In vitro dosimetry for assessment of Targeted-α-Therapy (TαT)

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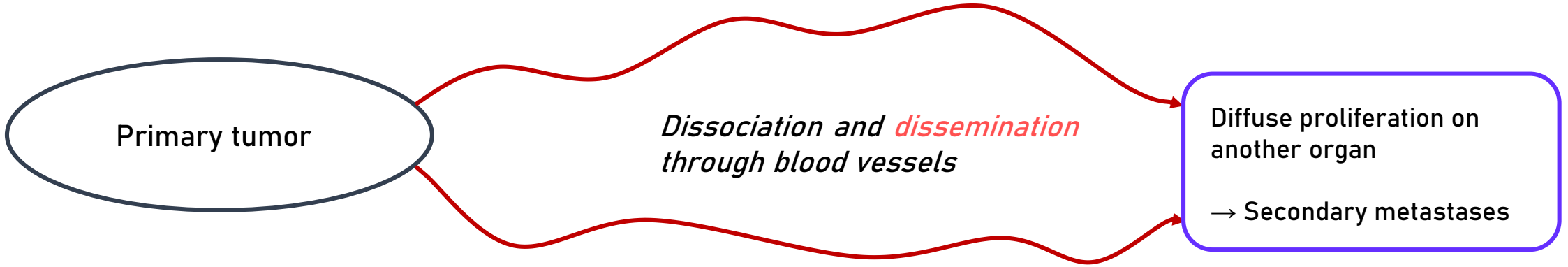
Origin and treatment of secondary brain metastases



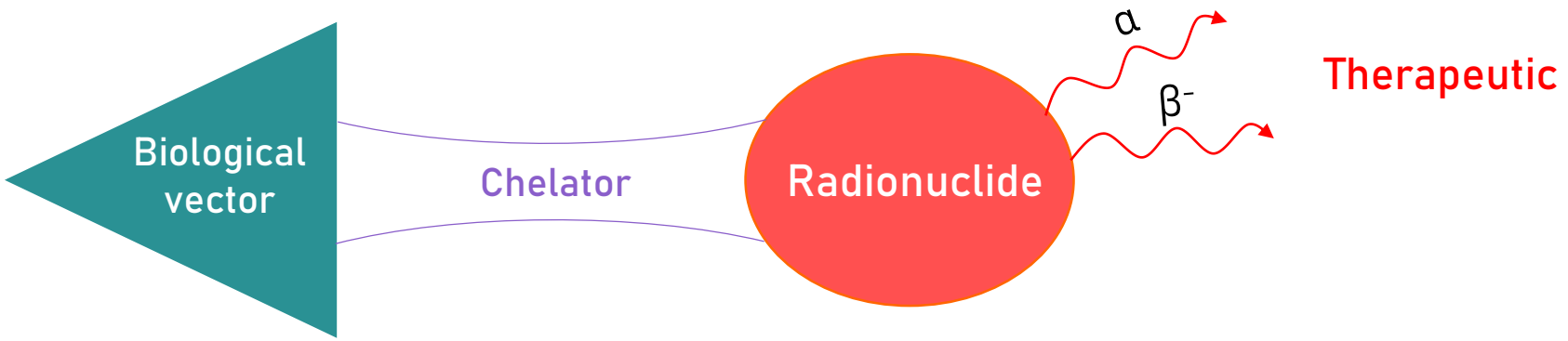
- Metastases are detectable once formed, treatment via radiosurgery, radiotherapy and/or chemotherapy.

  ↳ Multiple locations + potential radio-induced brain damage → poor prognostic (brain metastases: 6 months)

- Detection and treatment of early stages of brain metastasis formation: Targeted Radionuclide Therapy (TRT)

VCAM-1-based TαT

- Radiopharmaceutical structure:



- Over-expression of VCAM-1 observed near breast-cancer-induced brain metastases

→ Anti-VCAM-1 antibody

→ ^{212}Pb-αVCAM-1

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

N. Falzone et al., Theranostics (2018)

- Spatially restricted target + sensible environment (few dozens µm in brain)
- Compromise between clinical usability and short physical period (radioprotection)

→ ^{212}Pb (10.1 h)
→ ^{212}Bi (60.5 min): 6.1 & 8.8 MeV α
= 50 & 91 µm range in water

In vitro assessment of TRT

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

▪ MIRD formalism:

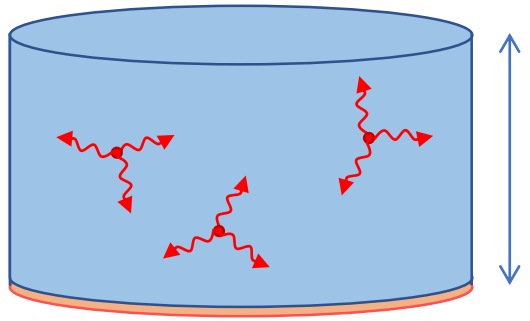
$$Dose \propto A_0 \times \phi(target \leftarrow source)$$

- Injected activity
- Fraction of energy emitted by the source absorbed by the target

Simulated dosimetry under **homogeneous distribution hypothesis**

- β ✓ (range > mm)
- α ✗ ^{212}Bi : 6.1 & 8.8 MeV = 50 & 91 µm in water

▪ *In vitro* configuration:



~2 mm : Culture medium

~20 µm : Cell medium

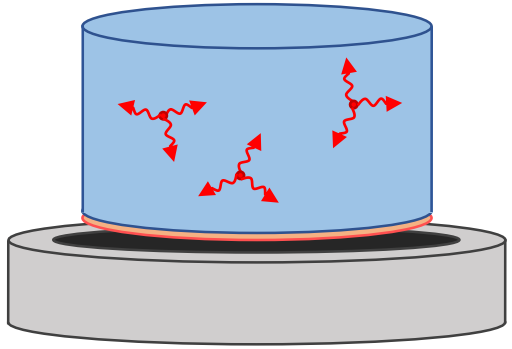
→ Need to determine the spatial distribution of the radionuclides in the culture medium and its evolution during the time of the irradiation.

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

From spectral acquisitions to delivered doses

➢ Development of a new TαT dosimetry system:

→ Acquisition of energy spectra of the alpha particles emitted through the culture medium and cell layer ;



α-detector under culture well

→ Application of a spectral deconvolution method to estimate the spatial and temporal distribution of the radionuclides ;

→ Reconstruction of the dose deposited on the cells through Monte-Carlo simulations.

Detection of α-particles

▪ Dimensions compatible with in vitro cultures

▪ High efficiency (low activities)

Silicon semiconductor detectors

(PIPS, Mirion, U.S.A.)

▪ Specific conditions of T (noise, stability)

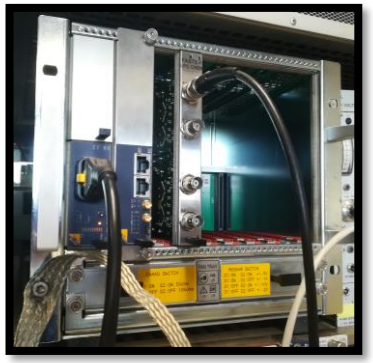
▪ Good energy resolution for α < 10 MeV and response linearity

σ_E(E = 5 486 MeV) = 12,3 keV

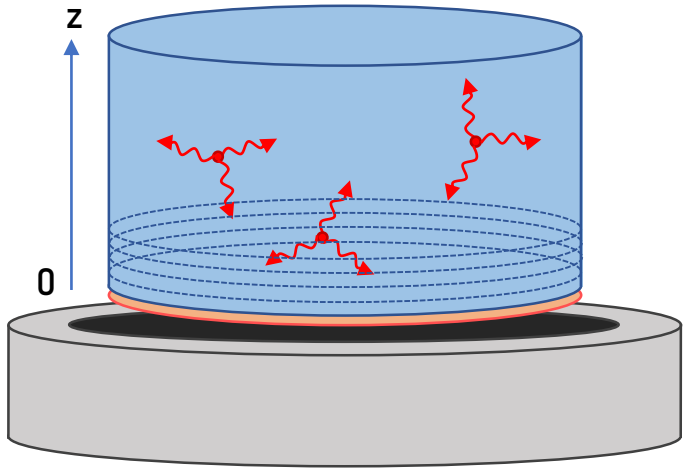
⇒ spatial resolution < 0,5 µm

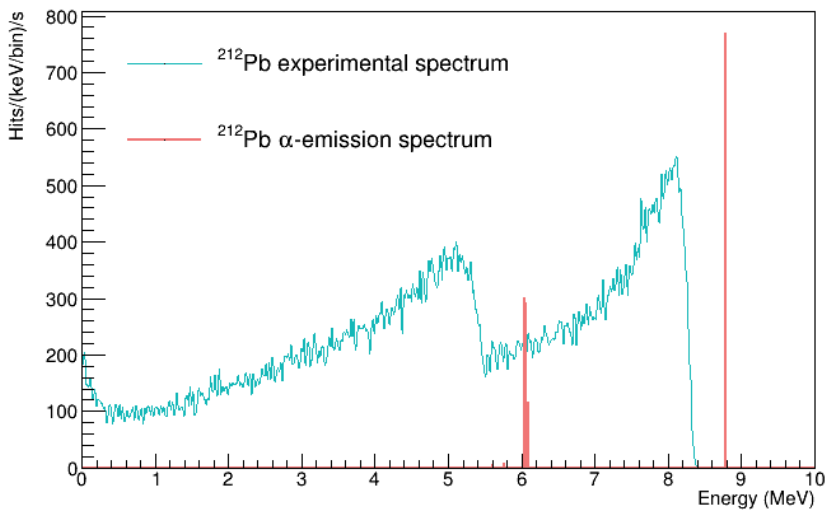
(cell medium: 20 µm, range: 50 to 100 µm)

▪ Coupled with **FASTER** *(LPC Caen)* acquisition system



Deconvolution following a parametric model





- Time evolution: t-discretization

- Decomposition of experimental spectra as a sum of elementary spectra: z-discretization

$$SP_{exp}(t_k, E) = \sum_i A(t_k, z_i) \cdot SP_{elem}(z_i, E)$$

- Constraints: Parametric description of activities

$$A(t_k, z_i) = A(z_i, p_1(t_k), p_2(t_k), \dots)$$

- A satisfying model: exponential distribution

$$A(t_k, z_i) = a(t_k) \cdot e^{-b(t_k) \cdot z_i} + h(t_k)$$

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

3 parameters

Deconvolution as a matrix optimization: notions

- $SP_{exp}(t,E) = \sum_i A(t,z_i) \cdot SP_{elem}(z_i,E)$ —For each time interval→ $Y = Xa\,, \quad a_{sol} = \min_a \|Xa - Y\|^2$

- Additionnal physical constraints on a
  (positivity, limited sum of activities, …) →

$$\begin{cases} Ca_{sol} = c \\ d_{min} \leq Da_{sol} \leq d_{max} \\ a_{min} \leq a_{sol} \leq a_{max} \end{cases}$$

(Quadratic programming)

- Examples

No constraints on a	a ≥ 0
Least Squares (LS)	Non-Negative Least Squares (NNLS)
Algebraic resolution	Iterative resolution
Pseudo inverse : $a_{LS} = (X^T X)^{-1} X^T Y$	*Law & Hanson algorithm*

Deconvolution as a matrix optimization: NNLS-based methods

- The objective function can be modified to adapt a particular modelization :

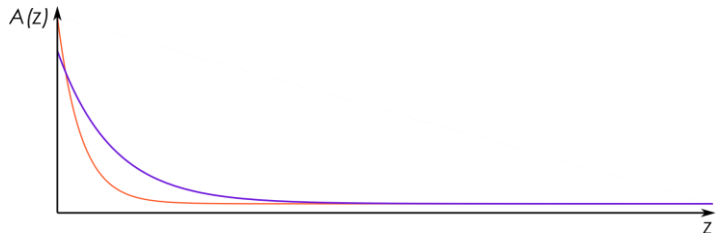
$$A(t_k, z_i) = a(t_k) \cdot e^{-b(t_k) \cdot z_i} + h(t_k)$$

→ Monotonicity of successive derivatives, property of the exponential model

- Other possibilities (can be conbined):

→ Removal of constraints
near the bottom culture wells

→ Separation of the spatial distributions
of different radionuclides

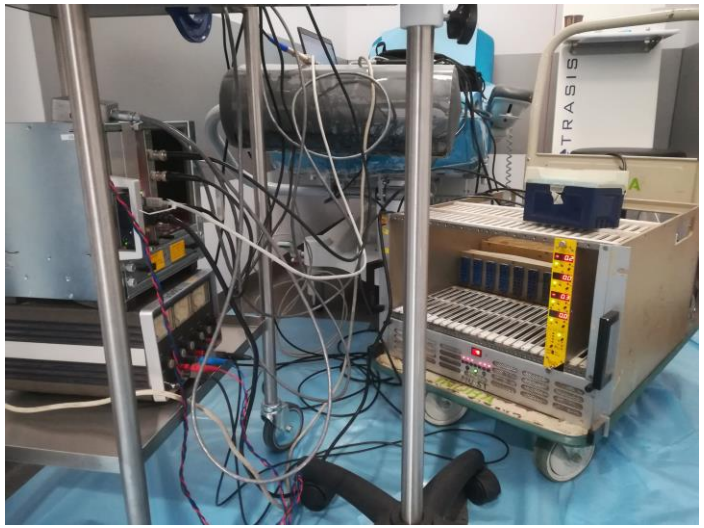


→ Likelihood maximisation criterion
instead of least squares

→ Irregular spatial sampling
of the elementary spectra (adaptative resolution)

Application to a clinical radiopharmaceutical

➢ Goal : assessment of the experimental set-up and of the deconvolution methods



FASTER module and voltage supplies

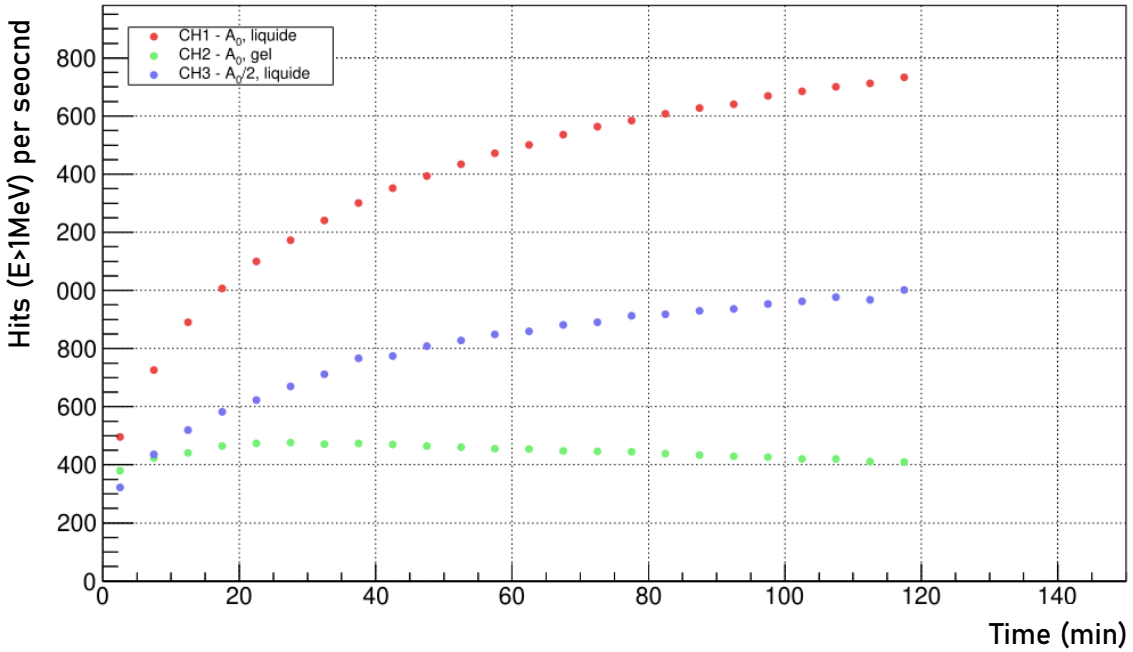
Light-tight container

Diode support and culture wells

- Measurements with an α-emitter radiopharmaceutical: Xofigo ($Cl_2{}^{223}Ra$), at the CLCC François Baclesse (Caen, France).
- 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).

Measurements with ^{223}Ra (1/4) – Radionuclides mobility

Hitrates comparison



- 3 configurations studied:

- Liquid solution of activity A_0
- Liquid solution of activity $A_0/2$
- Gelified solution of activity A_0 with SuperAbsorbent Polymer (SAP, Curas)

- A_0 = 9,3 kBq

- Higher stability of hitrate in time with the gelified solution

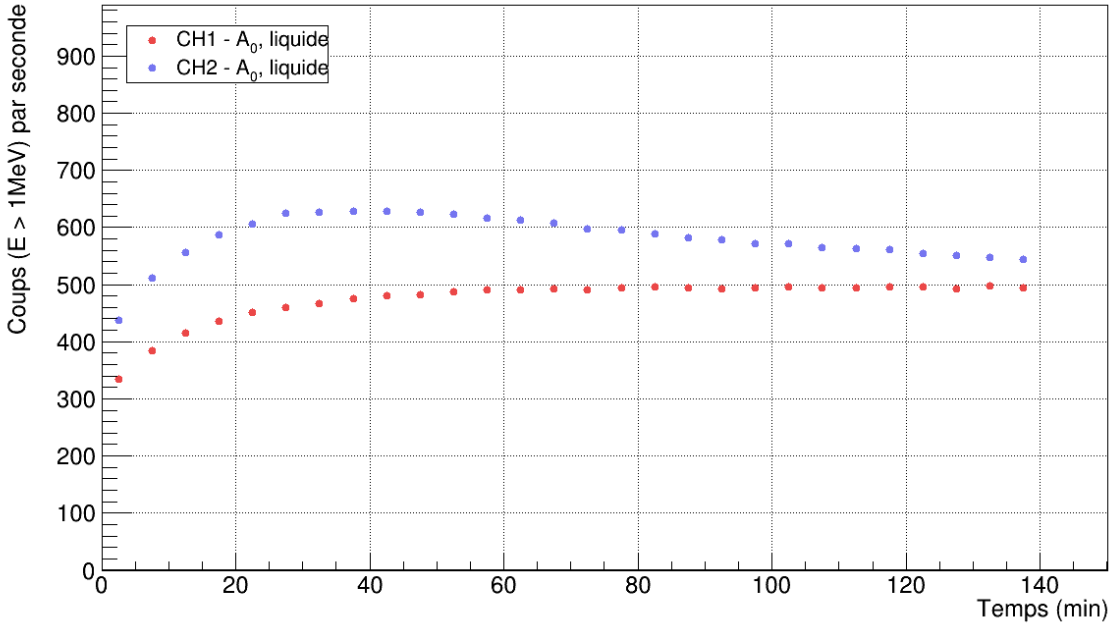
→ Showcases the displacement of radionuclides during *in vitro* experiments

Measurements with ^{223}Ra (2/4) – Reproducibility

▪ Both spectra sets correspond to two separate wells filled with 9,3 kBq of the same liquid solution of ^{223}Ra.

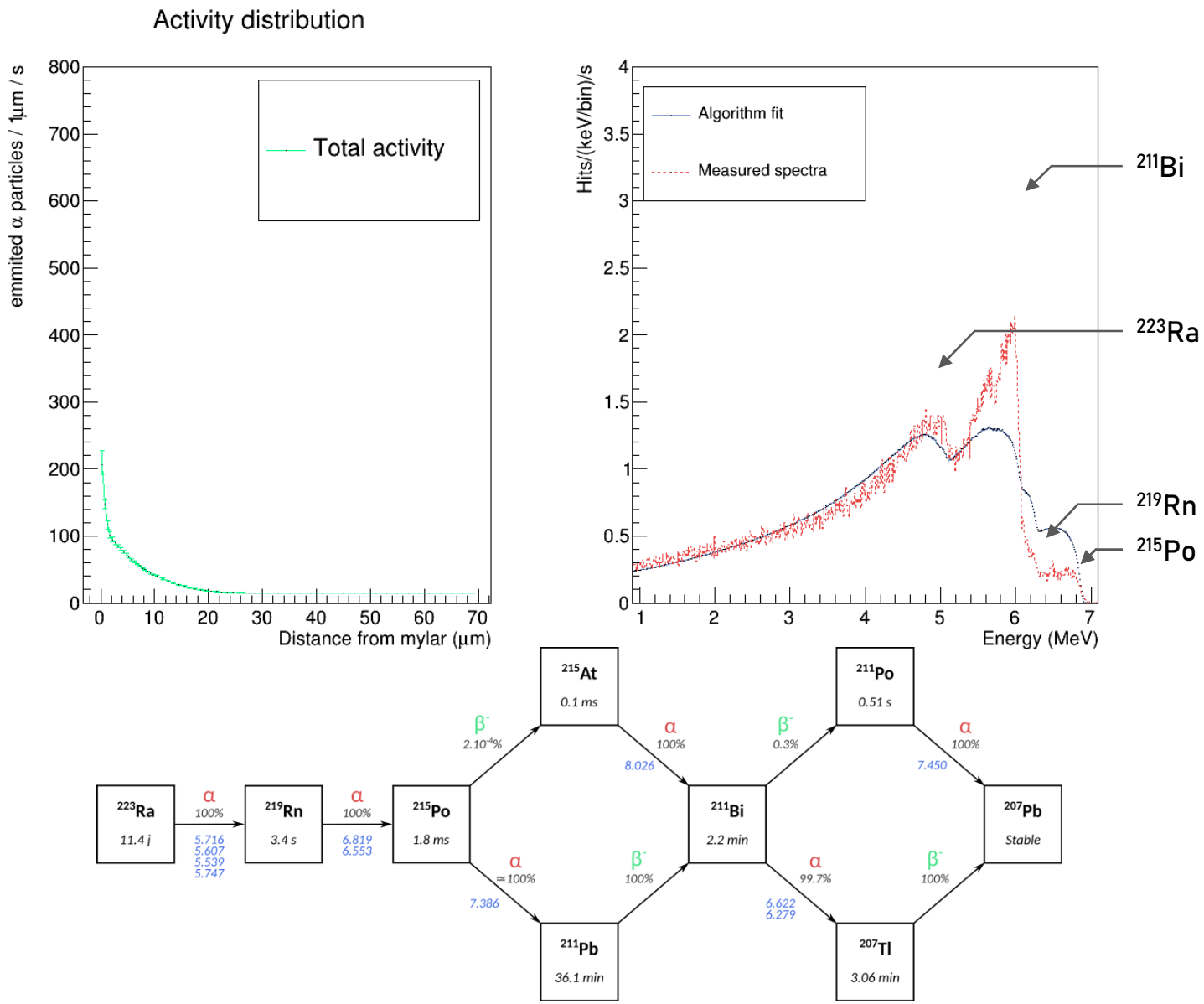
▪ Different hitrate profiles hint at different distribution kinetics for each well.

Hitrates comparison



→ Dose uncertainty estimations must also consider potential lack of reproducibility of the tests

Measurements with ^{223}Ra (3/4) – Deconvolutions



➢ Matrix deconvolution methods application

▪ Set of spectra obtained for a well filled with an activity A_0 = 9,3 kBq of ^{223}Ra

▪ ^{211}Bi distribution strongly differs to the rest of the decay chain ($T_{1/2}$,^{211}Pb = 36 min)

▪ A three-way sepration of the spatial distributions leads to the best experimental spectra reconstructions
(based on information criteria)

▪ Majority of the information lies in a short energy range : overfitting issues

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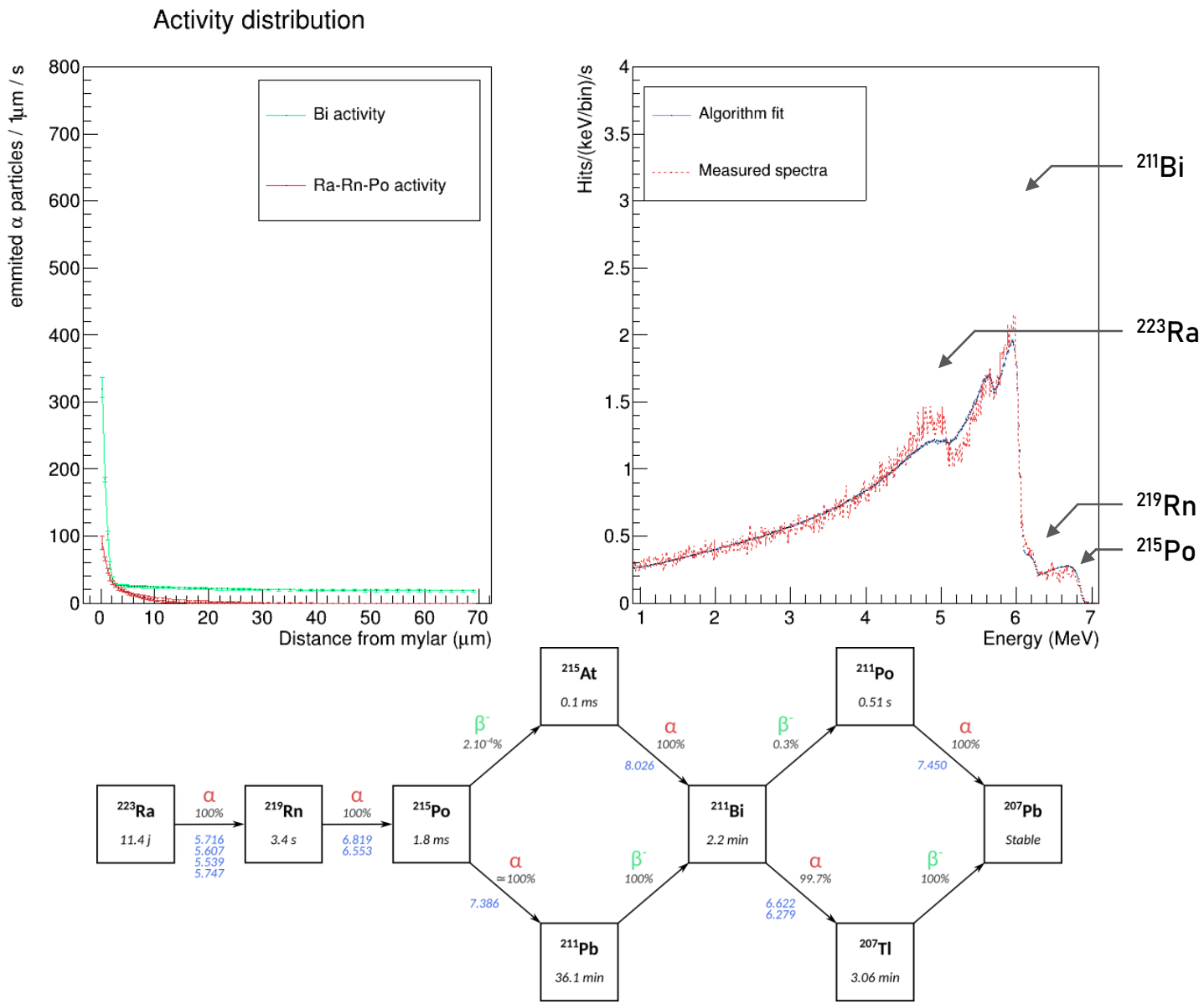

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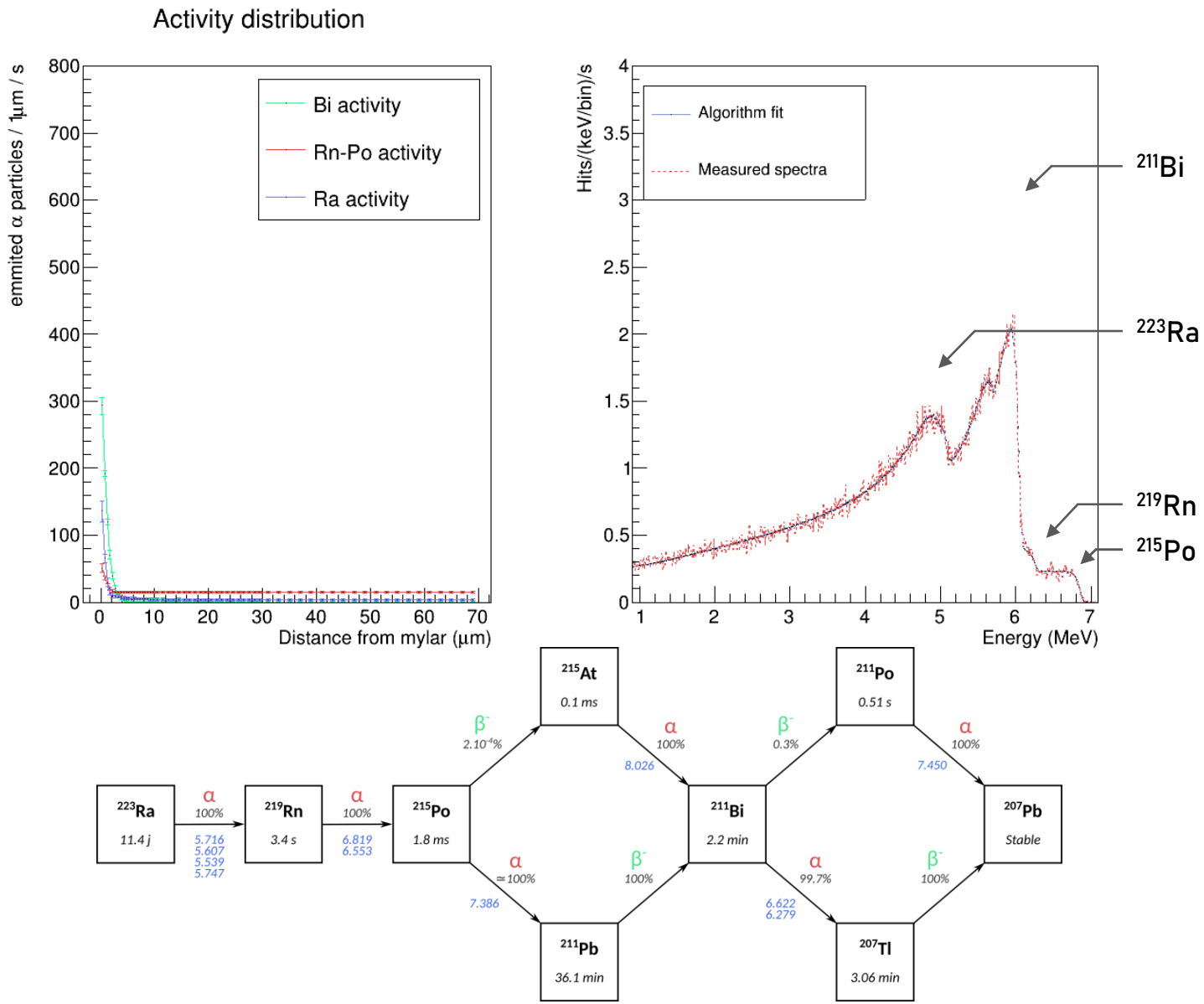

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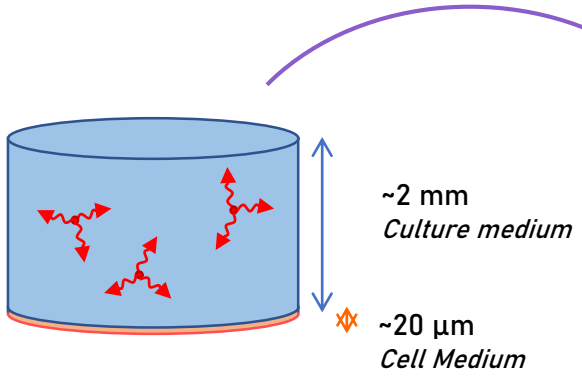
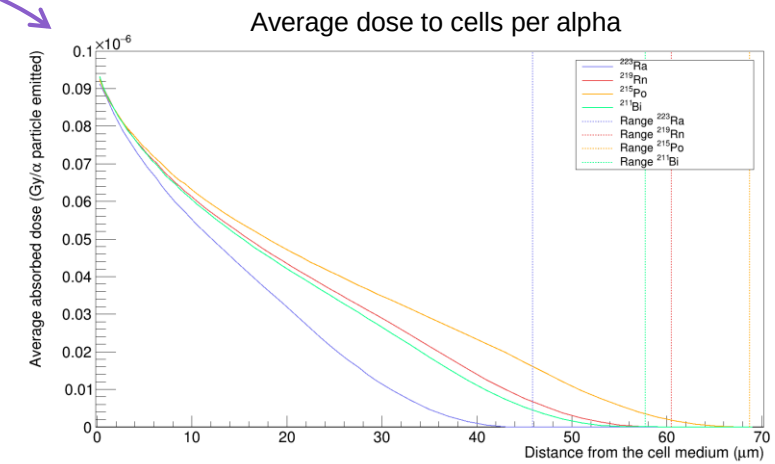
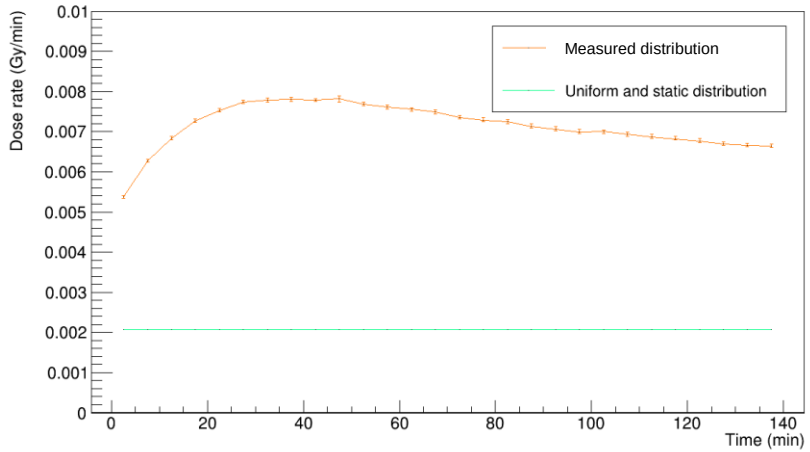
Measurements with ^{223}Ra (4/4) – Dose computation



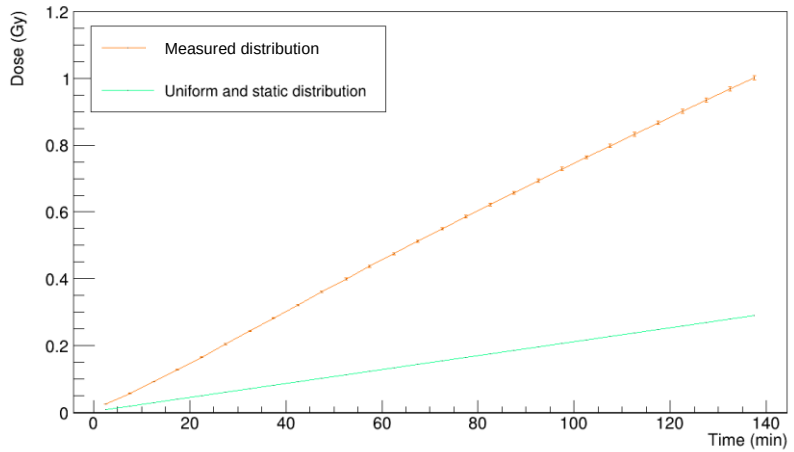


- Simulated cell geometry: 20 µm-high water cylinder.
- For every sampled height, mean delivered dose to the cells per α emitted is computed.
- Continuous aspects of dose rate and cumulated dose graphs: limited overfitting impact.
- Ongoing study.

Dose rates to a 20 µm water cylinder



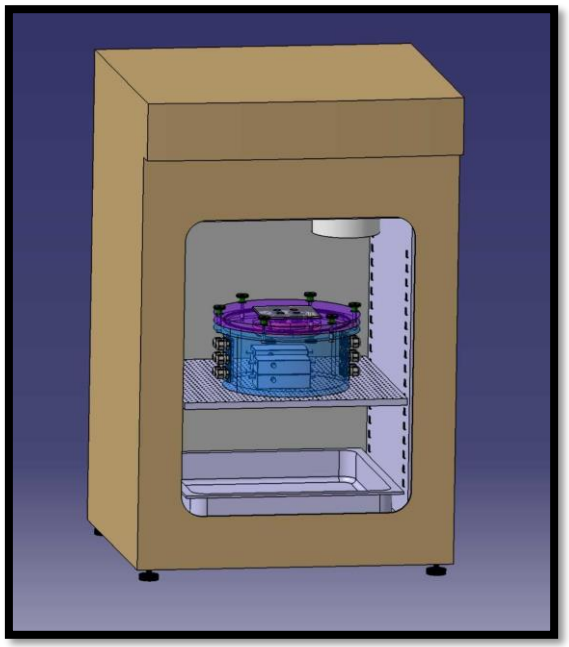
Cumulated dose to a 20 µm water cylinder



3 to 4-fold underestimation

Conclusion - Outlooks

- Short α emissions range: source of important *in vitro* dosimetry errors under homogeneity assumptions.
- Matrix deconvolution easily adjusts physical or hypothetical needs. Computational speed and portability of the set-up: on-site dose estimations.
- Noticeable overfitting for complex decay schemes.
  Consequences on dose computation uncertainties are currently evaluated.
- Cell modelling impact on dose computation is currently studied.
- First measurements of ^{212}Pb injected in cell cultures under *in vitro* conditions: end of 2021.



Thank you for your attention.