In vitro dosimetry for assessment of Targeted-α-Therapy

Journées de Rencontres Jeunes Chercheurs 2022

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Alexis Doudard[1], Aurélien Corroyer-Dulmont[2,3], Cyril Jaudet[2], Myriam Bernaudin[3], Samuel Valable[3], Xavier Ledoux[1], Anne-Marie Frelin-Labalme[1]

[1]*Grand Accélérateur National d'Ions Lourds (GANIL), CEA/DRF CNRS/IN2P3, 14076 Caen, France*

[2]*Medical Physics Department, CLCC François Baclesse, 14000 Caen, France*

[3]*Normandie Univ, UNICAEN, CNRS, ISTCT, GIP CYCERON, 14074 Caen, France*

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Introduction – Radiotherapy, radiotherapies

- In France, 2018 : **382 000** new cancer cases, and **157 000** attributed deaths (French National Cancer Institute)
- Different organs, different cancer types… → Different treatments, including **radiotherapy**
- Radiotherapy is a vast domain :

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External radiotherapy

LINAC

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Internal radiotherapy

Brachytherapy
(source deposit)

Source projector

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Internal radiotherapy

Brachytherapy
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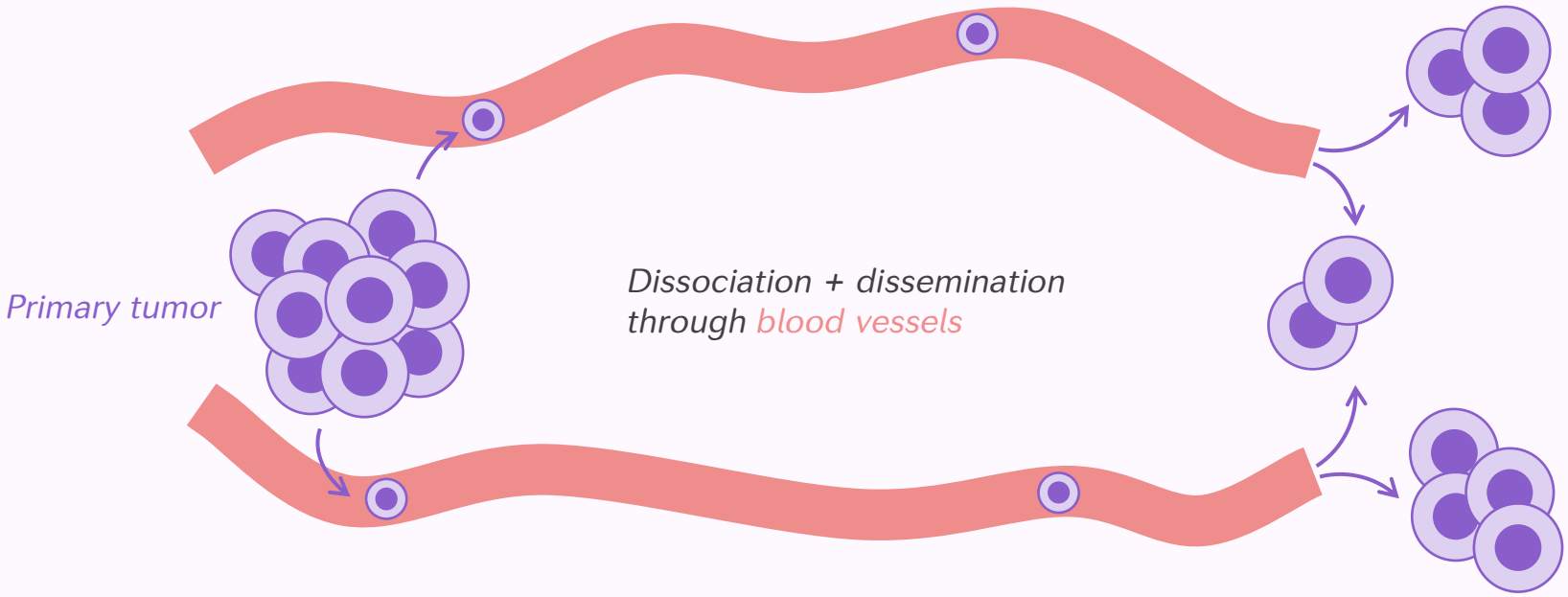
Targeted radiotherapy
(injection)

Internal (💉) and vectorized (🎯)
radiotherapy targeting diffuse targets

Xofigo ($Cl_2^{223}Ra$)

Introduction – Secondary brain metastases



Diffuse fixation on multiple sites in another organ :

Secondary metastases

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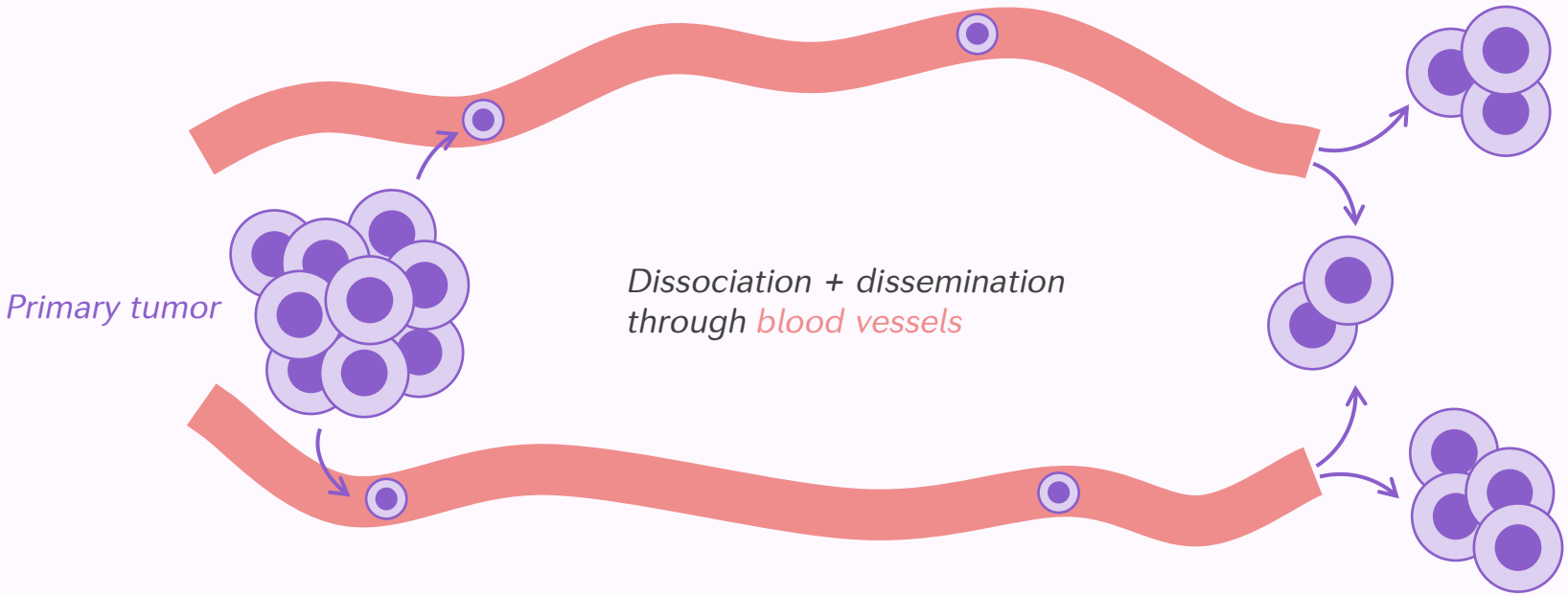


Diffuse fixation on multiple sites in another organ :

Secondary metastases

- Metastases are hard to detect and to treat (external beam therapy, surgery)

  ↳ Multiple lesion sites + Radio-induced damage: **poor prognosis** (6 months for brain metastases)

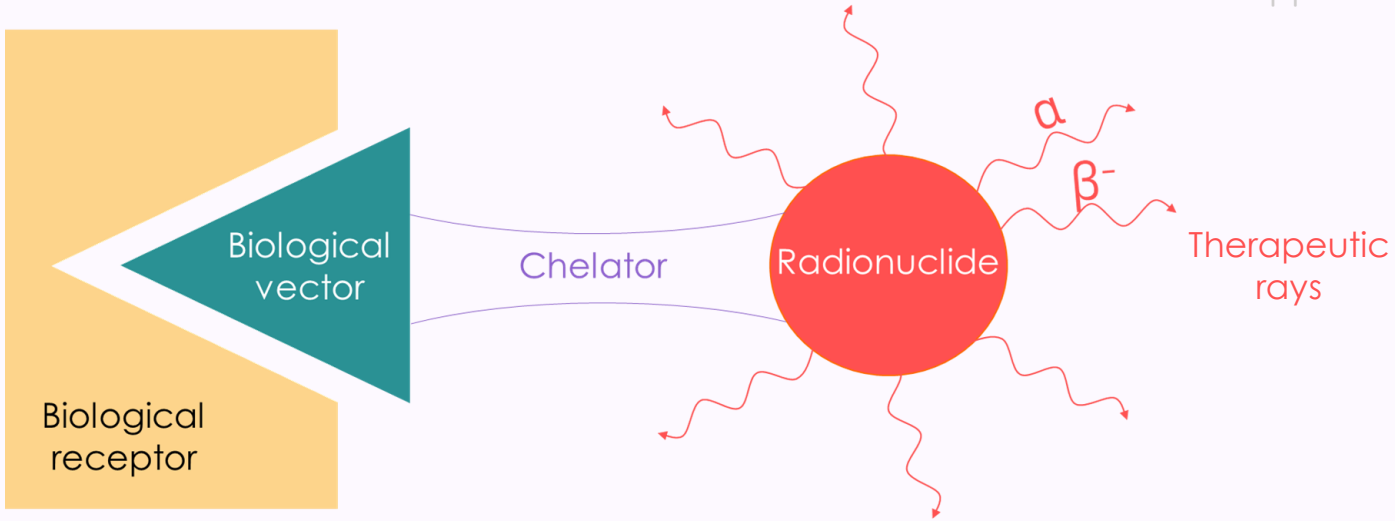
  QT Ostrom et al., Handb. Clin. Neurol. (2018)

- Local and specific treatment of the metastases: **Targeted-Radionuclide-Therapy(TRT)**

Introduction – VCAM-1 based targeted-alpha-therapy

- **Radiopharmaceutical** structure:

Internal (💉) and **vectorized (🎯)**
radiotherapy targeting diffuse targets



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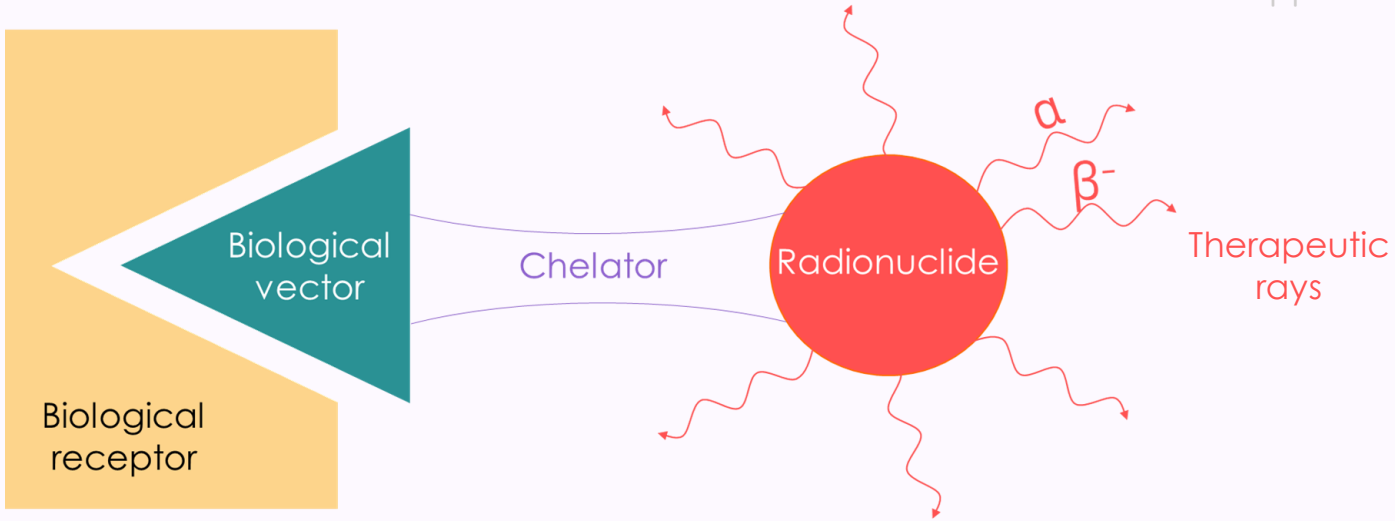


- **Over-expression of VCAM-1** observed in blood vessels **near** brain metastases → Anti-VCAM-1 antibody

- **Spatially restricted** target + sensible environment (**~100 µm in brain**)
- $T_{1/2}$ compatible with **clinical usability** and **radioprotection**

→ ^{212}Pb-αVCAM-1

N. Falzone et al., Theranostics (2015)

A. Corroyer-Dulmont et al., Neuro-Oncology (2020)

^{212}Pb ($T_{1/2}$ = 10.1 h) → ^{212}Bi (60.5 min) : **6.1** or **8.8 MeV α**
= **50** or **91 µm** in water

Introduction – *In vitro* assessment of targeted-alpha-therapy

➢ **Goal of *in vitro* assays**: assess **biological effectiveness** as a function of the **delivered dose** **to the cells**.

• Dose → **Medical Internal Radiation Dosimetry** formalism:

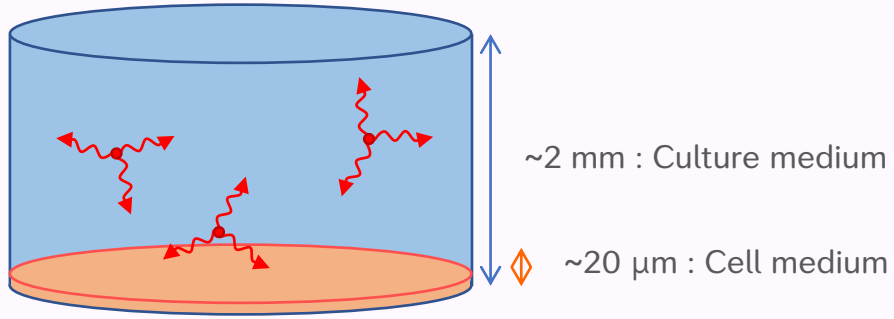
$$\dot{D} \propto \sum_{source} A(source, t) \times \phi(target \leftarrow source)$$

Activity in a source

Fraction of energy emitted by the source absorbed by the target

Sources :
- Cell nuclei
- Cytoplasm
- Cell membrane
- **Surrounding culture medium**

• ***In vitro*** configuration:



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Activity at position pos

Fraction of energy emitted by the medium at position pos, absorbed by the target

Activity distribution ?

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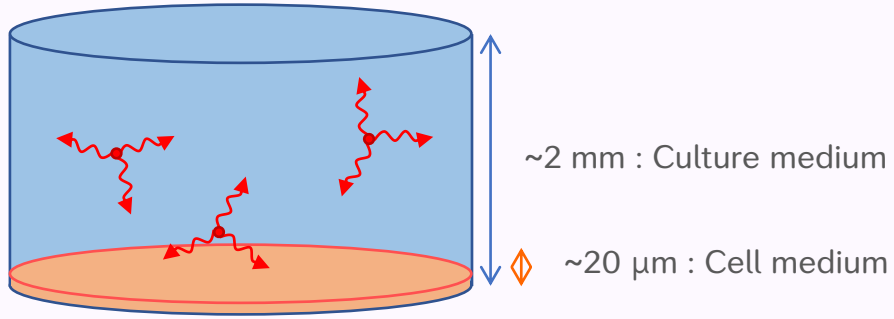

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Simulated dosimetry under homogeneous distribution hypothesis

β ✓ (range ~ mm)

α ✗ (range < 100 µm)

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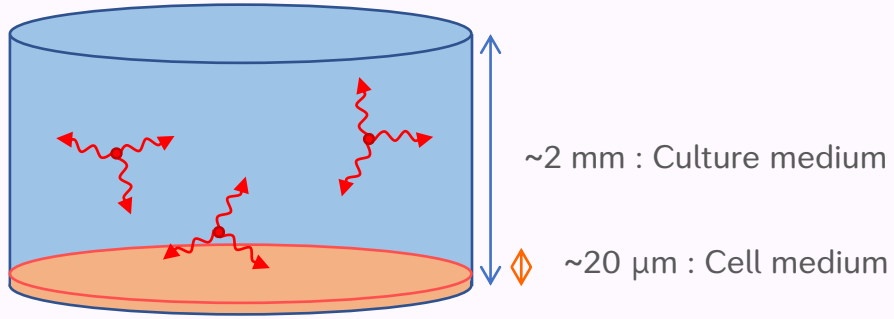


→ **Spatial and time distribution** of the radionuclides is needed for an accurate *in vitro* dosimetry of TAT

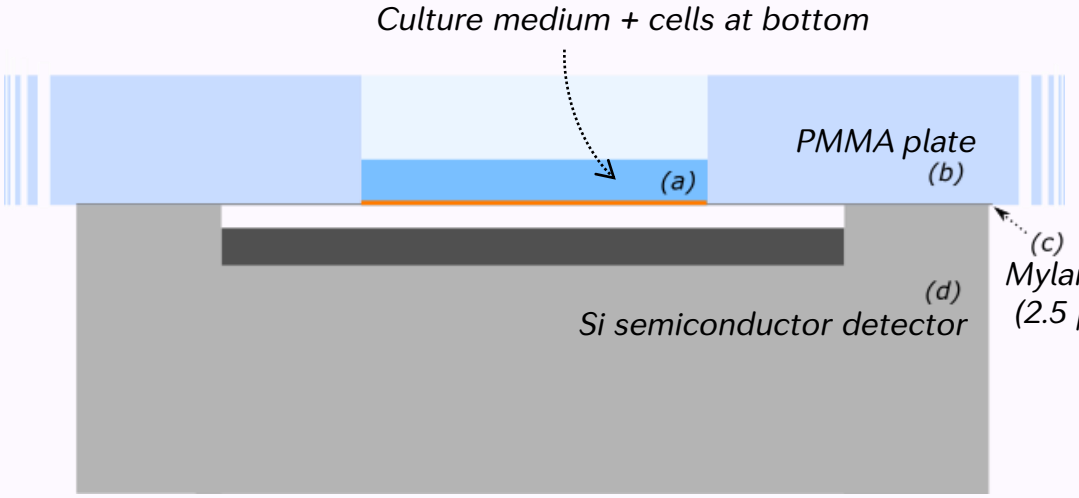
A.M. Frelin-Labalme et al., Med. Phys. (2020)

Introduction – *In vitro* dosimetry methodology

➢ Development of a new TAT dosimetry system:

- Acquisition of **energy spectra** of the α particles emitted through the culture medium and cell layer ;

- Conception of **dedicated culture wells** : transmission of α-particles through the bottom of the well ;



Silicon semiconductor detector under custom made culture well

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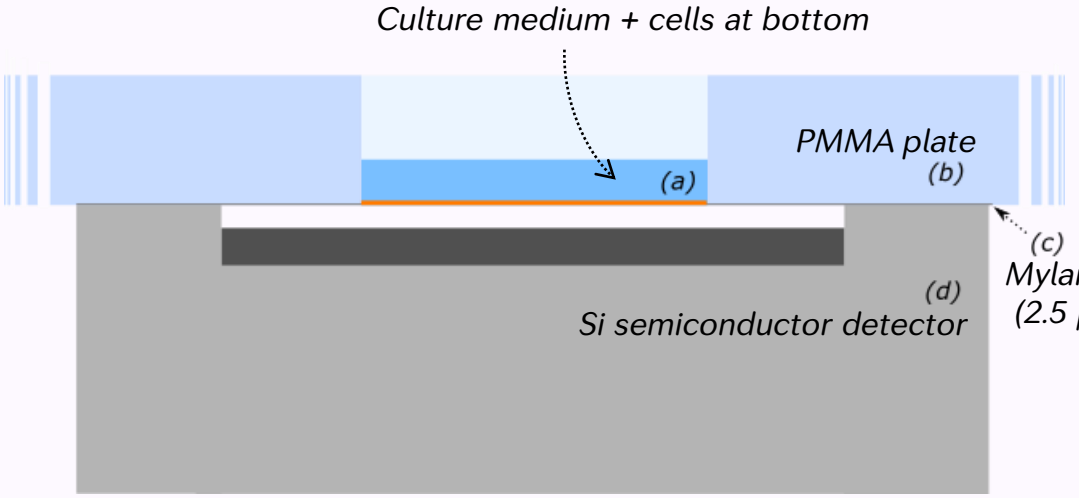
- Spectral **deconvolution** method : estimate the **spatial and temporal distribution** of the radionuclides ;



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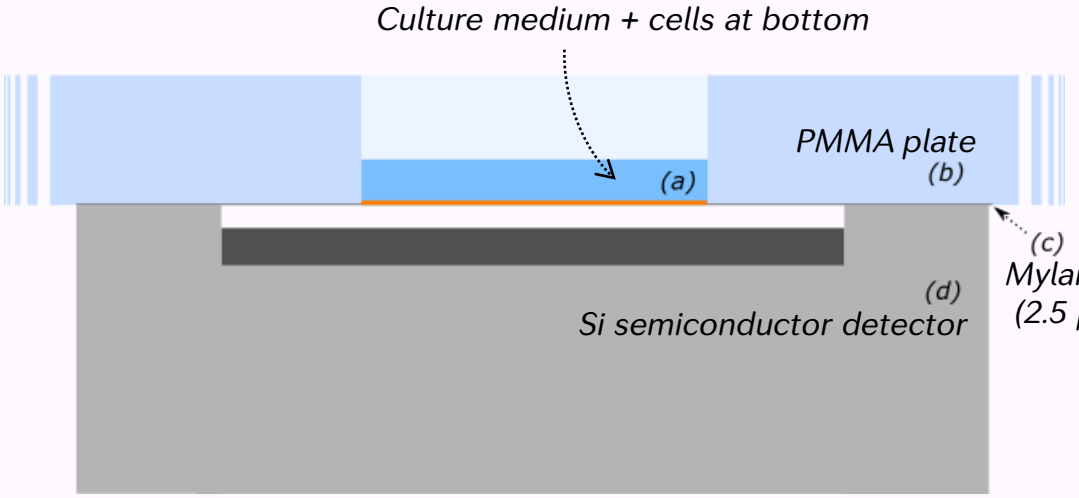

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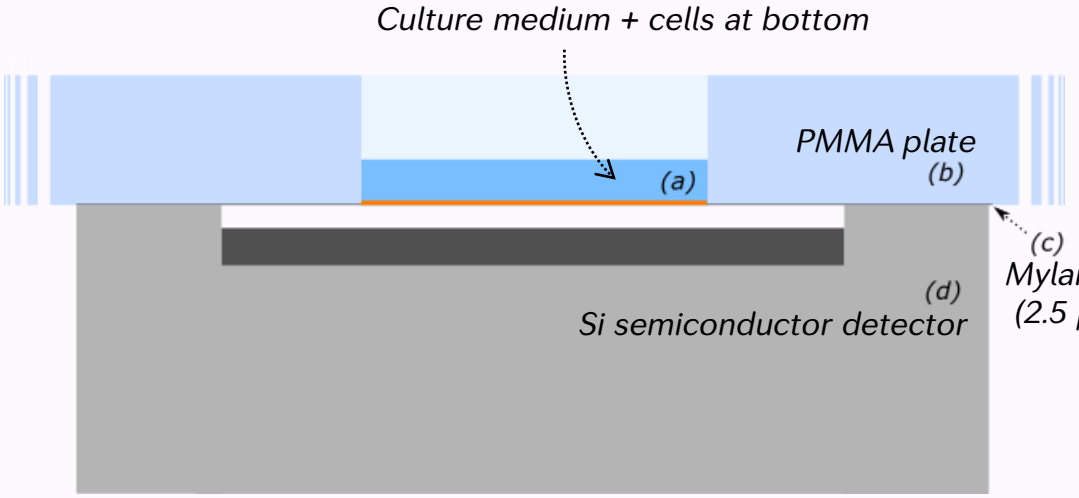

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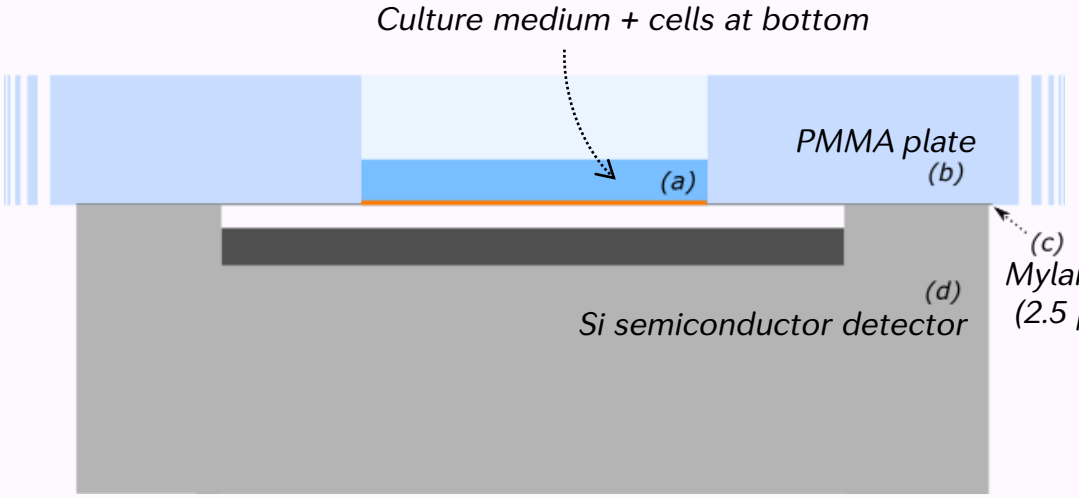

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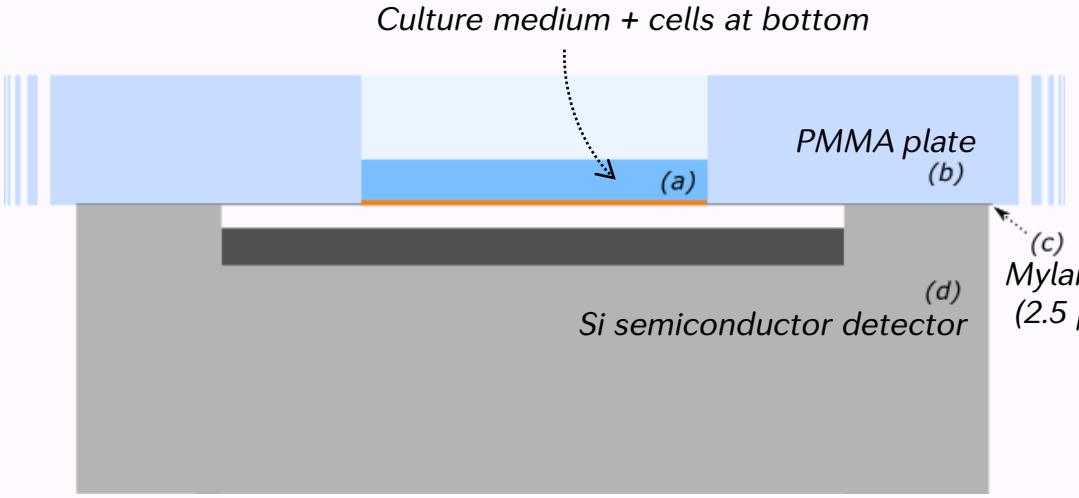
- Computation of the delivered dose to the cells.



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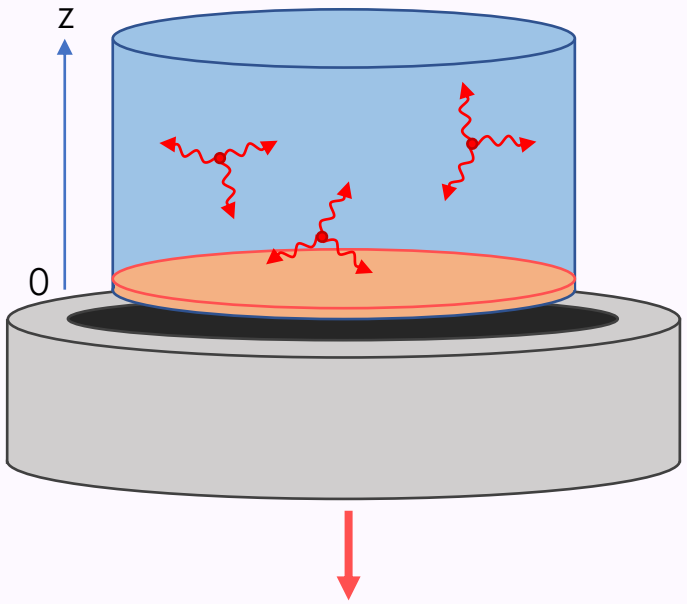
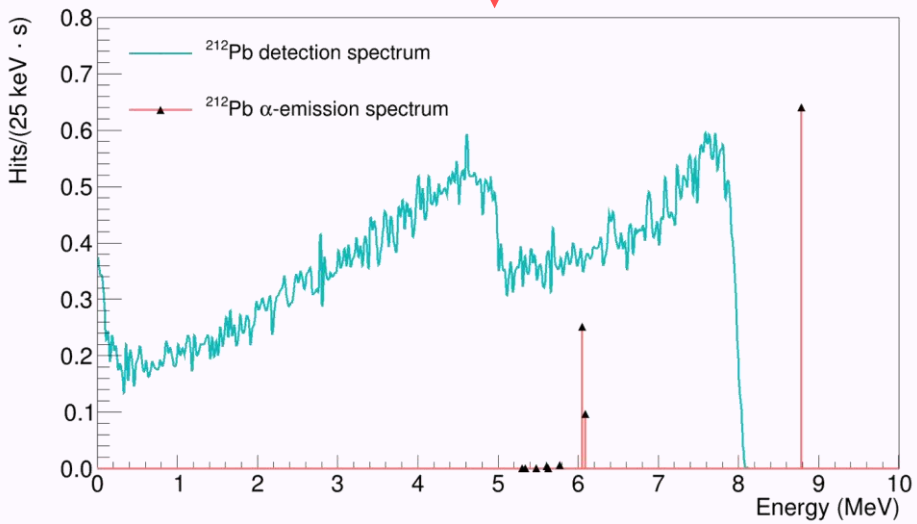
Deconvolution method – Principles





- **Detection spectrum ≠ Emission spectrum**
- The **remaining energy of the α-particles** reaching the detector **depends on their path** in the culture medium
- Detection geometry → **z-discretization (vertical) of the well**

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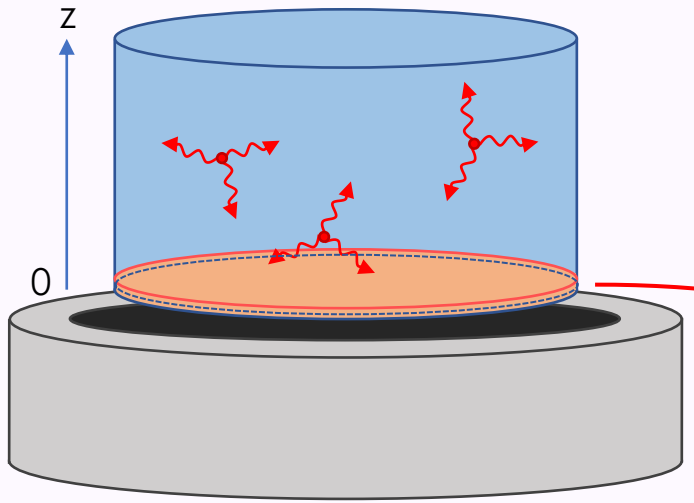

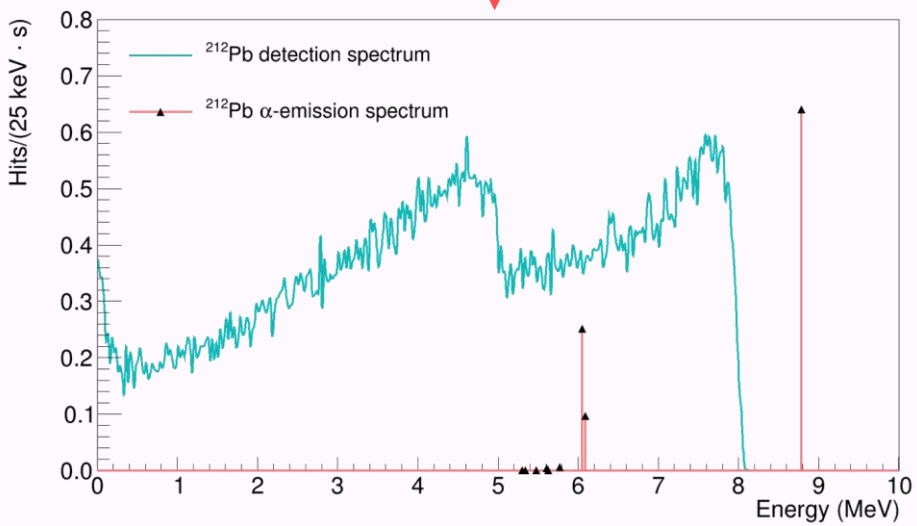

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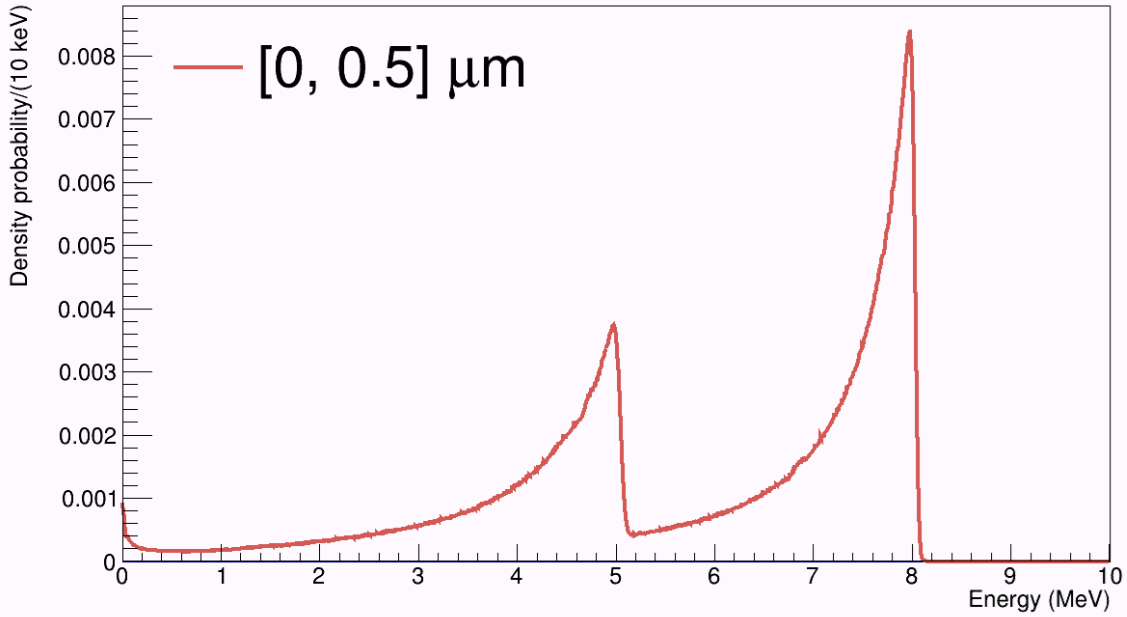

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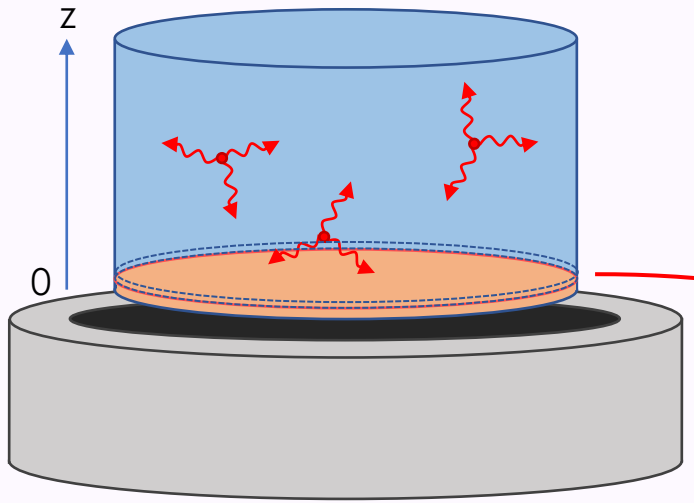

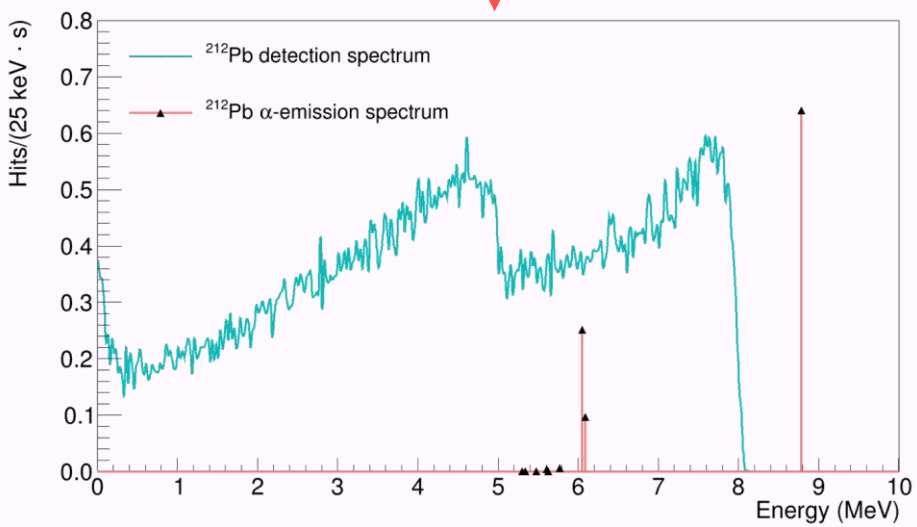

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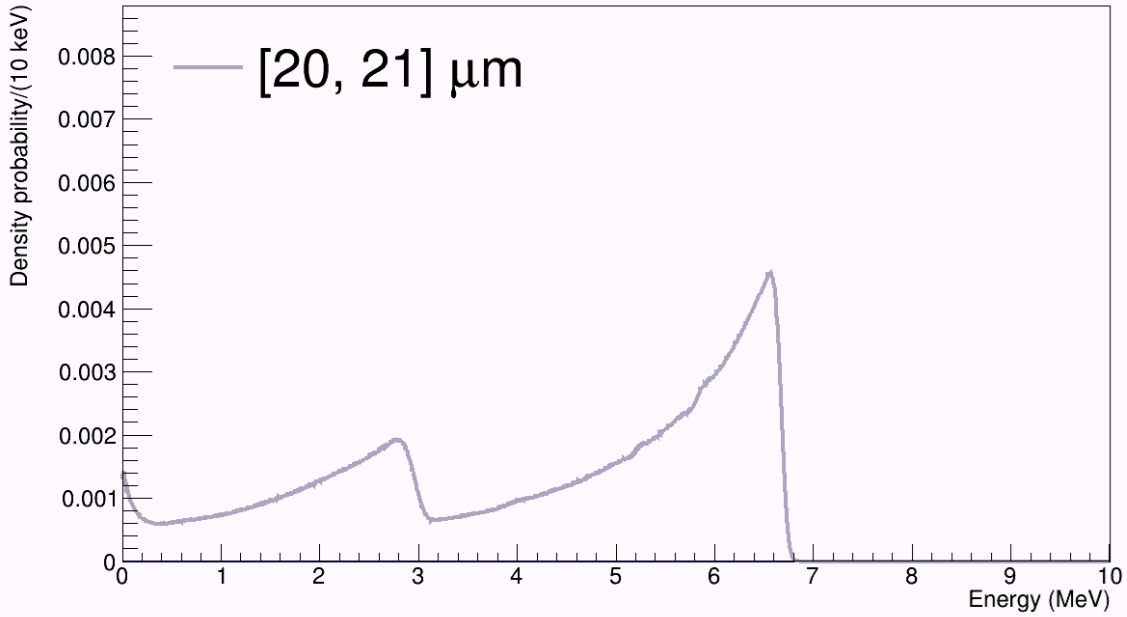

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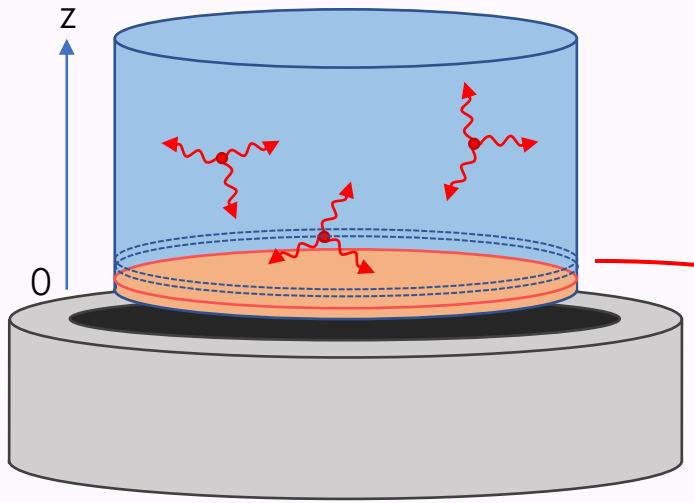

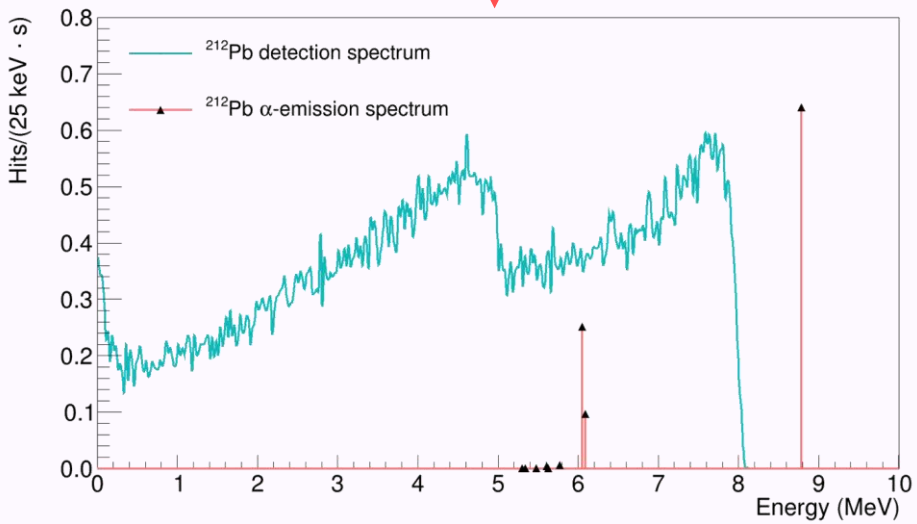

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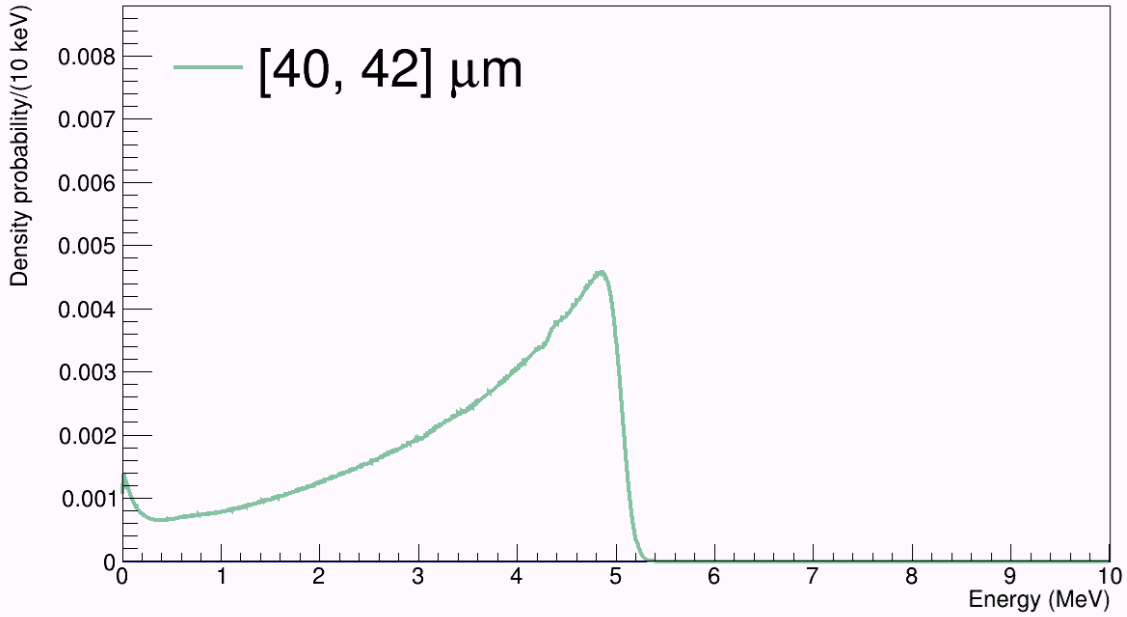

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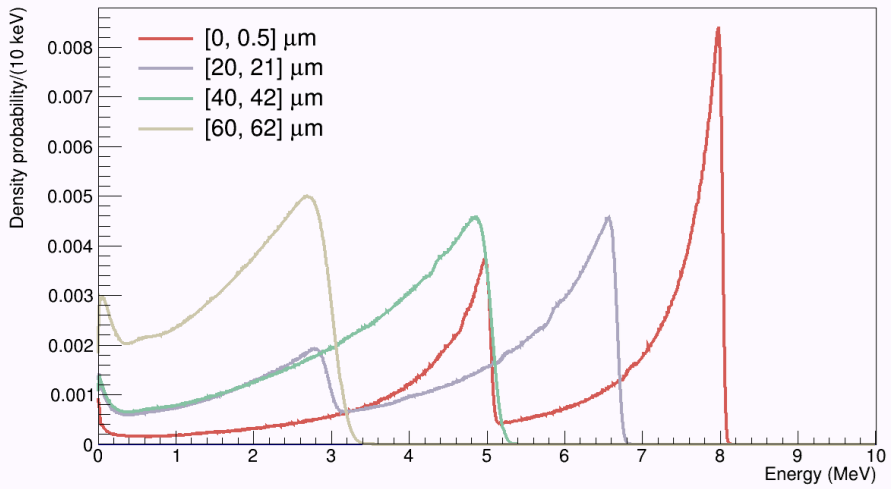
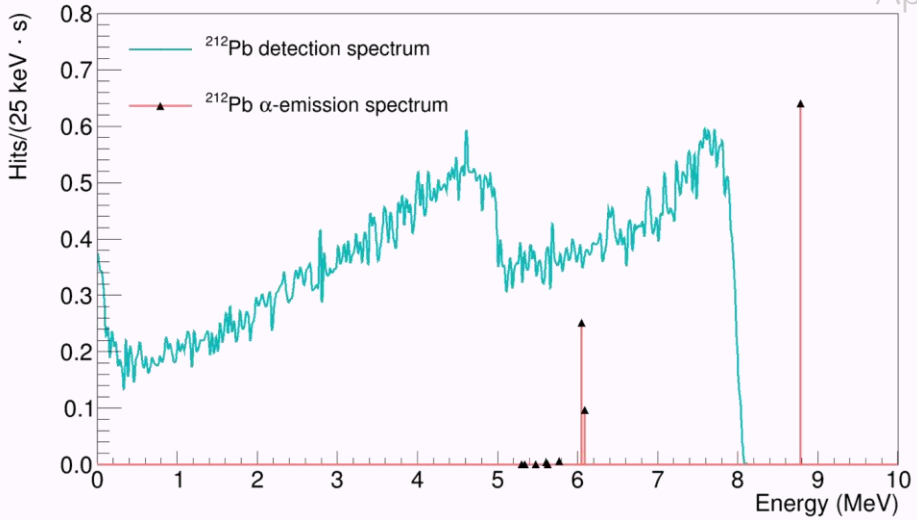


Basis of elementary spectra



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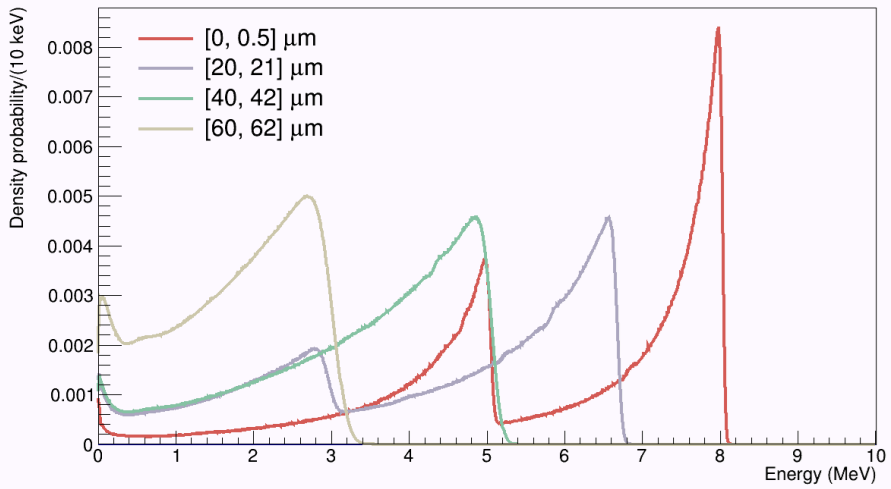

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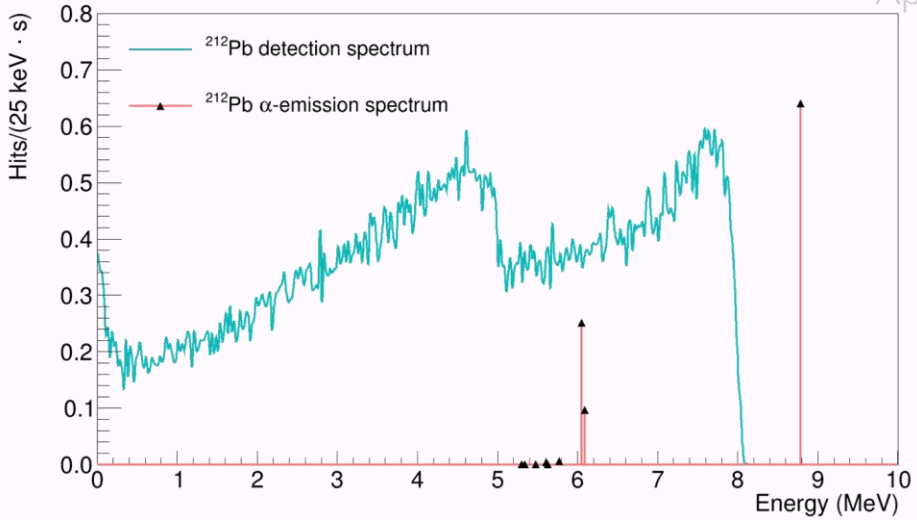

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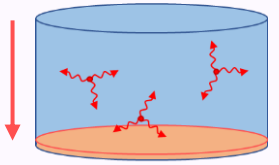
  - ^{212}Pb spectra **incompatible with a homogeneous activity distribution**
  - **Vertical gradient towards bottom** (z-discretization)

→ Satisfying fit



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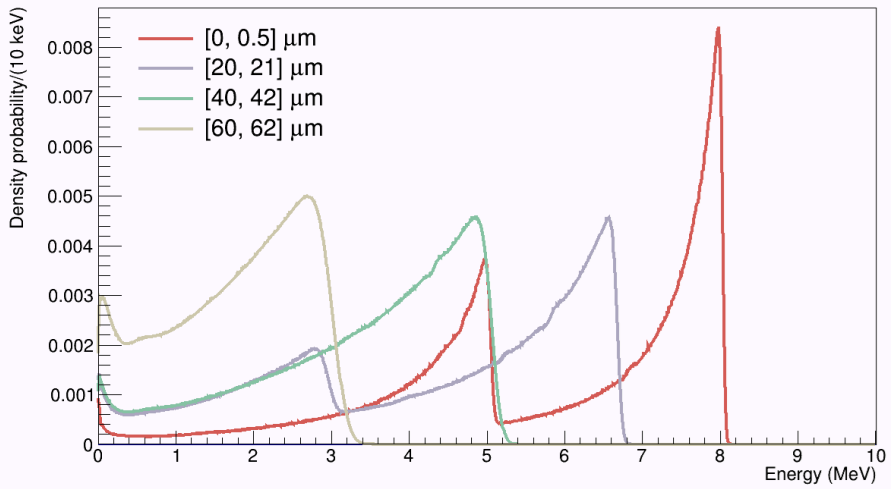

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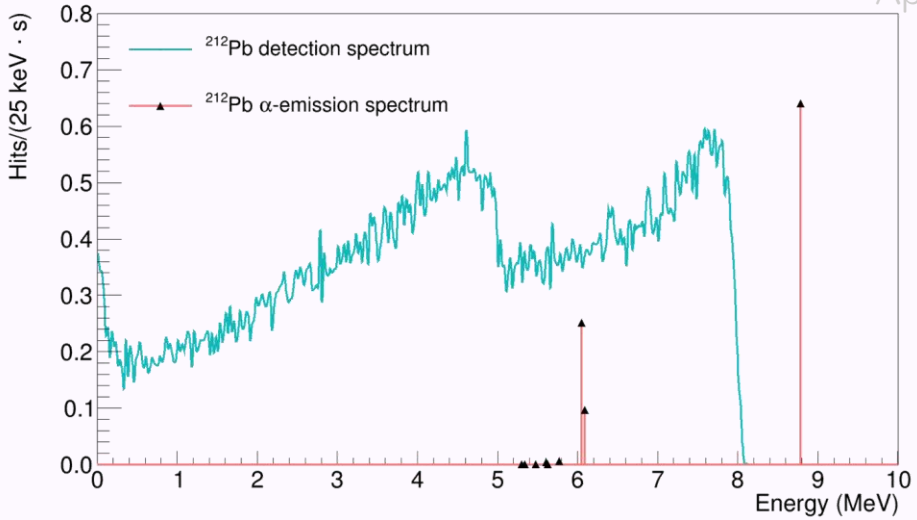

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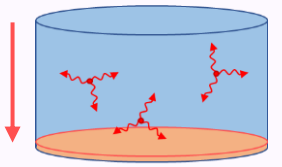

- **Requirements**

Online dosimetry → Fast spectral analysis

Reliable dosimetry → Realistic activity distributions

Deconvolution method – Matrix optimization

- Matrix optimization : generally **fast** and allows **flexible** modelling
  - $SP_{exp}(t,E) = \sum_i A(t,z_i) \cdot SP_{elem}(z_i,E)$ $\xrightarrow[\text{time interval}]{\text{For each}}$ $\boldsymbol{y} = \boldsymbol{X}\boldsymbol{a}$, $\boldsymbol{a}_{sol} = \min_{\boldsymbol{a}} \boldsymbol{f}(\boldsymbol{a}, \boldsymbol{X}, \boldsymbol{y})$

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- The **minimization function** was built around **physical considerations** :

  ① Enforcing **positivity** of the activity distribution

  ② Enforcing a **continuous gradient toward the bottom** of activity concentration

  ③ **Likelihood maximization criterion** (Poisson statistics of the spectral counts)

  ④ **Total cumulated activity** of the solution compatible with reality

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- The minimization is iterative due to the condition ③ :

$$\boldsymbol{a}_{n+1} = \boldsymbol{D}_{\boldsymbol{k}}^{-1} \cdot \min_{\boldsymbol{a}^{(k)} \geq 0} \frac{1}{\boldsymbol{\Lambda}_{\boldsymbol{n}}} \left\| \begin{pmatrix} \boldsymbol{X} \\ p \cdot \boldsymbol{h}^{\boldsymbol{T}} \end{pmatrix} \cdot \boldsymbol{D}_{\boldsymbol{k}}^{-1} \boldsymbol{a}^{(k)} - \begin{pmatrix} \boldsymbol{y} \\ p \cdot A_0 \end{pmatrix} \right\|_2^2$$

→ **A(z,t) needed for dosimetry via MIRD formalism**

(Object of a paper currently being written)

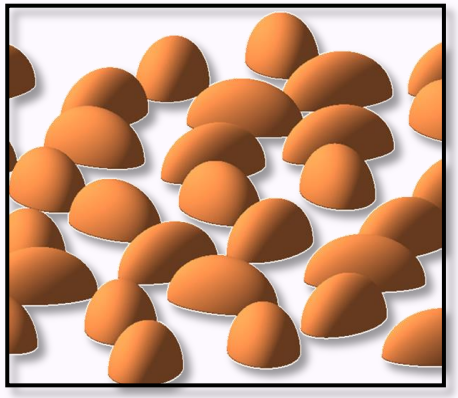
Validation of the method – Simulation of *in vitro* irradiations

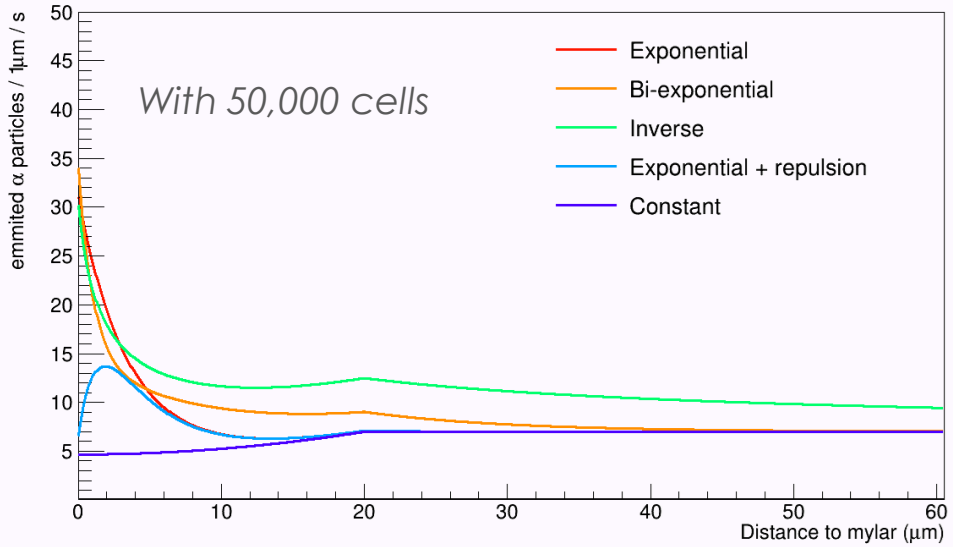
- **Is the deconvoluted activity distribution equal to the real activity distribution ?**
- **If there are discrepancies, what is the impact on dose calculation ?**

- Simulation of **known activity distributions** of ^{212}Pb.
- **50.000 cells** evenly distributed at the bottom of the well + **Silicon detector**

Identical half-ellipsoïd cells

(not mogettes !)



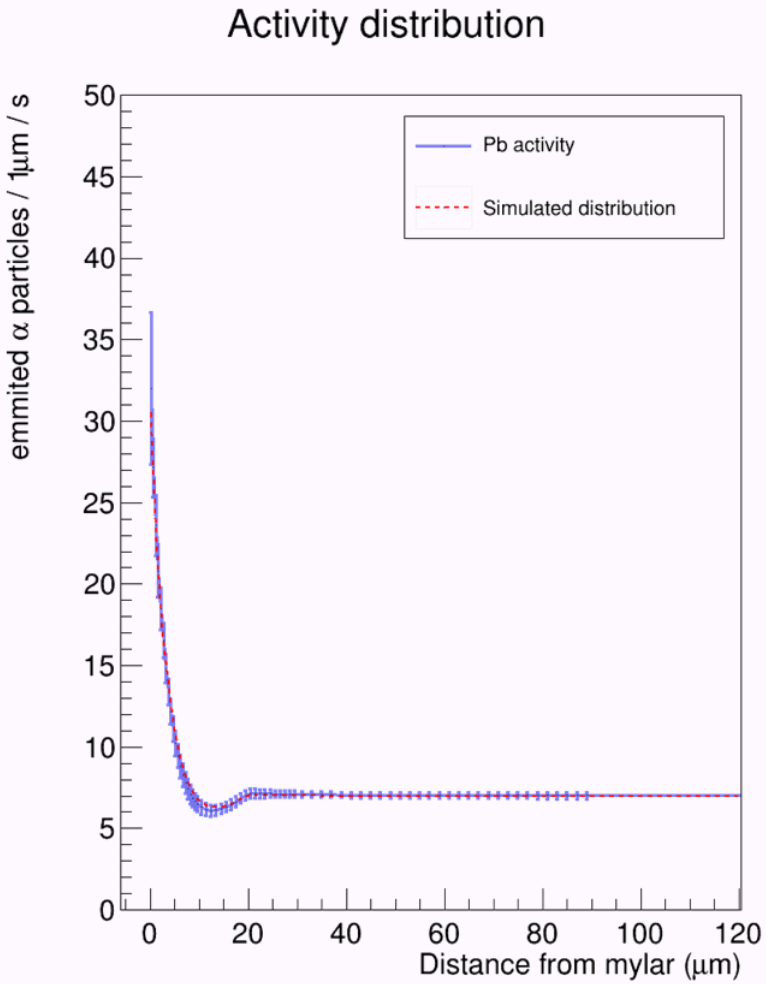


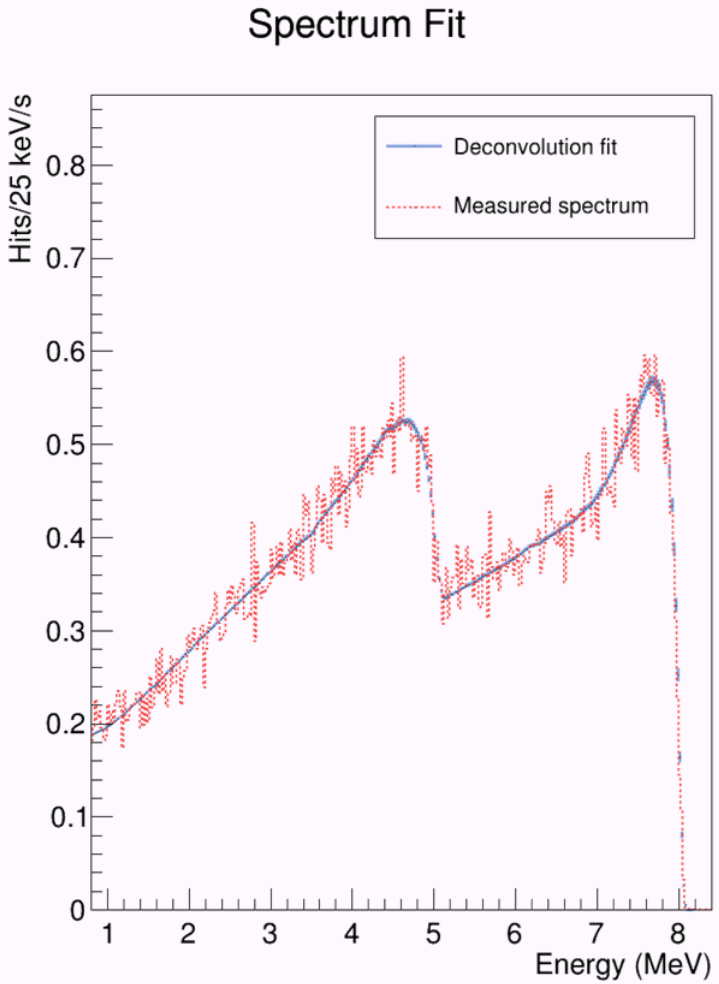
- **Spectra and corresponding "Ground Truth" doses database.**
- Application of the deconvolution method → **"Computed" doses.**

Dose comparisons

Validation of the method – Spatial distributions

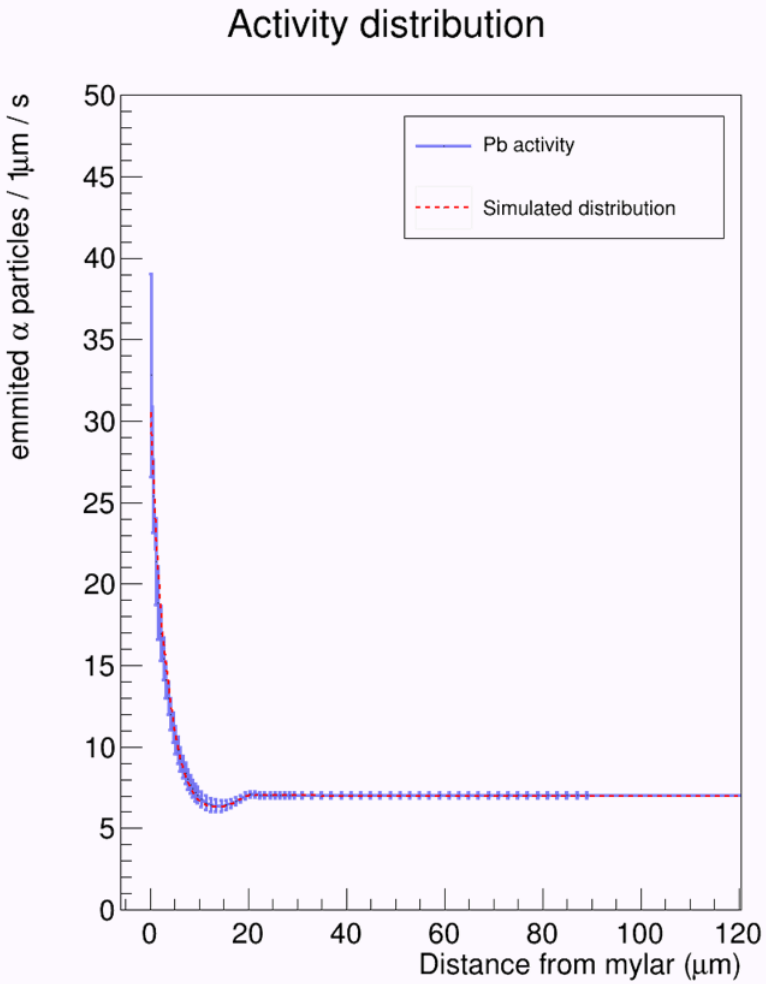
- Exponential distribution, ^{212}Pb

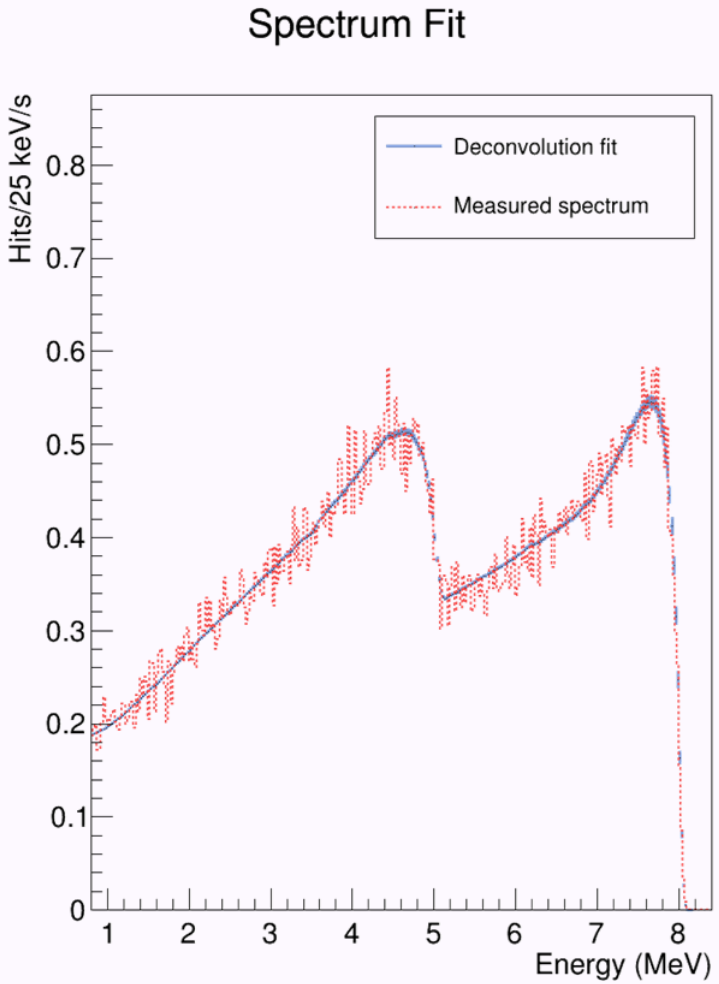




Validation of the method – Spatial distributions

- Exponential distribution, ^{212}Pb



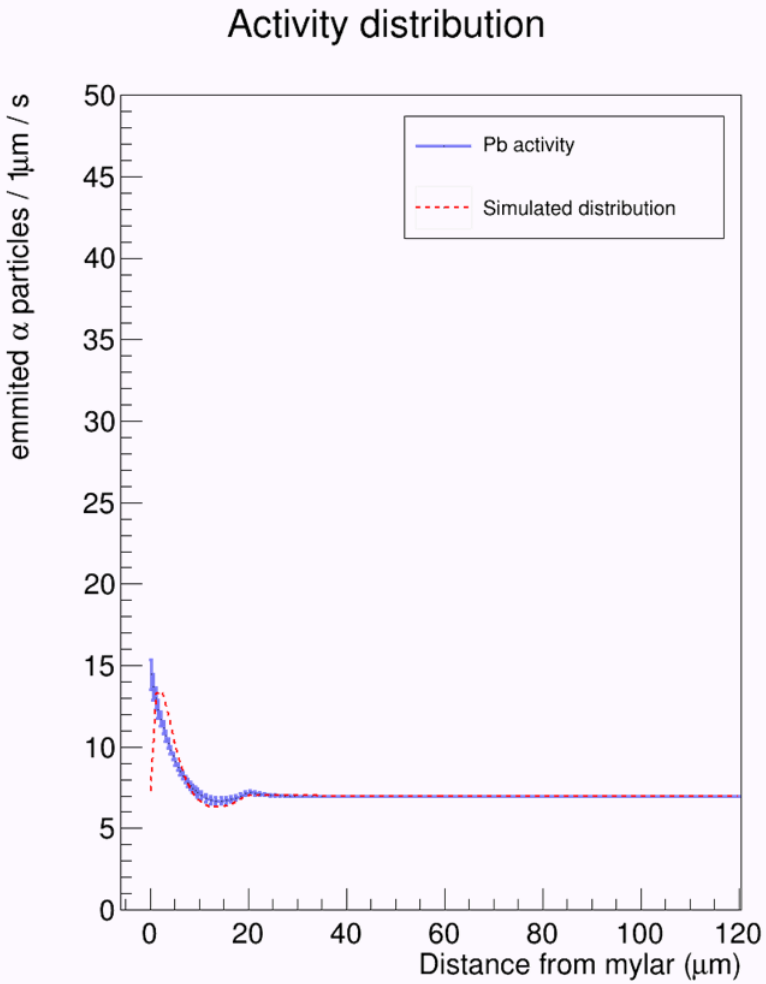


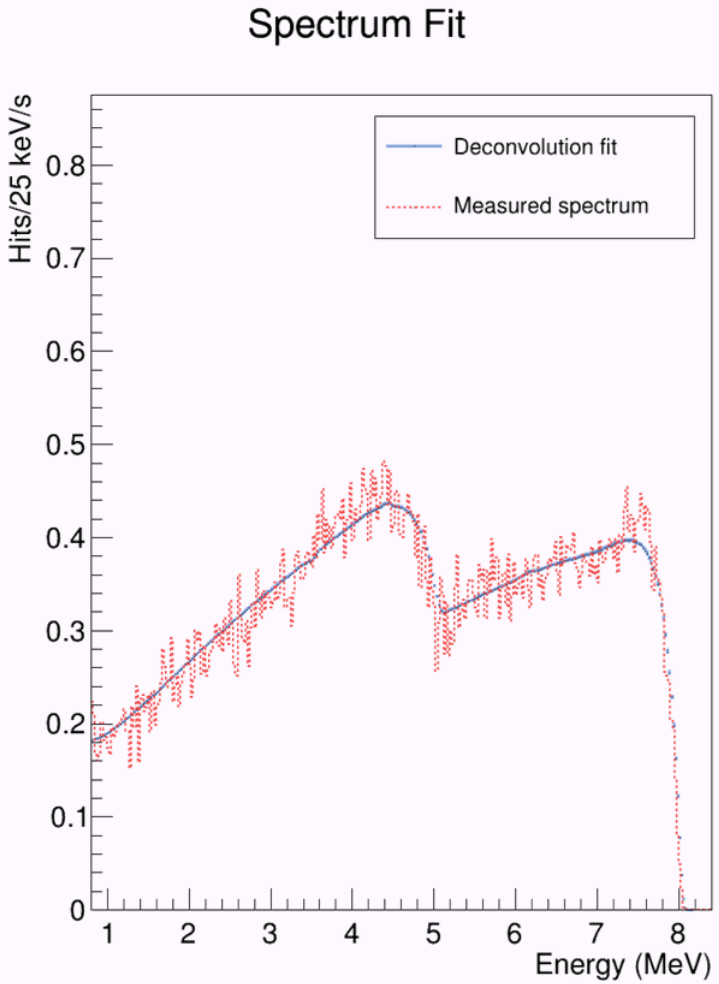
→ Dose bias :

-0.05 % ± 0.43 %

Validation of the method – Spatial distributions

- Exponential & repulsion distribution, ^{212}Pb





Dose bias :

+0.22 % ± 0.45 %

Validation of the method – Dose computations

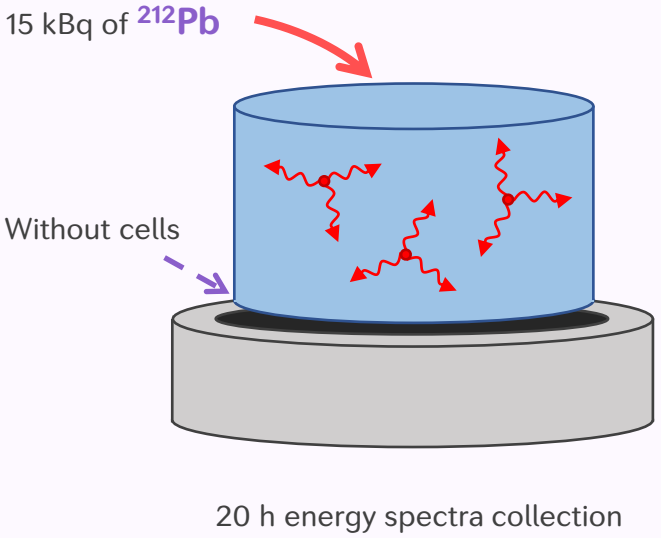
➢ With ^{212}Pb

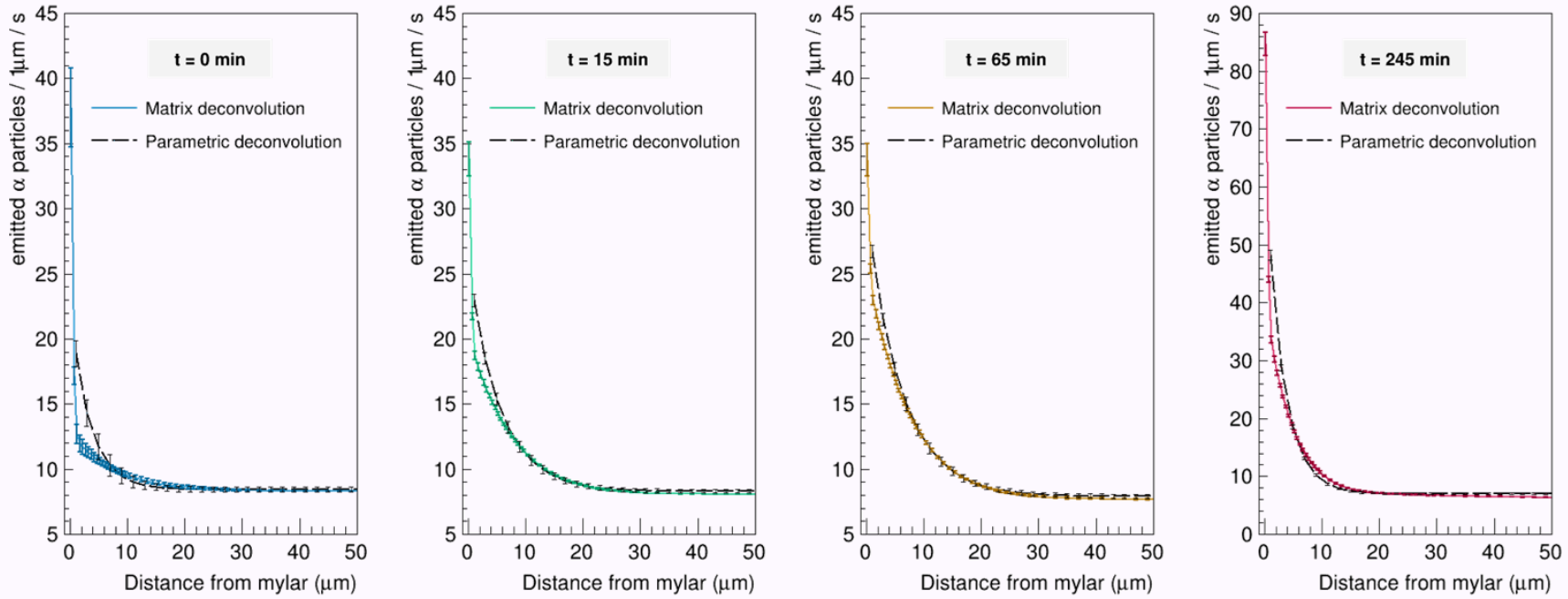
Dose

- **No conclusive evidence for bias** for any function (global bias : **-0.01 % ± 0.19 %**)
- "Computed" vs "Ground Truth" **error < 3 % for all simulations**
- **Uncertainties** are **reliable** (69.3 % of discrepancies within 1σ, 94.0 % within 2σ, 99.3 % within 3σ)

Application of the method – Analysis of ^{212}Pb kinematics assays

➢ **Study of the kinetics of radioisotopes in conditions similar to *in vitro* experiments**





Activity distribution gradients

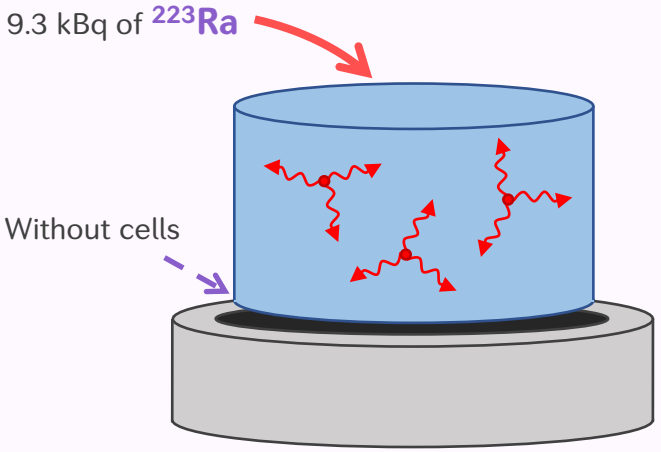
- Retrieval of **spatial activity gradient**
- Time evolution ≠ radioactive decay

Methodology improvements

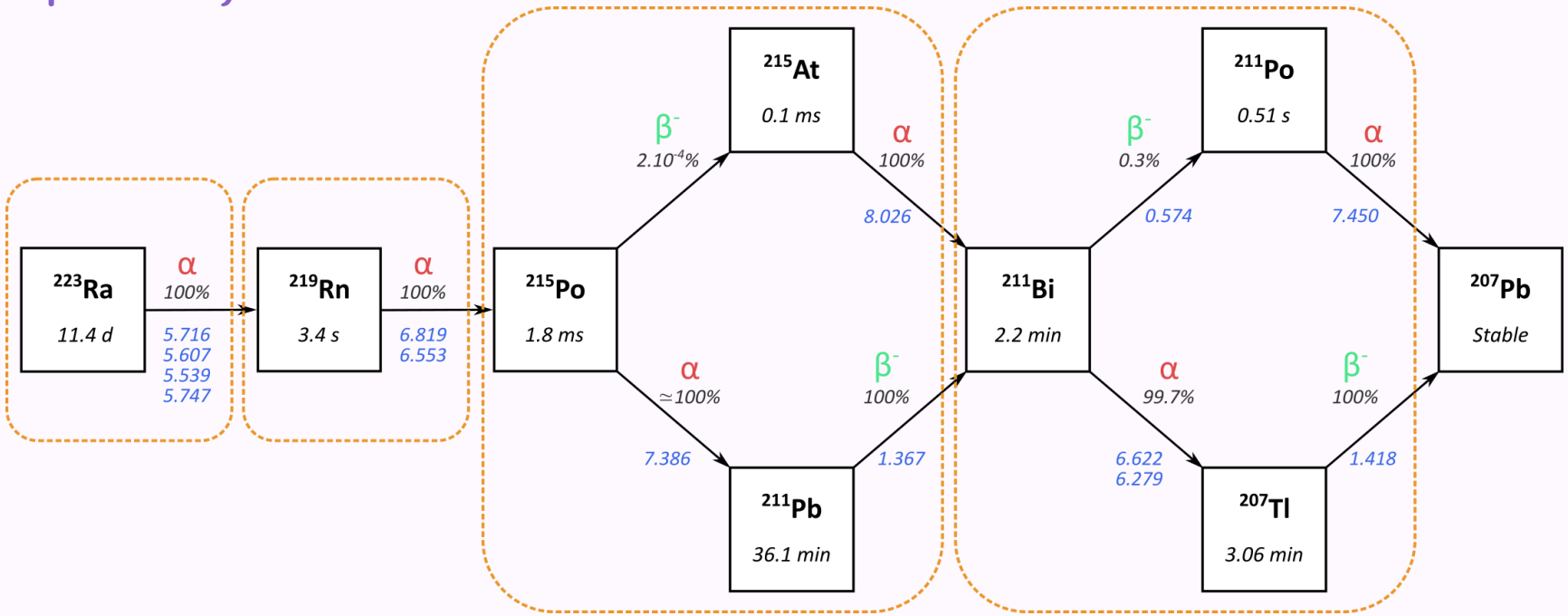
- **Improved spatial resolution** at the bottom of the well
- **Flexible gradient** reconstruction

Application of the method – Analysis of ^{223}Ra kinematics assays

➢ **Study of the kinetics of a more complex decay chain**

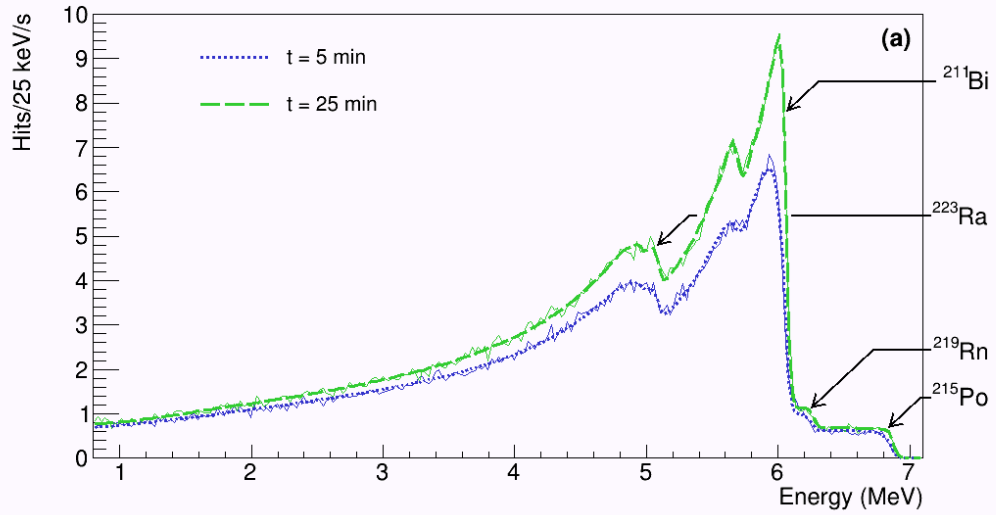


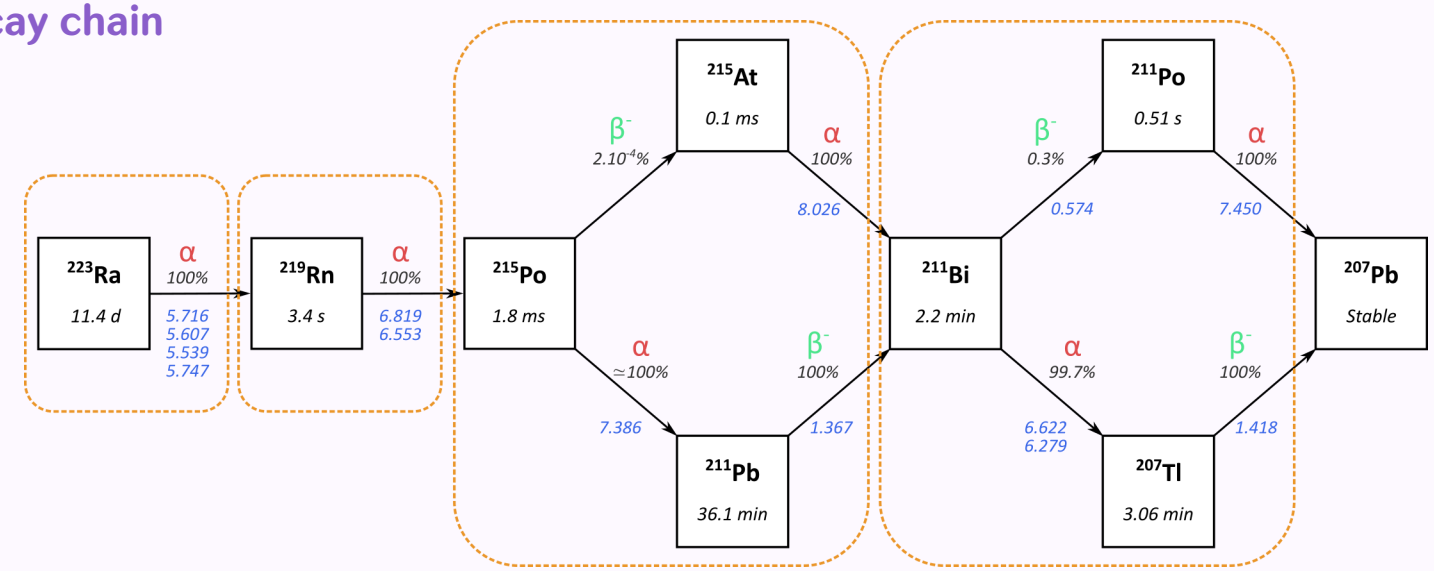
2 h energy spectra collection

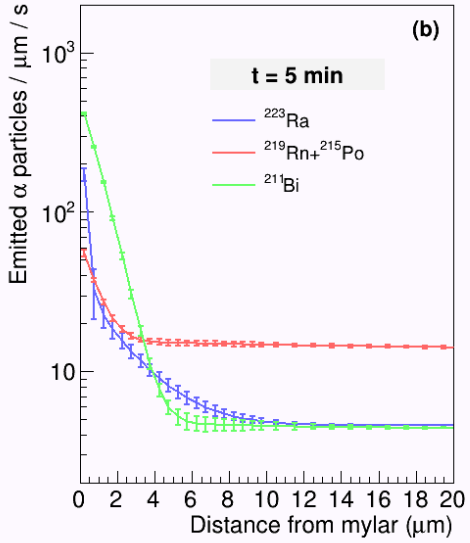


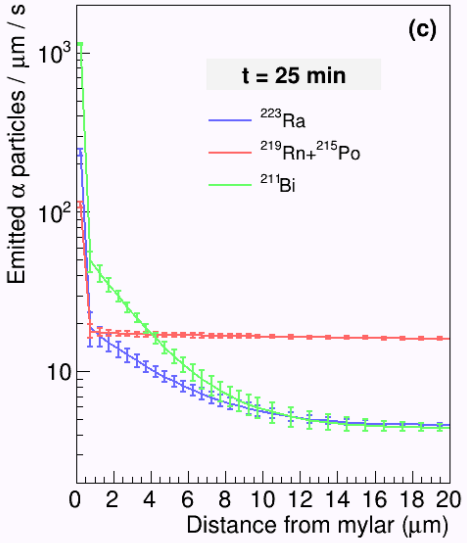
Application of the method – Analysis of ^{223}Ra kinematics assays

➢ Study of the kinetics of a more complex decay chain









Complexity of the kinetics

- Necessity to distinguish distributions the ≠ α-emitters
- **≠ distributions, ≠ time evolutions**

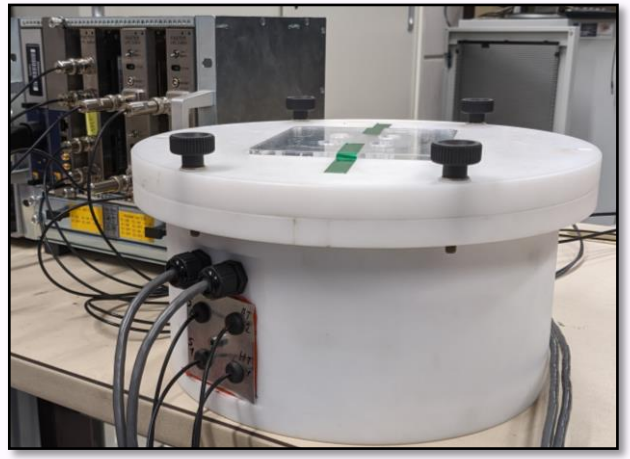
Increase in degrees of freedom → Risks of overfitting

- Spatial distributions less reliable (from validation)
- What matters : the total distribution
- **Good spectral fit → good dose computation**

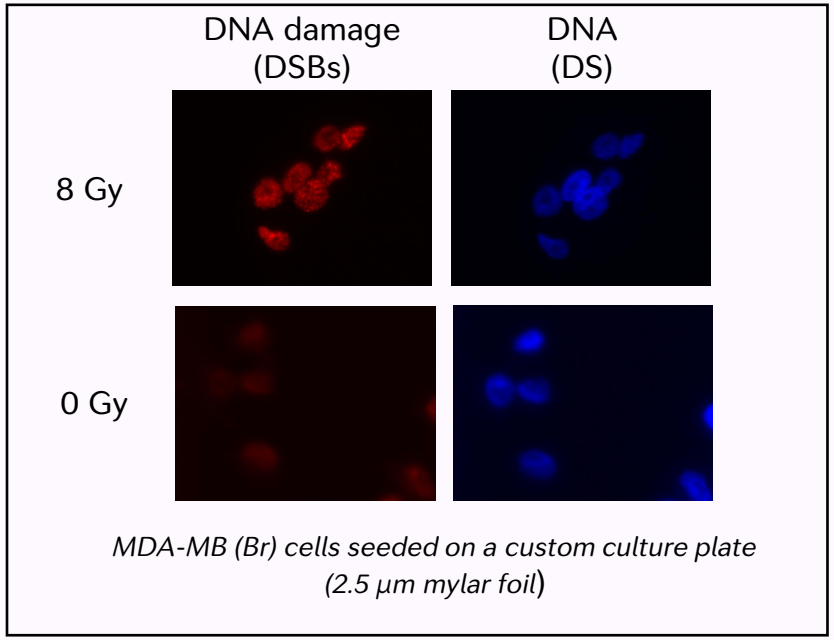
Conclusions

- We developed a **fast** and **flexible** spectral deconvolution process for ***in vitro* dosimetry assessment**
- Validation of the framework showed **dose errors limited to +/- 3%** with **limited bias due to the framework**
- ^{212}Pb and ^{223}Ra kinetics assays → highlighted the **spatial concentration gradient**, and **complex kinetics**

Perspectives



- Prototype of a **measurement chamber** compatible with in vitro assays
  - Mylar foil compatible with cell culture incubation and imaging
  - Electronics behavior assessment in an *in vitro* culture chamber
- So far, measurement without cells → In the following month, **assays with cells**
- Reliable computation of **dose deposition in cells**
  - **Cell modelling** from cell imaging
    - Shape
    - Spatial Density
    - Confluence
- α-particles biological effects must be considered
  - Computation of **other metrics of interest** on top of average dose



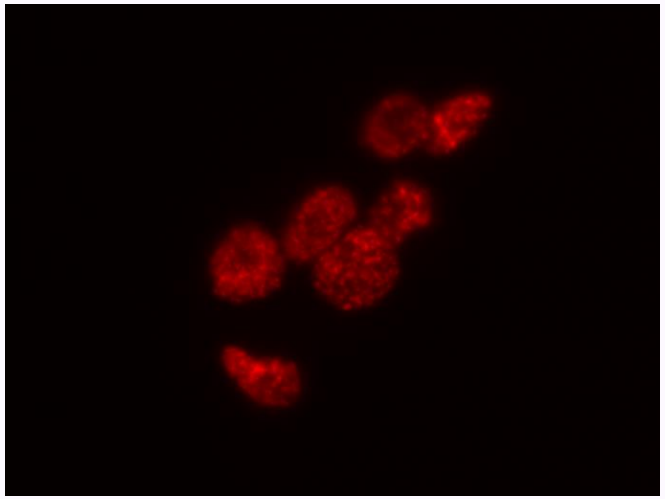
MDA-MB (Br) cells seeded on a custom culture plate (2.5 µm mylar foil)

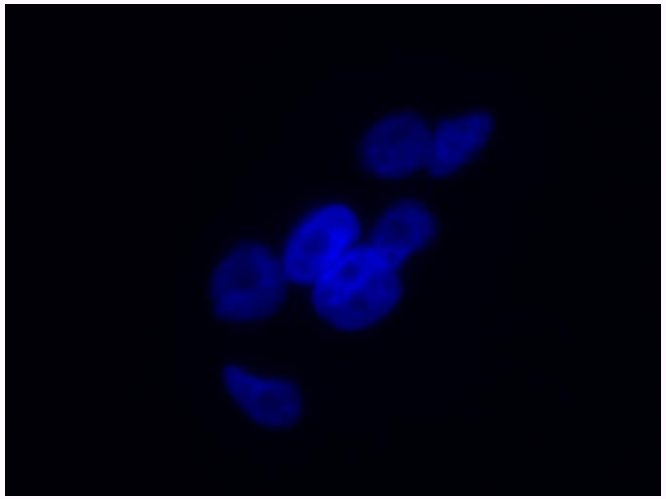
Thank you for your attention !

Supplementary Materials – Cell seeding and imaging

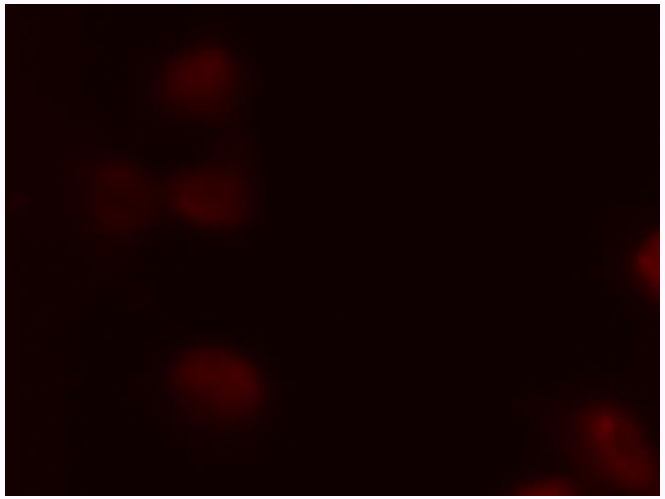
γ-H2AX (DNA DSBs) | Hoescht 33342 (DNA)

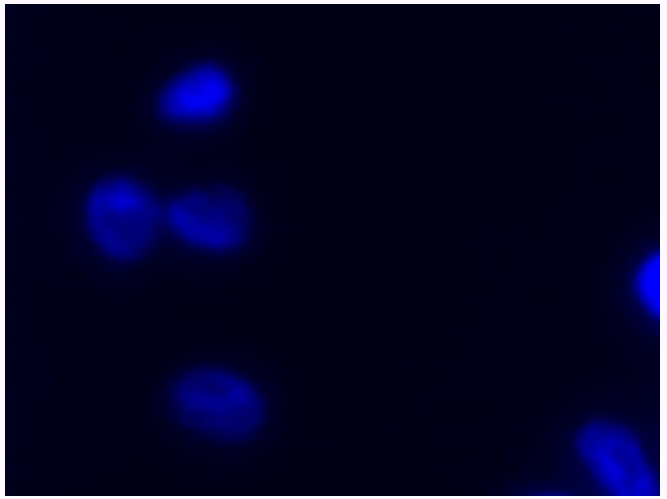
8 Gy





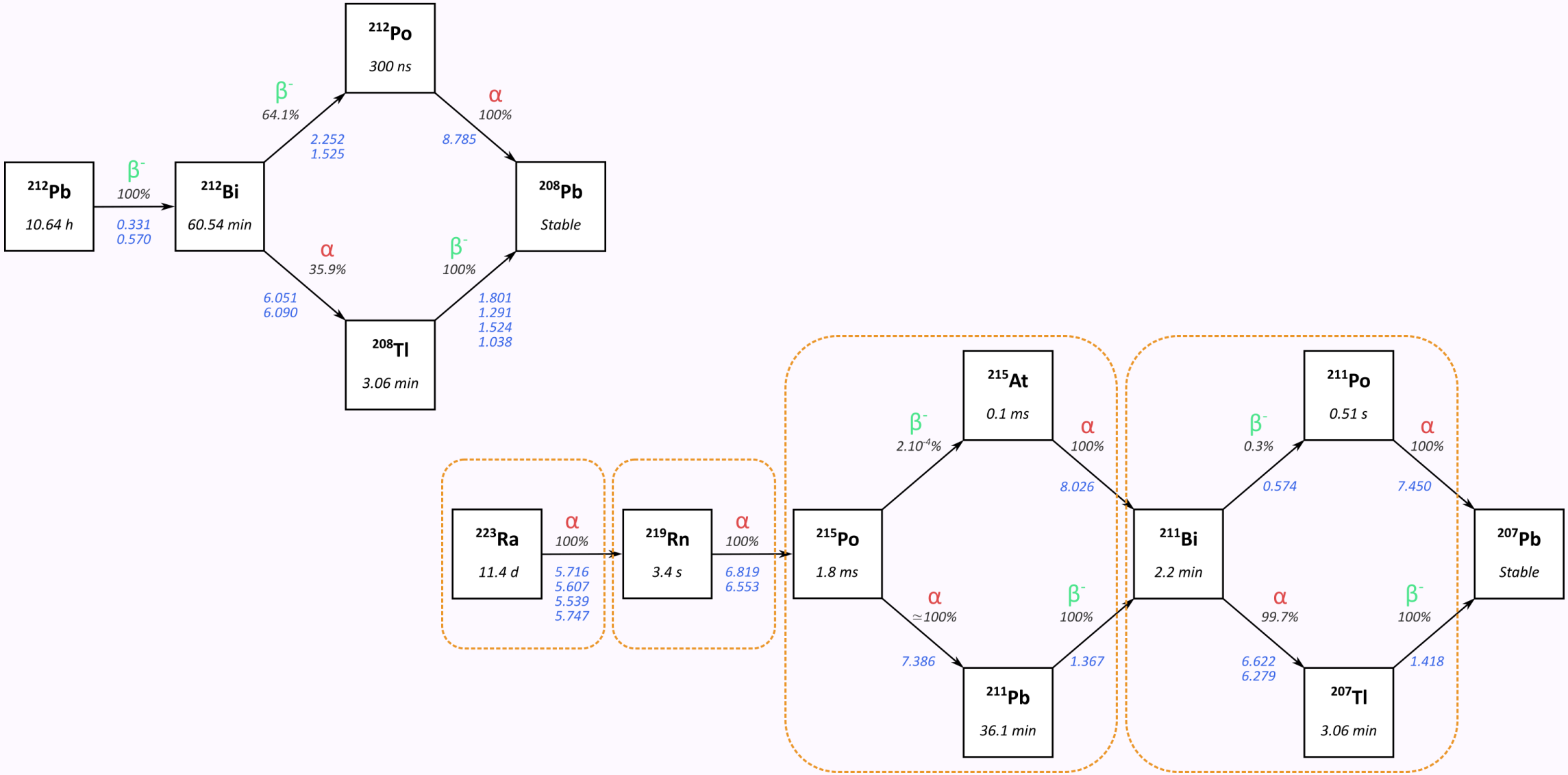
0 Gy



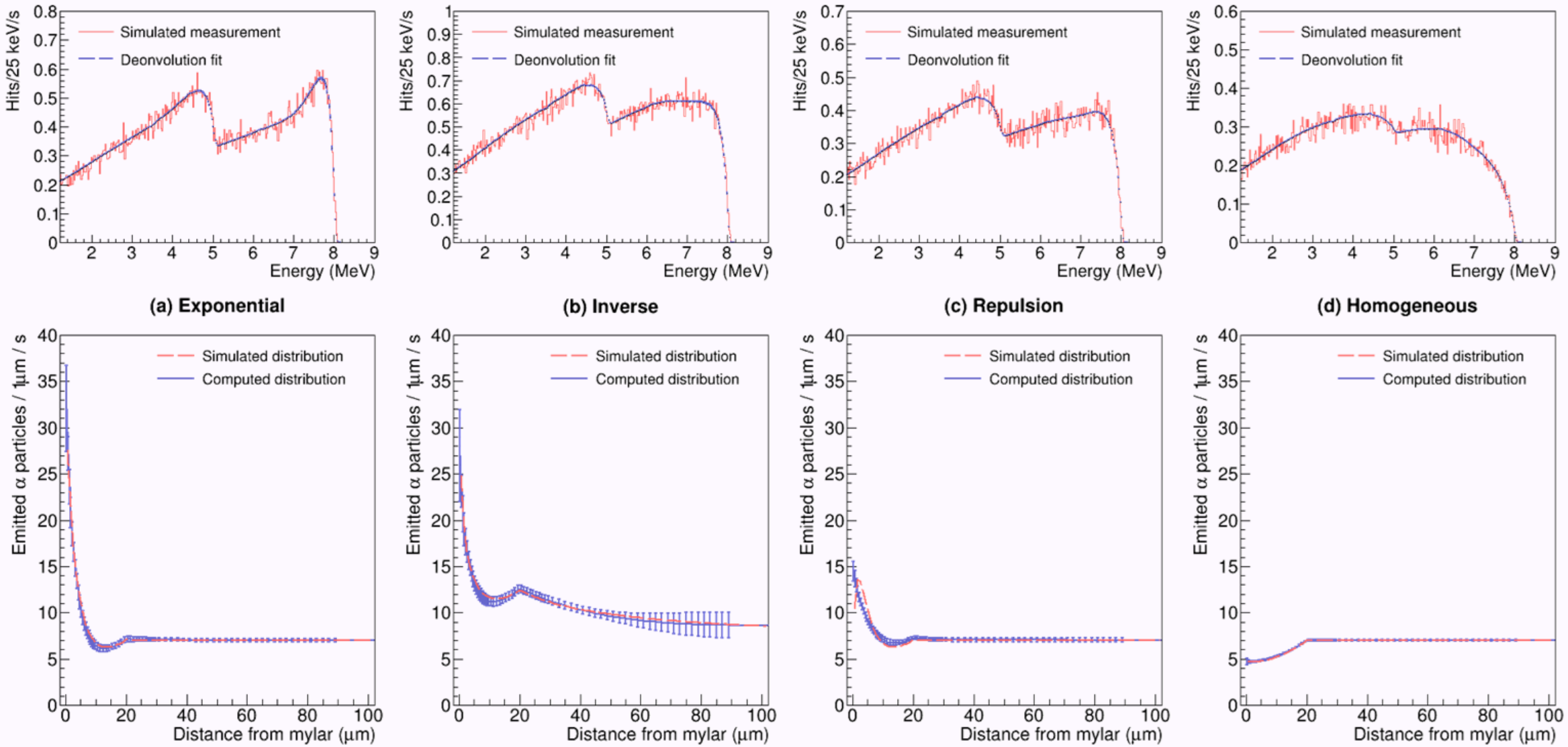


- MDA-MB (Br) cells seeded on a custom culture plate (2.5 µm mylar foil)
- Cell iraddiator (150 kV, 8 Gy)
- Fixation at +2 h

Supplementary Materials – ^{212}Pb & ^{223}Ra decay chains

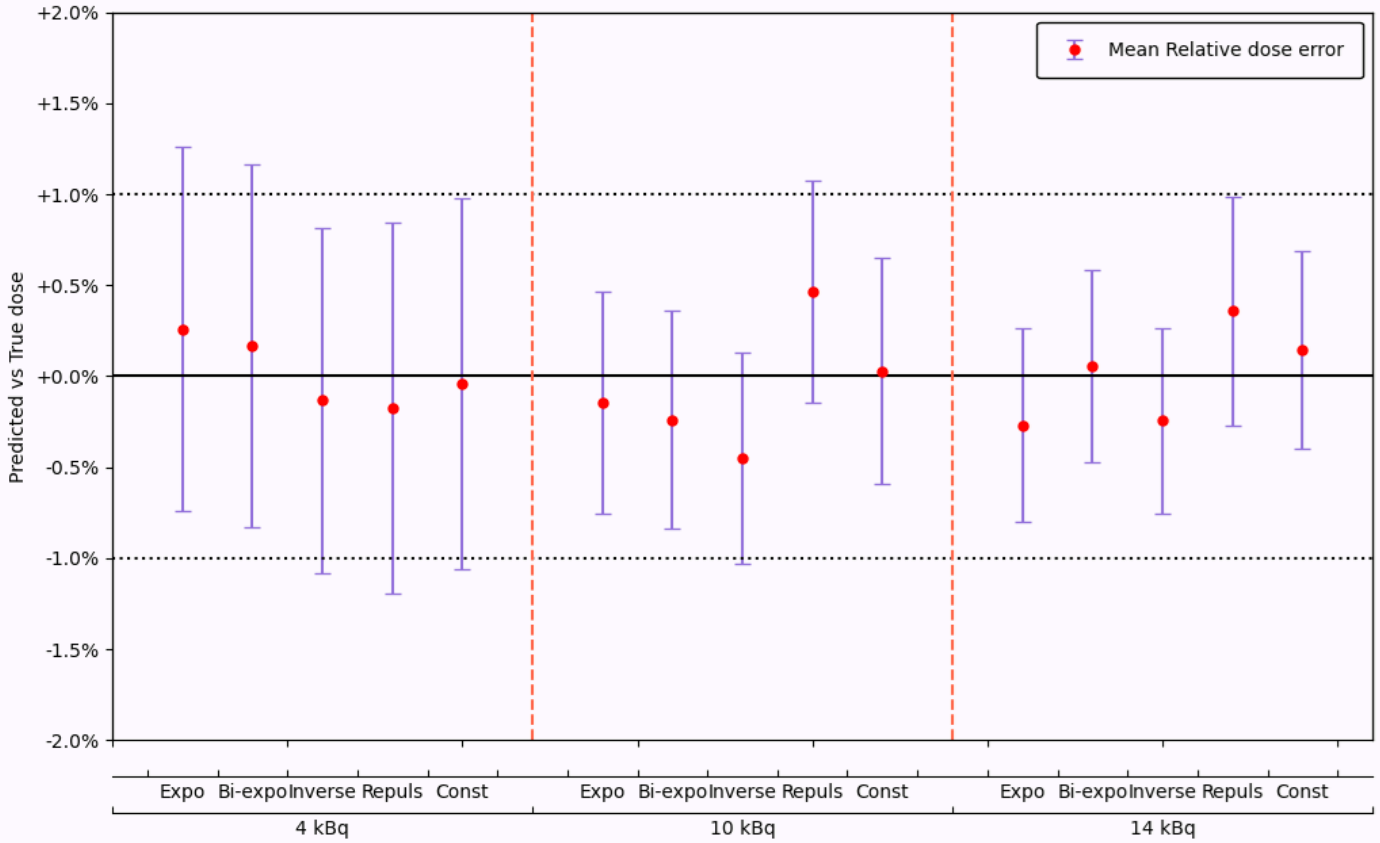


Supplementary Materials – Spatial distributions



Supplementary Materials – Dose computations

- **Mean dose error** per activity distribution **(bias)** and its uncertainty (3σ)

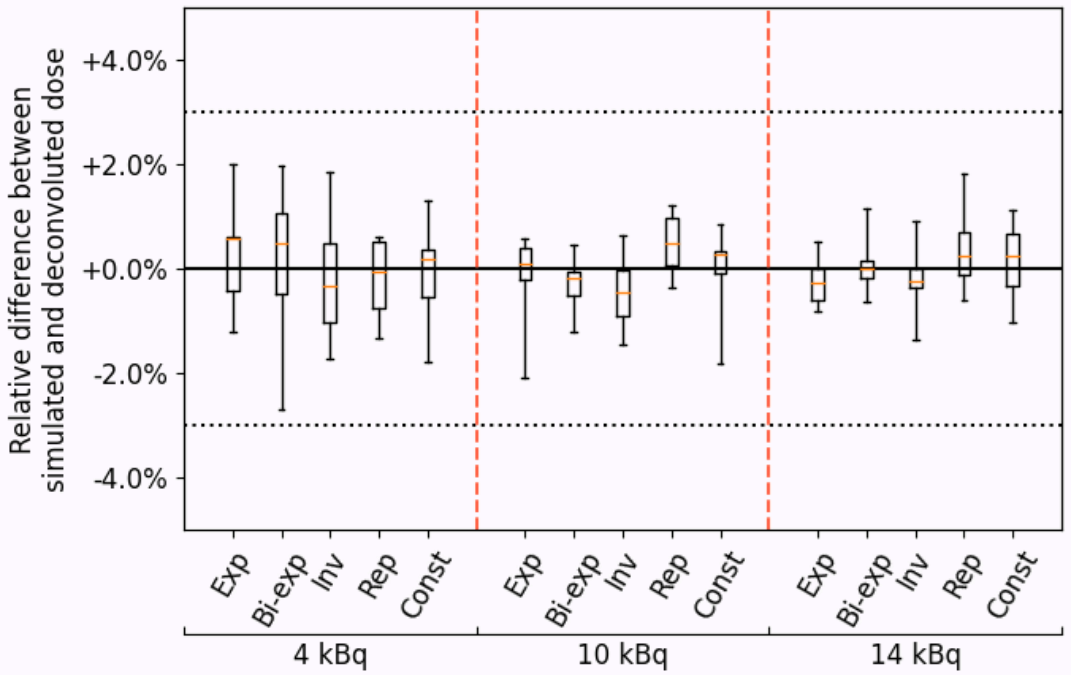


- **No conclusive evidence for bias** for any function (-0.01% ± 0.19%)
- "Computed" vs "Ground Truth" **error < 3% for any run**
- **Uncertainties** are **reliable** (69.3% of discrepancies within 1σ, 94.0% within 2σ, 99.3% within 3σ)

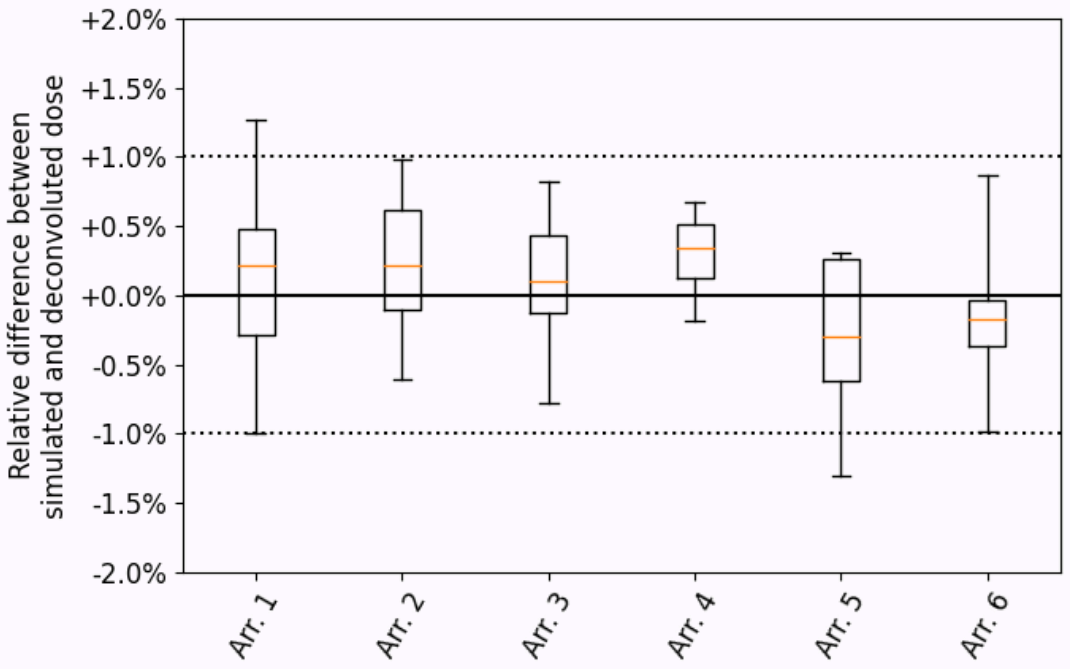
Supplementary Materials – Validation errors

- **Error distributions** per activity distribution

^{212}Pb



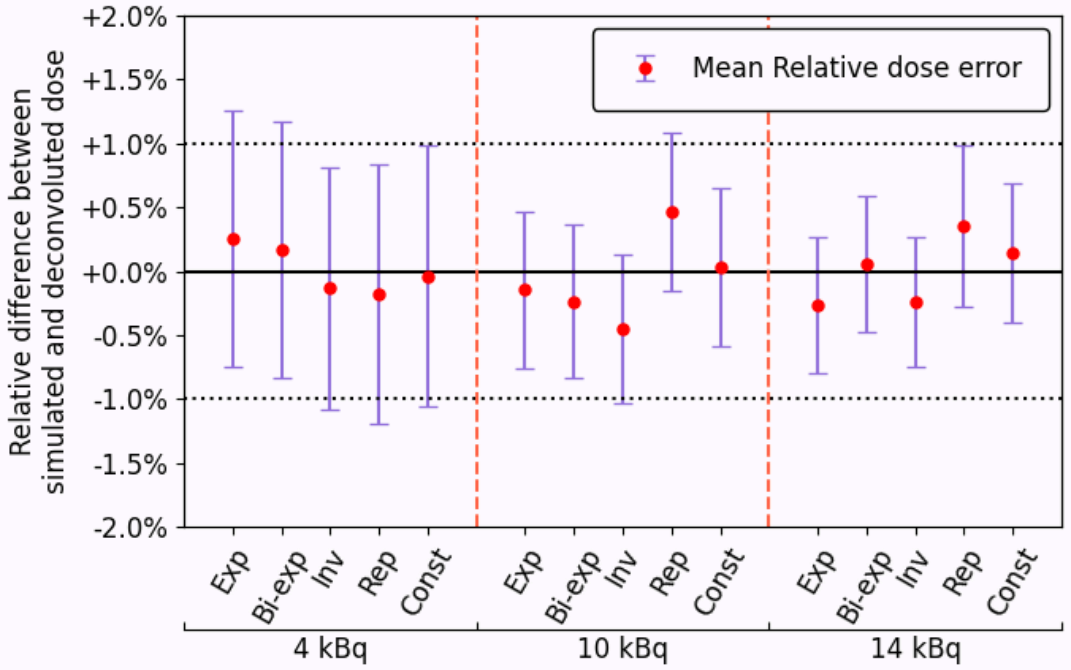
^{223}Ra



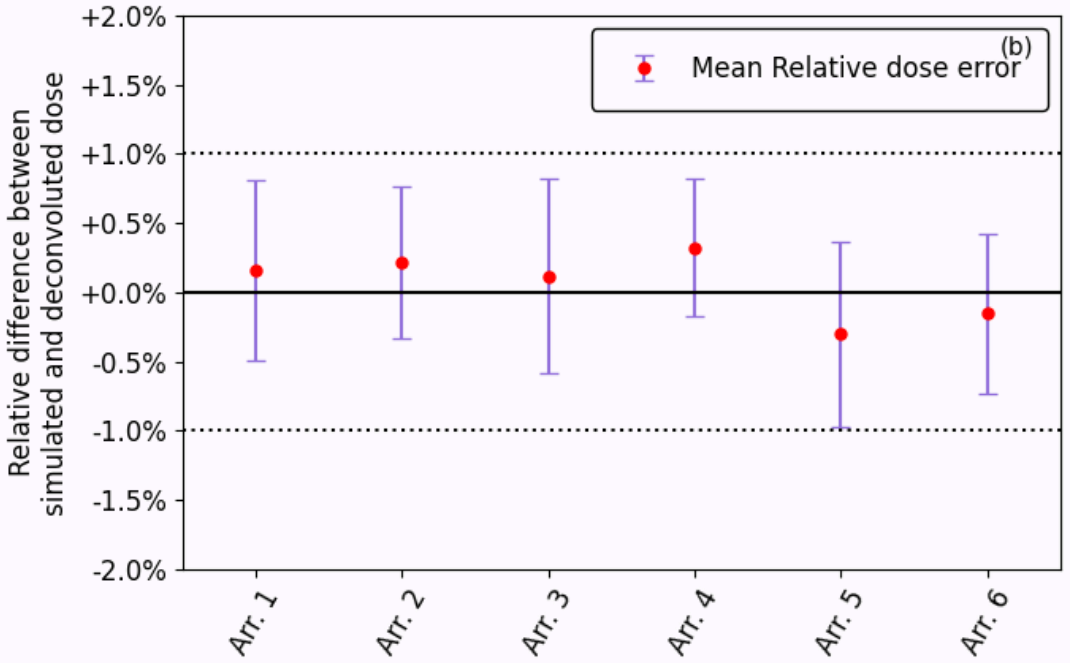
Supplementary Materials – Validation errors

- **Mean dose error** per activity distribution **(bias)** and its uncertainty (3σ)

^{212}Pb

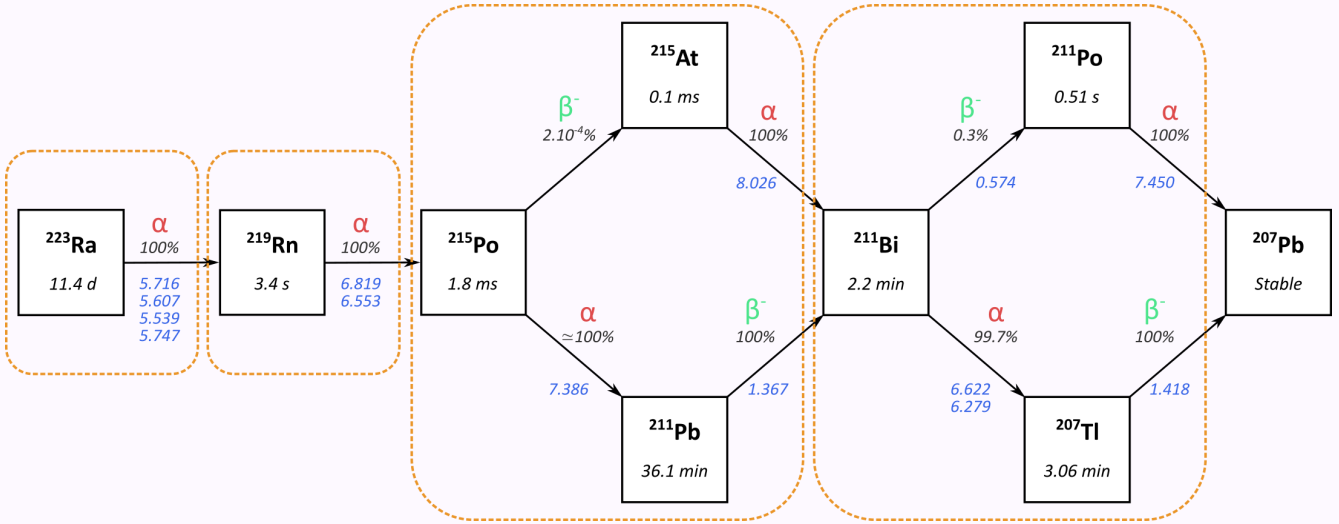


^{223}Ra

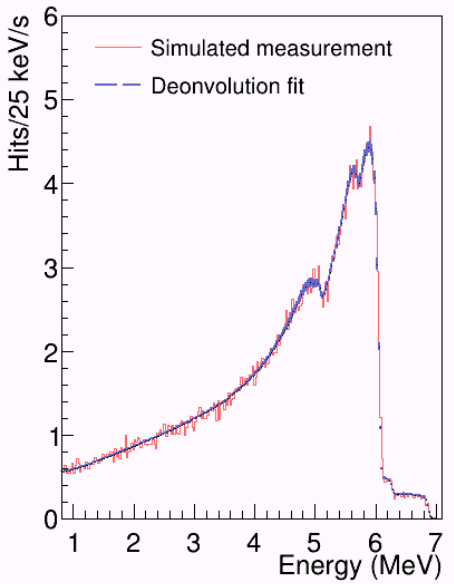


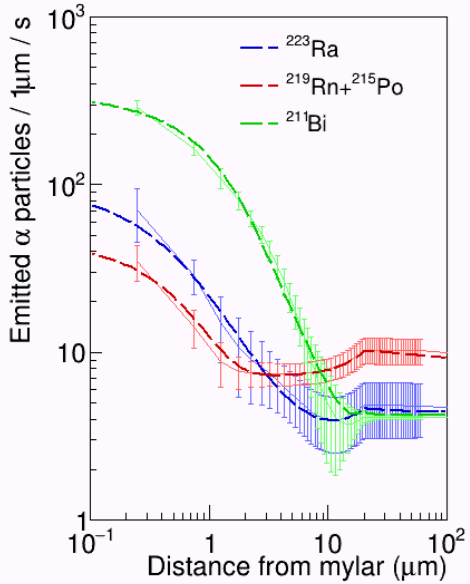
Supplementary Materials – With a more complex decay chain

- Validation with Xofigo (Cl_2 ^{223}**Ra**)
- **4 distinct** α-emission groups
- From distribution kinematics assays :
  - ^{219}Rn and ^{215}Po groups share the same distribution
  - Attribution of realistic distributions to each group



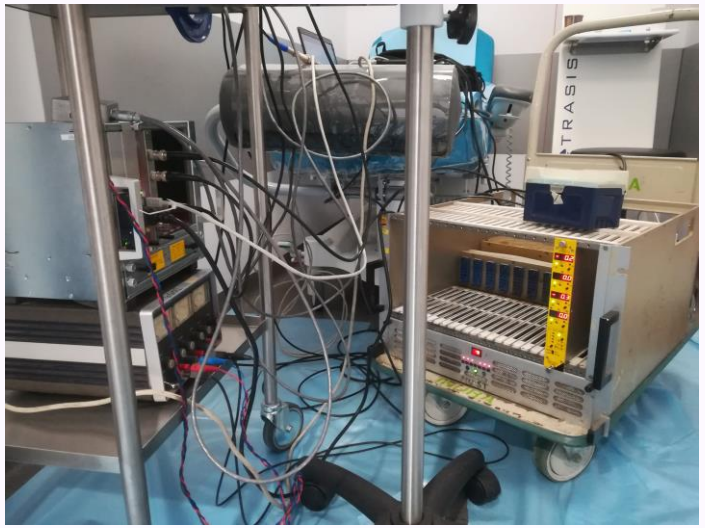
- **Relative dose error systematically below 2%**
- Dose biases observed for α and non-α contributions :
  - α : +0.56 ± 0.26 %
  - non-α : -1.72 ± 0.26 %
- "Per isotope group" contribution subject to large errors:
  - Similar dose deposition for all nuclides (similar LET values)
  - **The total distribution and dose is what matters**





Supplementary Materials – Distribution kinetics assays of ^{223}Ra

➢ **Goal** : application of our deconvolution framework on spectra acquired with our dedicated setup



FASTER *module (LPC Caen) and voltage supplies*

Light-tight container (not the one conceived for culture chambers)

Diode support and culture wells

- **Measurements with an α-emitter radiopharmaceutical**: Xofigo ($Cl_2{}^{223}Ra$), at the CLCC François Baclesse (Caen) *(2021)*
- **4α-emission spectrum** (5.6 MeV, 6.7 MeV, 7.4 MeV, 6.4 MeV) (^{212}Pb : 1α, 2 decay paths, 6.1 MeV & 8.8 MeV).