MAPSSIC, a CMOS Intra-Cerebral Probe for Brain Imaging in Awake and Freely Moving Rat

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Fifth French-Ukrainian workshop on the instrumentation developments for HEP

LAL, Orsay, France
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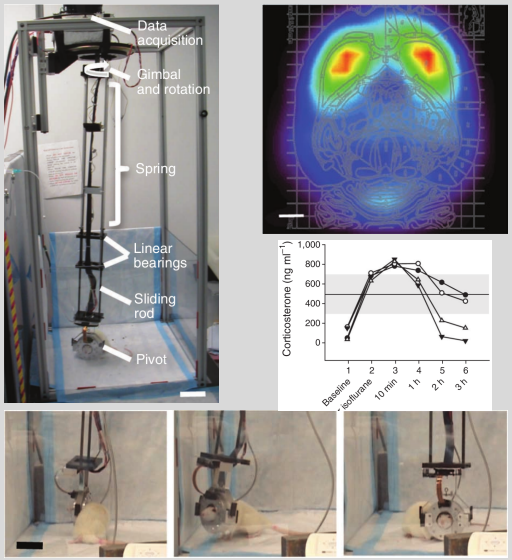
Imaging brain on freely moving animal

How anesthesia affects neuroimaging?

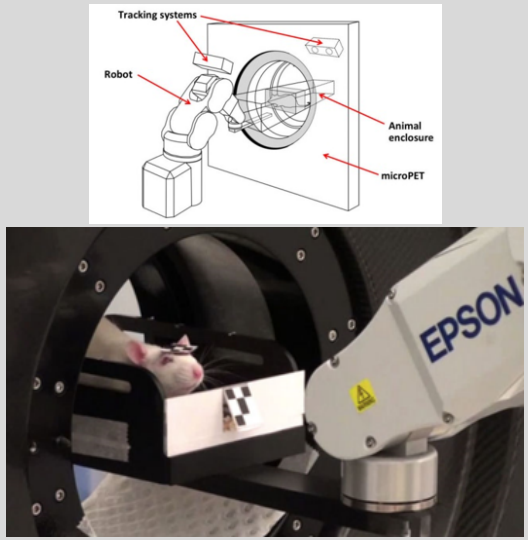
How to study molecular processes and behavior simultaneously?

RatCAP



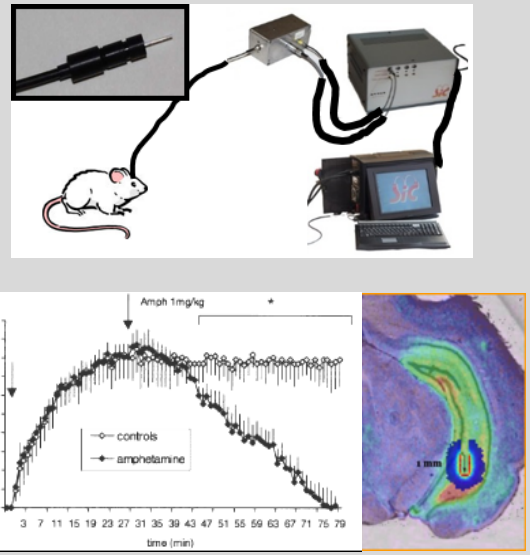
Schulz *et al.*, *Nature Methods*, 2011.

Motion tracking



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

Beta Microprobe



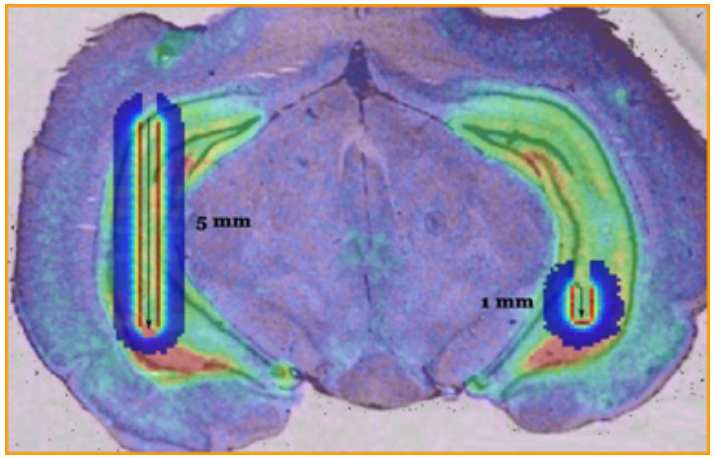
Pain *et al.*, *PNAS*, 2002.

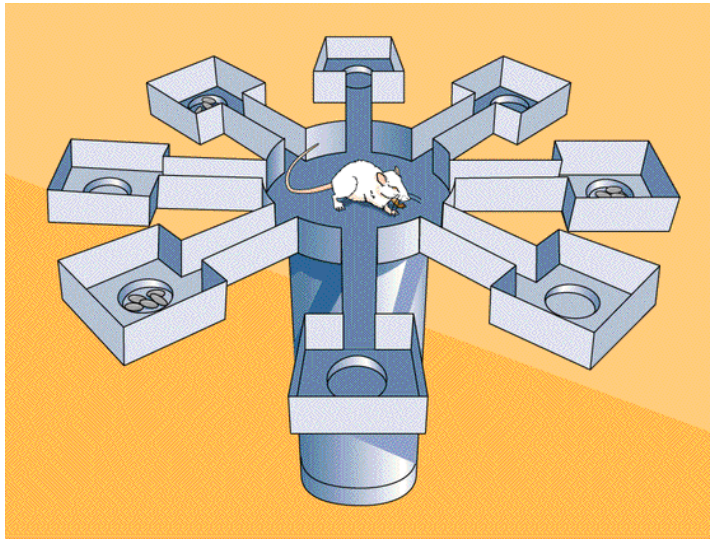
Project goals

To develop a pixelated β^+ sensitive imaging device

To limit sensitivity to annihilation γ rays and visible light

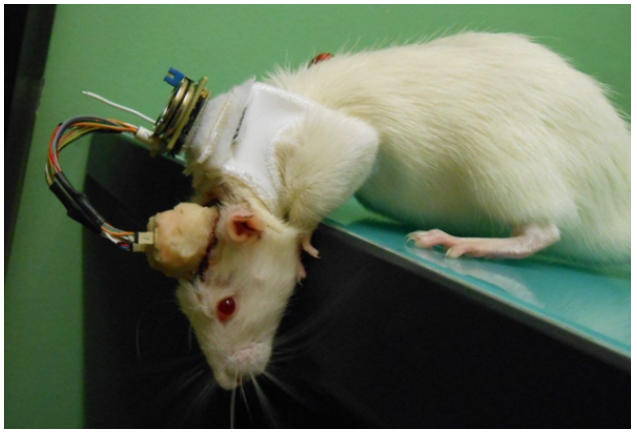
To study fully freely-moving rodents



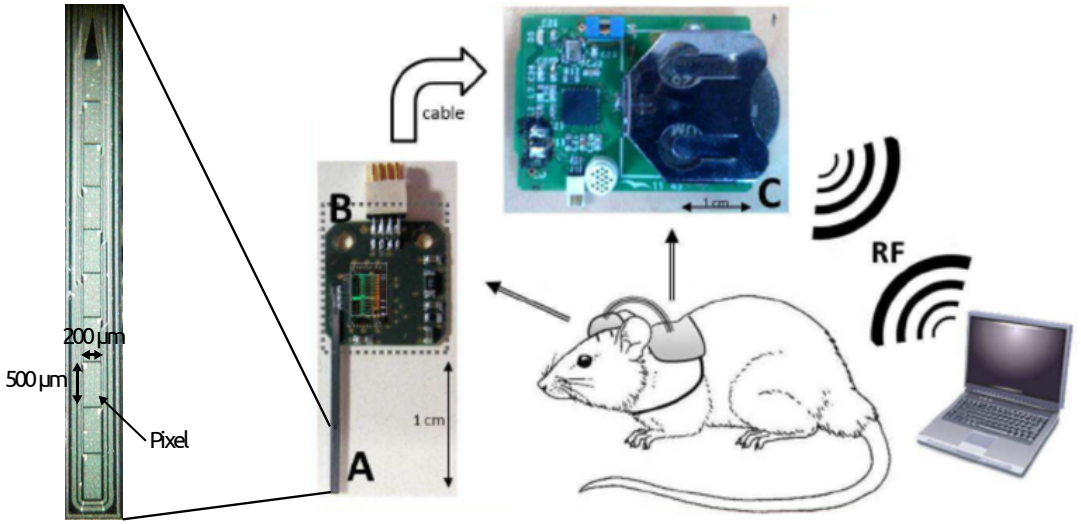


PIXSIC, the first pixelated β^+ microprobe

- ✓ good sensitivity to β^+
- ✓ Pixellated structure (10 pixels)
- ✓ Wireless communication

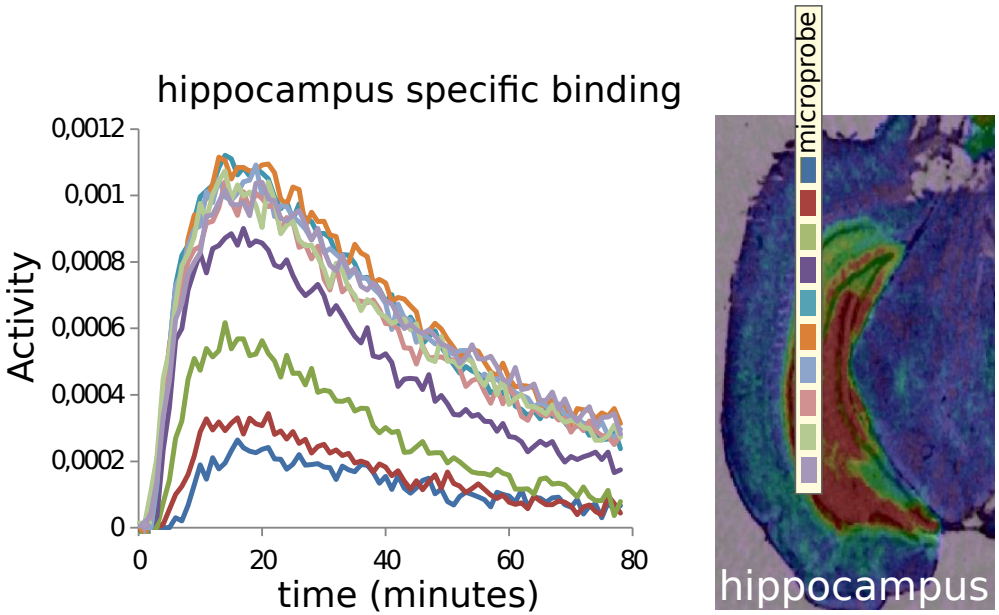


Fully freely moving animal with PIXSIC



A: Pixellated probe ; *B* : Readout electronic ; *C* : Battery and communication system

Several experiments validated PIXSIC biological and pharmacological suitability.

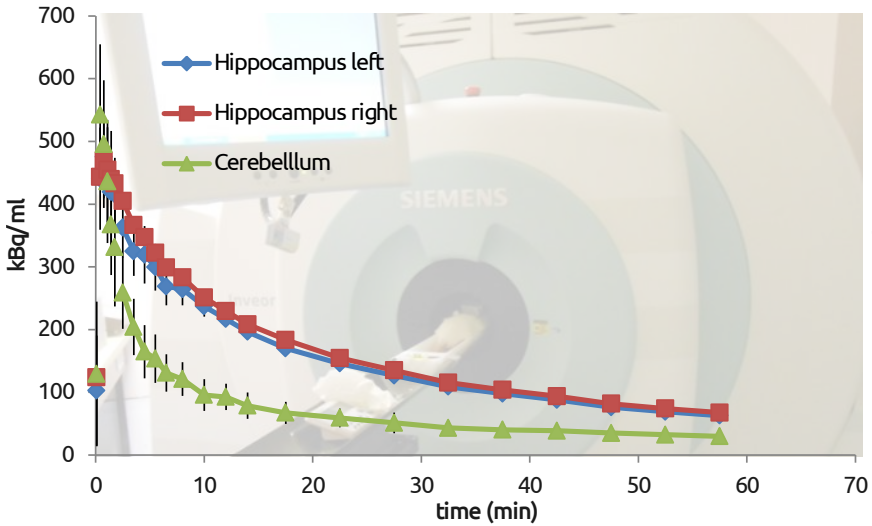


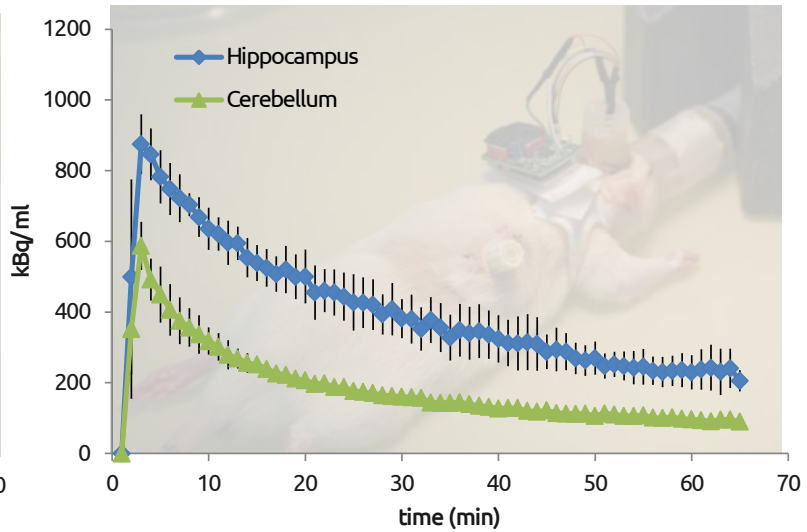
[18F]-MPPF injection - Hippocampus implantation.

Evaluation of the tracer spatial distribution validated !

PIXSIC pharmacological validation

Several experiments validated PIXSIC biological and pharmacological suitability.

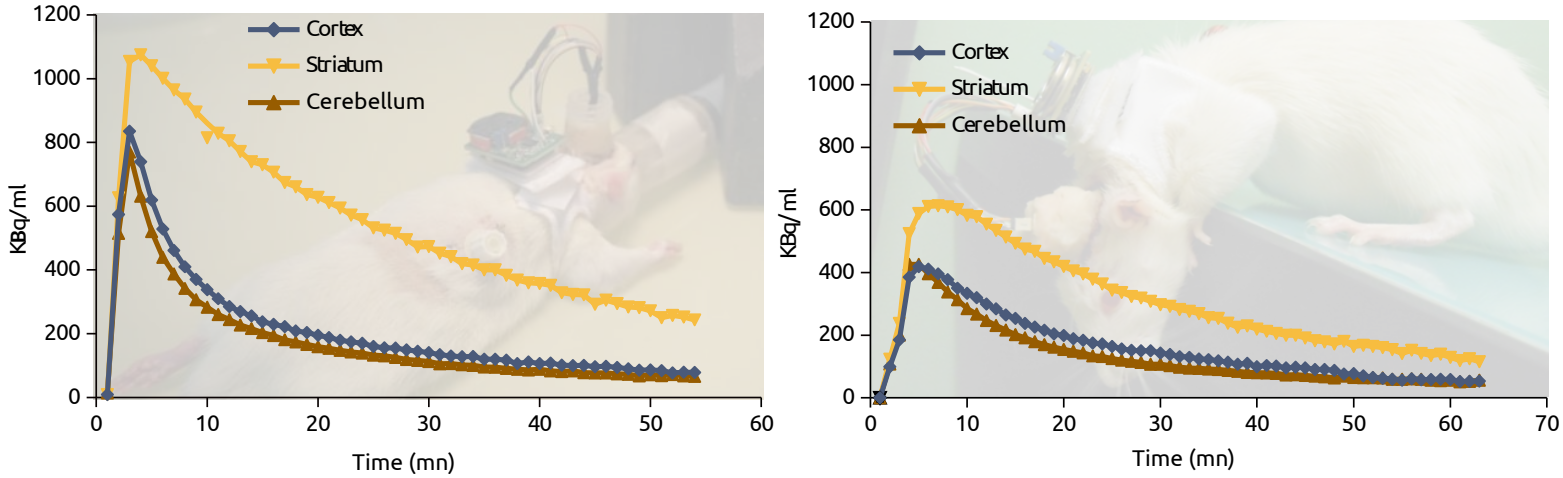




[18F]-MPPF 2 mCi injection - Hippocampus and cerebellum implantations.

Uptake measurement validated !

Several experiments validated PIXSIC biological and pharmacological suitability.



[11C]-raclopride 2 mCi injection - Striatum and cerebellum implantations.

PIXSIC shows anesthesia bias on neuroimaging results !

CMOS MAPS: towards an ideal probe

PIXSIC: It works!

- First autonomous β^+ probe
- Validated in pharmacological studies
- Biocompatibility validated

... but it shows major limits :

- Mechanical robustness.
- Electronic noise.
- γ rays sensitivity.

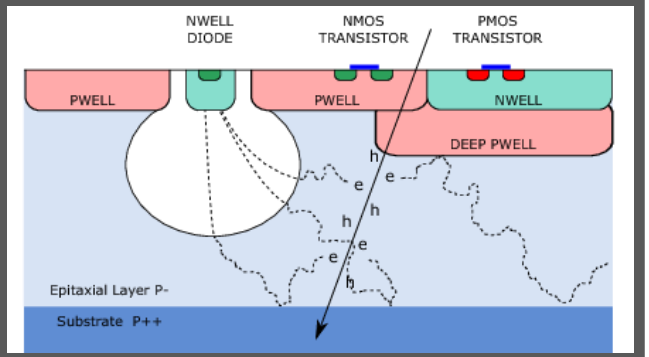
CMOS MAPS technology

$\rightarrow$ Highly pixelated sensors

$\rightarrow$ Direct amplification on the pixel

$\rightarrow$ Data processing on the sensor

$\rightarrow$ Low thickness of the sensitive volume



Charged particles detection in MAPS

MAPSSIC project aims to:

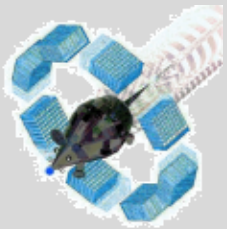
- Develop a CMOS MAPS sensor
- Develop front-end electronics
- Create an autonomous system on the animal head and back
- Validate the biological compatibility (temperature, size ...)
- Ensure mechanical and electrical robustness

First sensor prototype

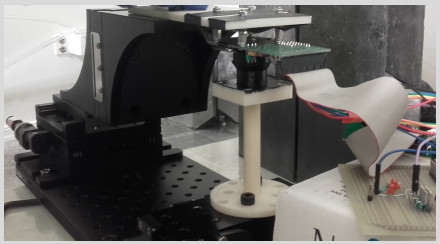
First prototype

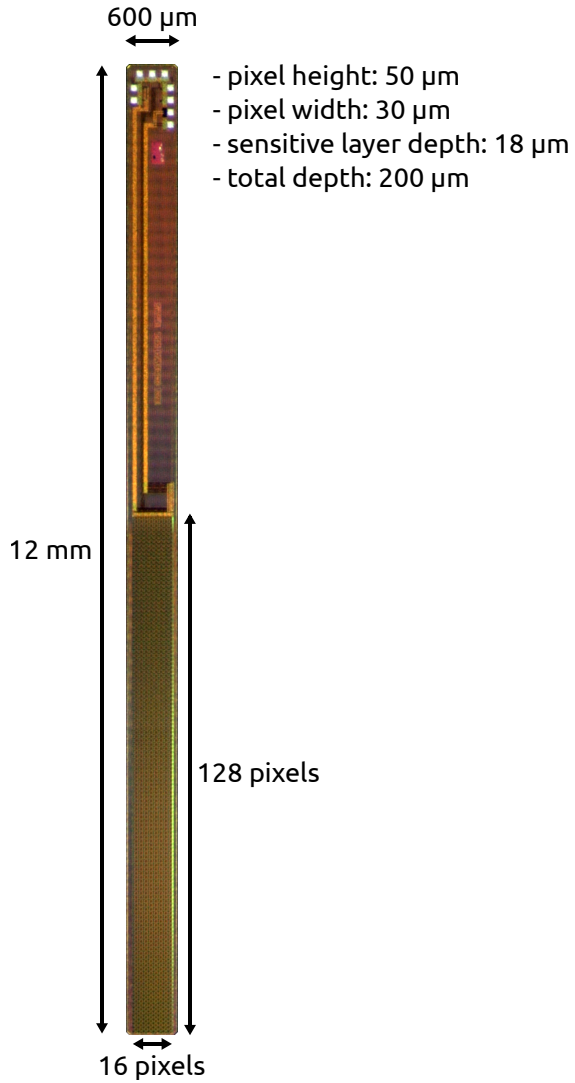
- 18 µm sensitive layer
- digital sensor
- 1 bit memory per pixel per frame
- Low power consumption (160 µW)

Monte Carlo simulations



Experimental measurements

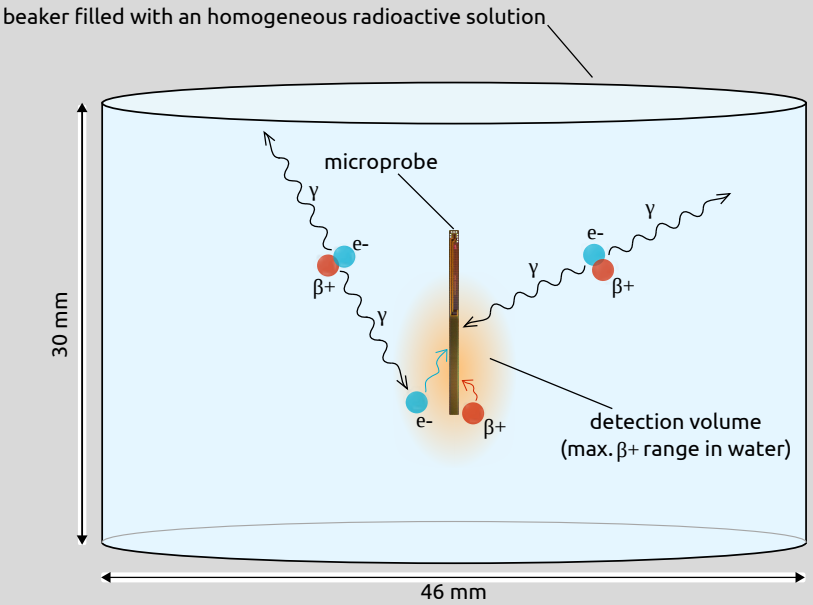


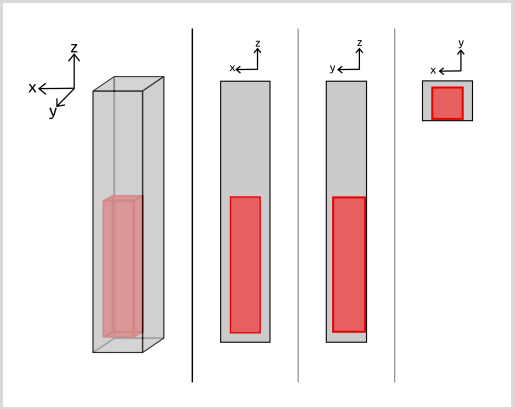


MAPSSIC sensor photography

Monte-Carlo simulations

Geometry of the simulation

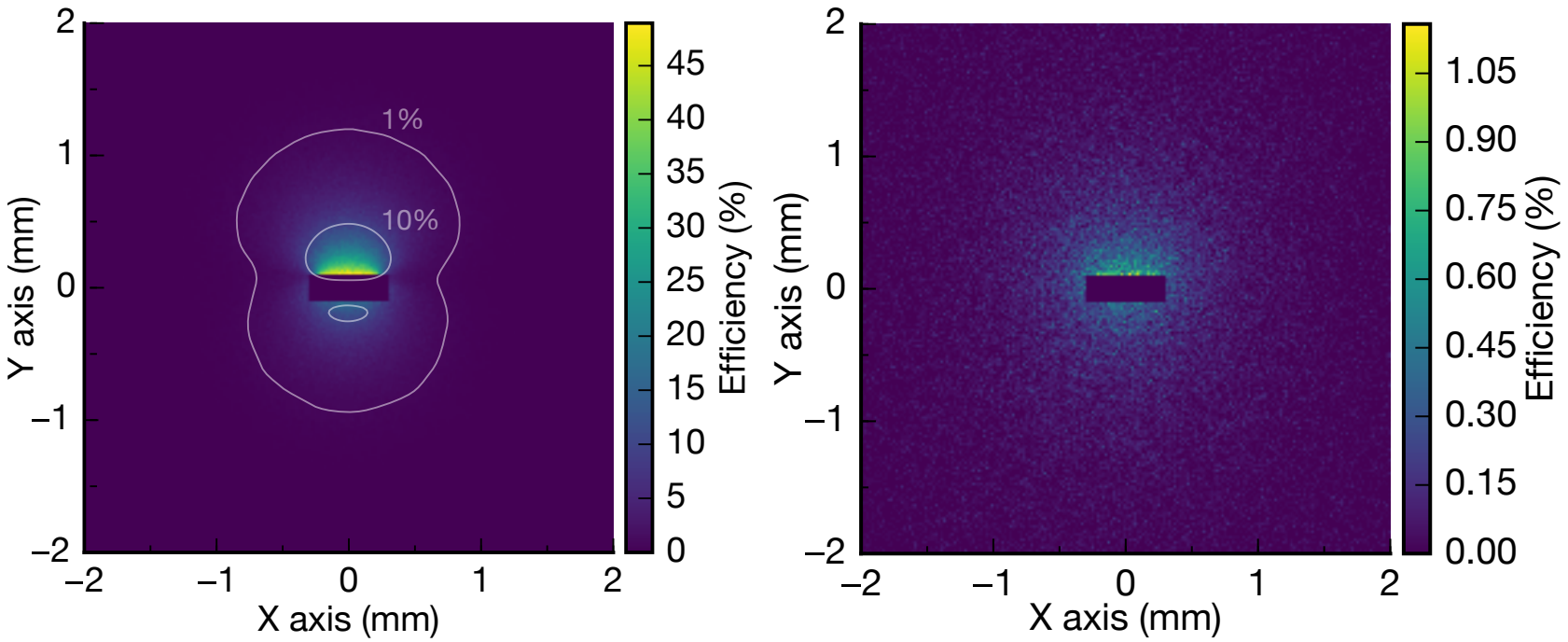




Radioactive sources

- Homogeneous sources: 18F, 11C and 15O
- Water cylinder : H=30 mm, R=23 mm
- Ability to modify *a posteriori* the activity distribution

Efficiency

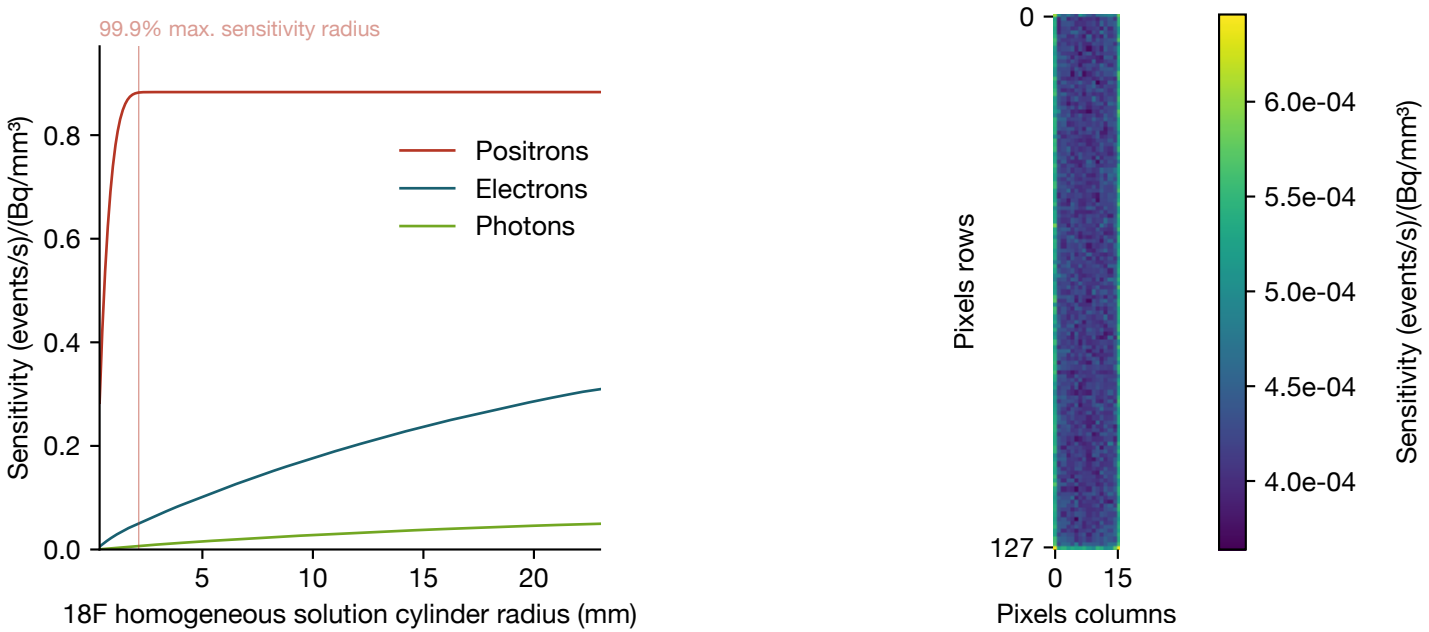


Direct β^+ detection efficiency (left) and indirect detection efficiency (right) (18F in water)

Results

- Low indirect detection efficiency, decreasing with distance to the sensor
- Volume > 1% efficiency is comparable to cerebral structures of interest

Sensitivity



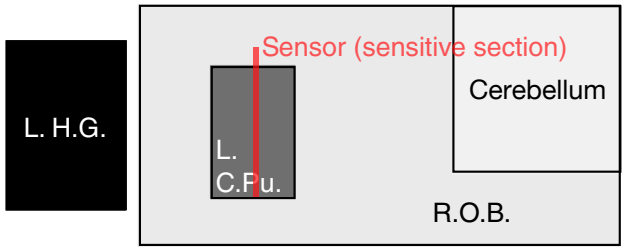
Sensitivity as a function of source radius and pixels sensitivity map

Results

	18F	11C	15O
Sensitivity to β^+ ((events/s)/(Bq/mL))	0.88	1.79	4.34

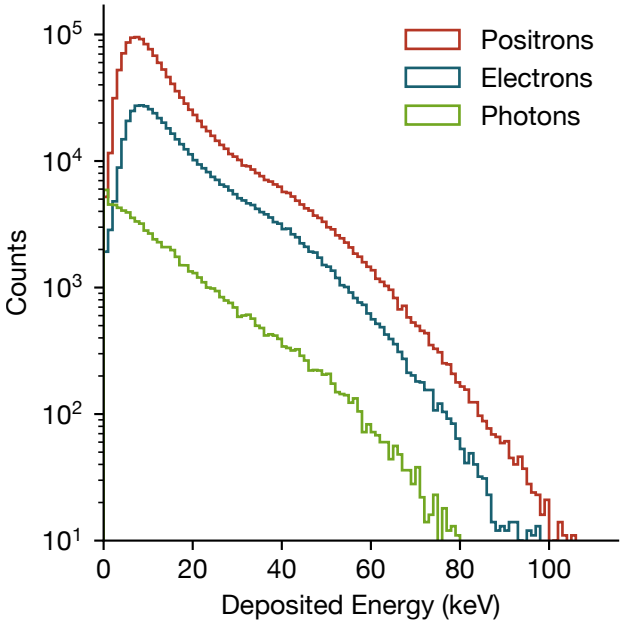
- Over the same sensor height, MAPSSIC sensor is 21% more sensitive than PIXSIC
- Integral non-uniformity: 7.53%

Sensitivity in a brain shaped source distribution



Structure name	Direct sens. ((evts/s)/(Bq/mm3)) contribution to the total	Indirect sens. ((evts/s)/(Bq/mm3)) contribution to the total
R.o.B.	$7.19 \times 10^{-2} \pm 0.21 \times 10^{-2}$ 7.67%	$1.42 \times 10^{-2} \pm 0.01 \times 10^{-2}$ 25.8%
Cereb.	$< 1 \times 10^{-5}$	$3.60 \times 10^{-4} \pm 0.15 \times 10^{-4}$ 0.65%
L. CPu.	$8.66 \times 10^{-1} \pm 0.01 \times 10^{-1}$ **92.3 %**	$2.98 \times 10^{-2} \pm 0.01 \times 10^{-2}$ **54.1%**
R. CPu.	$< 1 \times 10^{-5}$	$2.38 \times 10^{-3} \pm 0.14 \times 10^{-3}$ 4.32%
L. HG.	$< 1 \times 10^{-5}$	$3.03 \times 10^{-3} \pm 0.04 \times 10^{-3}$ 5.51%
R. HG.	$< 1 \times 10^{-5}$	$5.27 \times 10^{-3} \pm 0.06 \times 10^{-3}$ 9.57%

Deposited energy



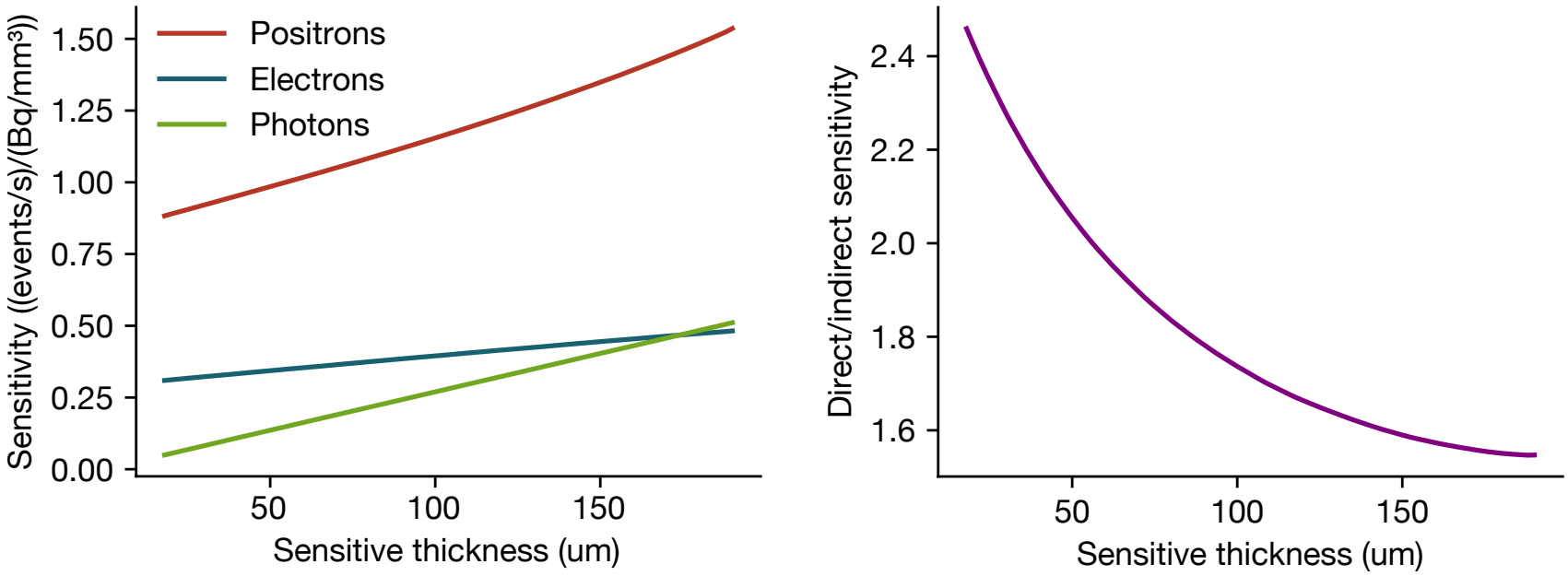
Deposited energy in pixels (18F in water)

Isotopes	18F	11C	15O
E_{peak} (keV)	6.9	7.2	6.1
E_{median} (keV)	11.0	9.51	8.72
E_{mean} (keV)	15.1	12.9	11.4
fraction < 1 keV	0.37 %	0.44 %	0.59 %
fraction < 10 keV	44.3 %	52.9 %	59.0 %

Results

- Peak ≈ 7 keV $\rightarrow$ energy threshold will be critical
- 24.3% of the γ spectrum is under 4 keV, 7.15% for the β^+ spectrum

Sensitive thickness variation



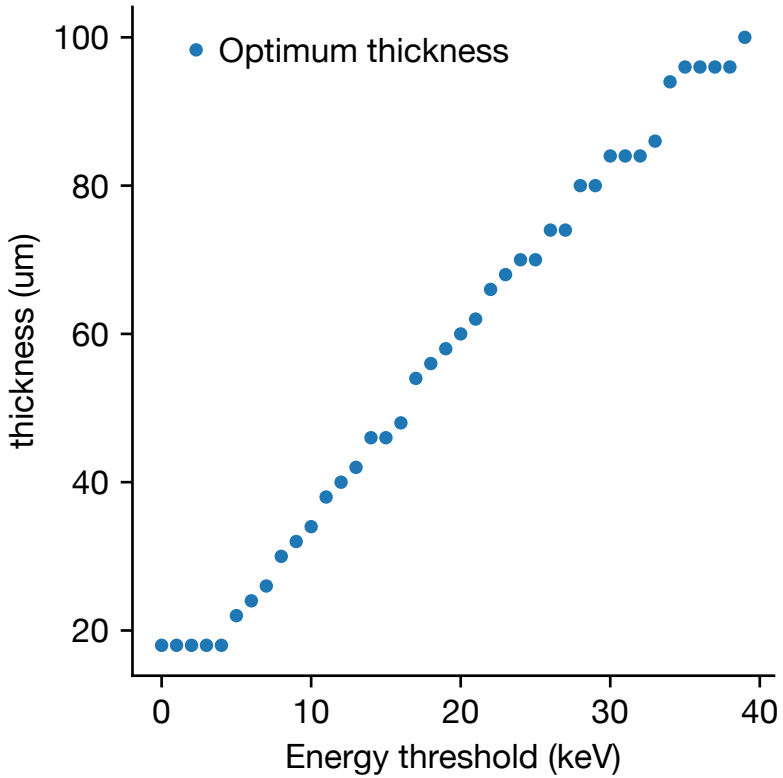
Sensor sensitivity as a function of sensitive thickness

Results

- 18 µm is the best thickness for direct β^+ detection over indirect detection (1.58 times better than 190 µm)
- But sensitivity is reduced by a factor 2.34

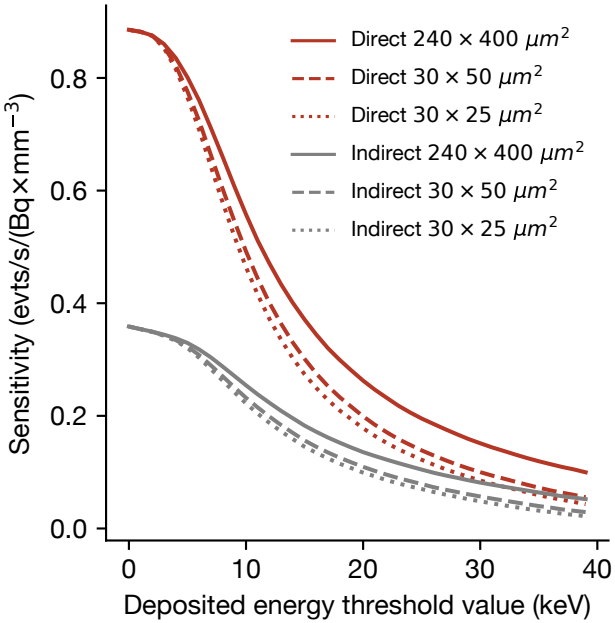
Sensitive thickness and energy threshold

The ratio between direct β^+ detection and indirect detection is not always maximum at lowest thickness values



Optimal thickness for a given energy threshold

Pixels size variation



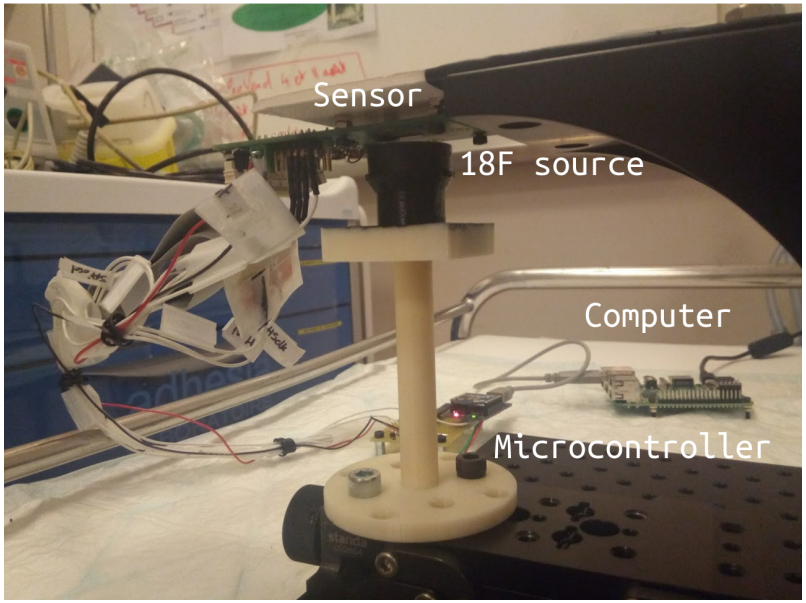
Sensitivity as a function of pixels dimensions and energy threshold

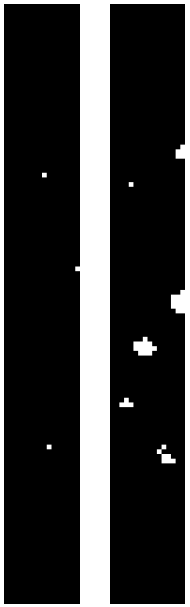
Results

- Without energy threshold, pixels dimensions doesn't affect sensitivity
- With threshold, variations still limited. (10 keV threshold $\rightarrow$ 17% increase of sensitivity with a $\times 128$ pixel surface increase

Experimental testings on first prototype

Experimental testing setup

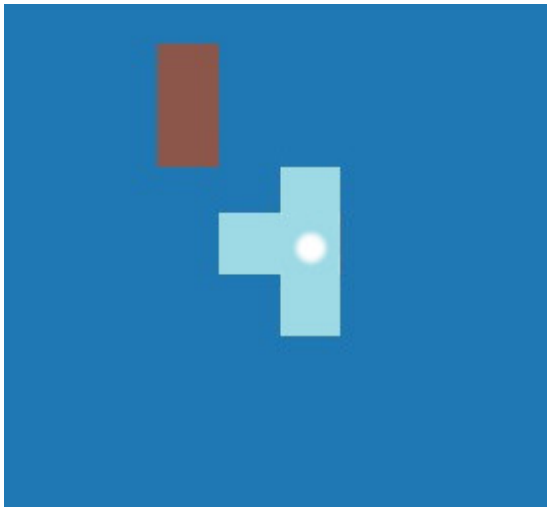


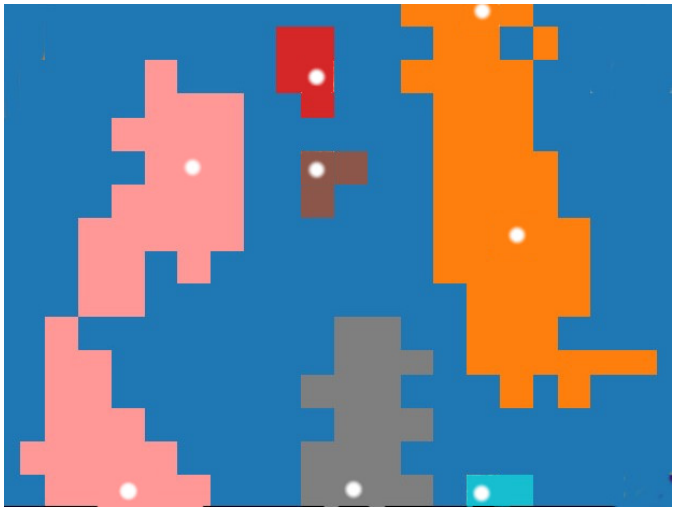


→ Mean clusters size (18F): 3.57 pixels
→ Most clusters (38%) are 1 pixel large

Left: ^{55}Fe X-ray source image
Right: ^{18}F beta^{+} source image

- 18F liquid sources (FDG or AV-1451) into an ABS container
- First MAPSSIC sensor prototype
- XBee microcontroller with Zigbee communication capability (450 ms duration frames)

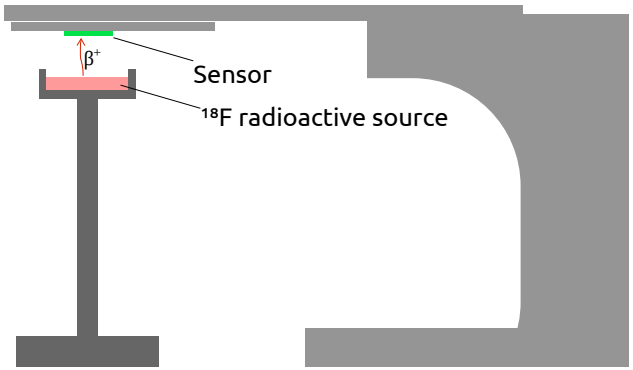


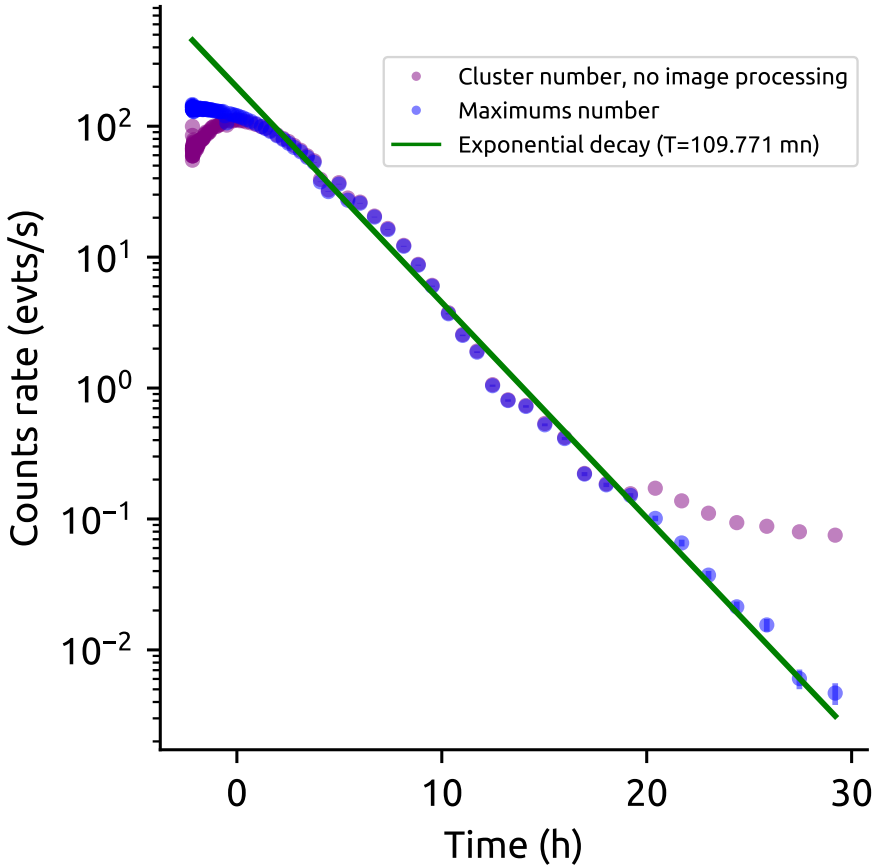


Left: scattered clusters example. Right: Piled-up clusters example. Dots are local maxima found by our image processing algorithm

- Removal of noisy pixels based on their relative activation frequency
- Filtering with a 3×3 gaussian kernel ($\sigma = 1$)
- Searching for local maxima within 3×3 kernels

Count rate

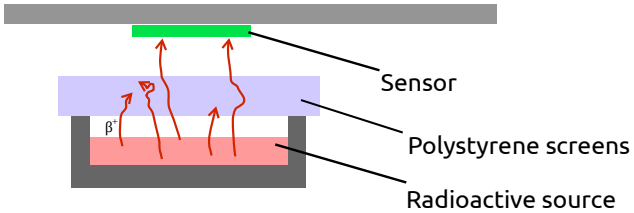


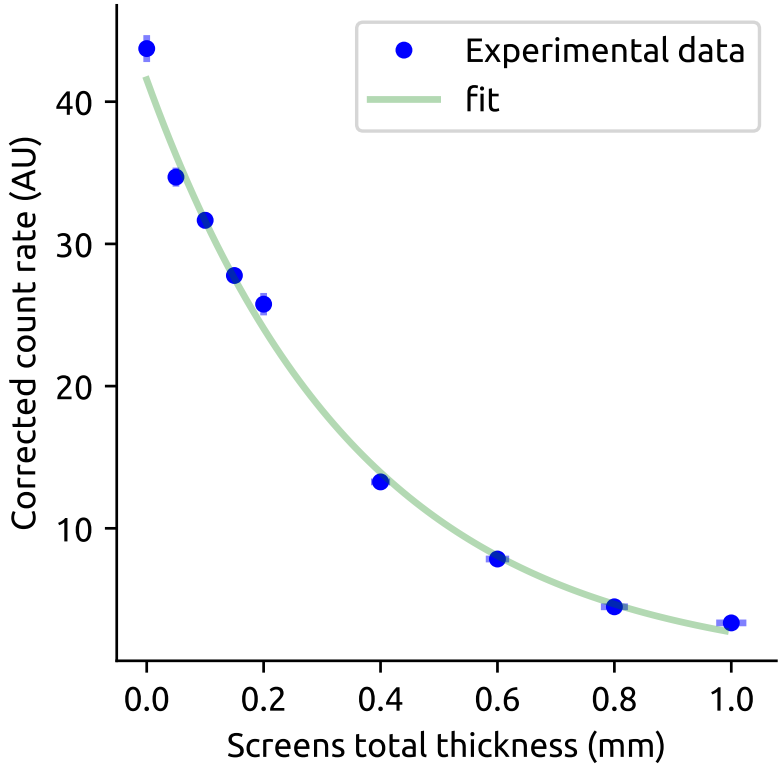


Results

- Events pile-up at high count rates (over 40 events/frame)
- Accordance with MC simulation in the linear region (2% difference)

Attenuation

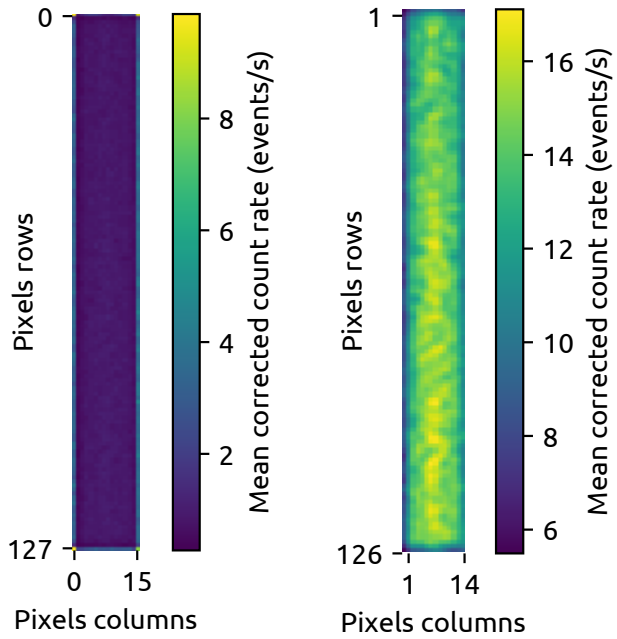




Results

- Attenuation in polystyrene follows an exponential decay law with a linear coefficient $\mu_{exp} = 2.82 \pm 0.18$ mm^{-1}
- Good agreement with empirical formulas ($\mu_{th} = 2.84$ mm^{-1})

Uniformity



Left: Uniformity map, obtained for all the positions of clusters maxima within the linear region
Right: Uniformity map after the removal of the edge pixels and 9 points filtering

Results

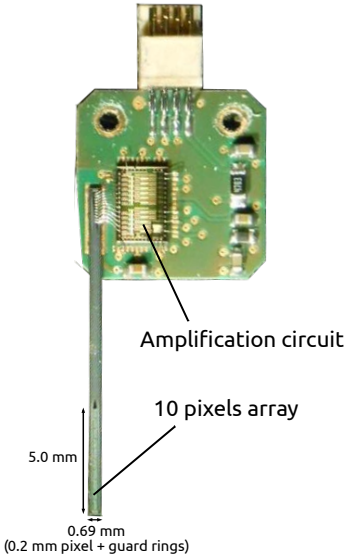
- The mean value on the edge is 2.92 times higher than the central region
- In the central region, the mean value of the two central columns is 19.5 % higher than the mean value of the other ones

Ongoing work

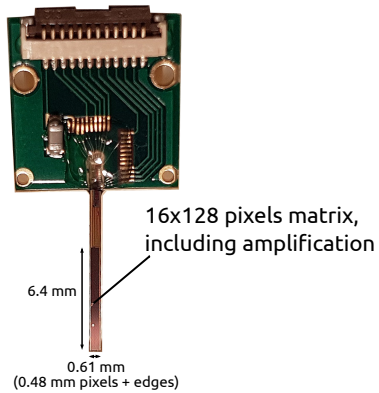
- Merging sensors back to back to increase the implant sensitivity and efficiency
- Parylene cover to protect the sensor from moisture
- Head PCB for connecting the sensors
- Autonomous module and wireless communication
- New optimized sensor design based on the first experimental feedbacks
- More realistic Monte Carlo simulations
- Experimental measurements into water phantom then into brain tissues

Conclusion

- We succesfully built a CMOS sensor β^+ for intracerebral β^+ microprobes
- Monte Carlo simulation demonstrated its suitability for in-vivo measurements
- Experimental testings confirmed its ability to measure β^+ emissions



PIXSIC sensor photography



MAPSSIC prototype photography

Thank you for your attention

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