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Latest development of α emitter imaging and quantification on a large Field Of View for Targeted Alpha Therapy applications

Arthur Bongrand, Samuel Duval, Jérôme Donnard, Julie Champion

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Arthur Bongrand, Samuel Duval, Jérôme Donnard, Julie Champion. Latest development of α emitter imaging and quantification on a large Field Of View for Targeted Alpha Therapy applications. 11th International Conference on Isotopes (11ICI), Sylvia Fedoruk Canadian Centre for Nuclear Innovation (the Fedoruk Centre); University of Saskatchewan; Tourism Saskatoon, Jul 2023, Saskatoon, Saskatchewan, Canada. hal-04403997

HAL Id: hal-04403997

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Submitted on 18 Jan 2024

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Arthur BONGRAND

Samuel DUVAL, Jérôme DONNARD & Julie CHAMPION

PRISMA



Physics of Radiation InteractionS with Matter and Applications

Latest development of α emitter imaging and quantification on a large Field Of View for Targeted Alpha Therapy applications



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Nantes
Université





Physics of Radiations InteractionS with Matter and Applications

Basic and applied research around 3 main scientific expertise's with potential strong societal impacts:

RaMI → Radionucléides Médicaux Innovants – Innovative Medical Radionuclides

- ✓ Health
- ✓ Nuclear medicine
- ✓ Radionuclides

IRMa → Interaction Rayonnement Matière – Radiation-Matter Interaction

- ✓ Ion Beam Analysis, materials → *IBA platform: visible, X, γ*
- ✓ Non Destructive Testing → *Nuclear data X, γ: PIXE/PIGE - High Resolution X-Ray Tomography System*
- ✓ Detector development and characterization → *profilers, diamond detectors, dosimeters...*

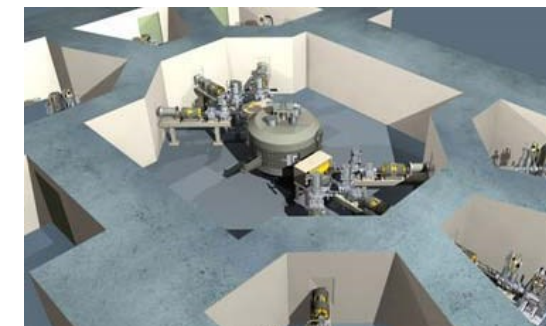
HB → HadronBiologie – HadronBiology

- ✓ Health, Radiobiology, Dosimetry, Flash Hadrontherapy → *In-situ dose monitoring*

Irradiation platform: proton and α



| Beam | Particules | Energy [MeV] | Intensity [μA] | Double beam? |
|----------|------------------|--------------|----------------|--------------|
| Proton | H ⁻ | 30 to 70 | ≤350 | Yes |
| | HH ⁺ | 17 | ≤50 | No |
| Deuteron | D ⁻ | 15-35 | ≤50 | Yes |
| Alpha | He ²⁺ | 68 | ≤70 | No |



⁸²Sr

²¹¹At

⁶⁴Cu

⁴⁴Sc

⁶⁸Ge

⁶⁷Cu

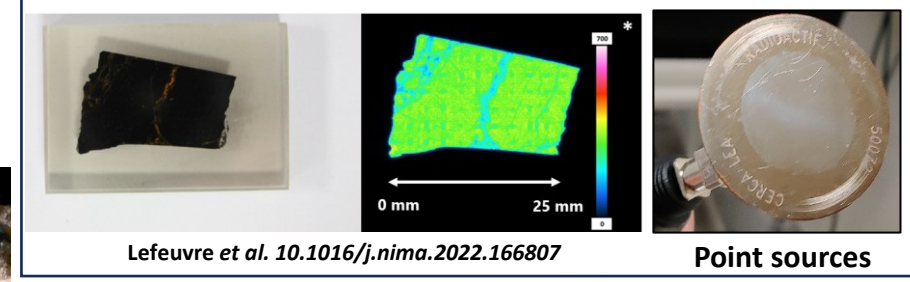
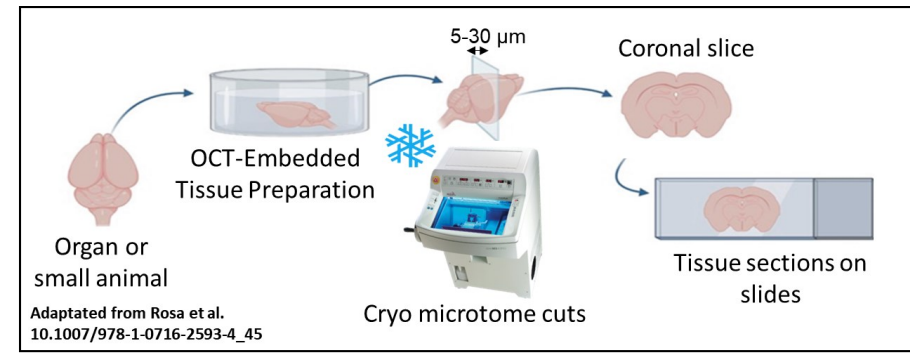
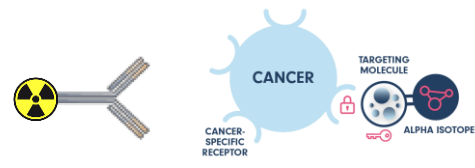
⁴⁷Sc



- **Autoradiography, an emission imaging technique !**
 - Allows to study and locate in 2D the radioactivity emanating from a sample
 - Area of interest located at the surface ($\approx 10 \mu\text{m}$ deep)

Applications

- **Pre-clinical** (oncology + drug discovery)
Visualization of molecules or fragments of molecules labeled with radioactive elements
- **Geology** (study of uraniferous rocks, environmental pollution...)



Samples

- "Thin" (<1 cm thick) \approx size of a small sugar square
- Can be electroplated on a glass slide, a “sugar”, a metal foil...



Specificities of the BeaQuant

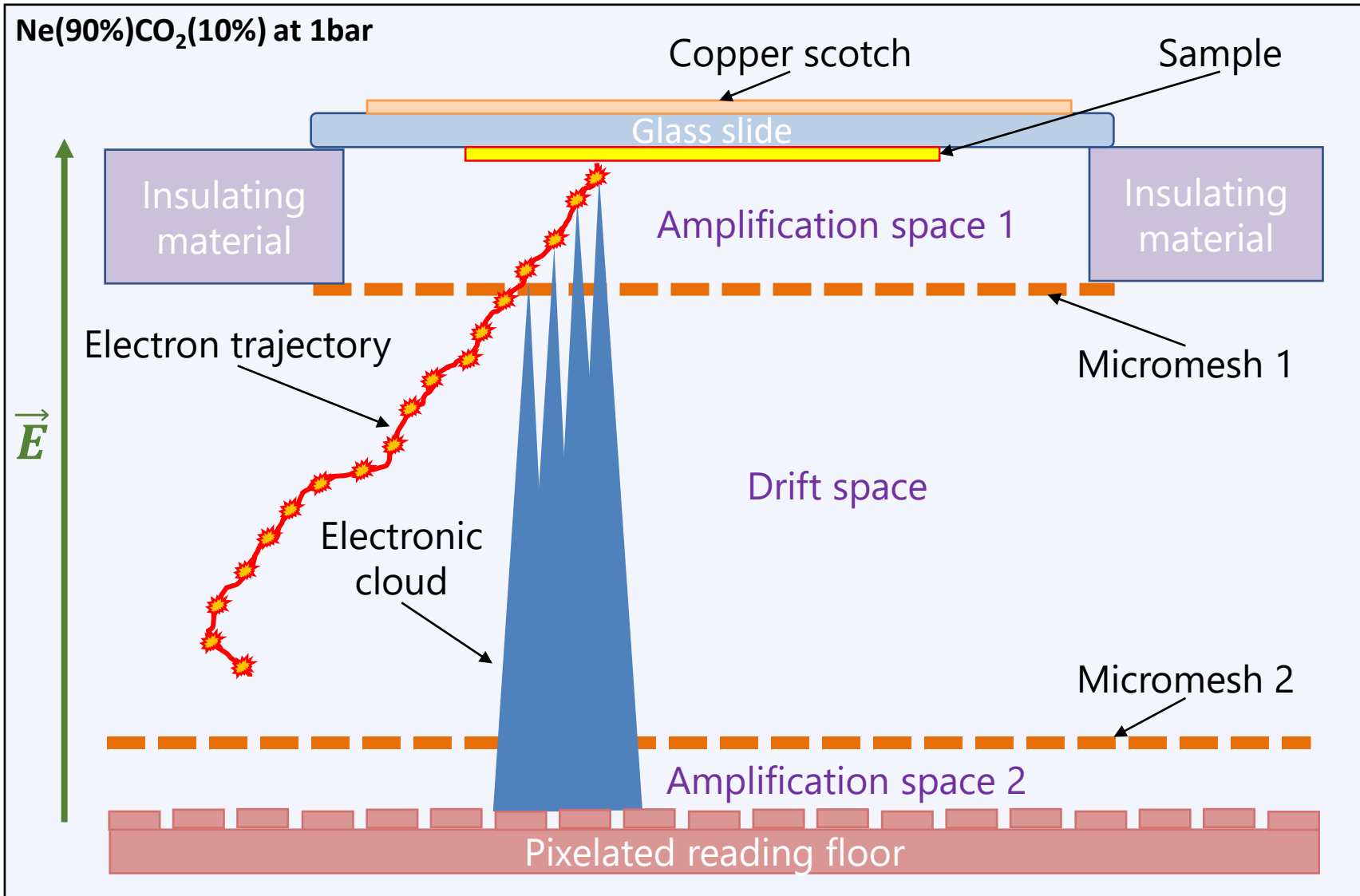
- Real-time direct counting
 - ✓ Quantification
 - ✓ Tracking

| | |
|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Technology | Direct gaseous counter |
| Performance | <ul style="list-style-type: none"> •Spatial: α (alpha) 20 μm – β (Beta) 20 μm – High energy β or β^+ 50 μm •Linearity over 5 orders of magnitude •Sensitivity: 0.0005 cpm/mm² (\approx mBq) •Large Field Of View 20x20 cm² |
| Markers | All radioisotopes |

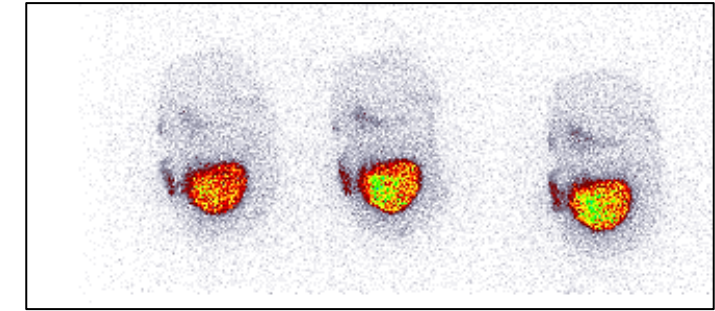


27/07/2023

Sectional view

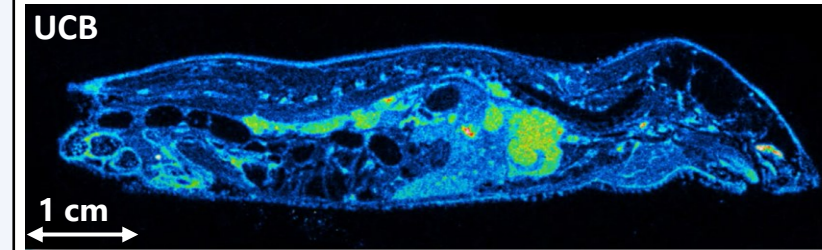


Laboratoire Imagerie et Cerveau, Unité Inserm
930 Université François-Rabelais de Tours



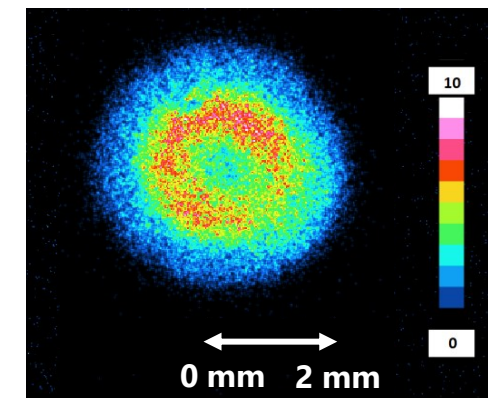
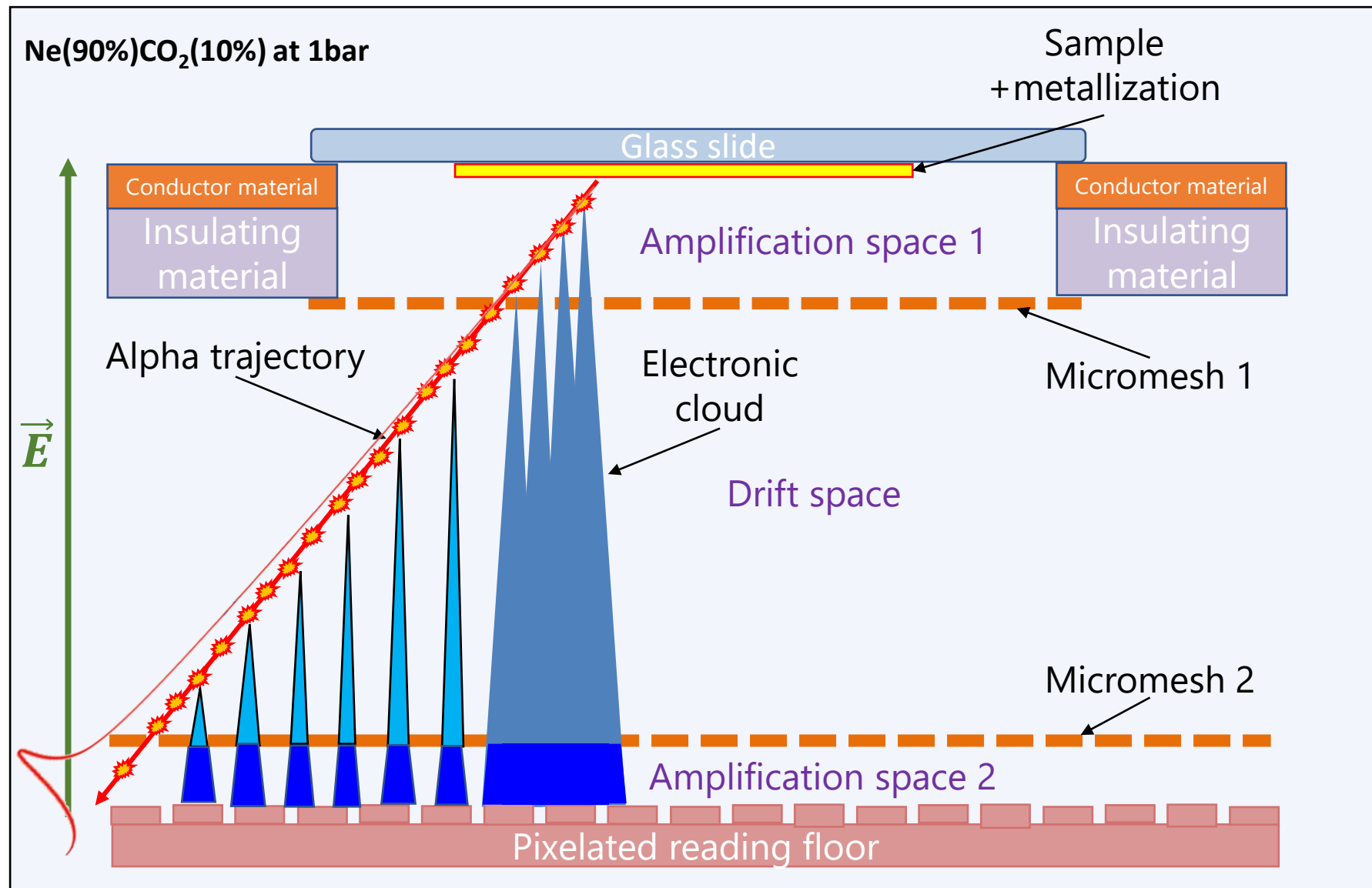
In vivo rat brain labelled with LBT999 - ¹⁸F

¹⁸F Spatial resolution: 50 μ m

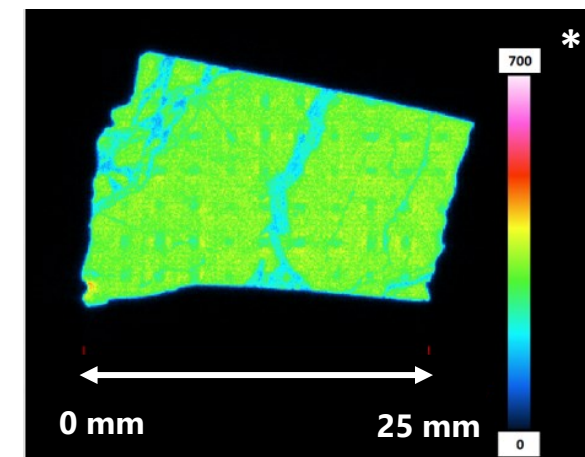


¹²⁵I QWBA
Spatial resolution: 50 μ m

Sectional view



Isotope: ²²⁵Ac PSMA
Spatial resolution : 20 μ m

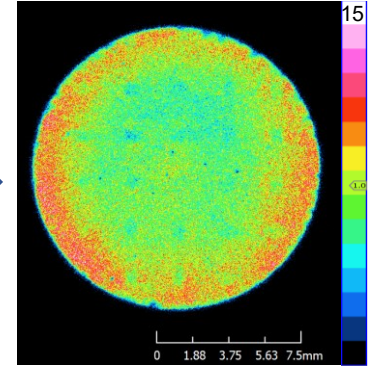
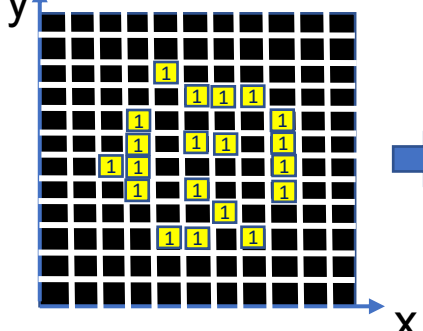
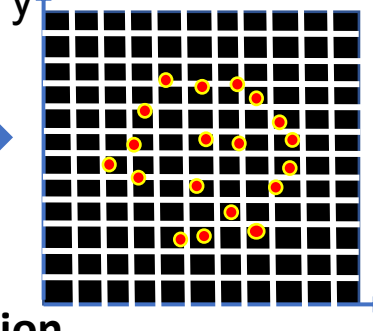
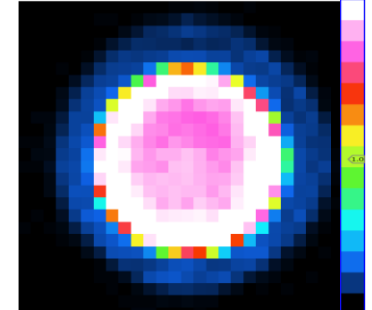
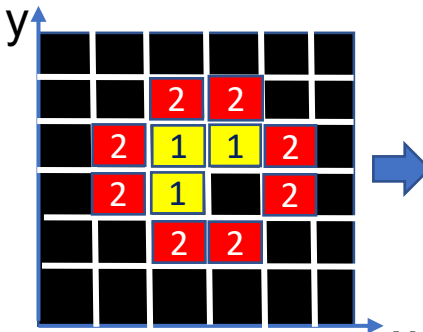
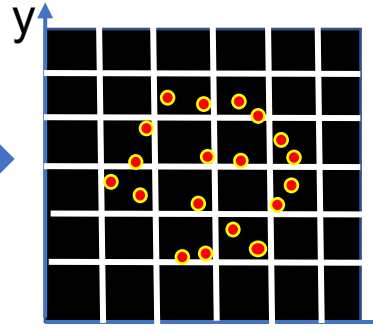
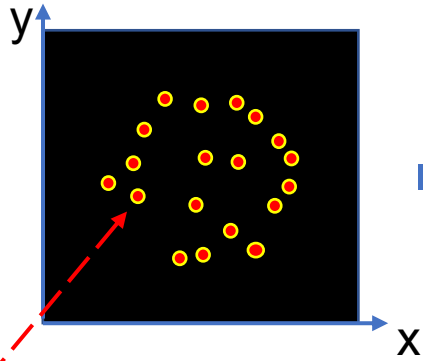
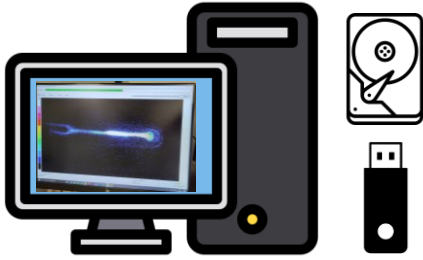
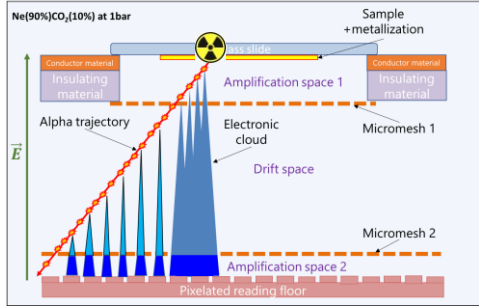


Uranium ore sample (²³⁸U, ²³⁵U, ²³⁴U)
Spatial resolution: 20 μ m

*Lefevre et al. 10.1016/j.nima.2022.166807

Digital autoradiography → Ability to analyze and reanalyze endlessly!

Autoradiograph



Tri alpha point source (²³⁹Pu, ²⁴¹Am, ²⁴⁴Cm)

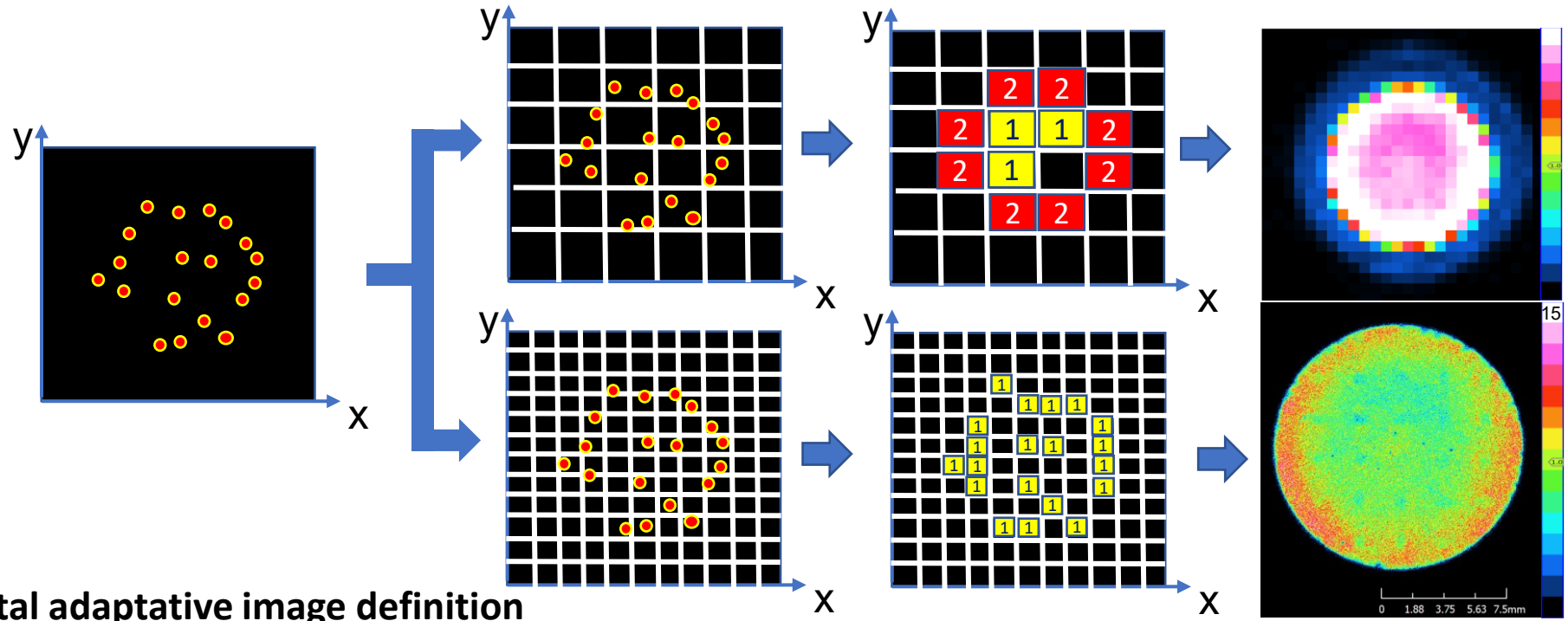
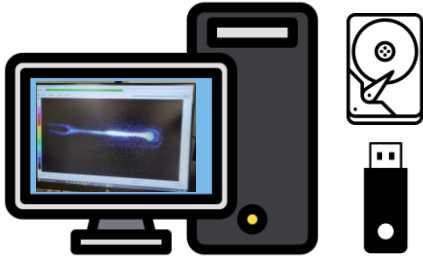
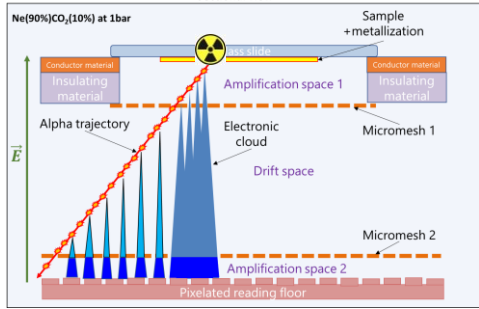
Digital adaptive image definition

DataFile

```
Ascii_Output.txt - Notepad2
File Edit View Settings ?
1 X; Y; A; T
2 6.993324e+04;4.232566e+04;1.403000e+03;9.770000e+02
3 8.085247e+04;4.233055e+04;2.773000e+03;9.880000e+02
4 3.051850e+04;4.315222e+04;1.503000e+03;1.135000e+03
5 3.003613e+04;4.303467e+04;7.310000e+02;1.164000e+03
6 7.303848e+04;4.258221e+04;3.789000e+03;1.168000e+03
7 7.116055e+04;4.153960e+04;5.870000e+02;1.188000e+03
8 8.847627e+04;4.183154e+04;2.319000e+03;1.197000e+03
9 7.199740e+04;4.361172e+04;1.717000e+03;1.241000e+03
10 3.221283e+04;4.560778e+04;1.505000e+03;1.317000e+03
11 8.333140e+04;4.226087e+04;3.920000e+03;1.319000e+03
12 6.820509e+04;4.269427e+04;8.210000e+02;1.388000e+03
13 7.000938e+04;4.203142e+04;2.385000e+03;1.422000e+03
14 6.811284e+04;4.221139e+04;2.793000e+03;1.438000e+03
15 2.930108e+04;4.269967e+04;3.010000e+03;1.467000e+03
16 3.366449e+04;4.408017e+04;1.543000e+03;1.507000e+03
17 7.060286e+04;4.325380e+04;1.347000e+03;1.512000e+03
```


Digital autoradiography → Ability to analyze and reanalyze endlessly!

Autoradiograph



DataFile

```

Ascii_Output.txt - Notepad2
File Edit View Settings ?
1 X; Y; A; T
2 6. 993324e+04; 4. 232566e+04; 1. 403000e+03; 9. 770000e+02
3 8. 085247e+04; 4. 233055e+04; 2. 773000e+03; 9. 880000e+02
4 3. 051850e+04; 4. 315222e+04; 1. 503000e+03; 1. 135000e+03
5 3. 003613e+04; 4. 303467e+04; 7. 310000e+02; 1. 164000e+03
6 7. 303848e+04; 4. 258221e+04; 3. 789000e+03; 1. 168000e+03
7 7. 116055e+04; 4. 153960e+04; 5. 870000e+02; 1. 188000e+03
8 8. 847627e+04; 4. 183154e+04; 2. 319000e+03; 1. 197000e+03
9 7. 199740e+04; 4. 361172e+04; 1. 717000e+03; 1. 241000e+03
10 3. 221283e+04; 4. 560778e+04; 1. 505000e+03; 1. 317000e+03
11 8. 333140e+04; 4. 226087e+04; 3. 920000e+03; 1. 319000e+03
12 6. 820509e+04; 4. 269427e+04; 8. 210000e+02; 1. 388000e+03
13 7. 000938e+04; 4. 203142e+04; 2. 385000e+03; 1. 422000e+03
14 6. 811284e+04; 4. 221139e+04; 2. 793000e+03; 1. 438000e+03
15 2. 930108e+04; 4. 269967e+04; 3. 010000e+03; 1. 467000e+03
16 3. 366449e+04; 4. 408017e+04; 1. 543000e+03; 1. 507000e+03
17 7. 060286e+04; 4. 325380e+04; 1. 347000e+03; 1. 512000e+03
    
```

Digital adaptive image definition

Data analysis

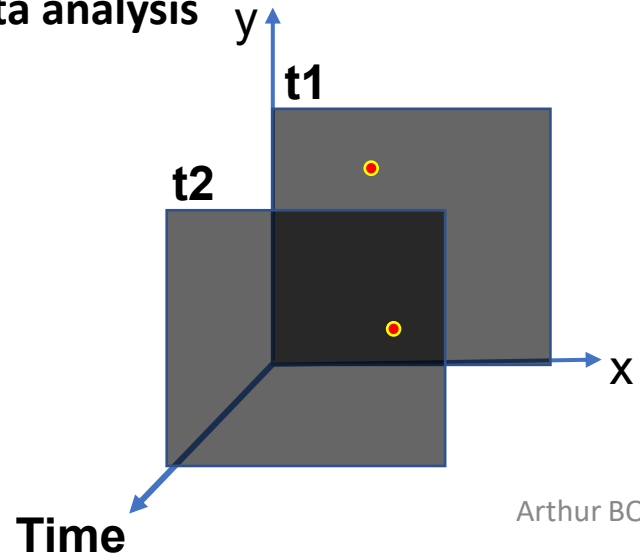


Image processing:

- ✓ Localization (ROI)
- ✓ Quantification

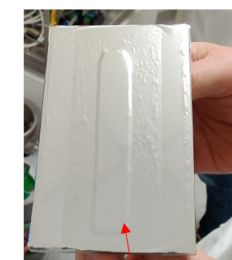
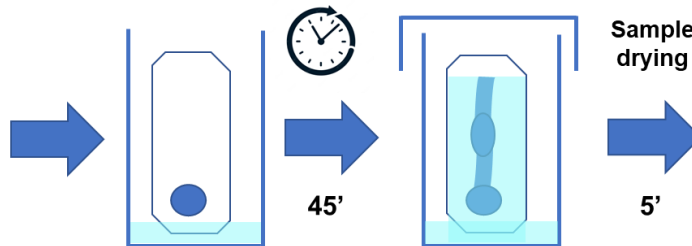
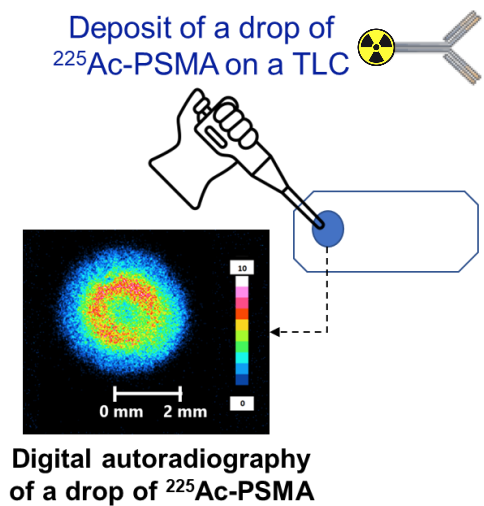
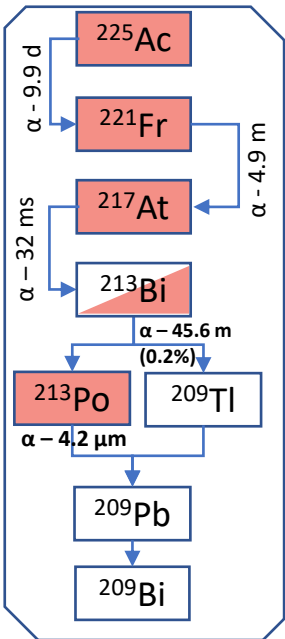
Additional data available of each detected particle:

- ✓ Time
- ✓ Kinetic energy (α)

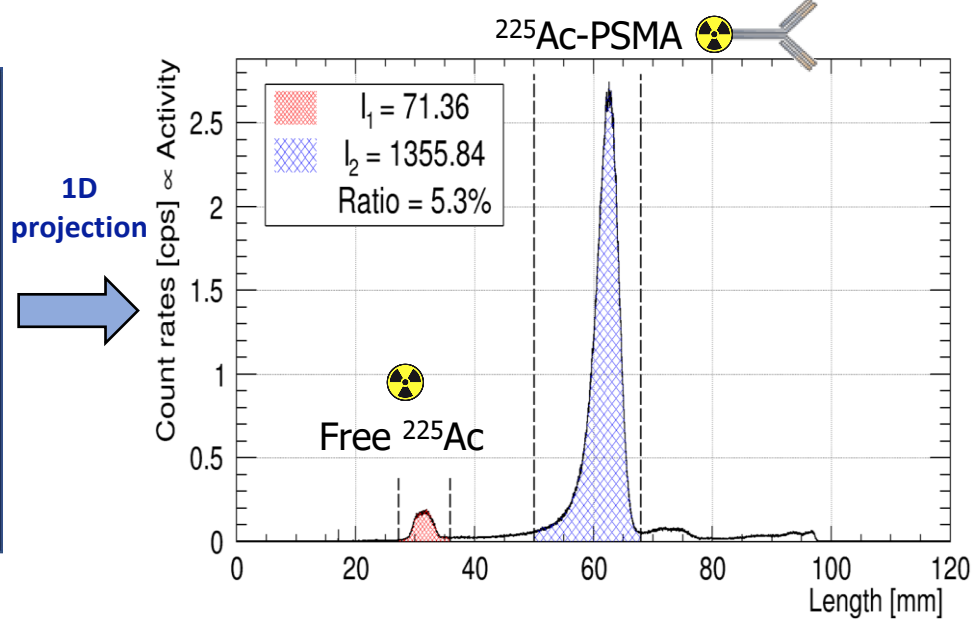
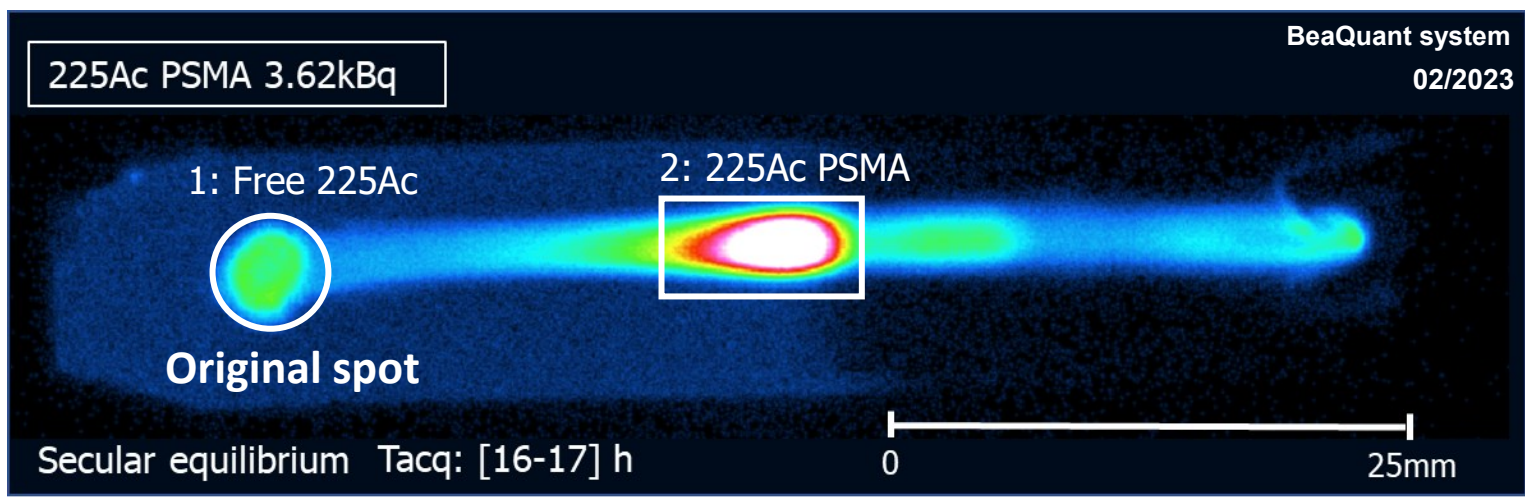
Quality control of ^{225}Ac -PSMA with Digital Autoradiography!



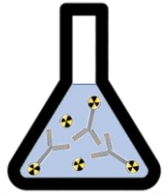
Protocol: Deposit of a drop of ^{225}Ac -PSMA on a TLC → Migration (45min)



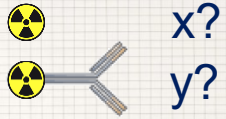
Sample preparation: Protection of the TLC with a foil



Quality control of ^{225}Ac -PSMA with the TLC method !

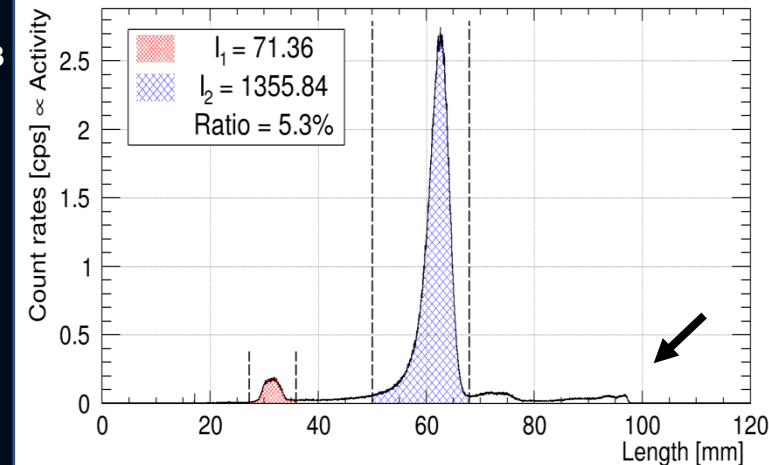
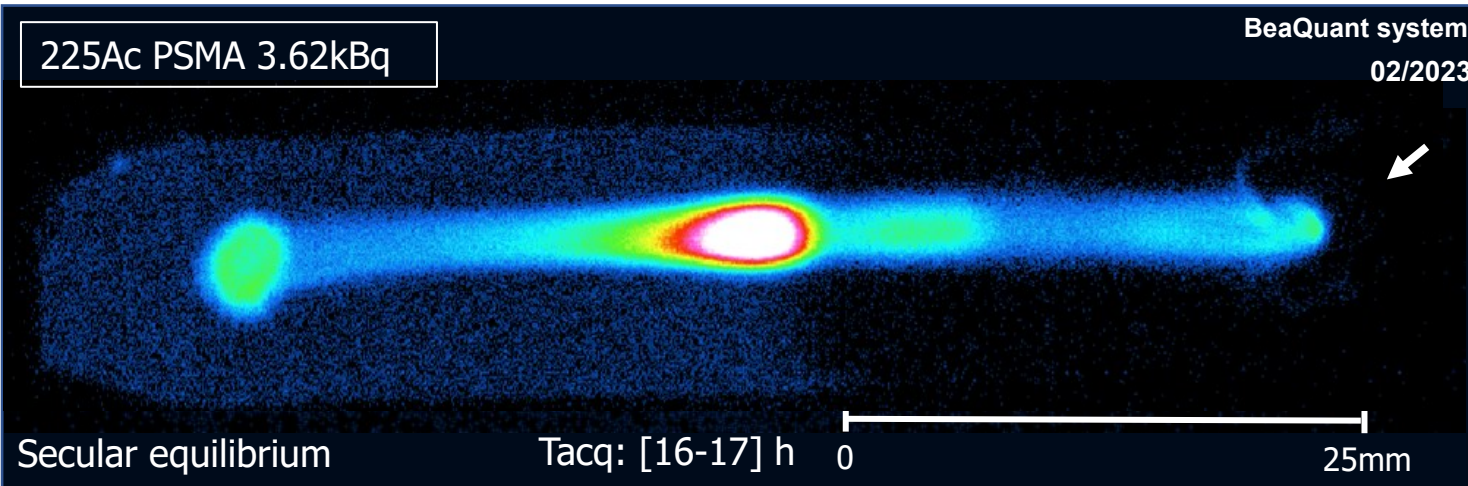
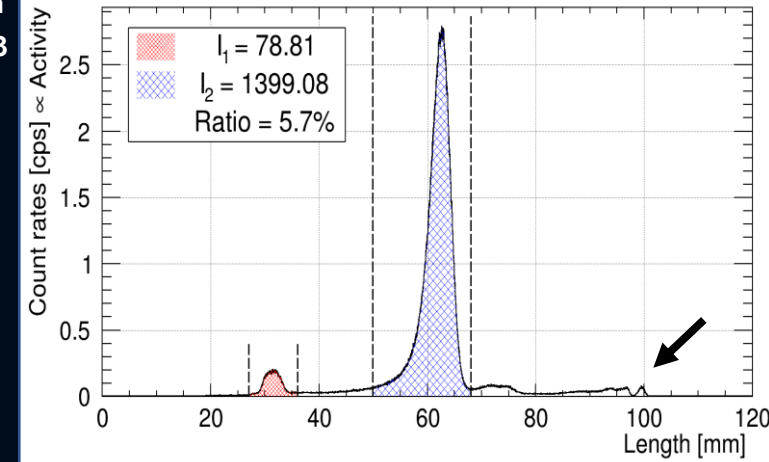
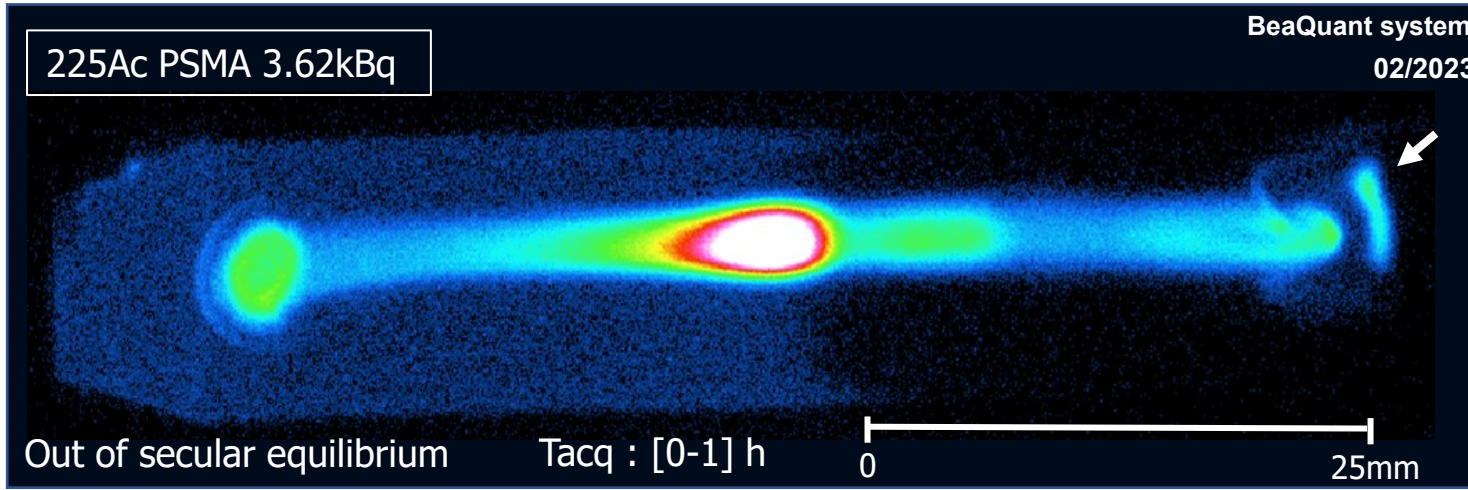
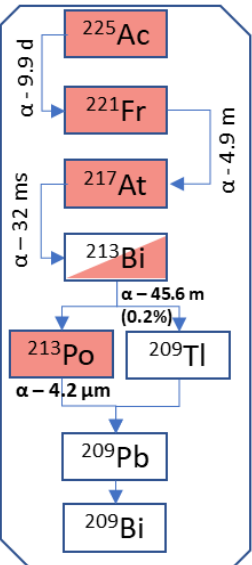


Quality control



$$\text{Ratio} = x/y$$

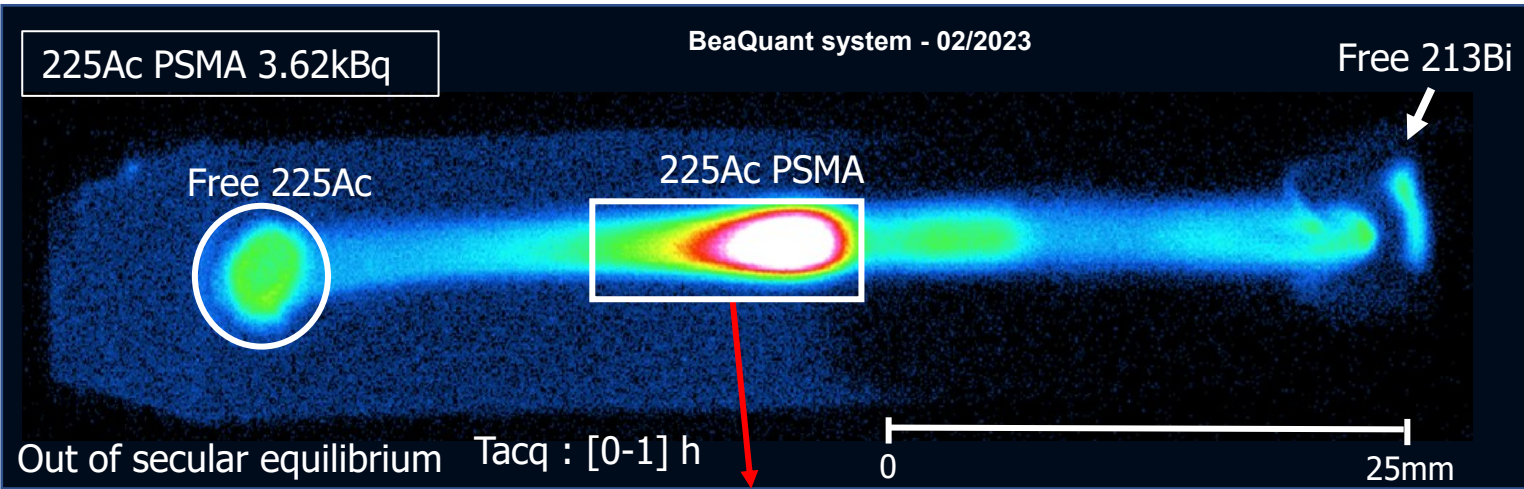
Ratio < 5%!




Can we identify the contributions of the different elements of the decay chain?




Quality control of ^{225}Ac -PSMA with the TLC method & **Temporal Spectro'** 10

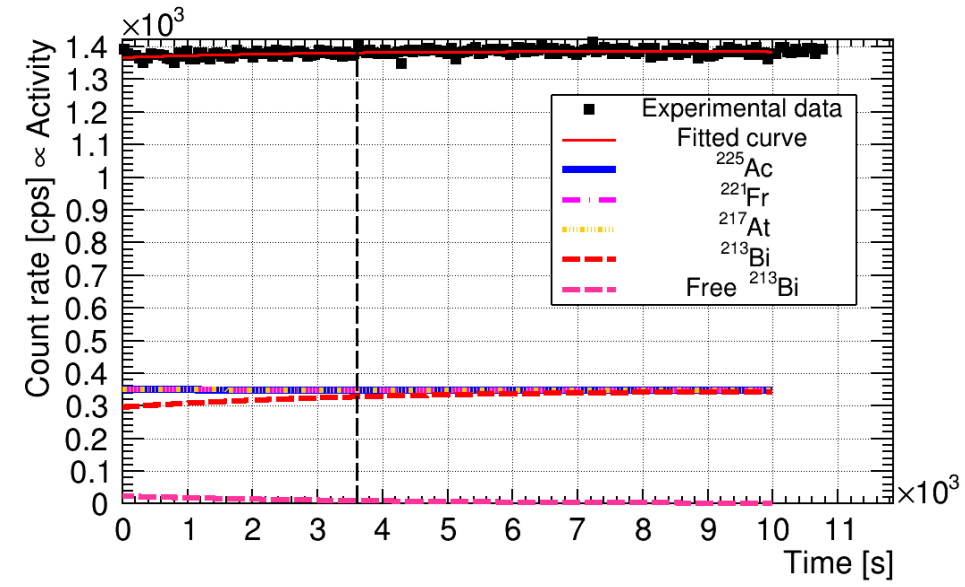
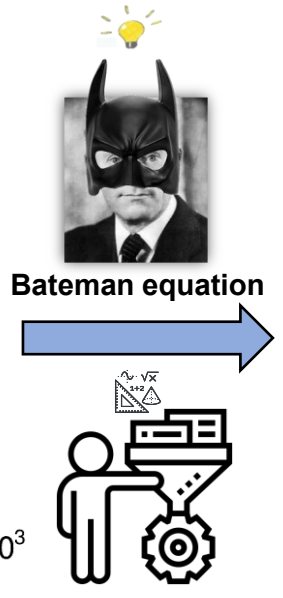
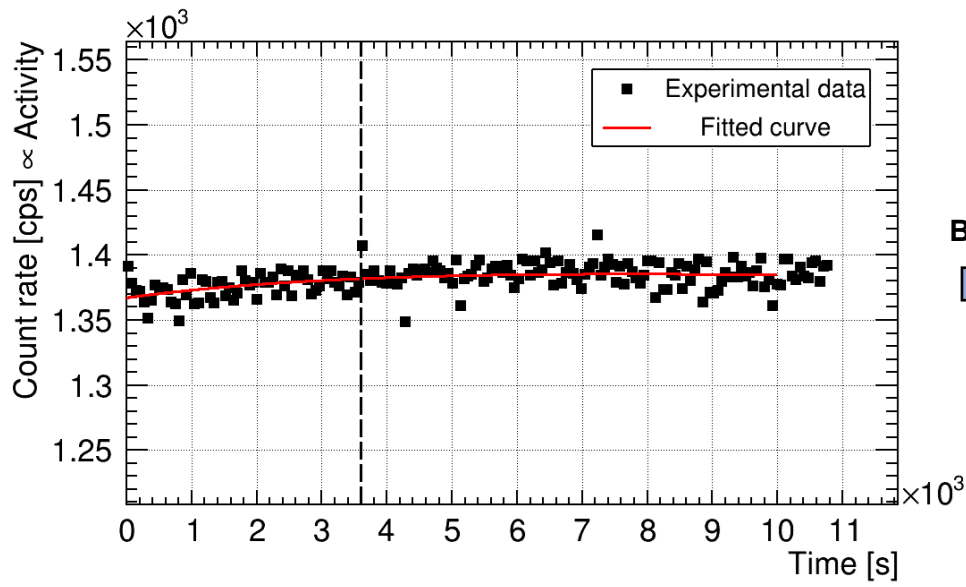
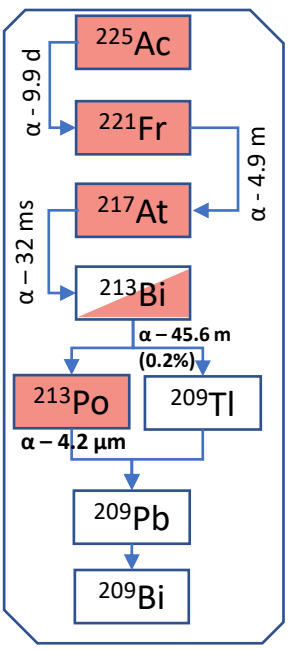


Digital autoradiography: 

Digital image + Exploitation of time data

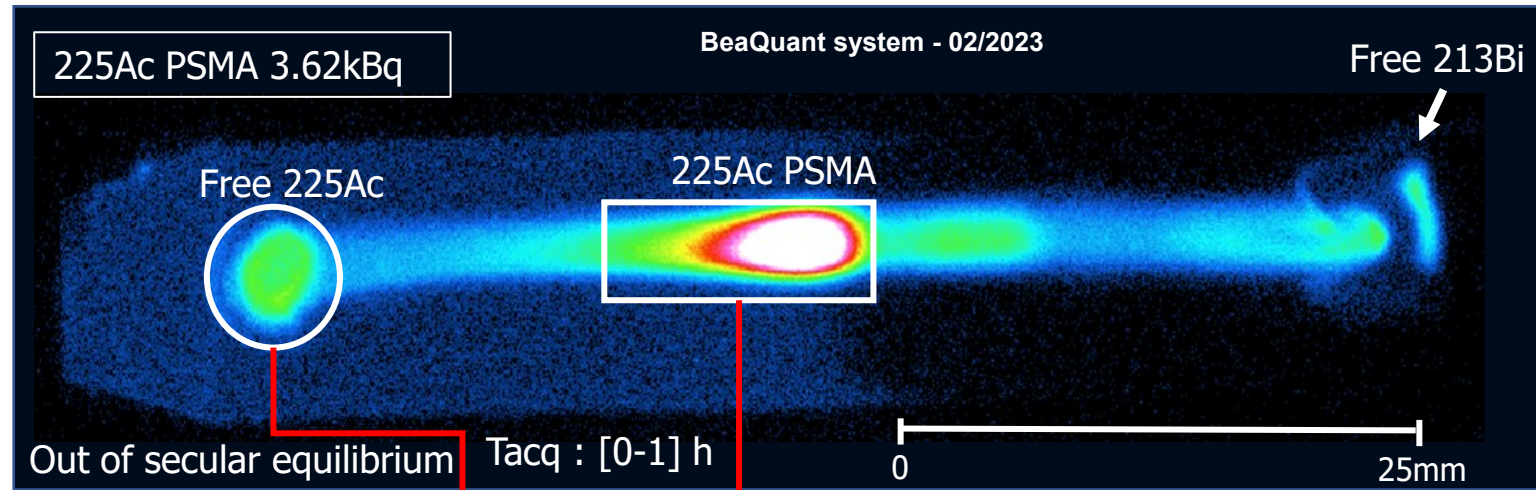
↓

Localized Identification of the different α isotopes of the decay chain 



The activity of the different α isotopes can be determined at any time!

Quality control of ^{225}Ac -PSMA with the TLC method & **Temporal Spectro'** ¹¹



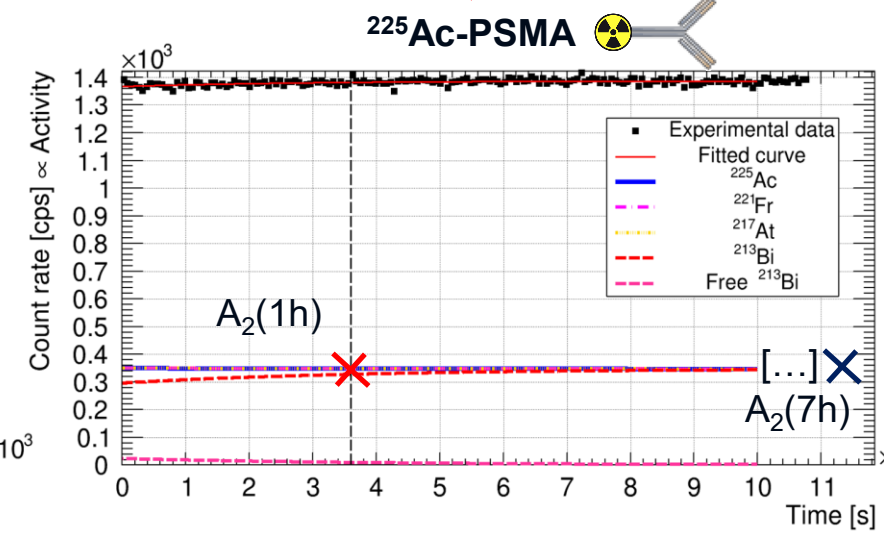
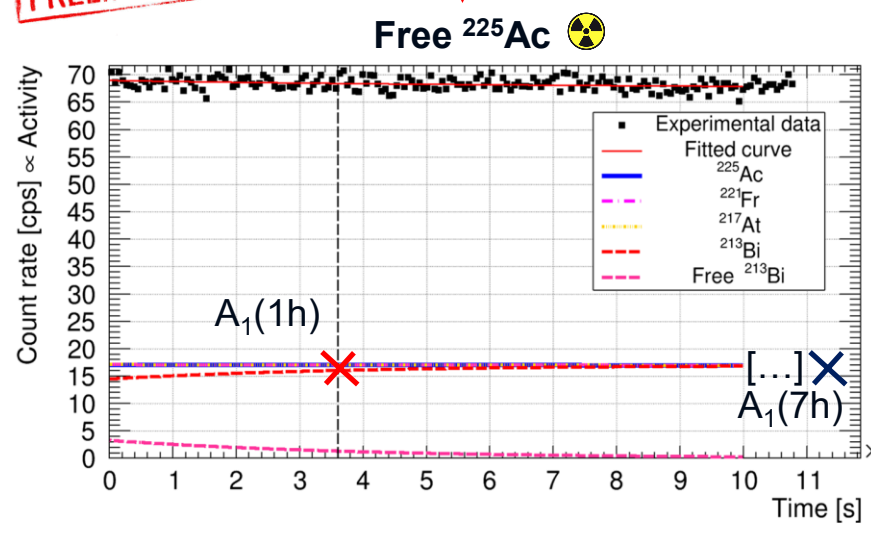
Digital autoradiography:

Digital image + Exploitation of time data

↓

Localized Identification of the different α isotopes of the decay chain

PRELIMINARY



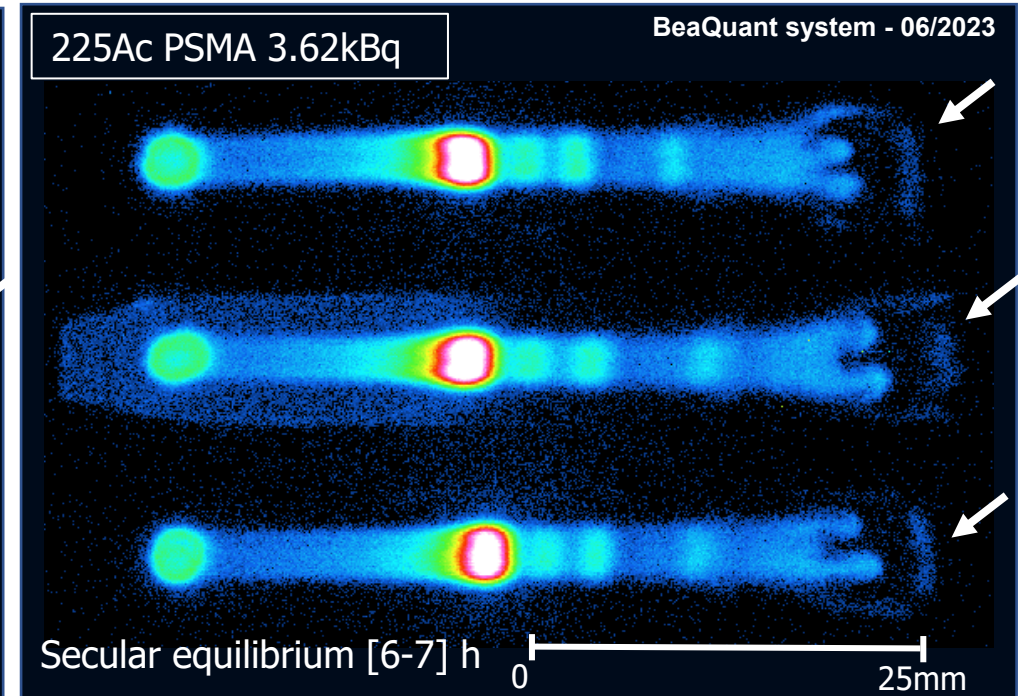
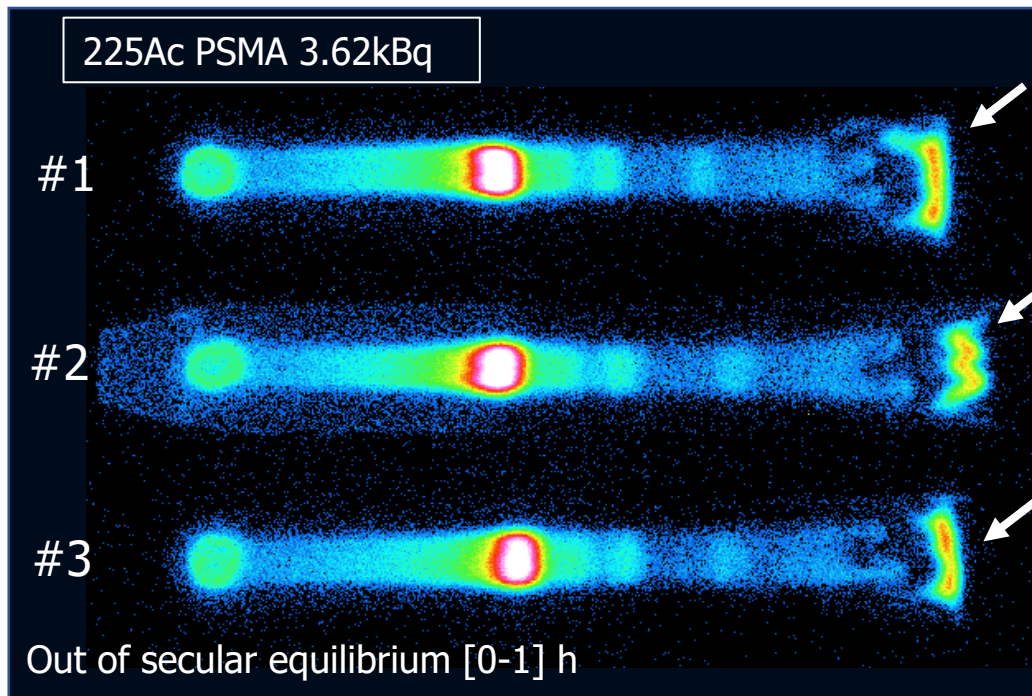
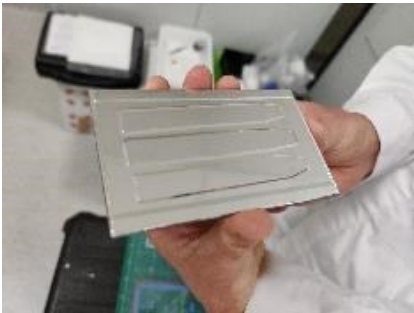
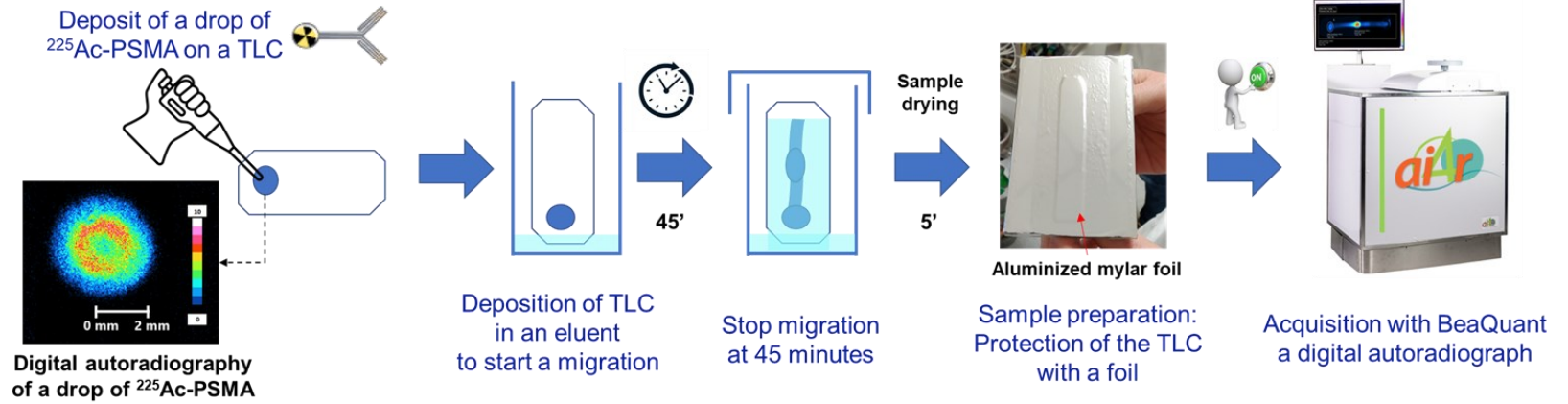
| | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>✗</p> <p>Out of secular equilibrium (1h)</p> <p>$A_1(1h) = 17,13$ $A_2(1h) = 348,28$ Ratio = 4,91%</p> | <p>VS</p> | <p>✗</p> <p>Secular equilibrium</p> <p>$A_1(7h) = 16,78$ $A_2(7h) = 346,76$ Ratio = 4,83%</p> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------|

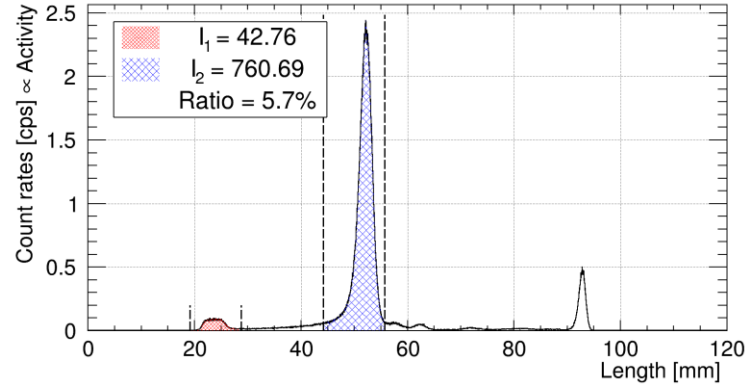
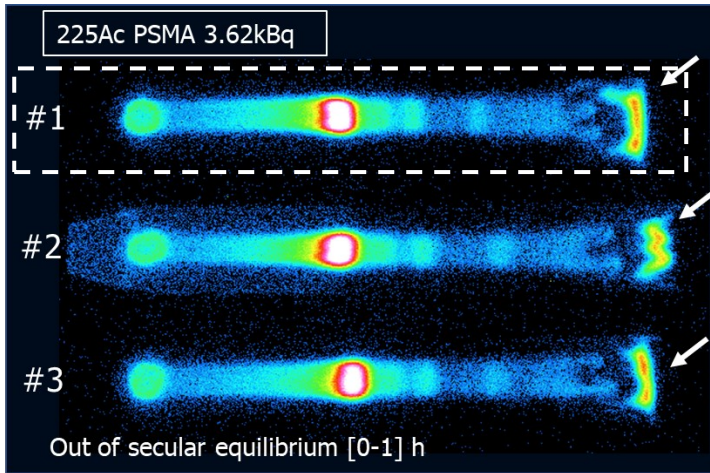
Very promising ! 😊

Simultaneously combining autoradiography with a time spectral measurement
 → **Spatio temporal spectroscopic autoradiography**

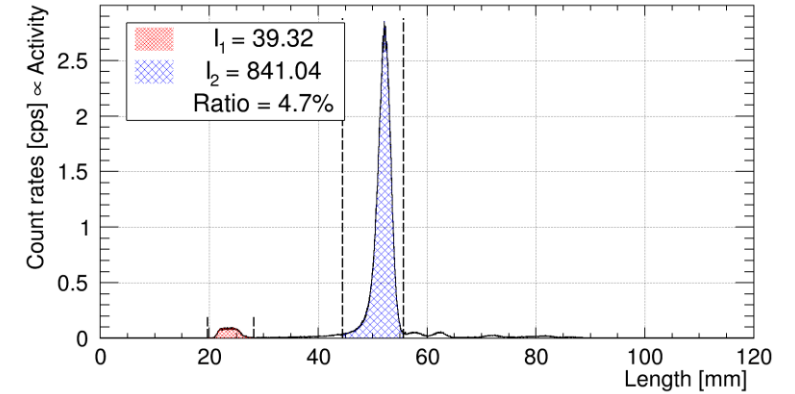
Campaign n°2

- ✓ Same protocole
- ✓ 3 TLC simultaneously !
- Very thin foil of aluminized mylar: $2\mu\text{m}$



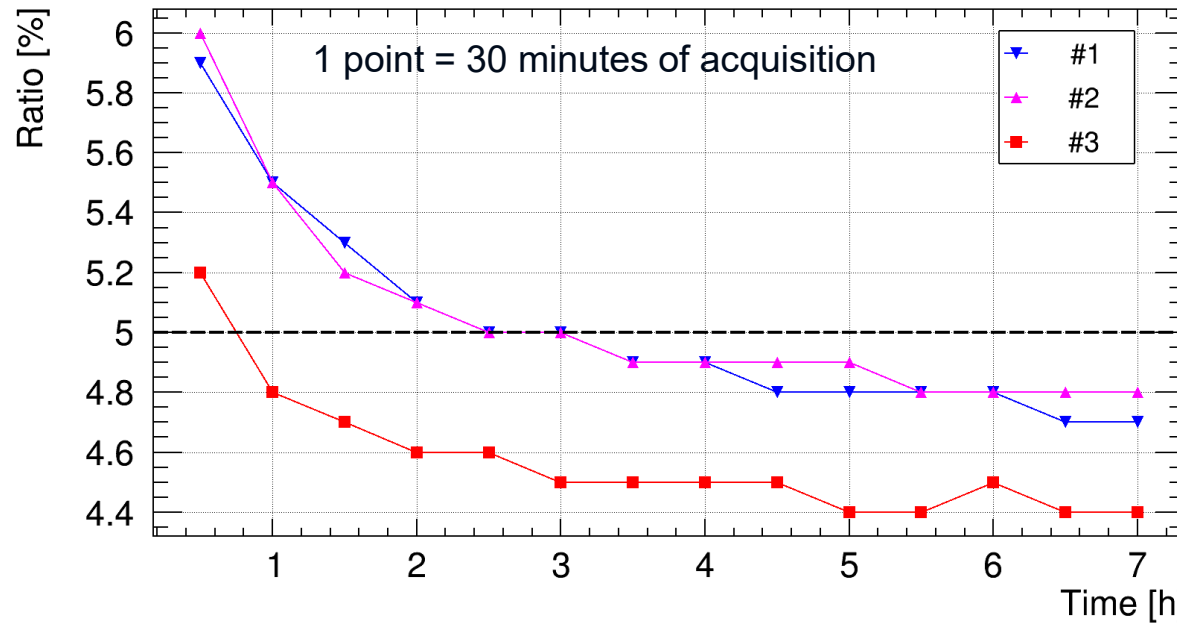


Out of secular equilibrium [0-1] h



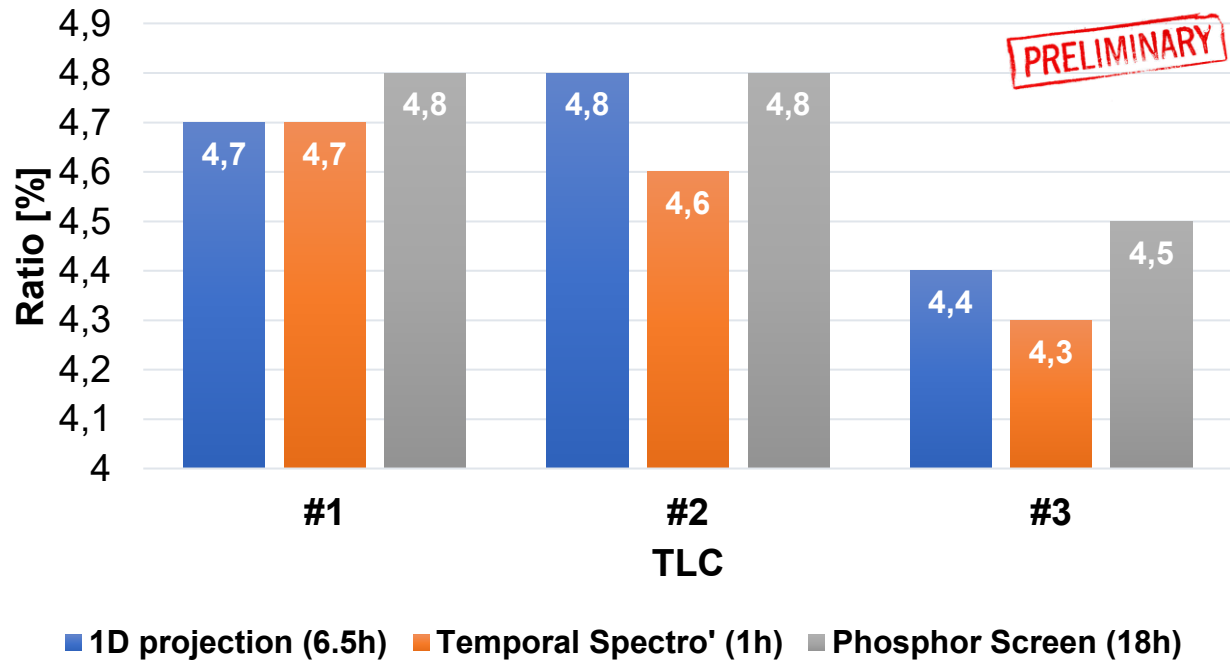
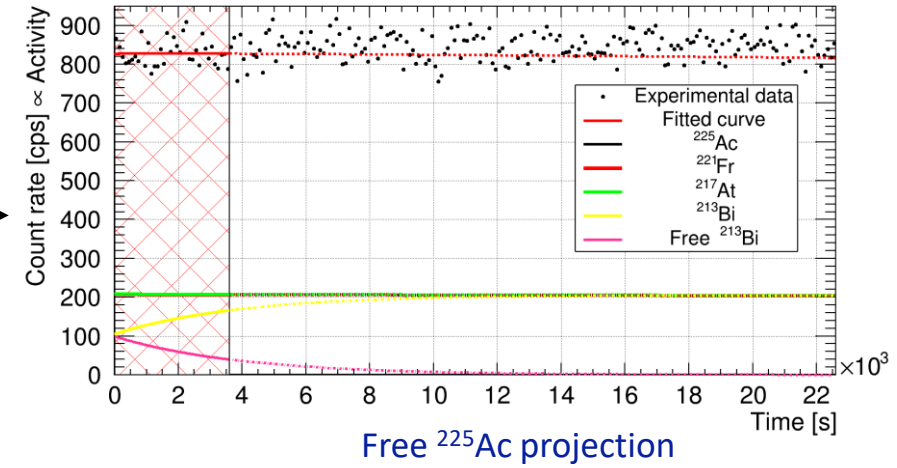
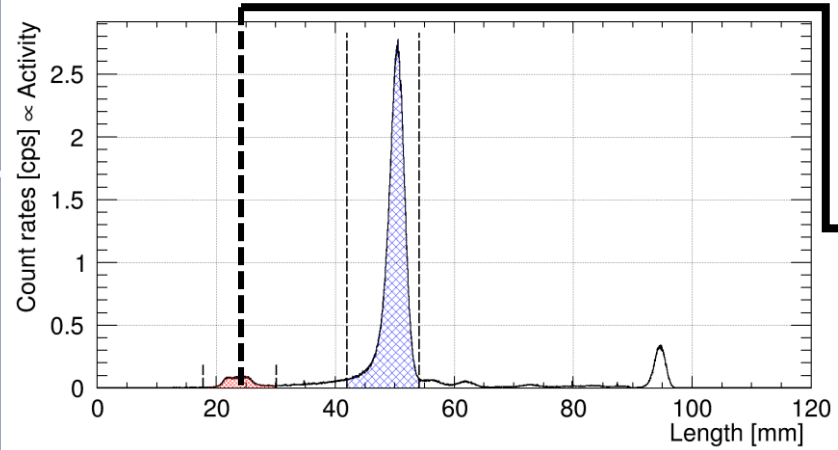
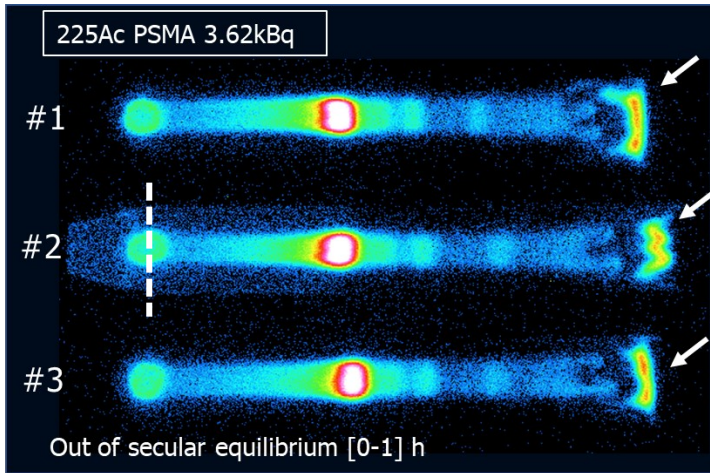
Secular equilibrium [6-7] h

PRELIMINARY



1D projection method:
 Classic and visually appealing
 But:
 Accuracy is dependent on Free Bismuth decay...

Quality control of ^{225}Ac -PSMA with the TLC method & **Temporal Spectro'** ¹⁴



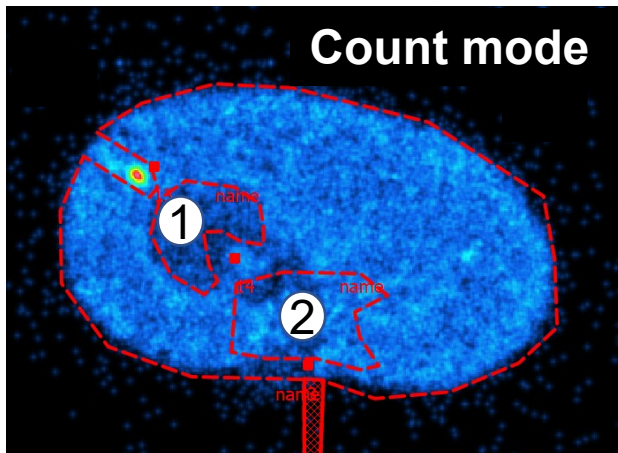
1D projection method:
 Classic and visually appealing
 But: accuracy is dependent on Free Bismuth decay...

Temporal Spectro' method
 Complex and hard to conceptualize
 But:
 Accuracy is not dependent on Free Bismuth decay...
Accuracy can be achieved in only 1 hour of acquisition time

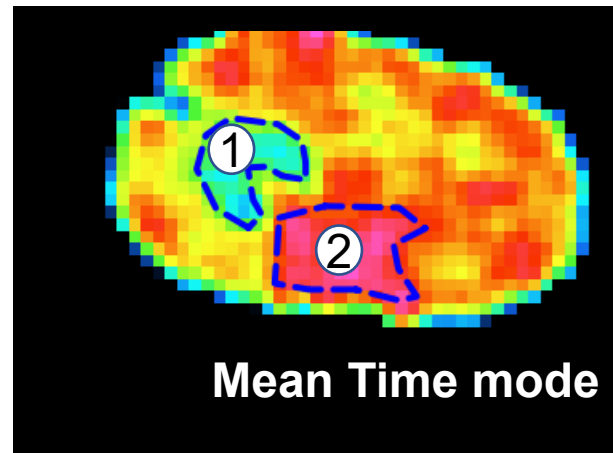
Mouse kidney labelled
with ^{225}Ac -PSMA



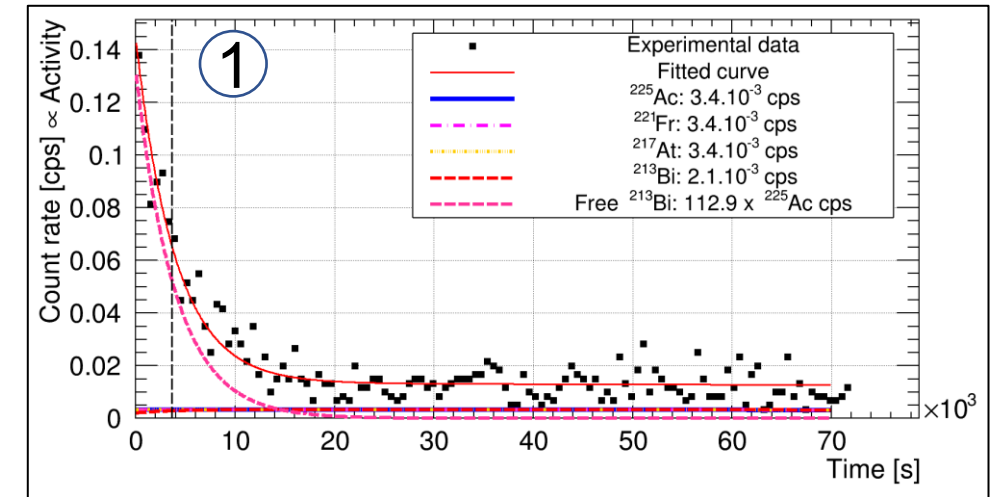
2D digital image



Data analysis



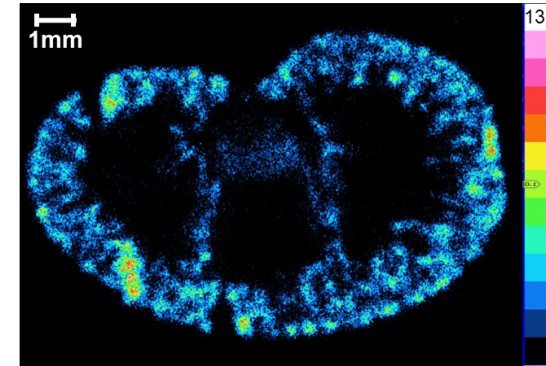
Spatio temporal spectroscopic autoradiography



Simultaneously combining autoradiography with a time spectral measurement
→ Spatio temporal spectroscopic autoradiography

Digital Autoradiography with spectroscopic method:

- ✓ **Promising** in the acquisition of nuclear data for the production of radionuclides for nuclear medicine applications like **quality control of radiopharmaceuticals** !
- ✓ A **precise tool** to understand the **temporal behavior** of a chain of labeled isotopes
- ✓ Precise image & **quantification** from **mBq to kBq**

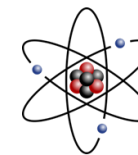


BeaQuant system
Mouse kidney labelled with ^{227}Th

BeaQuant's perspectives

More experiments !

- Perform simultaneous **comparisons** with **standard quality control methods**
- Perform **multiple quality controls** of the same batch **simultaneously** using the **BeaQuant's large Field Of View**
- **Explore the method for other radiopharmaceuticals**



| At 211 | Tb 149 |
|---------------------|----------------------|
| 7.2h | 4.1h |
| ϵ 5.867... | ϵ 3.97 |
| α (687) | β^+ |
| γ (687) | γ 352; 165... |





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