

Simulation of a neuroimaging acquisition with MAPSSIC, an implantable β^+ microprobe for rat brain imaging

S. El ketara^{a,b}, P. Lanièce^{a,b}, M.-A. Verdier^{a,b}

^aUniversité Paris-Saclay, CNRS/IN2P3, IJCLab, 91405 Orsay, France

^bUniversité Paris Cité, IJCLab, 91405 Orsay France



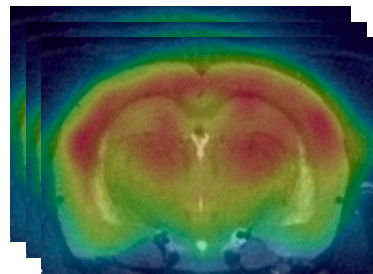
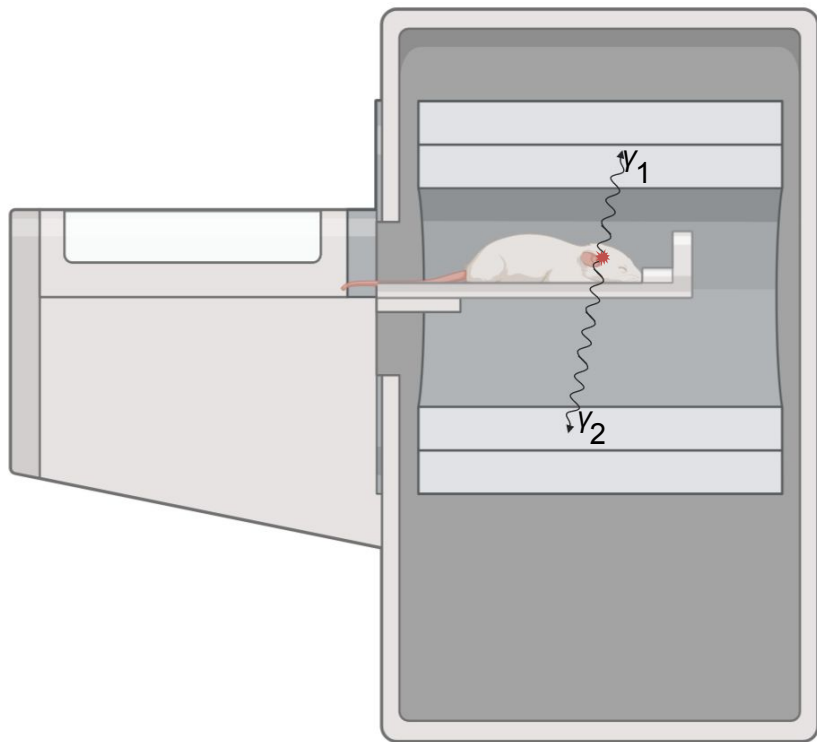
PHENIICS
Fest 2024



Preclinical neuroimaging with micro-PET

micro-**Positron Emission Tomography** (micro-PET):

- Use injected β^+ radioisotopes
- Detects gamma rays from β^+ /e⁻ annihilation
- High sensitivity
- Allows for quantification

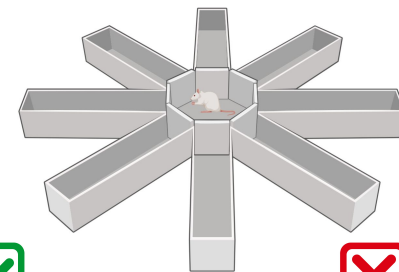
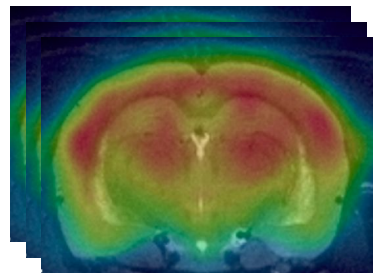
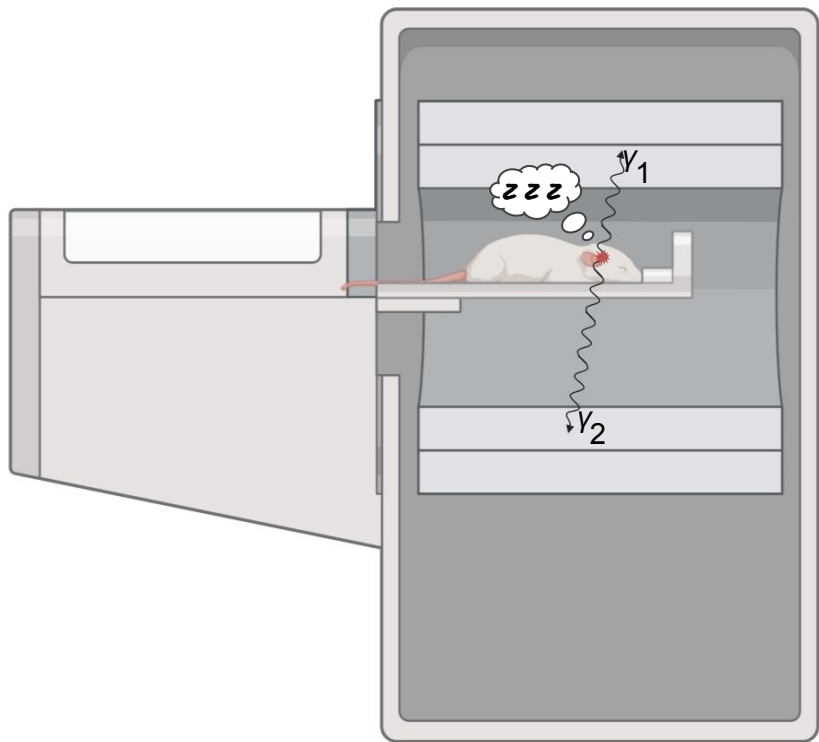




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- Use injected β^+ radioisotopes
- Detects gamma rays from β^+ /e⁻ annihilation
- High sensitivity
- Allows for quantification
- **Requires anesthesia**

→ Need for **awake imaging** data



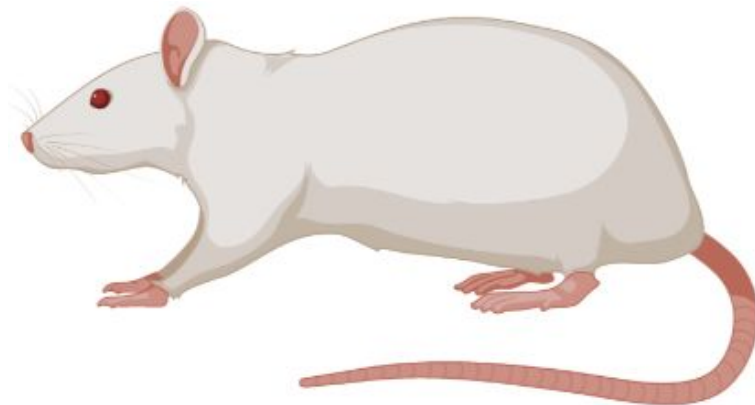


Neuroimaging of awake and freely moving rats, why?¹

*Majority of preclinical imaging performed under
anesthesia*

Effect of anesthesia

- Potential biases
- Many anesthetics²



¹Y.R. Gao et al, *NeuroImage*, 2017

²J. Silverman, *Laboratory animal science*



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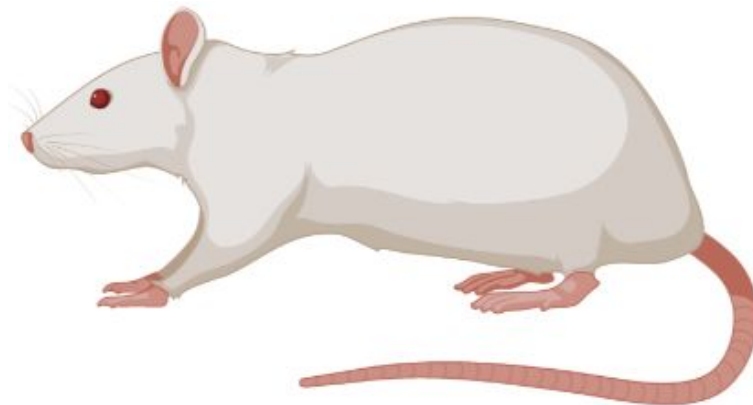
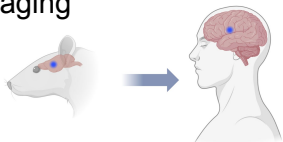
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Get closer to clinical practices

- No anesthesia in clinical imaging



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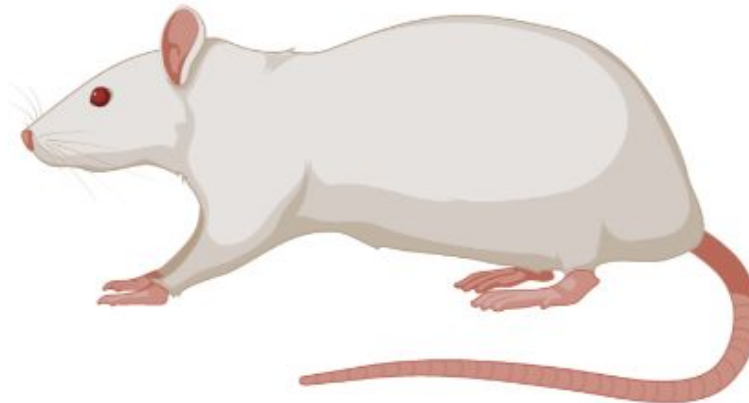
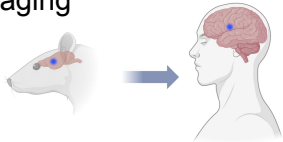
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Effect of anesthesia

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Get closer to clinical practices

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Perform **simultaneous neuroimaging** and **behaviour** studies

- Correlation between behavior and brain images
- Molecular processes allow better understanding of behavior

Effort made for **all modalities** (MRI, ultrasound and optic imaging)

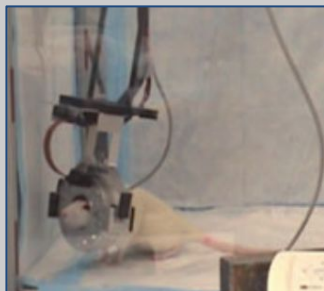
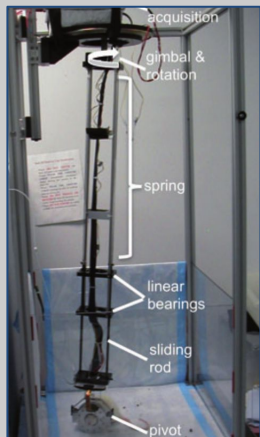
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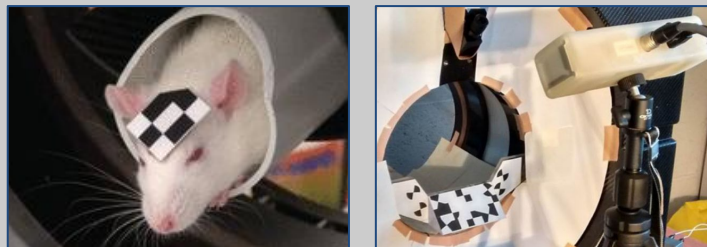
Neuroimaging on awake and freely moving rats: 3 approaches

1 mini microPET

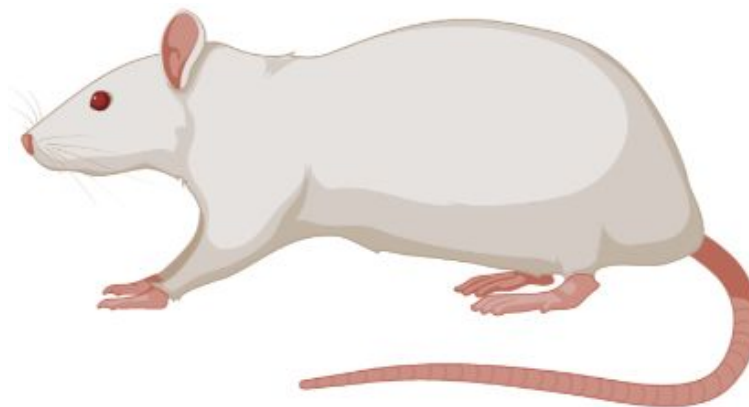


Schulz et al., Nature methods, 2011.

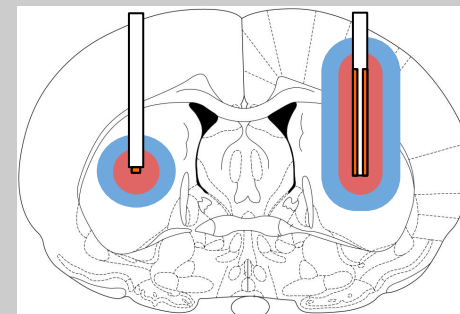
2 Regular microPET with Motion tracking



Spangler-Bickell et al., Phys. Med. Biol., 2016.



3 Implantable Microprobe



Pain et al., PNAS, 2002.

L. Balasse et al., Mol Imaging Biol, 2015



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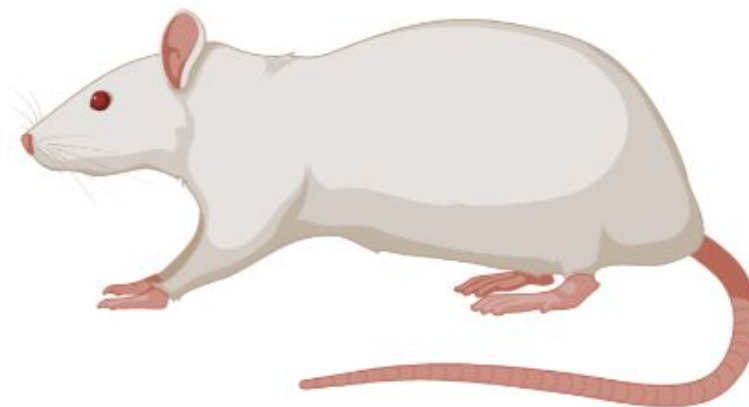


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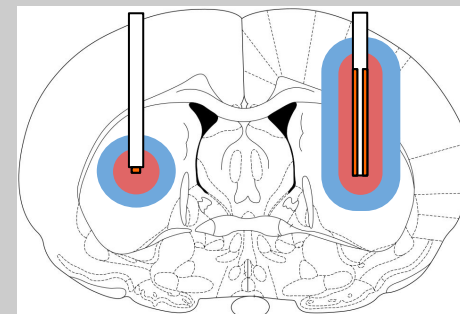
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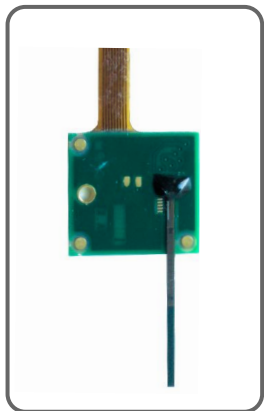


Mean range of ^{18}F
Mean range of ^{11}C
Sensitive areas
Not to scale



Pain et al., PNAS, 2002.

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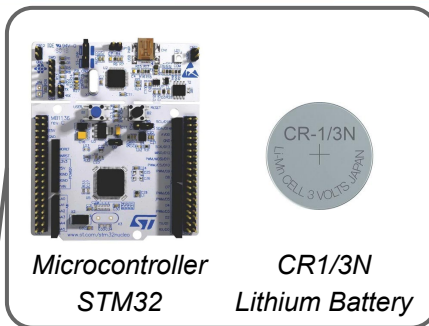


1. Sensitive probe

Features:

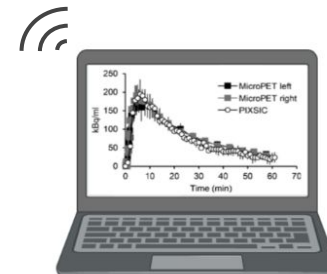
- Sensitive to **short range β^+**
- Record **kinetic** of **radiotracers**
- **Autonomy** to the rat
→ **Wireless**

- ## 2. Backpack
- Microcontroller
 - Power supply
 - RF antenna



Microcontroller
STM32

CR1/3N
Lithium Battery

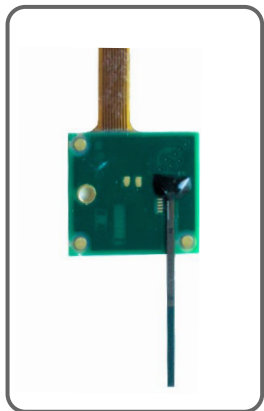


Constraints:

- **Gamma transparency**
- **Light:** < 10% of rat weight
- **Biocompatible**
- **Low power consumption**



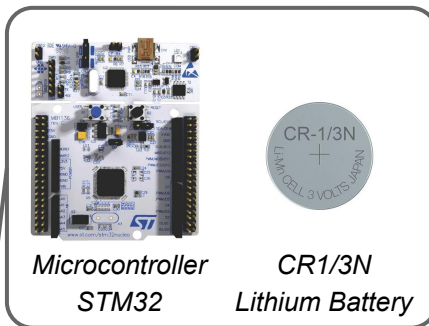
MAPSSIC project



1. Sensitive probe

2. Backpack

- Microcontroller
- Power supply
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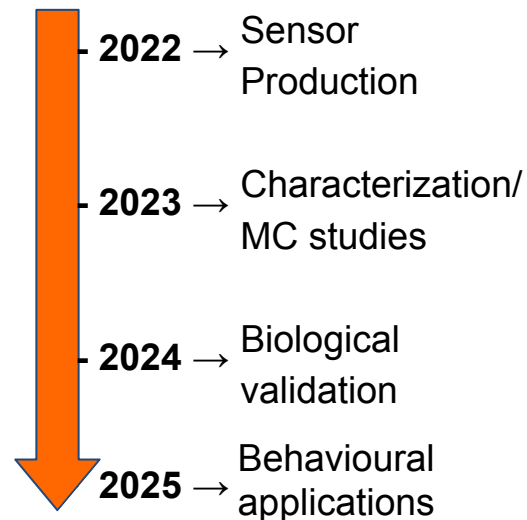
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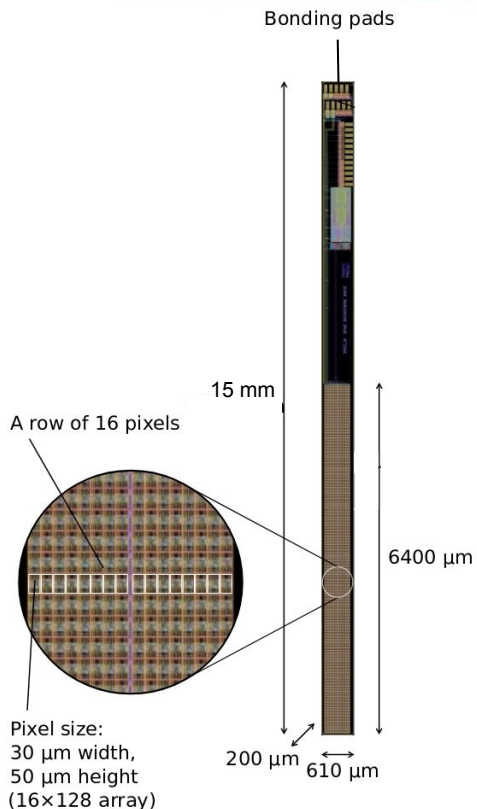


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MAPSSIC probe



New digital sensor prototype (**IMIC**, 2022) based on a first prototype^{1,2} (2018):

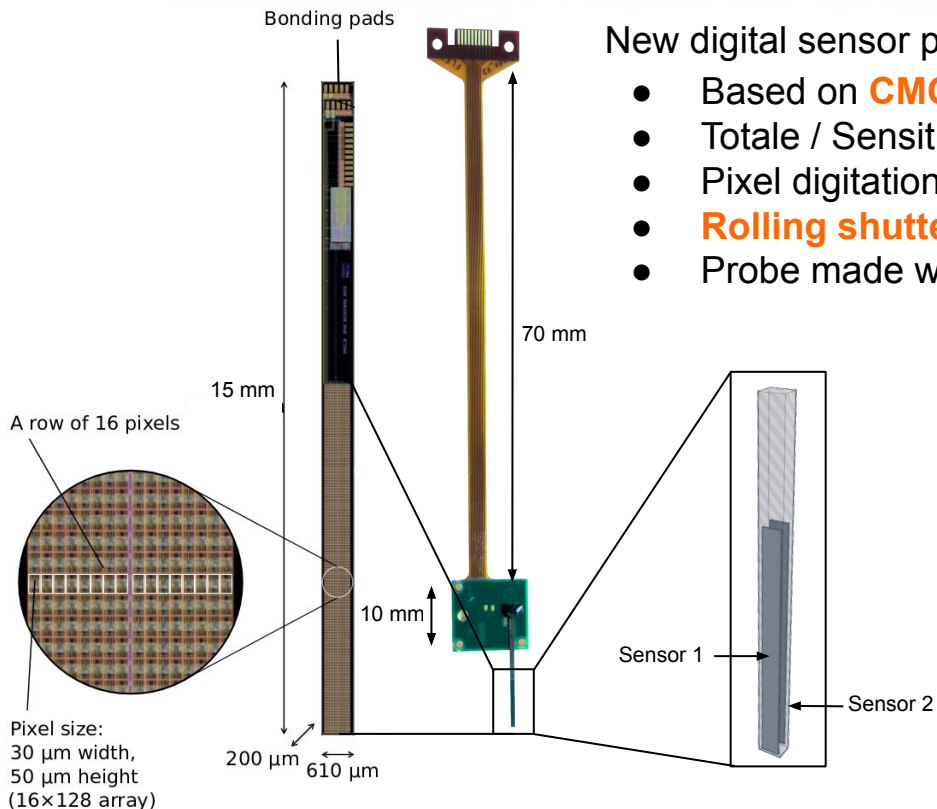
- Based on **CMOS-MAPS technology**
- Totale / Sensitive thickness: 200 μm / **25-50 μm**
- Pixel digitation: **1 bit**
- **Rolling shutter** readout

¹L. Amour et al., *IEEE Transactions on Radiation and Plasma Medical Sciences*, 2019

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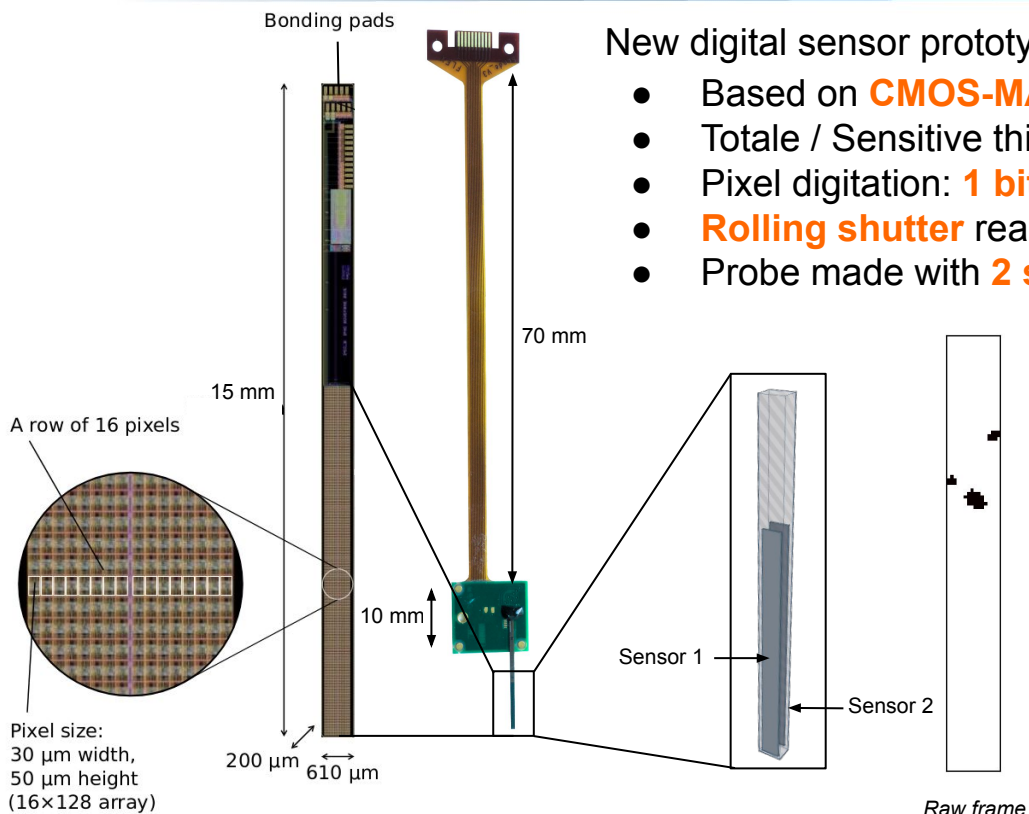
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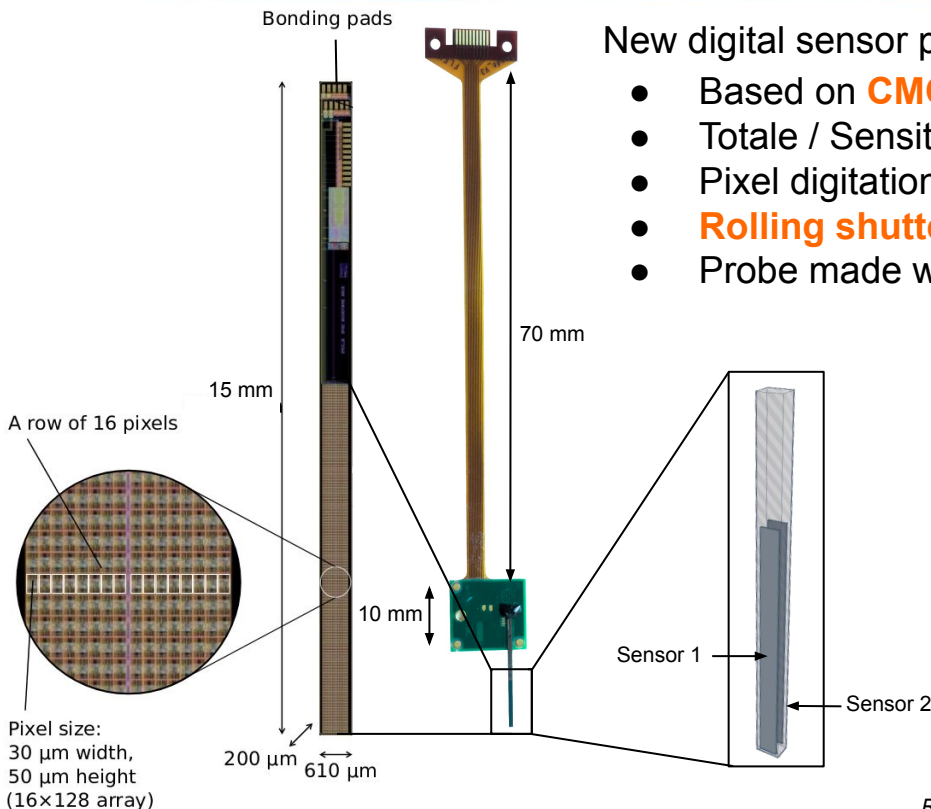
Raw frame

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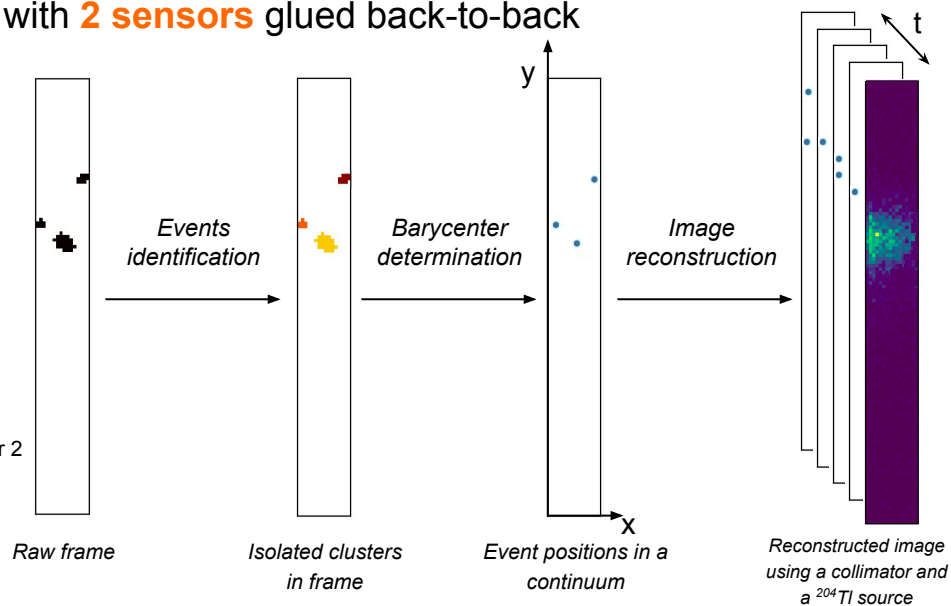


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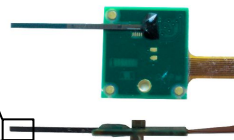
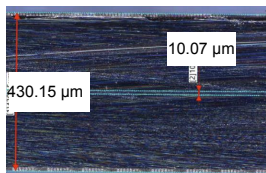
MAPSSIC overview

Probe mounting



Wire connections

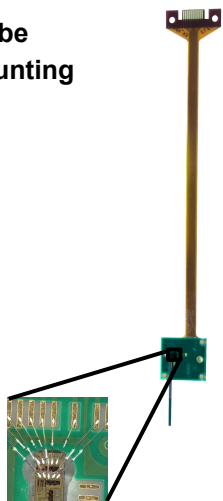
Back-to-back sensor assembling





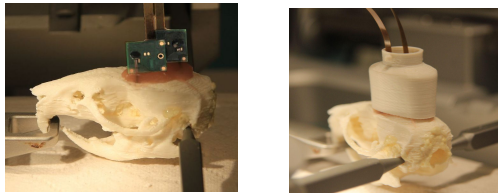
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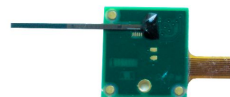
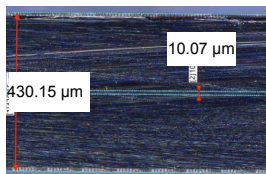
Wire connections

Biology



3D printed rat skull

Back-to-back sensor assembling





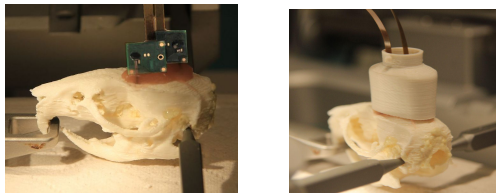
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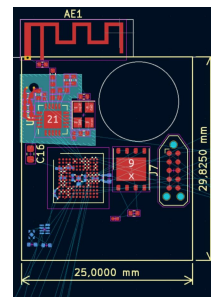
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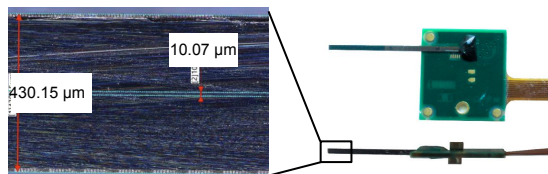
3D printed rat skull

Electronics



Microcontroller scheme

Back-to-back sensor assembling





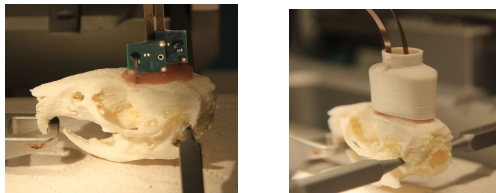
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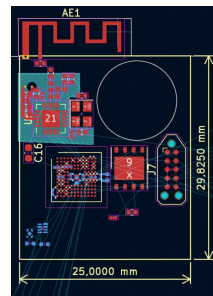
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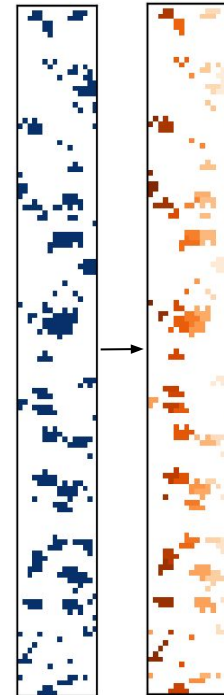
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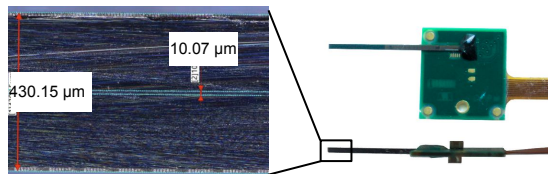
Microcontroller scheme

Clustering analysis



Machine learning method for event reconstruction

Back-to-back sensor assembling

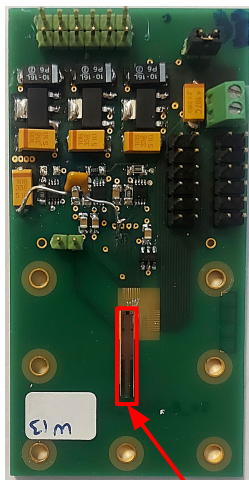




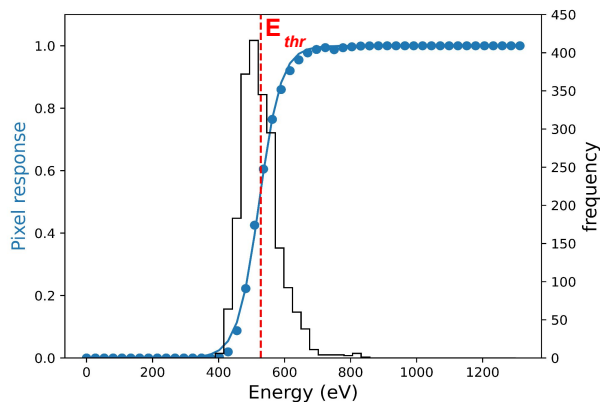
Physical validation and sensor optimisation

→ Energy threshold

Testing PCB



IMIC sensor



Understand the sensor's characteristics

Set nominal parameters

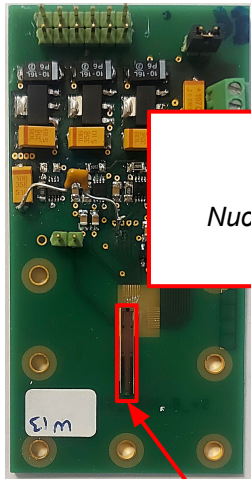
- **Charge injections**
- **Sealed sources**
 - beta: ^{204}Tl , ^{22}Na
 - X ray: ^{55}Fe



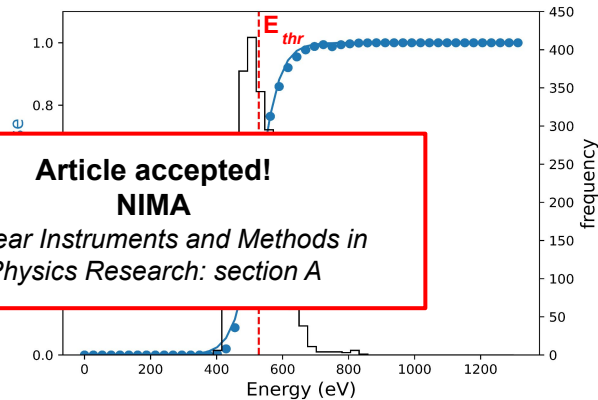
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Article accepted!
NIMA
*Nuclear Instruments and Methods in
Physics Research: section A*

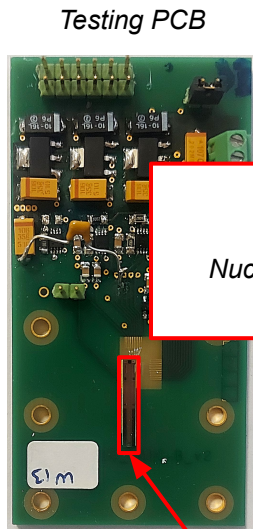
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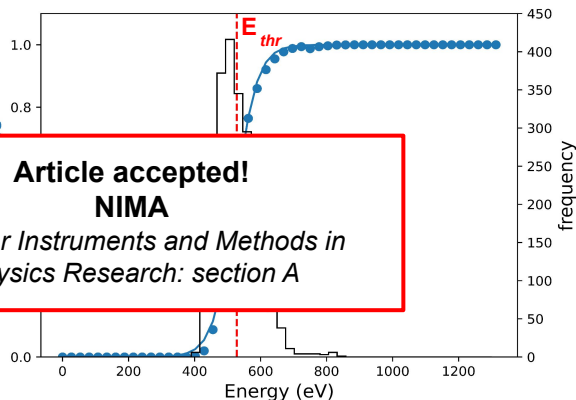


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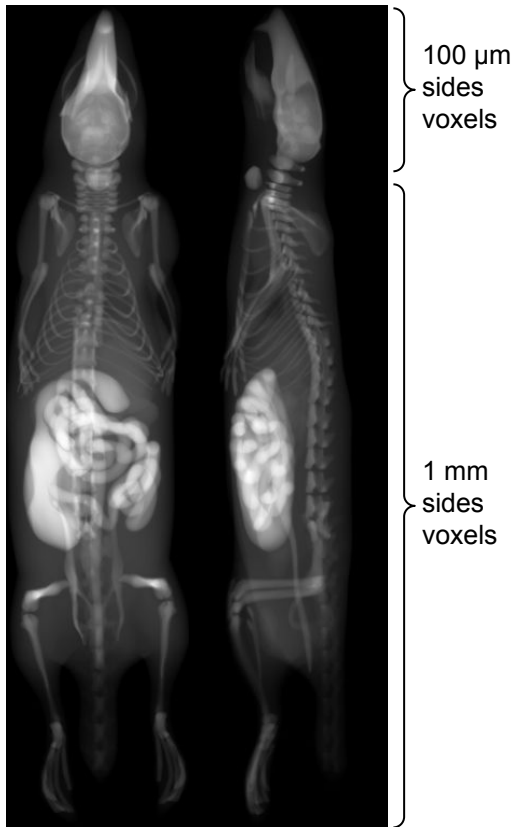
- **Charge injections**
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Simulations

- Confirm the probe relevance
- Predict its *in vivo* performances
- Explore segmentation methods

→ **Monte Carlo simulations using GATE**



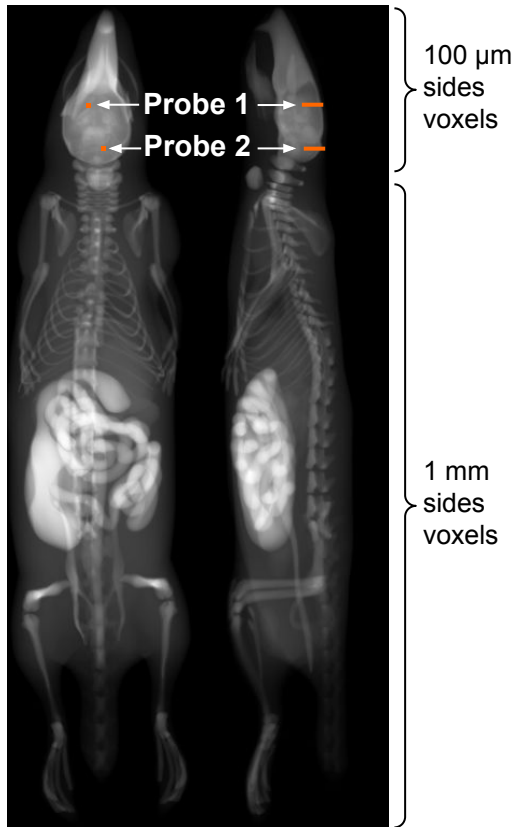


ROBY phantom¹

Voxelized rat phantom:

- Generated with the **ROBY program**¹
 - Skull area: cubic voxels of 100 μm sides
 - Body area: cubic voxels of 1 mm sides
- Used for both **attenuation** and **activity** ranges
- Addition of **Harderian glands** from MRI images

¹W. P. Segars, *Molecular Imaging and Biology*, 2004.



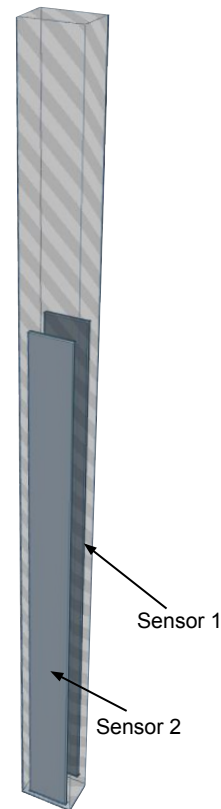
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Probes geometry:

- **2 Silicon boxes** of 9500 μm x 450 μm x 700 μm
- Physical volume inserted within the voxelized phantom using the **Merge Volume Actor**
- In the **cerebellum** and **striatum** region
- **Sensitive areas** of 6400 μm x 25 (and 50) μm x 480 μm (2 per probe) filtered post simulations

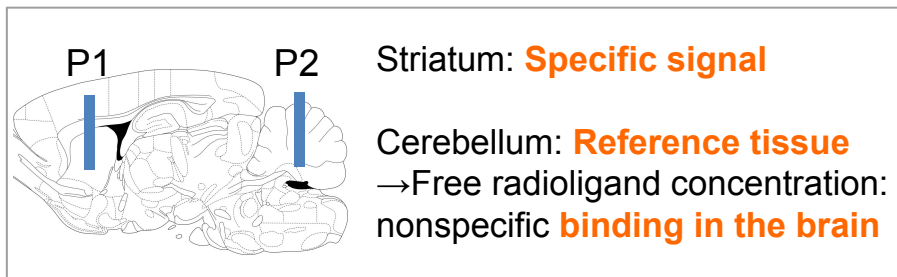


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Radiotracer: [^{11}C]Raclopride

- ^{11}C Carbon radiolabeled **dopamine D2 receptor antagonist**^{1,2}
- Preclinical/clinical research **schizophrenia, addictions**
- **Uptake in Harderian glands** (potential source of noise)
- Mean **range** of ^{11}C positrons \approx **1.1 mm** ($>$ $^{18}\text{F} \approx 0.6$ mm)



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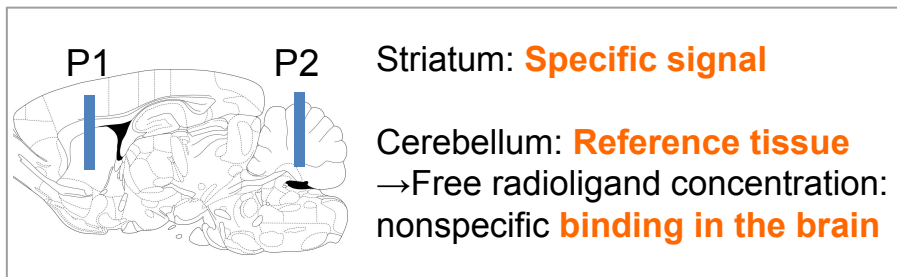
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Input - Source

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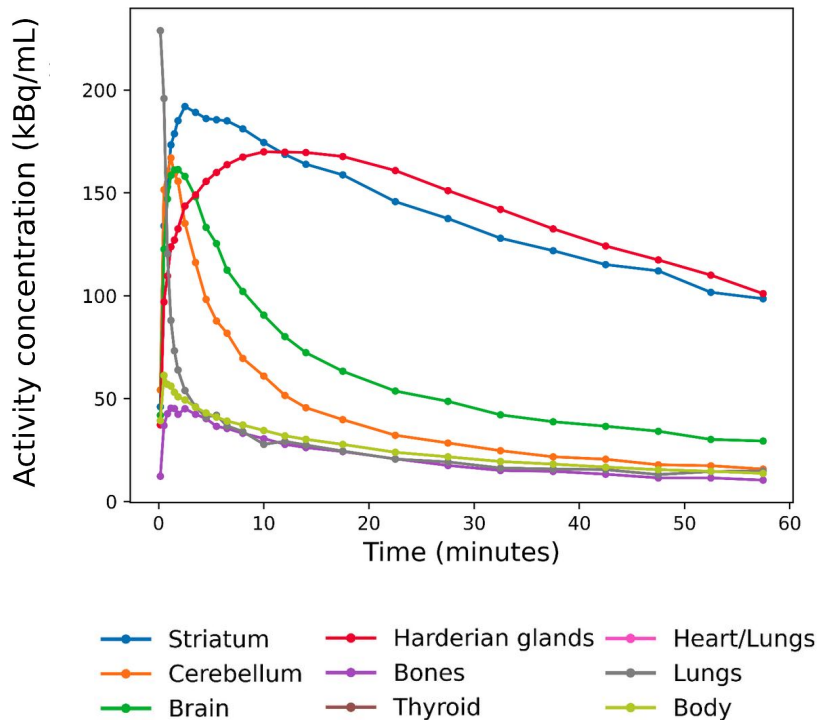


- [^{11}C]Raclopride time activity curves of **anesthetized rat**
→ 9 MBq injection, dynamic **micro-PET** acquisitions

¹H. Hall et al, *Prog Neuropsychopharmacol Biol Psychiatry*. 1988

²N. Ginovart et al, *Mol Imaging Biol*, 2005

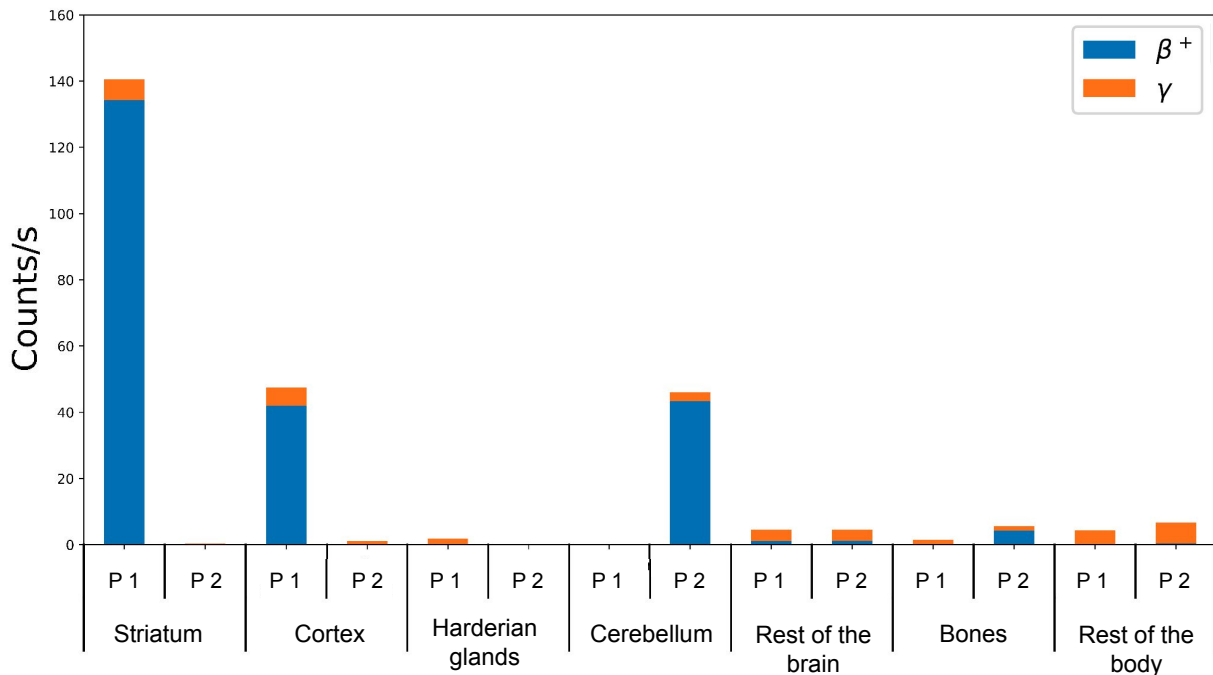
Time-activity curves





Results - Organ/particle contributions

27.5 minutes after a 9 MBq injection (25 μm epitaxial layer)



Emission of detected particles:

→ 99% of detected particles from **skull area**

→ Count rate:

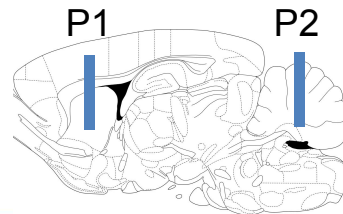
$\approx 265 \pm 0.2$ cps (25 μm)

→ High **direct sensitivity**

$\approx 89\%$ of events in probe 1 (25 μm)

→ Low **gamma sensitivity**

→ Harderian glands signal **< 1%**

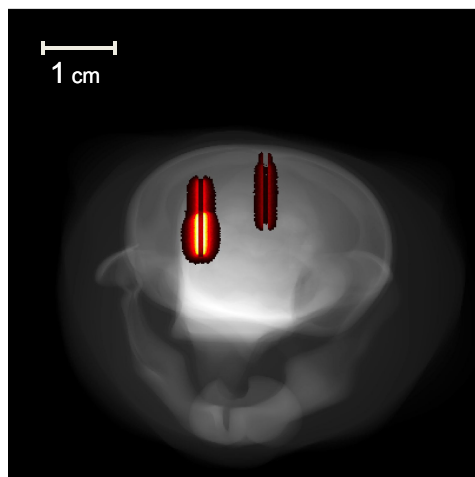




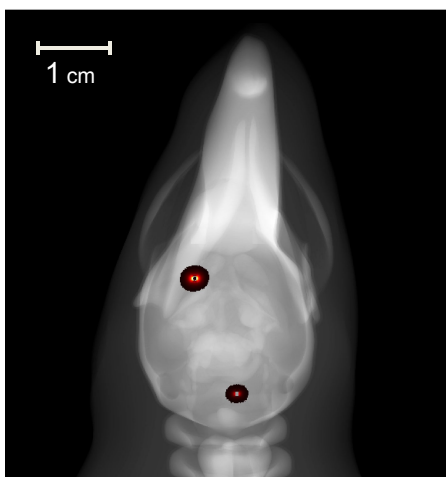
Results - Organ/particle contributions

Source position of detected particles:

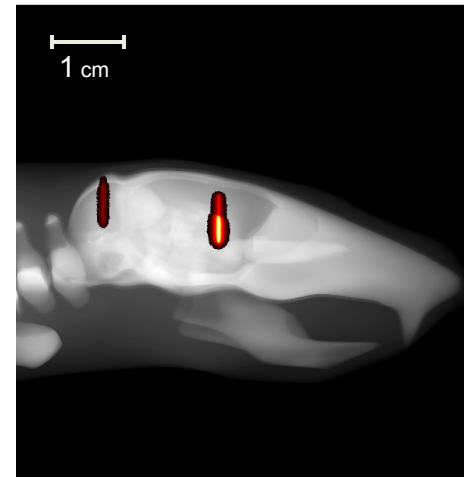
→ **Local information**: more than **93%** of detected particles emitted within the first **2 mm surrounding** the probe 1



Coronal



Axial

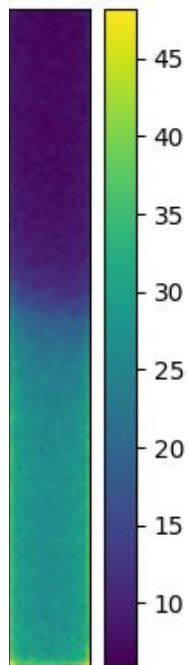


Sagittal

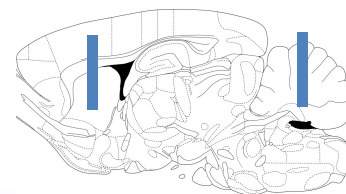
Integration over 1 minute, 27 minutes after injection (25 μ m sensitive layer)



Probe 1

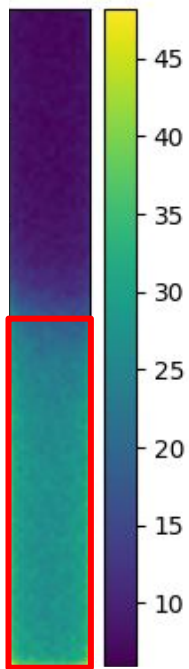


*Probe 1 integrated image
over 1 minute
(striatum + cortex)*

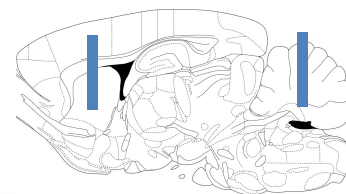




Probe 1



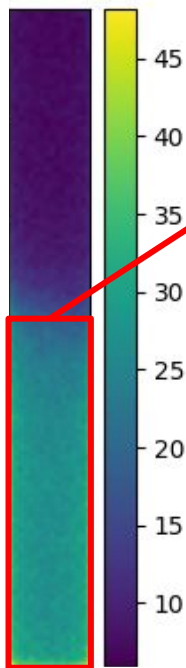
*Probe 1 integrated image
over 1 minute
(striatum + cortex)*





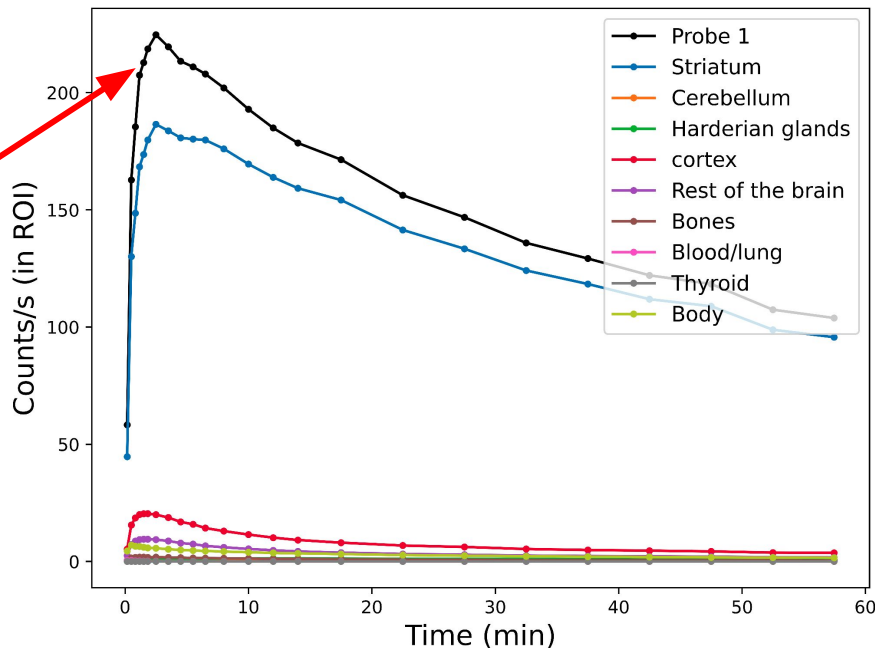
Results - Kinetic study

Probe 1

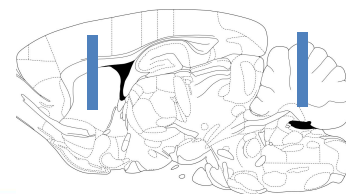


Probe 1 integrated image over 1 minute (striatum + cortex)

Probe 1 organs contributions in ROI



Input BP variation	Measured BP variation	Error on BP variation
- 5 %	- 4.81 %	- 3.8 %
- 10 %	- 9.65 %	- 3.5 %
- 20 %	- 19.38 %	- 3.1 %



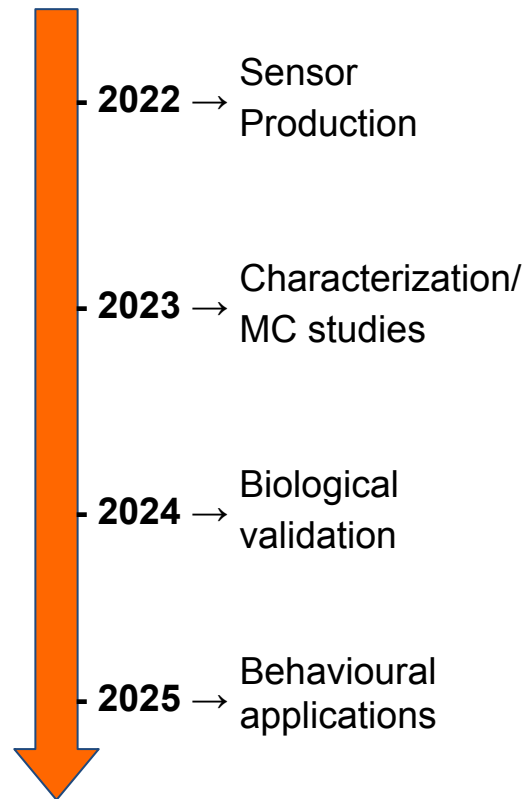


Conclusion

- **New implantable β^+ microprobe produced**
- Performances in line with the **intended application**
 - High **β^+ sensitivity**
 - Low **γ sensitivity** } → **Local radiotracer uptake**

Perspectives

- **Probe physical validation**
- **Biological validation** aimed for early 2024
 - Comparison MAPSSIC / micro-PET
- **Behavioral applications** aimed for early 2025



THANKS FOR YOUR ATTENTION

MAPSSIC Collaboration

*Franck Agnese
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Caroline Bouillot
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Samir El ketara
Fabrice Gensolen
Maciek Kachel
Philippe Lanièce
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Marc-Antoine Verdier
Christophe Wabnitz
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Luc Zimmer*



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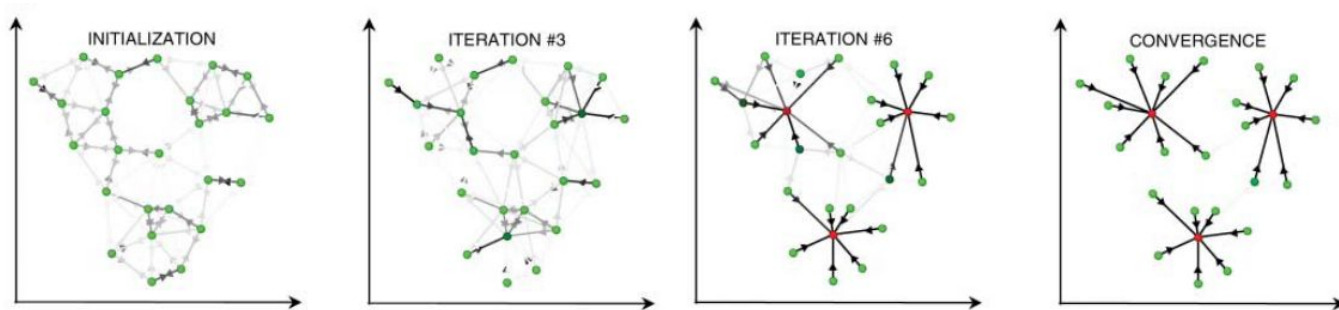


Results - Kinetic study

Input BP _{ND}	Measured BP _{ND}	Error on BP _{ND}	BP _{ND} variation	Measured BP _{ND} variation
3.0941	2.3919	22.7 %	0	-
2.9394	2.2769	22.5 %	- 5	- 4.81 %
2.7847	2.1611	22.4 %	- 10	- 9.65 %
2.6300	2.0442	22.3 %	- 15	- 14.54 %
2.4753	1.9283	22.1 %	- 20	- 19.38 %
2.3206	1.8109	22.0 %	- 25	- 24.29 %
2.1659	1.6936	21.8 %	- 30	- 29.19 %



Affinity propagation algorithm



Brendan J. Frey and Delbert Dueck, "Clustering by Passing Messages Between Data Points", Science Feb. 2007

- Influence parameter :
 - **Preference** : Calculated number of clusters is **directly influenced** by the *preference* value

→Need for **calibration** of the algorithm : Search for the optimal *preference* value for AP clustering on frames containing from 1 to 100 clusters



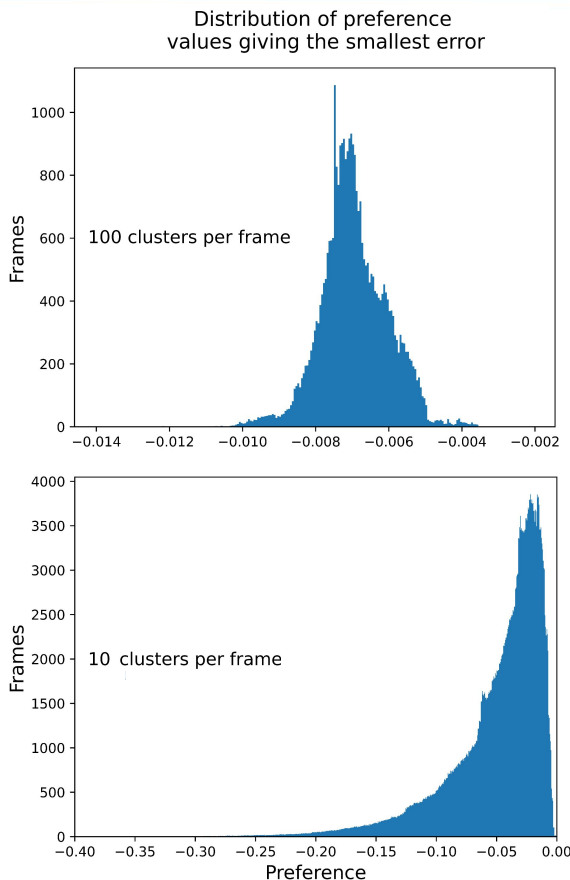
Data generation



Affinity propagation algorithm - Calibration

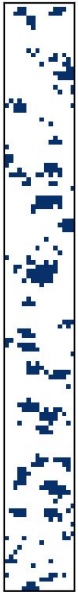
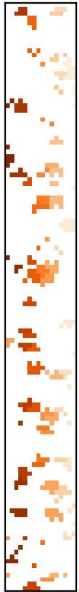
Data processing from AP calibration runs:

- Determination of the optimal *preference*:
 - AP runs on calibration frames **scanning** the previously determined **preference range**
 - **Mean** and **Mode** of the distribution *preference* values leading to the **smallest error** between calculated and actual cluster number for a given frame
 - Gaussian draw of a new *preference* value if the previous does not converge to an answer (400 times maximum)

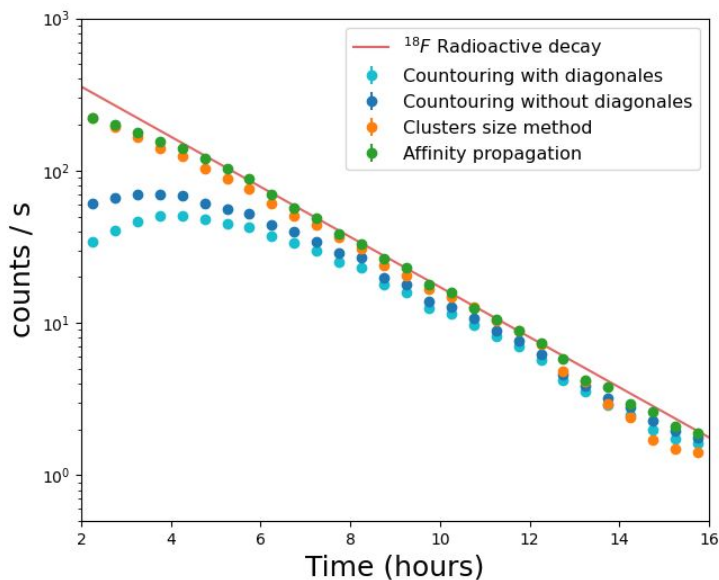




Data treatment

Raw Frame	Events
	

- Calibration of a machine learning algorithm (Affinity propagation algorithm)
- Application on **experimental Data** from ^{18}F radioactive decay measurement (IMIC-V1):



- **Achieved linearity** for the expected count rates for in vivo measurements
- Calculation time varies from **few milliseconds** to 0.5 seconds per frame
- **Spatial error** < 50 μm



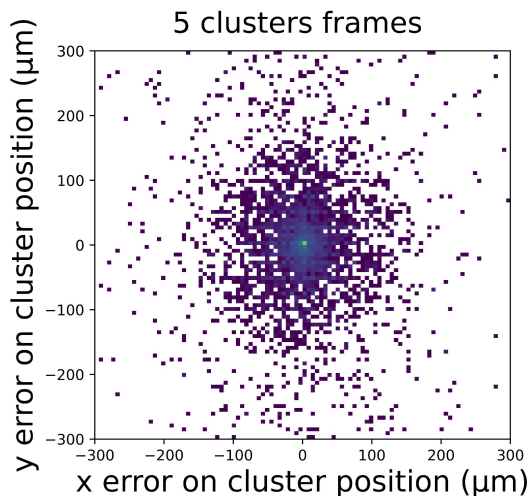
Results compatible with *in vivo* measurements



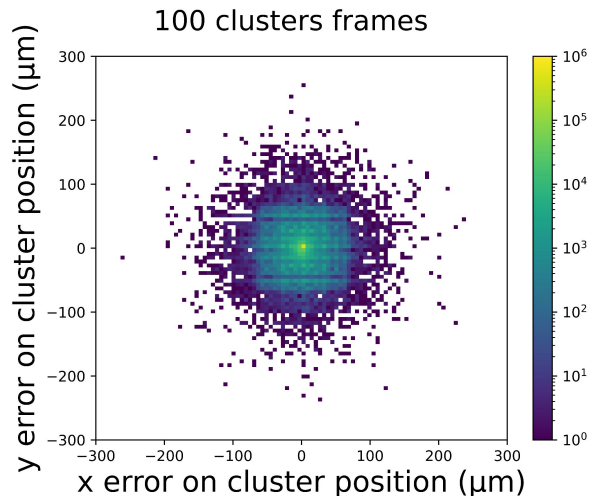
Affinity propagation algorithm - Spatial performances

Spatial study : Error on cluster barycenter

- **Errors** on x and y axis: mean σ of **16.5 μm** and **26.2 μm**
→ 95% error equal or smaller than pixels size (2σ)
- Error ($\approx \mu\text{m}$) < explored structures (ie: rat striatum $\approx \text{mm}$)



$\sigma_x = 23.9 \mu\text{m}$ $\sigma_y = 88.9 \mu\text{m}$

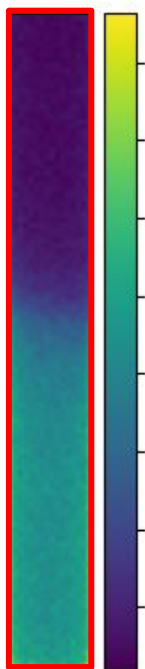


$\sigma_x = 15.5 \mu\text{m}$ $\sigma_y = 17.5 \mu\text{m}$

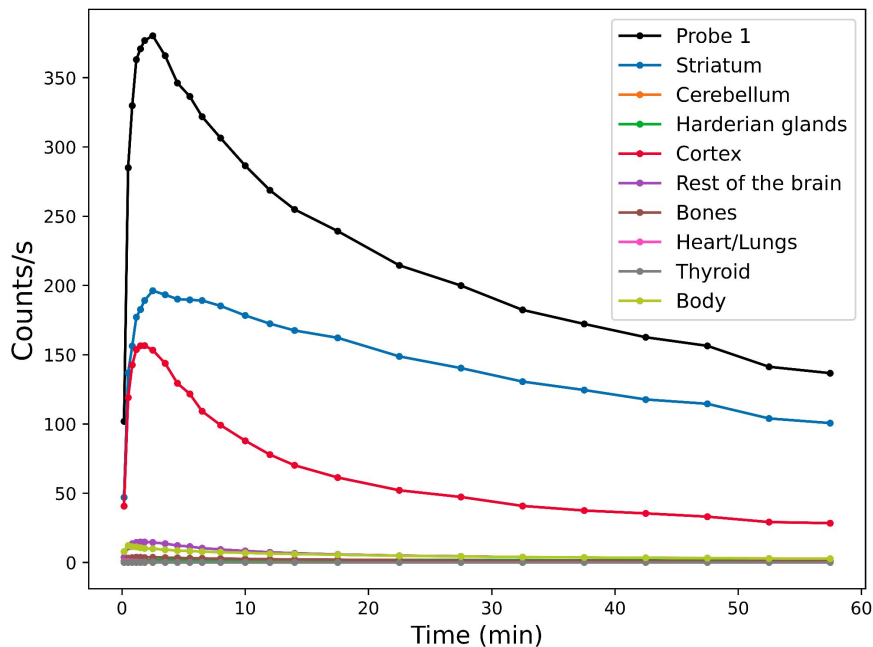


Probe 1

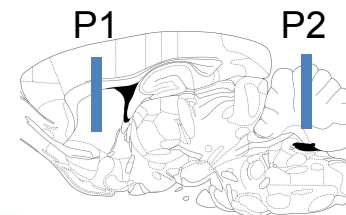
Probe 1 organs contributions



Probe 1 integrated image over 1 minute

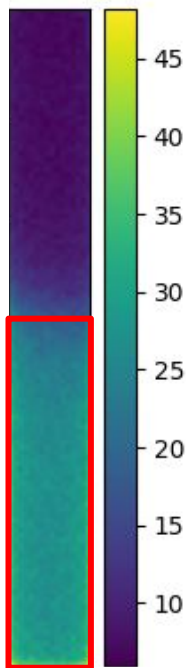


Striata signal in ROI vs overall striata signal in frame	Other organs contributions in ROI
100 %	30 %



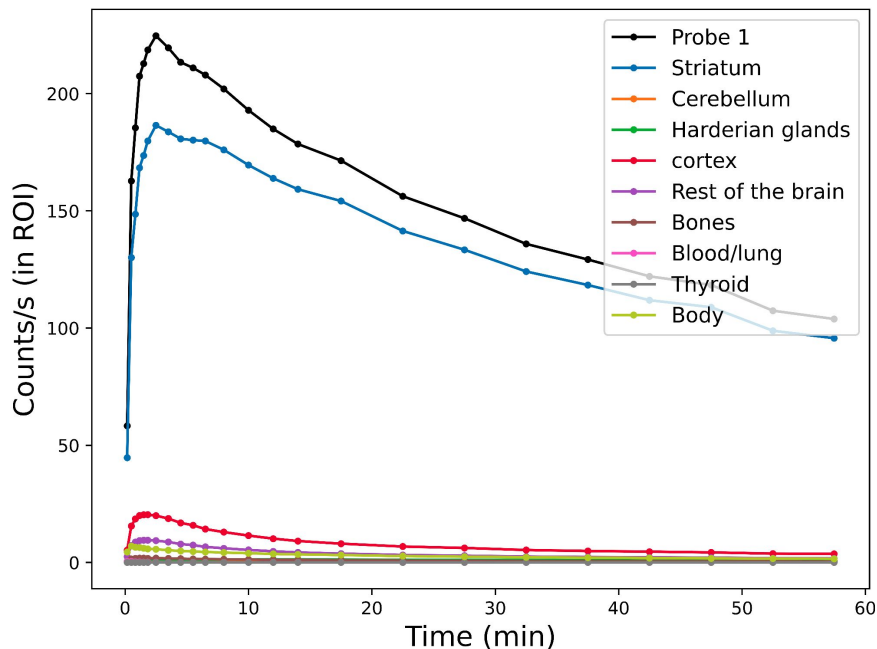


Probe 1



Probe 1 integrated image
over 1 minute
(striatum + cortex)

Probe 1 organs contributions in ROI



Striata signal in
ROI vs overall
striata signal in
frame

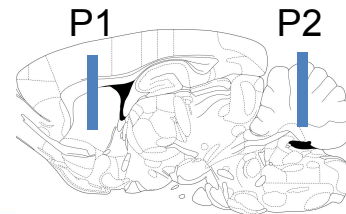
> 95 %

Other organs
contributions in
ROI

< 8 %

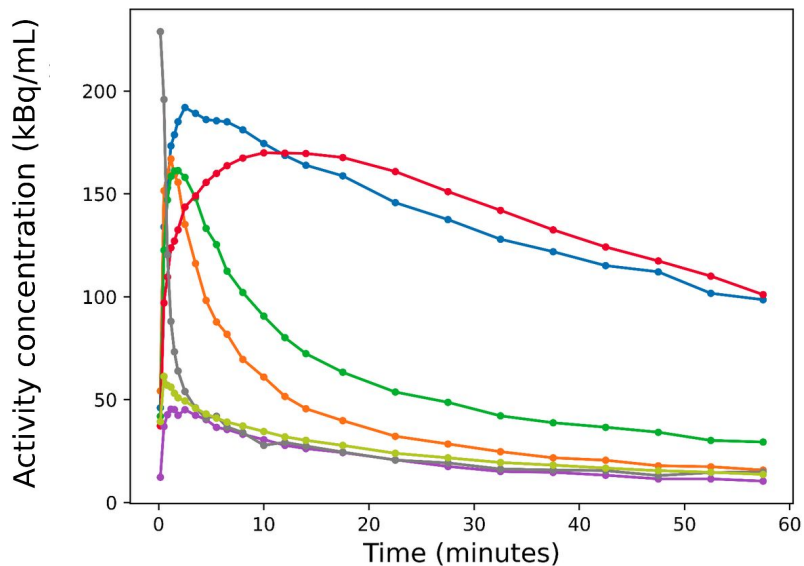
- Next steps:

- **kinetic modeling** with a compartmental model
- Next step: input data from **awake animals**





Time-activity curves



Time-activity curves (OSSI-PET data)

