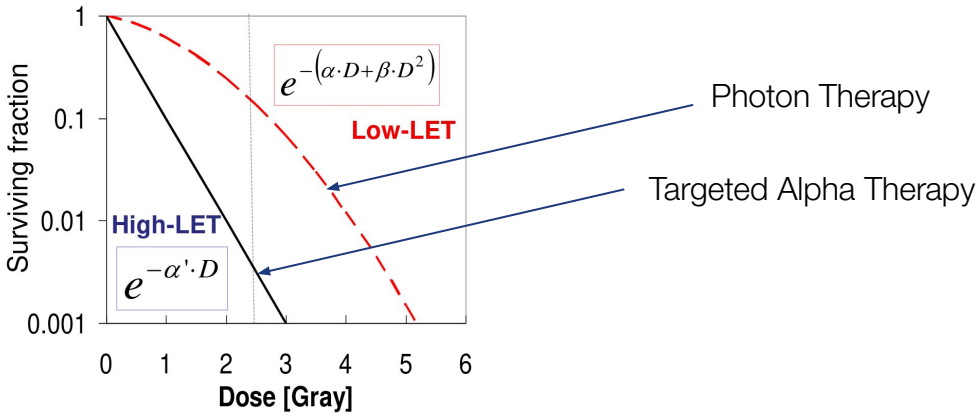
Sublethal damage : **oxidative stress**

β radiobiological coefficient



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)*

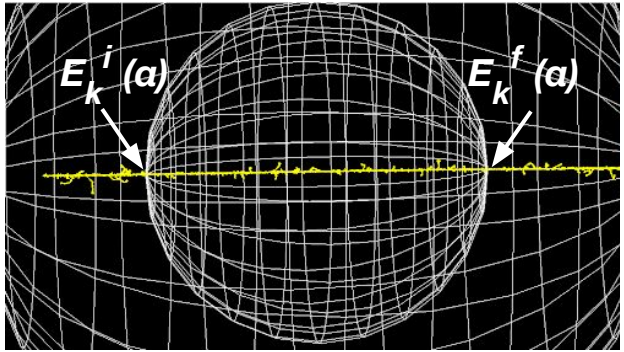
Adaptation of NanOx at low energies *(few MeV)*

Cell survival to lethal events =

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

n = number of lethal events

E_k = *Kinetic energy*



Homemade Monte-Carlo simulation of an helium ion crossing a nucleus

Adaptation of NanOx at low energies *(few MeV)*

Cell survival to lethal events =

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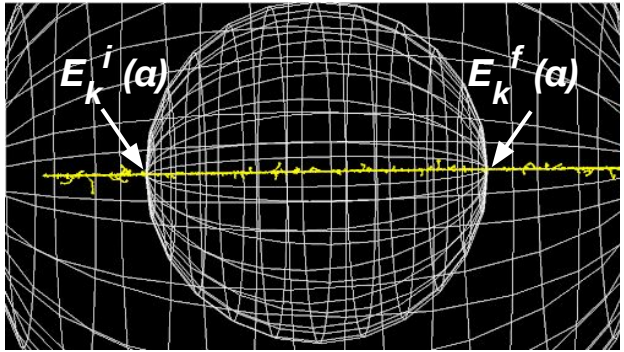
n = number of lethal events

E_k *= Kinetic energy*

Number of lethal events per energy =

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



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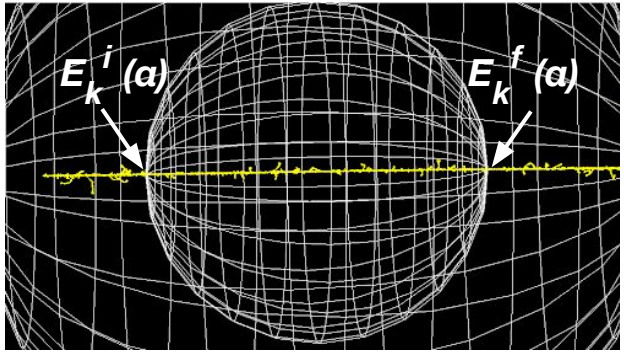
❖ If *Ei* ≃ *Ef* **(hadrontherapy)**,

$$n(E_k^i) = \frac{dn}{dE}(E_k^i) \cdot \Delta E_k$$



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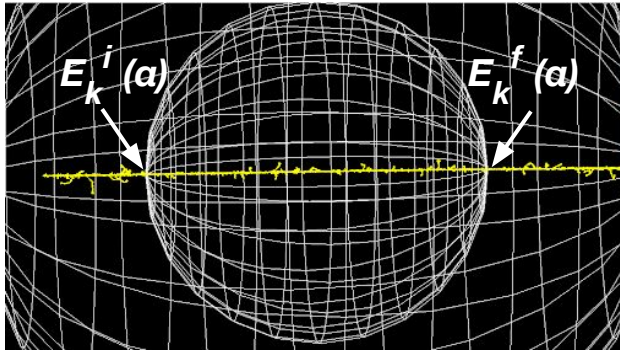
- If *Ei* ≃ *Ef* **(hadrontherapy)**,

$$n(E_k^i) = \frac{dn}{dE}(E_k^i) \cdot \Delta E_k$$

- If *Ei* ≠ *Ef* **(internal alpha therapy)**,

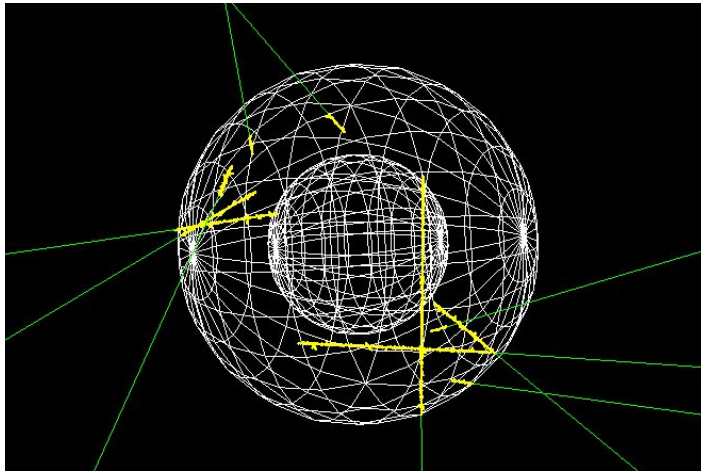
$$n\left(E_k^i, E_k^f\right) = \int_{E_k^f}^{E_k^i} \frac{dn}{dE}(E) \cdot dE$$



Homemade Monte-Carlo simulation of an helium ion crossing a nucleus

Geant4 simulations

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

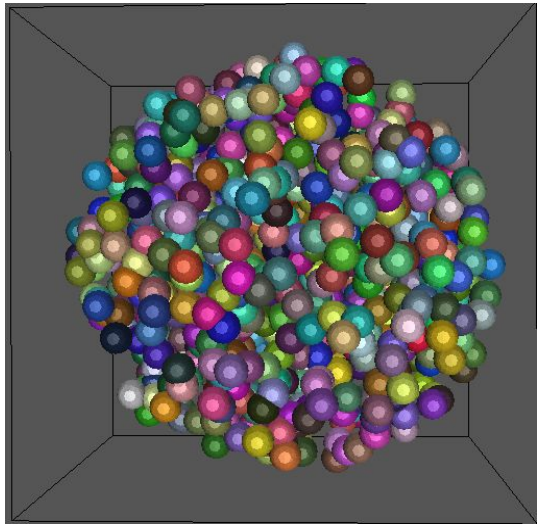


Homemade Monte-Carlo simulation of 10 helium ions emitted in the cytoplasm

- **Output :**
  - Physical doses in **nuclei** and cells
  - In (E_k^i) and out (E_k^f) energies of alpha particles in **nuclei**

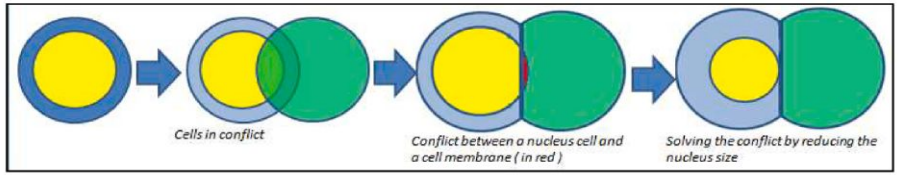
$$D = \frac{Energy}{Masse}$$

Complex geometry generation: CPOP



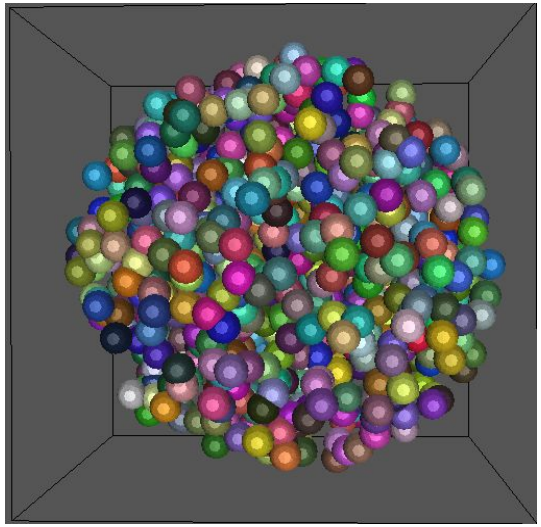
95 µm radius Spheroid generated by CPOP

- 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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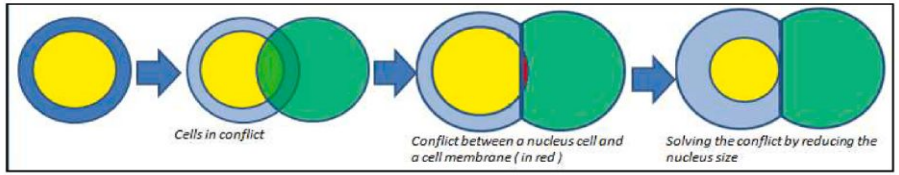
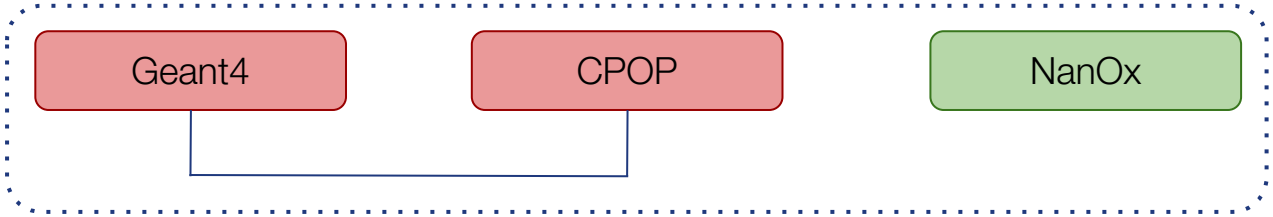


Maigne et al. 2021

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

A combined prediction model, using biophysical and physical tools

Existing models



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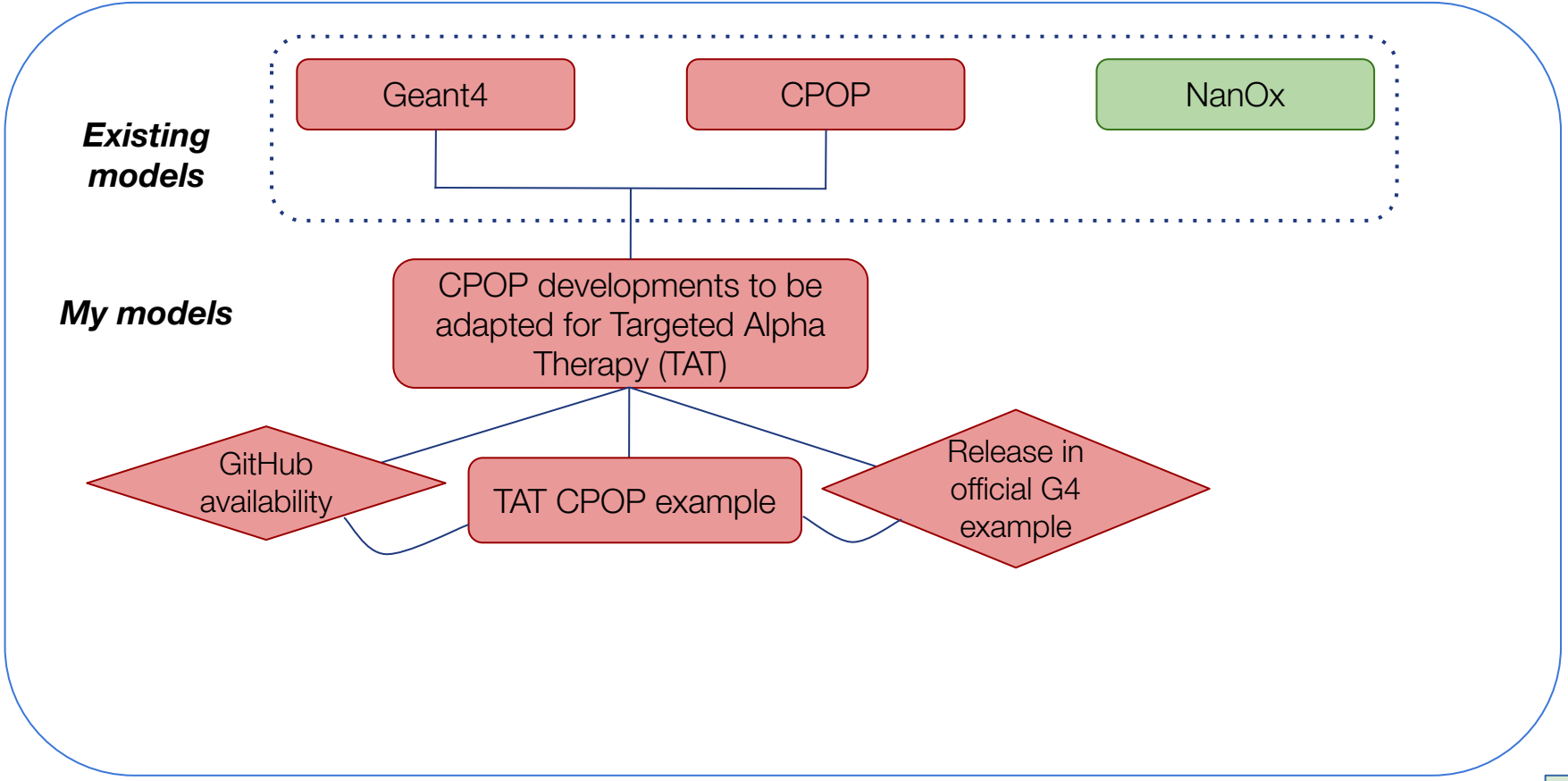

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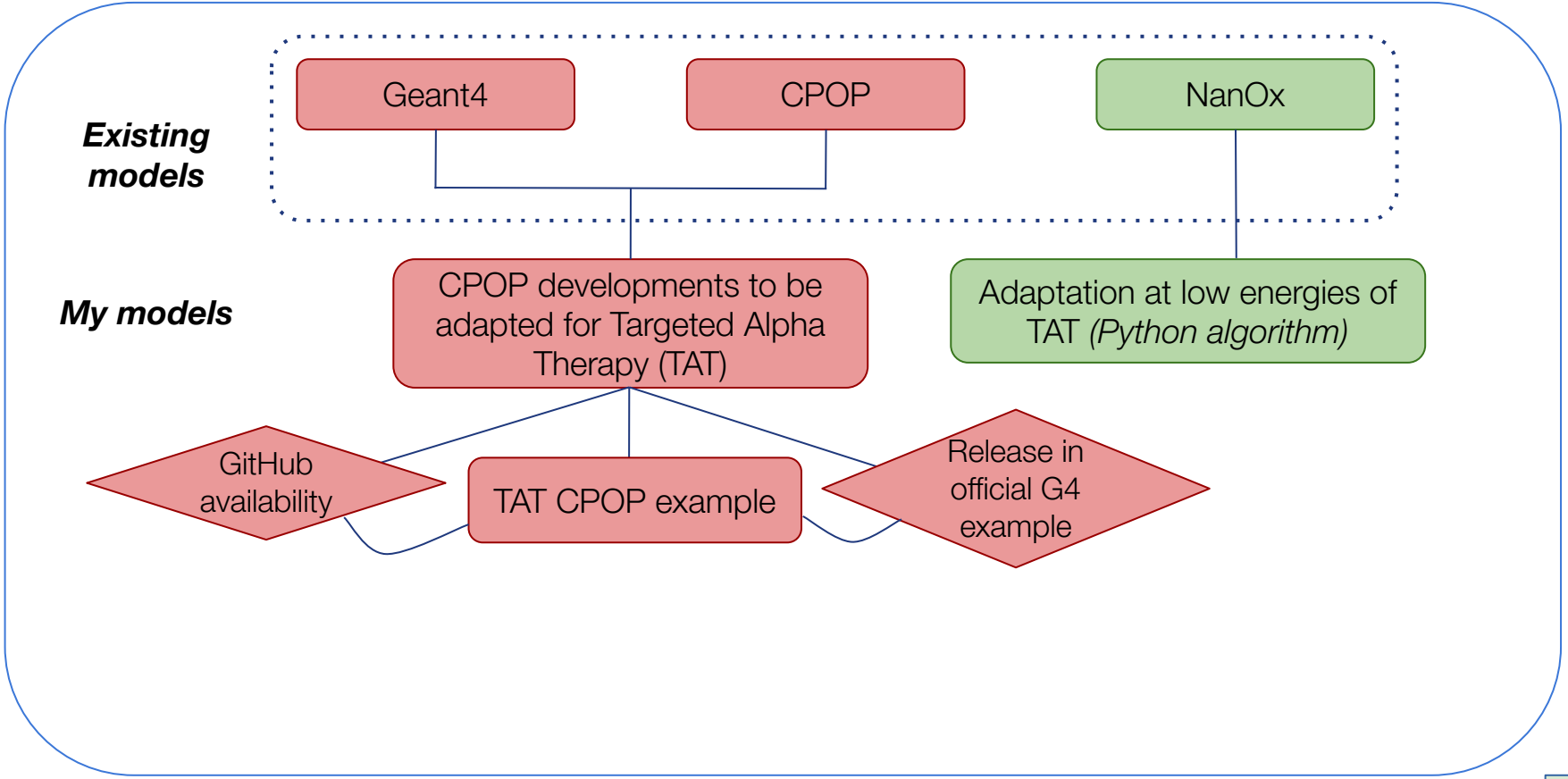

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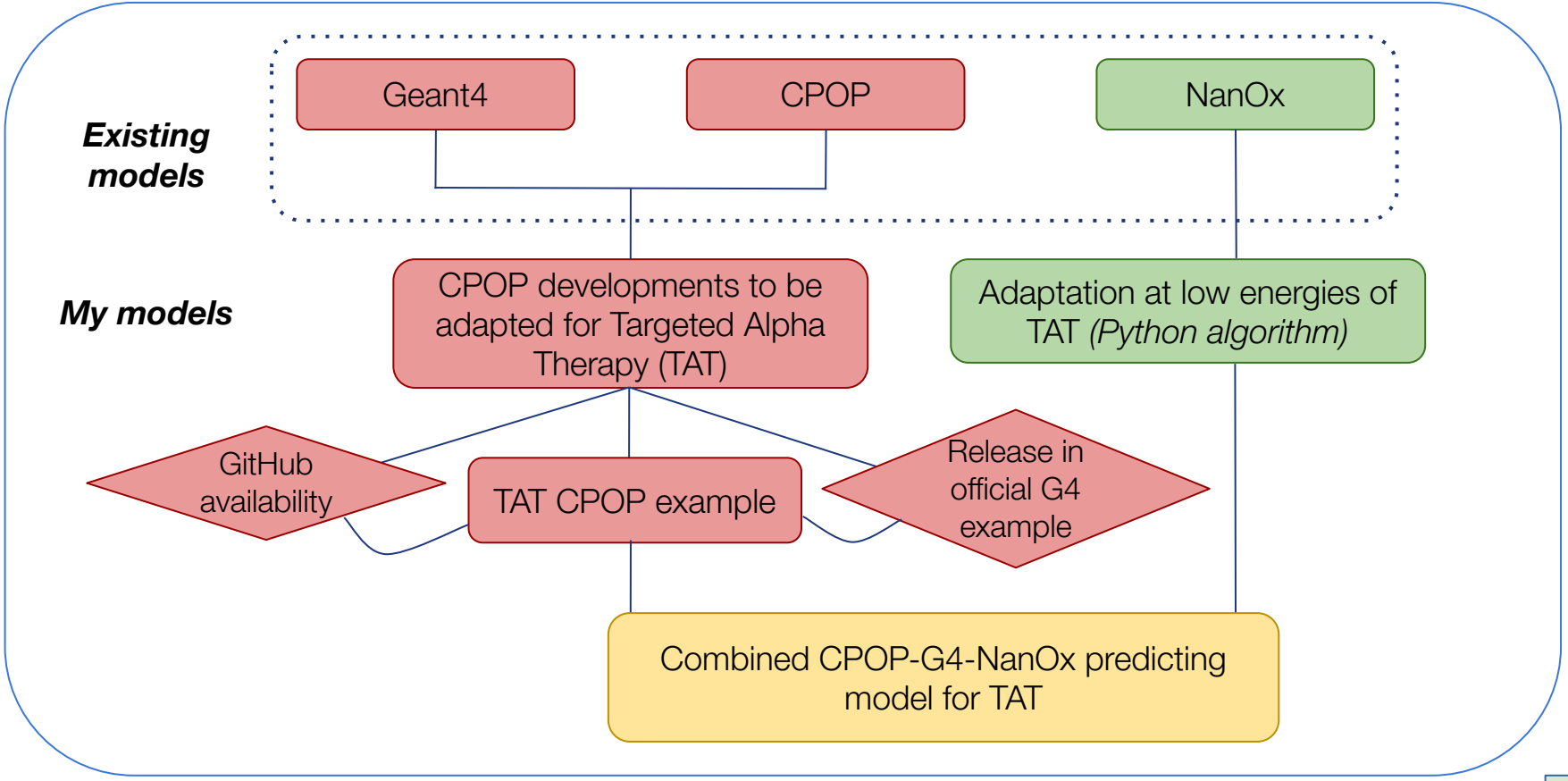

Results

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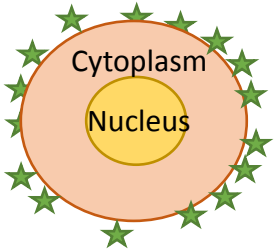
Impact of intracellular radionuclide distribution

In **Targeted Alpha Therapy**,
- Radionuclides can **enter in cells** because of the **chemical vector**
- **Radionuclide distribution cannot** be **known** during treatment

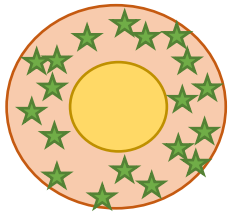
Different distributions studied :

α-emitter radionuclides

Membrane



Cytoplasm



Homogeneous

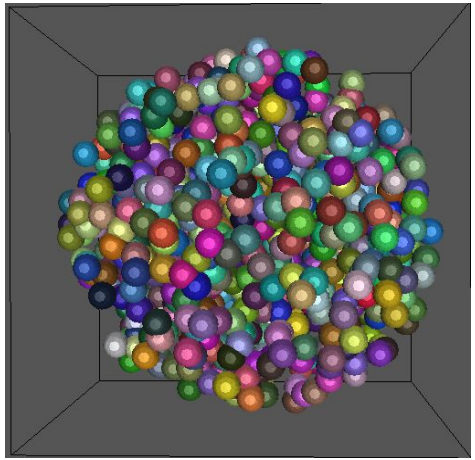
Nucleus

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

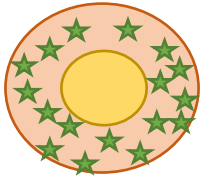
- **Number of alpha particles per cell :** 42
- **Studied parameters :**
  - **Spheroid compaction** : 25 - **75 %**
  - **Radionuclide** used : ^{210}Po, **^{211}At** , ^{213}Bi
  - **Spheroid radius** : 30 - **95 µm**



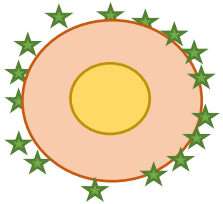
95 µm radius Spheroid generated by CPOP

Cell survivals calculated for the HSG cell line

Impact on nucleus physical dose



Cytoplasm only distribution :



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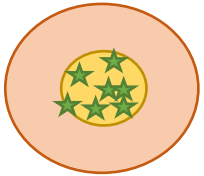

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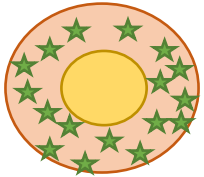

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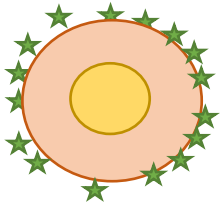

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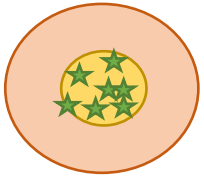
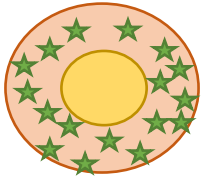


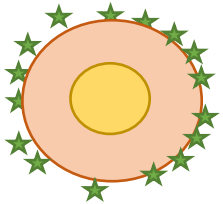
Spheroid radius :	**30 µm**	**50 µm**	**70 µm**	**95 µm**
$\frac{D_{nucleus}\ (cytoplasm\ source)}{D_{nucleus}\ (membrane\ source)}$	1.045	1.018	1.013	1.024
$\frac{D_{nucleus}\ (nucleus\ source)}{D_{nucleus}\ (membrane\ source)}$	1.301	1.168	1.130	1.116

Physical dose results for membrane, cytoplasm and nucleus distribution, with only the study of spheroid radius. Statistical errors are below 0.001.

Impact on nucleus absorbed dose



Cytoplasm only distribution :

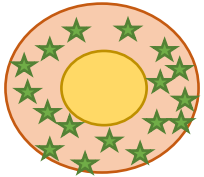


< 5 % mean **nucleus absorbed dose** increase compared to **no internalization**

Low influence of cytoplasm only internalization

- Spheroid compaction
- Alpha particles energy
- Spheroid radius

Impact on nucleus absorbed dose



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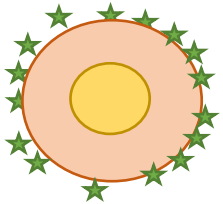

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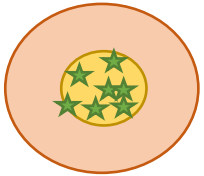


< 5 % mean **nucleus absorbed dose** increase compared to **no internalization**

Low influence of cytoplasm only internalization

- Spheroid compaction
- Alpha particles energy
- Spheroid radius

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

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

Small effect of nucleus internalization, but **higher** for low compaction and small spheroids.

Cross-fire effect : explanation

Cross-fire irradiation to a cell =

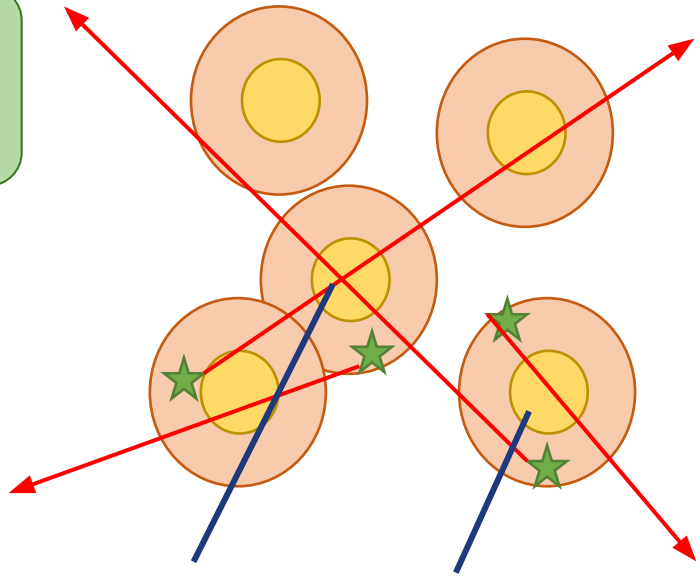
Irradiation coming **from radionuclides not fixed to this cell**

Cross-fire irradiation

100 %

Importance of the medium irradiation compared to self cell irradiation

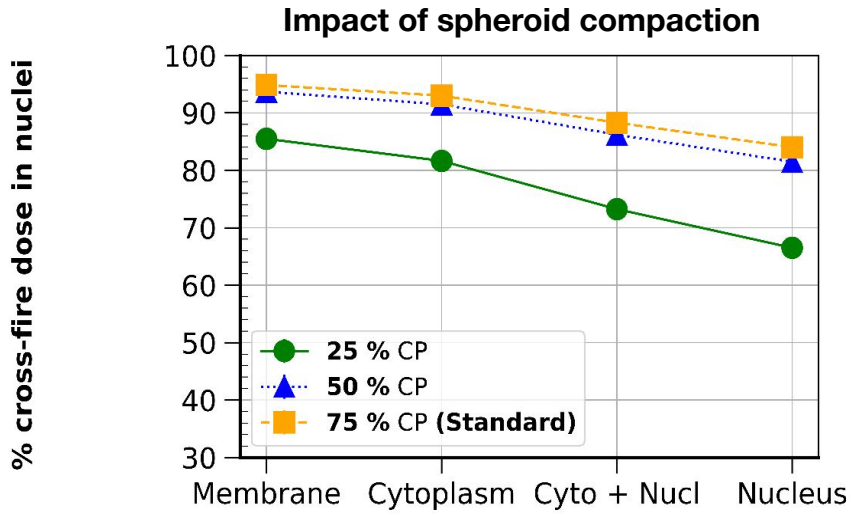
0 %



100 % cross-fire

0 % cross-fire

Quantification of cross-fire effect (1/3)



- **Spheroid compaction**
- *Alpha particles energy*
- *Spheroid radius*

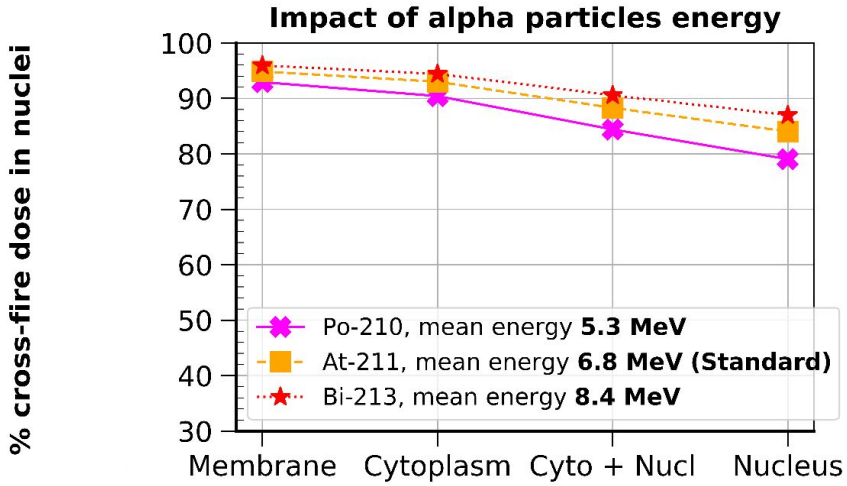
} **Fixed**

Strong **cross-fire effect**, between **68** and **96 %** nucleus cross-fire dose

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

High impact of low compaction spheroid on importance of radionuclide distribution

Quantification of cross-fire effect (2/3)



- *Spheroid compaction*
- ***Alpha particles energy***
- *Spheroid radius*

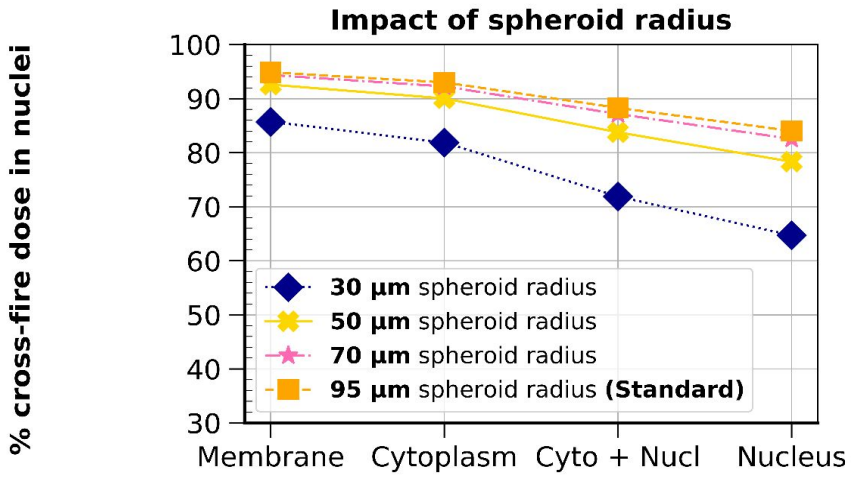
Fixed

Strong **cross-fire effect**, between **80** and **98 %** nucleus cross-fire dose

Less % cross-fire when particles are closer to nucleus

Low impact of alpha particles energy on importance of radionuclide distribution

Quantification of cross-fire effect (3/3)



- *Spheroid compaction*
- *Alpha particles energy*
- **Spheroid radius**

} **Fixed**

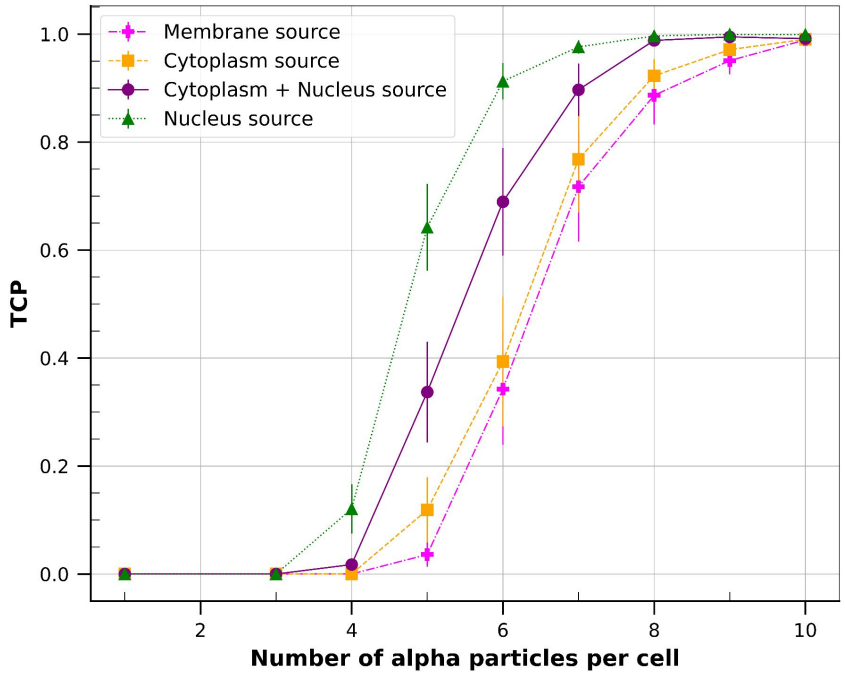
Strong **cross-fire effect**, between **65** and **98 %** nucleus cross-fire dose

Less % cross-fire when particles are closer to nucleus

High impact of small spheroid radius on importance of radionuclide distribution

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

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

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

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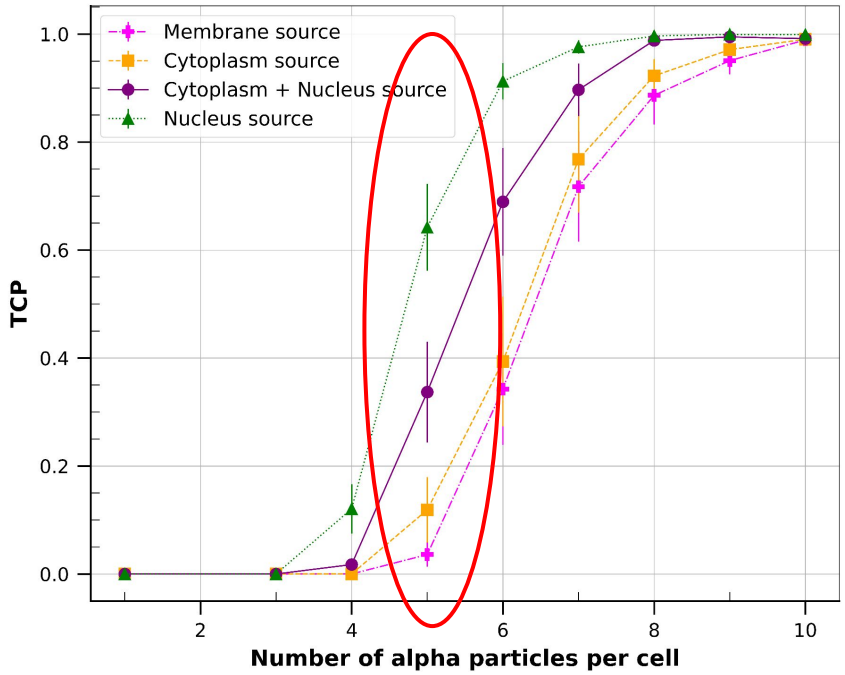

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Impact on biological effect (2/2)

Number of alpha particles per cell	3	5	7
$\frac{D_{nucleus}\ (nucleus\ source)}{D_{nucleus}\ (membrane\ source)}$	1.116 + 0.002	1.116 + 0.002	1.116 + 0.002

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Impact of radionuclide distribution is **not influenced** by number of alpha particles per cell **in term** of **physical dose**, but **is in term** of **Tumor Control Probability**

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RBEµ at 10% cell survival ≃ **6.9**, compared to external photon irradiation

Relative biological effectiveness = $\frac{D_{reference}}{D_{TAT}}$

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

Take-home messages

- ❖ **Low impact** of cytoplasm & nucleus internalization in **most cases**

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

- ❖ **Biological observables** are mandatory to take into account in **addition** to classical **physical ones**

General conclusions

- ❖ Combined predicting model NanOx - Geant4 developed for low energies
- ❖ CPOP model adapted and improved for Targeted Alpha Therapy modeling
- ❖ Parametric study with this model: impact of intracellular radionuclide distribution in Targeted Alpha Therapy

Ongoing work & Perspectives

- **Article** submission on the intracellular radionuclide distribution study
- **Article** writing and calculations for the NanOx adaptation at low energies ions

E.g. : validation of the NanOx hypothesis $Ek_i - Ek_f = Edep_{nucleus}$

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- Comparison of simulation results with experimental data

E.g. : Neti et al. 2007.
Biological Response to Nonuniform distributions of 210Po in Multicellular Clusters

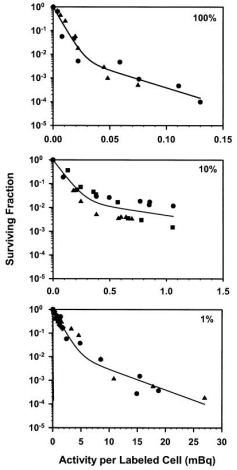


FIG. 3. Survival of V79 cells in multicellular clusters as a function of initial ^{210}Po activity per labeled cell when 100, 10 or 1% of the cells in the multicellular clusters were labeled with ^{210}Po-citrate. In each graph, different symbols correspond to independent experiments. Solid curves represent least-squares fits of the data by a two-component exponential function.

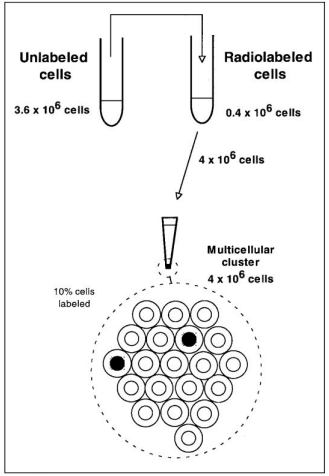
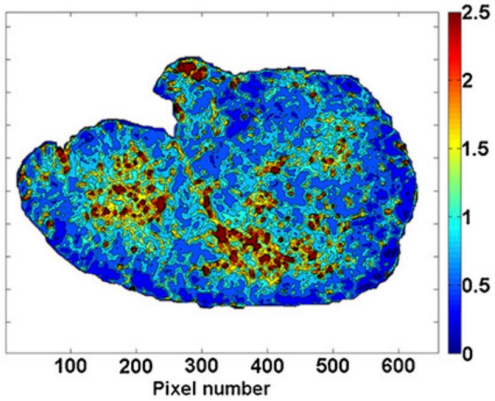


FIGURE 1. Assembly of multicellular cluster of V79 cells wherein 10% cells were radiolabeled with ^{131}IdU.

Ongoing work & Perspectives

❖ Study of the impact of intratumoral radionuclide distribution in Targeted Alpha Therapy

→ variation of **labeled cell %**
→ **cold regions of cells** protected by fibroblasts
→ heterogeneous tumor penetration
→ **kinetic model** of radionuclide diffusion



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

Ongoing work & Perspectives

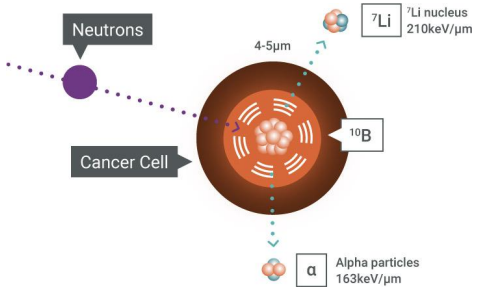
❖ Study of impact of boron intracellular distribution in BNCT:

$$^{10}B + n_{th} \rightarrow [11B]^{*}$$

$$[11B]^{*} \xrightarrow{6\,\%} {}^{4}He + {}^{7}Li \quad (2{,}79\ MeV)$$

$$[11B]^{*} \xrightarrow{94\,\%} {}^{4}He + {}^{7}Li \quad (2{,}31\ MeV) + \gamma \quad 0{,}48\ MeV$$

Range of ^{4}He and $^{7}Li \simeq 1$ cell



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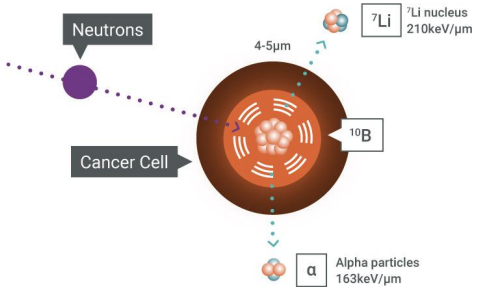
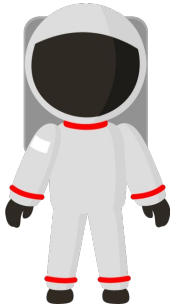
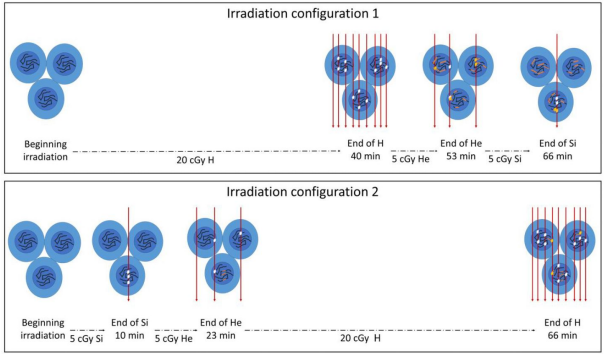


❖ IEA project in collaboration with Floriane Poignant (NIA/NASA):

"Mechanistic modeling of the impact of delivery order of low and high linear energy transfer ions on space radiation induced cancer risks"





Time for questions