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► **To cite this version:**

L. Ammour, J. Heymes, M. Bautista, S. Fieux, F. Gensolen, et al.. MAPSSIC, a Novel CMOS Intracerebral Positrons Probe for Deep Brain Imaging in Awake and Freely Moving Rats: A Monte Carlo Study. IEEE Transactions on Radiation and Plasma Medical Sciences, 2019, 3 (3), pp.302-314. 10.1109/TRPMS.2018.2881301 . hal-02165345

HAL Id: hal-02165345

<https://hal.science/hal-02165345>

Submitted on 25 Mar 2020

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MAPSSIC, a Novel CMOS Intracerebral Positrons Probe for Deep Brain Imaging in Awake and Freely-Moving Rats: a Monte Carlo Study

L. Ammour, J. Heymes, M. Bautista, S. Fieux, F. Gensolen, M. Kachel, A. Dubois, F. Lefebvre, F. Pain, P. Pangaud, L. Pinot, J. Baudot, P. Gisquet-Verrier, P. Laniece, C. Morel, L. Zimmer, M.-A. Verdier

Abstract—Preclinical behavior neuroimaging gathers simultaneous assessment of behavior and functional brain imaging. It is a potential key breakthrough to improve the understanding of brain processes and assess the validity of preclinical studies in drug development. Achieving such a combination is difficult, anesthesia or restraints inherent to conventional nuclear imaging preclude its use for behavior studies. In that context, we have proposed an original strategy using submillimetric probes to directly measure positrons inside the rat brain. This paper gives the results of Monte Carlo simulations of a new generation of intracerebral positron probe based on a CMOS Monolithic Active Pixel Sensor. We present the results obtained for a probe into a large homogeneous volume of radioactive water (^{18}F) leading to a sensitivity of $0.88 \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$ and a mean energy deposition by positrons of 15.1 keV. Simulation in simplified brain-shaped sources modeling a ^{11}C -raclopride experiment shows that the implanted volume modeling the left putamen contribute to 92.4 % of the signal from positrons. We also investigate the effects of the thickness of the sensitive layer, the energy threshold and pixel dimensions on the detection capacities of the sensor. We demonstrate that an increase in the sensitive thickness from 18 to 190 μm would lead to an increase of positrons sensitivity by a factor of 1.74, but to a decrease of the direct (positrons) to indirect (γ -rays and electrons) sensitivity ratio by a factor of 1.59. Finally we show that for a threshold lower than about 5 keV the effect of the pixel dimensions is negligible.

I. INTRODUCTION

AMONG the numerous methods developed to address neuroscience research needs, the combination of positron emission tomography (PET) with behavioral studies has been pointed out as a potential key breakthrough to go further in the understanding of functional processes in the brain [1]. Correlating *in vivo* molecular processes of neuronal communication with behavior in real time is of major interest. This complementarity is a critical step for comparing animal to human behavior and consequently assess the validity of

preclinical studies in drug development. For example, as explained in [2], behavior neuroimaging shows applications for the study of addiction in animal models, using ^{18}F -FDG for associating brain metabolism to a particular behavior or ^{11}C -raclopride to study the dynamic changes in the dopaminergic system in real-time.

Achieving such a combination is not straight-forward though, since general anesthesia or severe restraints historically used in small animal PET imaging precludes its use for behavioral studies.

Furthermore, previous works have highlighted that anesthesia or restraints on awake animals affect PET brain imaging studies ability to reflect the awake and freely moving rat brain [3, 4]. As pointed out by Alstrup and Smith, anesthesia effects doesn't preclude PET brain imaging, but the current procedures to evaluate its effects using PET show limitations. For instance, awake imaging with restraints may cause stress to the animals. This points out the relevance for new tools for radiotracers imaging on awake animals and without restraints.

To address these obstacles, several approaches have been studied but remain affected by important constraints. The simplest method, the sequential use of anesthetized PET imaging after behavior experiment (as described in [2]) is obviously counterbalanced by the lack of real time analysis. A second method, the tracking of the rodent position inside a PET gantry [5] restricts the rat movements within its field of view, thus limiting the ability to perform complex behavioral studies. The RatCAP, which relies on a wearable PET for imaging the entire brain on awake animals, still requires a mechanical arm to sustain the device [6].

In that context, a less cumbersome strategy was proposed to record the radiotracers time-activity curves: radiosensitive positron probes. Directly at the contact of rodent tissue, they allow to measure the radioactivity in the region of interest, *i.e.* the medium surrounding the sensor, while leaving the animal freely moving. Without providing a full brain image, they are a simple and cost effective tool with a good sensitivity. Hence, they are an effective way to assess local time activity curves.

The first probes used a scintillation detector coupled to an external photomultiplier tube [7, 8], then extended to fully autonomous systems thanks to reverse-biased, high-resistivity silicon diodes and wireless communication [9].

These probes, implanted by stereotaxic surgery or placed closed to the brain surface must have a reduced size compatible with those of studied brain structures and must be biocompat-

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ible. Their sensor has to be highly sensitive to β^+ particles and has to present a good transparency to annihilation γ -rays.

A first intracerebral wireless probe named PIXSIC was previously developed [10]. Although successfully validated in various biological contexts [11], providing promising results for behavioral neuroimaging, this probe design suffered from several issues. The probe sensitivity to γ -rays led on to substantial noise. Moreover, the thickness of the probe, reduced to $200\mu\text{m}$ to limit annihilation γ -rays interactions, made the device brittle and difficult to manipulate. Finally, the signal suffered from electromagnetic noise picked-up along the tracks, as the charge had to be transported on a distance of about two centimeters.

Taking into account these limits we considered complementary metal oxide semi-conductor (CMOS) monolithic active pixel sensor (MAPS) technology to develop a novel β^+ sensitive micro-probe called MAPSSIC. In particular, among other benefits, MAPS provides direct signal amplification at pixel level, leading to a high signal to noise ratio. Moreover, the thickness of the epitaxial sensitive layer, a few tens of micrometers thick, should provide a good transparency to 511 keV γ -rays.

In order to find the most suitable sensor for the probe, we conducted Monte Carlo simulations to optimize the sensor developments. We simulated a sensor based on first design guidelines, which will be described in section II-A, as biological, electronics and mechanical constraints. This model was placed at the center of a homogeneous aqueous solution of ^{18}F , ^{15}O or ^{11}C or into a simplified sources model of an ^{11}C -raclopride experiment. The simulations evaluated the physical detection properties, without accounting for signal processing nor charges diffusion.

II. METHODS

A. Sensor model

We have designed a first set of CMOS probes matching miniaturization requirements for brain implantation and technical feasibility of CMOS MAPS sensors.

To be inserted into the brain of a rat, the sensor is needle shaped. Its width should not be greater than approximately $500\mu\text{m}$ in order to limit the invasiveness in cerebral tissues while providing a large sensitive volume. Its length must exceed 1 cm in order to attach the implanted sensor to a head socket, which is set on the rodent skull. The MAPS sensor circuit was designed to be manufactured in a 180 nm CMOS image sensor technology, with a high resistivity epitaxial layer sensitive to charged particles. This epitaxial layer can be grown to a thickness ranging from $18\mu\text{m}$ to $40\mu\text{m}$ with pixel dimensions in the order of a few tens of micrometers. Moreover, polarization of the substrate to reach deep depletion is possible in this type of CMOS technology allowing a thicker sensitive region, up to the whole silicon thickness [12].

A first prototype of the sensor called IMIC was designed as a 12 mm long silicon parallelepiped, with a $610\mu\text{m}$ width and a thickness of $200\mu\text{m}$. The sensor architecture is based on the ALPIDE chip developed for the ALICE experiment at the CERN Large Hadron Collider [13]. The first $10\mu\text{m}$ in depth

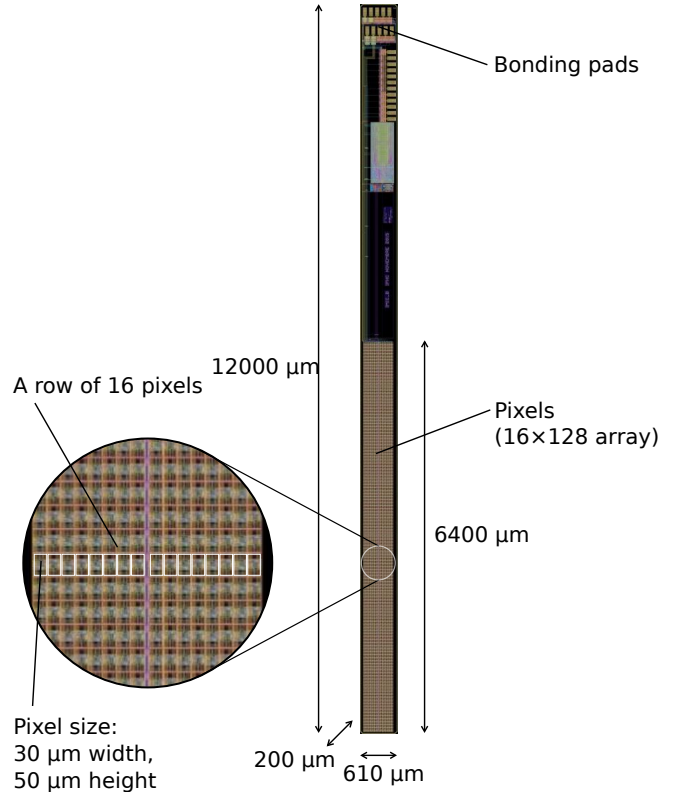


Fig. 1. Model of the first sensor prototype. It features a 16×128 pixels matrix for charged particles detection, each pixel surface is $30 \times 50\mu\text{m}^2$. The pixels are made into a thin $18\mu\text{m}$ epitaxial layer. The whole sensor dimensions are 12 mm length, $610\mu\text{m}$ width and $200\mu\text{m}$ thick.

receive the CMOS process, then comes the epitaxial layer over a $18\mu\text{m}$ thickness. The pixel matrix features 16 columns and 128 rows. The pixel dimensions are $50\mu\text{m}$ along the probe length (longest dimension) and $30\mu\text{m}$ along its width. The matrix of pixels is set on the lower half of the probe. The layout of the sensor model is presented in figure 1.

B. Detection properties

The first aim of this work was to validate the sensor concept, by demonstrating its ability to quantify the concentration of radioactivity in experimental context and exhibit improved performances, as compared to previous probes.

To evaluate the sensor design, we first studied several detection properties: detection efficiency, deposited energy, and sensitivity of the sensor.

The second goal was to optimize the design and the parameters of the probe, on the basis of these properties. We aimed to optimize the epitaxial layer thickness and pixel dimensions by using Monte Carlo simulations in order to create a set of parameter models.

1) *Direct and indirect detection*: In order to evaluate the detection properties, we distinguished the direct and indirect detection of positrons. When an event is created by a positron emitted by the source, directly interacting in the sensor, it gives information about the radioactive concentration in the

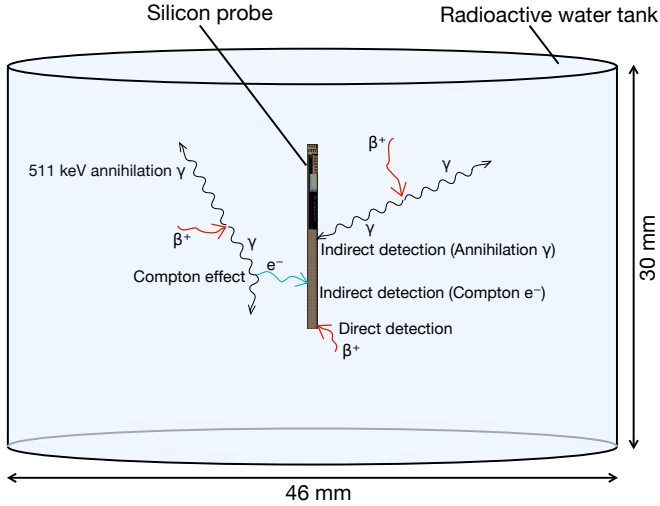


Fig. 2. The MAPSSIC sensor model into a cylindrical source of β^+ radioactive water. Three types of signal source in the sensor are illustrated here. From top to bottom: the detection of an annihilation γ -ray, the detection of an e^- consecutive to a Compton effect in the surrounding medium and the direct detection of a β^+ emitted by the source close to the pixels. The contribution to the signal from the first two types of events is called "indirect".

vicinity of the probe because of the short positron range in water or brain tissues. This corresponds to direct positron events. On the other hand, annihilation γ -rays and Compton electrons (issued from annihilation rays interacting within the surrounding medium) can also create events in the sensor, but their corresponding source emission location cannot be restricted to the close environment of the probe because of the high penetration of 511 keV annihilation γ -rays. They are consequently indirect positron events. Figure 2 illustrates these different signal components.

2) *Detection efficiency*: For a given small volume v at the position in a source volume, the detection efficiency e is defined as the ratio between the rate of counted events originating from v , N (cps), and the activity in this volume A (Bq).

$$e = \frac{N}{A} \quad (1)$$

3) *Sensitivity*: The sensitivity is defined as the counts rate of events N_{source} (cps) per unit of radioactivity concentration C_{ref} (Bq \cdot mm $^{-3}$) of a reference source.

$$S(\text{cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3) = \frac{N_{source}}{C_{ref}} \quad (2)$$

If a source volume is discretized into small elements (voxels) i with volumes v_i , activity concentrations C_i and efficiencies e_i , the sensitivity to this source volume is expressed by:

$$S = \frac{1}{C_{ref}} \sum_i e_i \times C_i \times v_i \quad (3)$$

We also define the direct sensitivity as the sensitivity to direct positron events and the indirect sensitivity when counts are related to indirect detection events. As the direct sensitivity

always provides useful information about radioactivity concentration in the surrounding medium whereas the indirect sensitivity could lead to signal originating from remote sources, the ratio between direct sensitivity and indirect sensitivity is considered as a metric of signal to noise ratio [7, 14].

4) *Deposited energy*: The deposited energy is measured in the sensitive part of the sensor. For a given event, it is the sum of the deposited energy by an incident particle and all the secondary particles created in the sensitive volume.

5) *Optimization of sensitive thickness and the pixel dimensions*: Considering the various sensitive layer thicknesses allowed by the CMOS technology ranging from 18 μm , up to the entire thickness except the wiring layer, we aimed to evaluate the effects of these sensitive thicknesses on detection properties. Moreover, the dimension of the pixels can also be adjusted. The first prototype used $30 \times 50 \mu\text{m}^2$ pixels. MAPS sensor would allow smaller pixels ($20 \times 20 \mu\text{m}^2$ with MIMOSA32 sensors [15] built with the same CMOS process).

C. Design of the simulation

1) *Sensor geometry*: Monte Carlo simulations were performed using GATE 7.0 [16, 17]. The probe model was defined according to the first design previously presented: a first $610 \times 200 \times 12000 \mu\text{m}^3$ parallelepiped of silicon, simulating the sensor, encapsulating an inner silicon $480 \times 190 \times 6400 \mu\text{m}^3$ parallelepiped, simulating the sensitive volume of the sensor (see figure 3). This latter parallelepiped was defined in the simulation as a sensitive volume, within which all the interactions of particles are stored. This volume is larger than the 18 μm thick epitaxial region to allow the study of models with a larger sensitive thickness.

2) *Source and phantom*: The simulated source was an aqueous homogeneous solution of either ^{18}F or ^{11}C or ^{15}O , radioactive β^+ emitters with energies of 633.9 keV, 960.5 keV and 1735.0 keV respectively. The source fills out a cylindrical volume of 30 mm height, and 46 mm diameter, as illustrated in figure 2. The simulated probes were located at the center of the source.

3) *Physical processes*: The physics processes were simulated using the *Penelope* model (the Geant4 implementation of the physics models developed for the PENELOPE code, including reliable electromagnetic processes for photons, electrons and positrons at low energies [16]). All energy cuts (minimum energy threshold of secondary particles production) were set to the energy corresponding to a 1 μm interaction path length in the medium.

We recorded all physical interactions, called *hits*, occurring in the sensitive inner volume: their type, particles involved, their location, the amount of deposited energy, a unique identification number of the source emission leading to this event and the location of this emission. When several recorded hits have the same primary particle for origin, this group of hits is called *event*.

D. Numerical analysis

1) *Sensitive thickness*: To fit the simulation model to the sensor design, we had to filter the recorded data. As we

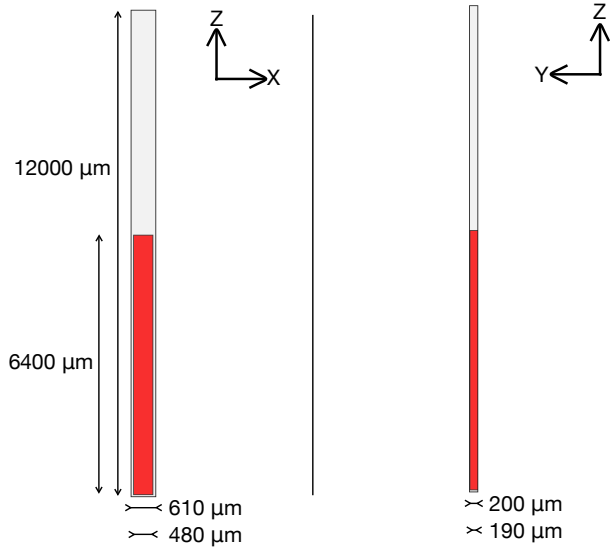


Fig. 3. GATE sensor model, made of two silicon parallelepipeds. The outer parallelepiped dimensions are $610 \times 200 \times 12000 \mu\text{m}^3$. The inner red parallelepiped dimensions are $480 \times 190 \times 6400 \mu\text{m}^3$. We recorded all the events occurring in the sensitive volume (in red). Pixels are not modeled in this GATE simulation but during data analysis with the required shapes and sizes. The left figure is a cross section in the (Z,Y) plan, the right figure is a cross section in the (Z,X) plan.

simulated a $190 \mu\text{m}$ thick sensitive area we filtered all recorded interactions occurring below a thickness of $18 \mu\text{m}$, corresponding to the epitaxial thickness of our first prototype, or thicker in order to study the effects of the sensitive thickness variation on the detection parameters.

2) *Pixels boundaries*: Although we did not model the individual pixel boundaries with GATE, all the positions of interaction were recorded. Consequently we were able to sort the recorded hits pixels by pixels during post-analysis. This allowed us to change the dimensions and number of the pixels to study their impact on the detection performances.

3) *Energy thresholds*: We have defined detection energy thresholds the following way: events were kept if the sum of deposited energy in at least one pixel was above a given value. While evaluating the detection properties we studied the impact of energy thresholds on detection properties, from no energy threshold up to a 40 keV threshold.

4) *Voxelized phantom*: Finally, by keeping or rejecting events based on the position of their primary particle emission, we were able to modify the spatial distribution of the source. We used a voxelized source file containing voxels activities as input. Each group of recorded events related to the same source emission were randomly kept with a probability equals to the relative voxel activity where this emission was located.

In order to model a realistic source distribution, we defined a simple voxelized brain phantom model of a rat brain (see figure 4). It is made of six parallelepiped volumes: left and right hardierian glands (L. HG. and R. HG.), left and right caudate putamen (L. CPu. and R. CPu.), cerebellum and rest of the brain (R.O.B.). Dimensions were based on the Paxinos and Watson rat brain atlas [18].

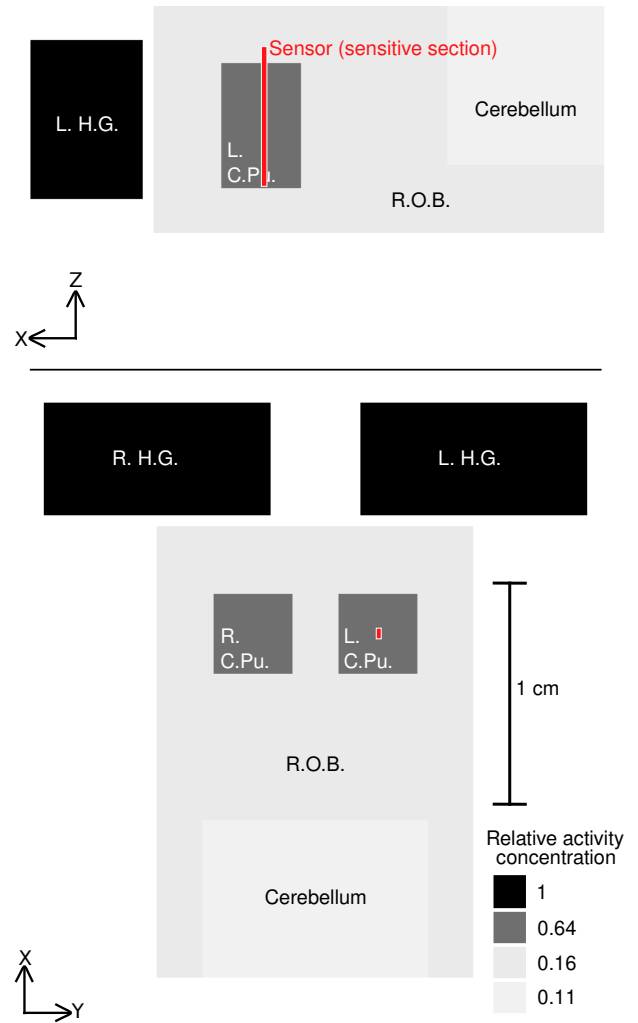


Fig. 4. Simplified simulated model of the rat brain including 6 volumes : left and right hardierian glands (L. HG. and R. HG.), left and right caudate putamen (L. CPu. and R. CPu.), cerebellum and rest of the brain (R.O.B.). The sensor properties are computed within this model. The probe (in red) is implanted in the middle of the L. CPu. structure. The activity concentration distribution follows a realistic ^{11}C -raclopride experiment, the gray level is proportional to the activity. The top cross section presents the model of the (Z,X) plan, the bottom figure is a cross section of the (X,Y) plan. Both cross sections use the same activity concentration and dimension scales.

In order to model ^{11}C -raclopride experiments, the phantom was based on the simulated ^{11}C source. The activity values were based on the reference time activity curve published in the OSSIPET database [19].

The sensor was placed vertically at the center of the simplified left caudate putamen region. As this region height is smaller than the sensitive volume height, a section of 5.5 mm height of the sensitive volume was into the L. CPu. and a section of 0.9 mm was into the R.O.B.. Figure 4 illustrates two cross sections of this phantom. The corresponding dimensions and activities are presented in table I.

5) *Efficiency spatial distribution*: Based on the simulations of the whole cylindrical source, with a $18 \mu\text{m}$ thick sensitive area and assuming no energy threshold, we have evaluated the detection efficiency within the source volume. The source positions of the recorded events were discretized into small

Structure	Relative activity concentration	Dimensions (X, Y, Z) (mm)
R.O.B.	0.16	(20, 14, 10)
Cerebellum	0.11	(7, 10, 7)
L. CPu.	0.64	(3.5, 3.5, 5.5)
R. CPu.	0.64	(3.5, 3.5, 5.5)
L. HG.	1.0	(5, 10, 7)
R. HG.	1.0	(5, 10, 7)

TABLE I
DIMENSIONS AND ACTIVITY CONCENTRATIONS OF THE SIMPLIFIED
BRAIN MODEL VOLUMES.

volume elements (voxels). We computed each voxel efficiency as the ratio between the rate of detected events originating from a given voxel and the total activity in the voxel volume defined in our simulation model. Our sources models only generated β^+ (branching ratio is 1).

We also computed the volume where efficiency exceed some values (10 %, 1 % and 0.1 %).

6) *Deposited energy*: The deposited energy was evaluated for the whole cylindrical sources, and for the three isotopes of interest. We compared the spectra of the deposited energy for each incident particles type. The incident and secondary particles can interact in different pixels, thus their energy can be deposited in several pixels. Since only one pixel hit is needed for an event to be detected, we studied only the pixel where the total deposited energy was the highest.

7) *Sensitivity*: The sensitivity was computed using equation 2. The activity concentration was defined in the GATE model, $1.60 \times 10^6 \text{ Bq} \cdot \text{mm}^{-3}$ for the cylindrical ^{18}F source, $0.80 \times 10^6 \text{ Bq} \cdot \text{mm}^{-3}$ for the cylindrical ^{15}O source and $1.59 \times 10^6 \text{ Bq} \cdot \text{mm}^{-3}$ for the ^{11}C cylindrical and brain phantom sources.

Direct and indirect sensitivities and their ratios were first evaluated for the homogeneous radioactive cylindrical sources. By adapting the spatial distribution of the source into a set of homogeneous cylindrical sources with different radii, we obtained sensitivity values as a function of the source radius.

We compared the results of the largest cylinder source with the previous PIXSIC probe. As the previous sensor geometry was different from the simulated one, we compared the sensitivity from equivalent heights h_{eq} . The equivalent sensitivity S_{eq} was computed as the mean sensitivity in a section of height h_{eq} , *i.e.* the sensitivity within the entire sensor multiplied by the ratio of the equivalent height to the sensor total height. The equivalent height was $h_{eq} = 500 \mu\text{m}$, as presented in [10].

We have also compared the sensitivity of each MAPSSIC sensor pixel for an array of 128×16 pixels. As for deposited energy computation, we took into account the events only in the pixel of maximum deposited energy. We have compared the mean sensitivity of edge pixels and center pixel. We have evaluated the non-uniformity of the sensor using the integral uniformity (*IU*) metric, defined as :

$$IU = \frac{S_{max} - S_{min}}{S_{max} + S_{min}} \quad (4)$$

Where S_{min} is the minimum pixel sensitivity value and S_{max} is the maximum pixel sensitivity value, after removing the edge pixels and applying a 9 points filter as described in [20].

Finally, we computed the sensitivities in the brain shaped voxelized phantom, with the sensor placed at the center of the L. CPu. region.

III. RESULTS

A. Efficiency

The spatial detection efficiency of the entire probe into a phantom filled with ^{18}F solution is shown in figure 5. Figure 5a presents the direct detection efficiency of the sensor while figure 5b shows the indirect detection efficiency. Efficiency isolines at 10 % and 1 % levels are drawn.

Each figure presents two slices of the detection efficiency, one along the sensor length (made of $0.1 \times 0.1 \times 5.5$ mm pixels) and the other one perpendicularly to it (made of $0.1 \times 0.1 \times 0.6$ mm pixels).

As expected, the low range of positrons in water strictly restricts the region of direct detection to a small region around the sensor. Moreover, the direct detection efficiency quickly decreases with the radius, demonstrating that the major contribution to the signal originates from the sensor vicinity. For ^{18}F , the efficiency drops to less than 1 % at 1.06 mm from sensor surface. Both the direct and the indirect efficiencies decrease with distance to the sensor due to the lower detection solid angle.

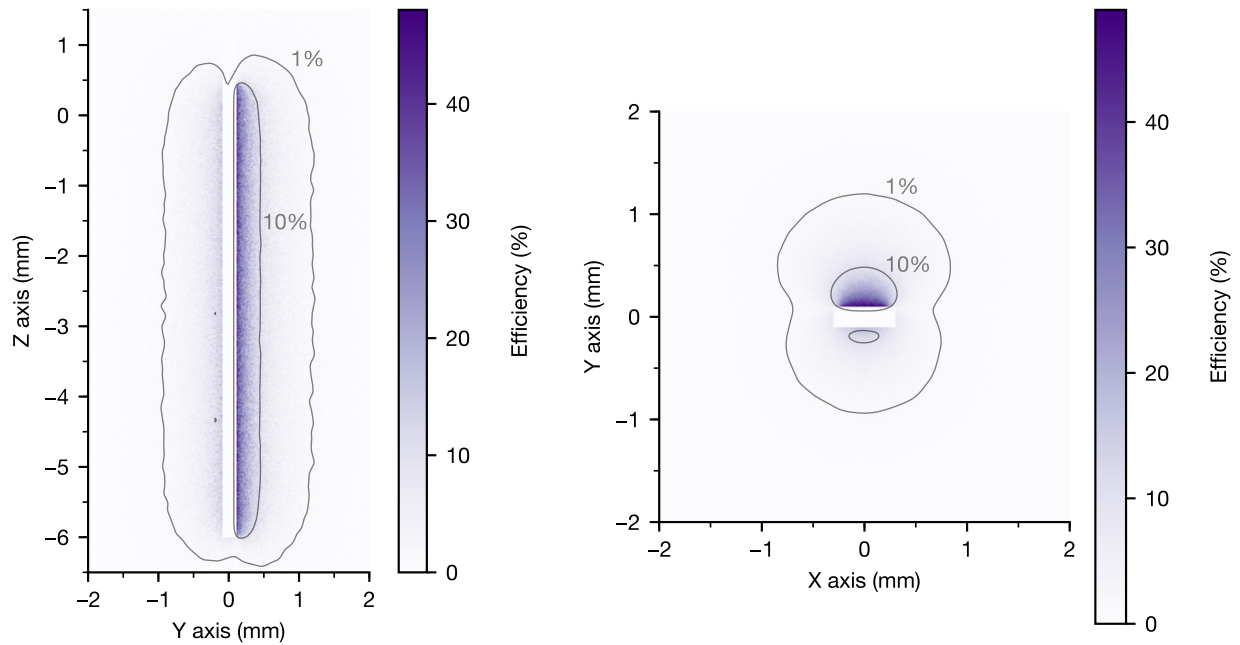
As the sensitive volume thickness is $18 \mu\text{m}$ and located between two very asymmetrical layers of silicon, of $10 \mu\text{m}$ on one side and $152 \mu\text{m}$ on the other side, this leads to a strong asymmetry on the efficiency along the Y axis.

The volume bounded by the 1 % efficiency isosurface (for direct events, in a ^{18}F water phantom) is as small as 17.34 mm^3 . Other isoefficiency volumes are presented in table II. As a matter of comparison, volumes of typical studied rat brain structures, hippocampus or caudate putamen, are respectively 39.5 mm^3 and 31.0 mm^3 according to [21] and [22]. Consequently we can expect a good detection efficiency of the radioactivity in the region of interest while limiting the efficiency to sources outside of this region.

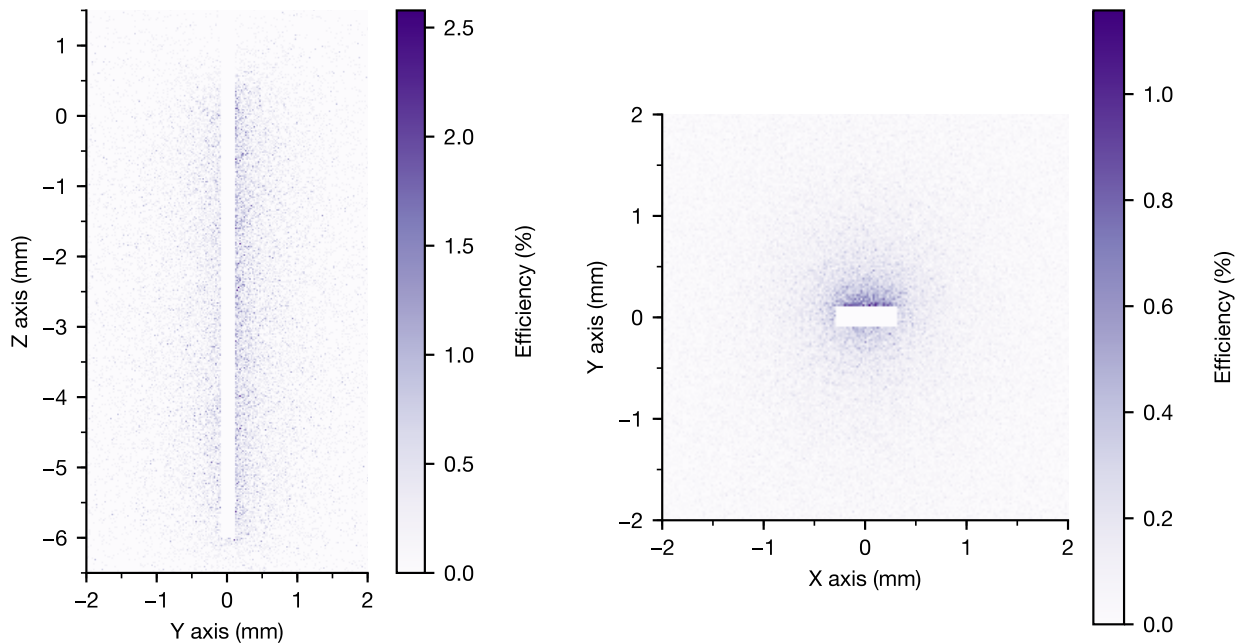
B. Sensitivity

The sensitivity varies greatly as a function of the source radius as shown on figure 6. Under radii close to the positron range in water (2.3 mm for ^{18}F according to [23]), the sensitivity to direct events quickly increases with the diameter of the source. For larger radii, the direct sensitivity stops increasing, as efficiency for the furthest points drops to zero.

For ^{18}F , this direct sensitivity limit was computed at $(8.83 \pm 0.01) \times 10^{-1} \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$. The maximum is obtained for a 2.71 mm cylinder radius, it reaches 99.9 % of this value for a 2.12 mm radius. The direct sensitivities for the three isotopes are summarized in table III. We observed a greater direct sensitivity for ^{11}C and ^{15}O sources than for ^{18}F sources. This difference arises from the positrons larger range in water for these isotopes.



(a) Direct efficiency map



(b) Indirect efficiency map

Fig. 5. Spatial distribution of the direct (top) and indirect (bottom) detection efficiency of the sensor into an homogeneous radioactive ^{18}F solution in water. The left figures present a lateral cross section including the complete sensitive region ((Z,Y) plan), the right ones present cross sections perpendicular to the sensor axis ((X,Y) plan). The sensor shape is displayed at the center of the figures, as a null efficiency area. The 10 % and 1 % efficiency isolines are drawn, smoothed to improve readability.

Indirect sensitivity continuously increases because of the high penetration of annihilation γ -rays in water. Even if we have demonstrated a low detection efficiency to indirect event in the remote medium (due to the solid angle), its integration over increasing cylinder volumes leads to a non negligible contribution to sensitivity for large radii. Table III presents

the radius of an homogeneous radioactive cylinder associated with direct to indirect sensitivity ratios of 20, 10 and 5. As for direct sensitivity, higher energy positron sources produce better direct to indirect ratios. These results cannot be directly interpreted as estimates of the direct to indirect sensitivity ratio in biological experiments since the source distribution differs

Source	Structure name	Volume (mm ³)
¹⁸ F	V10%	1.49 ± 0.01
	V1%	17.34 ± 0.05
	V0.1%	54.62 ± 0.08
¹¹ C	V10%	2.25 ± 0.02
	V1%	37.52 ± 0.07
	V0.1%	109.05 ± 0.08
¹⁵ O	V10%	3.12 ± 0.03
	V1%	80.13 ± 0.08
	V0.1%	120.68 ± 0.03

TABLE II

VOLUMES BOUNDED BY THE 10 %, 1 % AND 0.1 % ISOEFFICIENCY SURFACES FOR DIRECT POSITRONS DETECTION FROM THREE RADIOACTIVE SOURCES (¹⁸F, ¹¹C AND ¹⁵O) IN WATER.

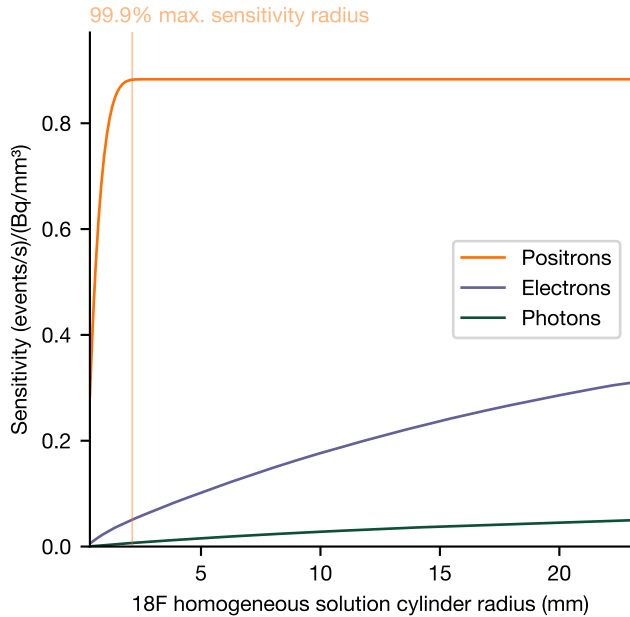


Fig. 6. Sensor sensitivity as a function of the cylindrical phantom radius. The phantom is filled with an homogeneous ¹⁸F solution. The vertical line illustrates the radius where sensitivity to positrons reaches 99.9% of its maximum, at 2.12 mm. Sensitivity is separated into three contribution: direct positron detection (the emitted positron reaches the sensitive area), indirect positron detection where a photon or an electron interact in the sensitive area.

from the homogeneous cylindrical case and does not model remote hot-spots resulting from the bladder or heart. However, we observe that an homogeneous cylinder of 7 mm radius and 30 mm height, which is roughly equivalent to a rat brain and nearby structures able to bind tracers like ¹¹C-raclopride or ¹⁸F-FDG, would lead to a 17.77 and 10.50 sensitivity ratio for ¹⁵O and ¹¹C sources, respectively, but only 5.71 for ¹⁸F. Thus, one should pay particular attention to the signal associated with the entire brain background radioactivity for ¹⁸F based tracers studies.

In order to compare the new sensor sensitivity to the previous PIXSIC one, we computed equivalent sensitivity (mean total sensitivity for a 500 μm height sec-

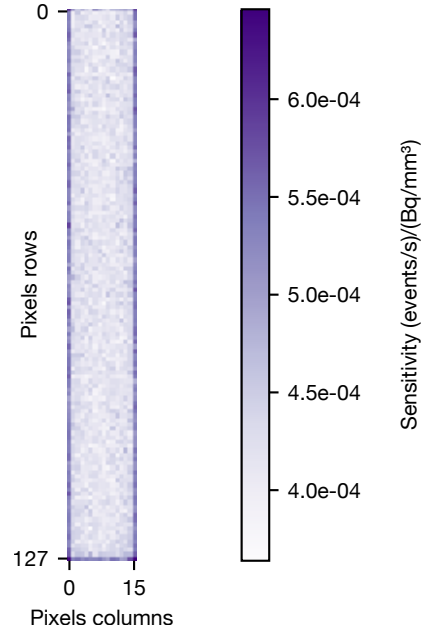


Fig. 7. Sensitivity map over the 16 × 128 pixels, each one featuring a 30 × 50 μm² area. The sensor was placed at the center of a homogeneous ¹⁸F cylindrical source.

tion of the sensor). Into the same large homogeneous water phantom of ¹⁸F, the PIXSIC equivalent sensitivity was computed by Monte Carlo simulations to $8.1 \times 10^{-2} \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$ and was experimentally measured to be equal to $(8.0 \pm 0.6) \times 10^{-2} \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$ for a 500 μm height section. For the new sensor we found a mean value of $(9.72 \pm 0.01) \times 10^{-2} \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$ for 500 μm height.

This comparison was done with different energy thresholds. PIXSIC simulation results were obtained using a 20 keV energy threshold [10] while our simulations did not accounted for any energy threshold. The PIXSIC diodes require an amplification circuit outside of the sensor, leading to high levels of noise, compensated in experimental studies by a high energy threshold. For MAPS pixels, we expect this energy threshold to be low: the ALPIDE pixels experimental studies used a threshold setting inferior to 1 keV [13].

Figure 7 presents the pixel sensitivity over an array of 16 × 128 pixels of 30 × 50 μm² each.

The mean sensitivity with one standard deviation in the central area (excluding the first outer edge pixels) is $(4.19 \pm 0.18) \times 10^{-4} \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$. The edge mean sensitivity value is $5.31 \times 10^{-4} \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$, with a standard deviation equals to $2.55 \times 10^{-5} \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$. We notice a higher sensitivity on the edge (mean sensitivity increased by 26.8%), because of geometrical and physical effects. The integral non-uniformity *IU* is equal to 7.53%. The edge to center difference and the center region integral non-uniformity may have to be taken into account for experimental quantification of radiotracer concentrations using uniformity corrections.

Source	^{18}F	^{11}C	^{15}O
S_{direct}^{max} (cps · Bq $^{-1}$ · mm 3)	$(8.83 \pm 0.01) \times 10^{-1}$	1.79 ± 0.01	4.34 ± 0.01
50% S_{direct}^{max} radius (mm)	0.50	0.77	1.6
99% S_{direct}^{max} radius (mm)	1.73	2.85	5.96
99.9% S_{direct}^{max} radius (mm)	2.12	3.53	7.36
$\frac{S_{direct}}{S_{indirect}} = 20$ radius (mm)	1.53	2.96	5.70
$\frac{S_{direct}}{S_{indirect}} = 10$ radius (mm)	3.55	7.48	20.3
$\frac{S_{direct}}{S_{indirect}} = 5$ radius (mm)	8.28	20.8	> 23

TABLE III

MAXIMUM DIRECT SENSITIVITY VALUES AND RADII ASSOCIATED WITH A GIVEN LEVEL OF DIRECT SENSITIVITY AND WITH VARIOUS RATIOS OF DIRECT TO INDIRECT SENSITIVITY VALUES, FOR THE ^{18}F , ^{11}C AND ^{15}O HOMOGENEOUS CYLINDRICAL SOURCES IN WATER.

Structure name	Direct sens. (cps · Bq $^{-1}$ · mm 3) contribution to the total	Indirect sens. (cps · Bq $^{-1}$ · mm 3) contribution to the total
R.o.B.	$(1.11 \pm 0.01) \times 10^{-1}$ 7.65%	$(2.27 \pm 0.05) \times 10^{-2}$ 26.05%
Cereb.	$< 1 \times 10^{-5}$	$(6.28 \pm 0.35) \times 10^{-4}$ 0.72%
L. CPu.	1.34 ± 0.01 92.35%	$(4.69 \pm 0.03) \times 10^{-2}$ 53.81%
R. CPu.	$(1.78 \pm 0.60) \times 10^{-5}$ 0.00%	$(3.73 \pm 0.09) \times 10^{-3}$ 4.28%
L. HG.	$< 1 \times 10^{-5}$	$(5.59 \pm 0.11) \times 10^{-3}$ 6.41%
R. HG.	$< 1 \times 10^{-5}$	$(7.61 \pm 0.12) \times 10^{-3}$ 8.73%

TABLE IV

SENSITIVITIES VALUES FROM RAT SIMPLIFIED BRAIN SHAPED ^{11}C SOURCES: LEFT AND RIGHT CAUDATE PUTAMEN (L. CPU. AND R. CPU.), LEFT AND RIGHT HARDERIAN GLANDS (L. HG. AND R. HG.), CEREBELLUM AND REST OF BRAIN. THE SENSOR IS IMPLANTED INTO THE LEFT CAUDATE PUTAMEN REGION. THE SENSITIVITY IS THE NUMBER OF DETECTED EVENTS RELATIVE TO THE ACTIVITY CONCENTRATION IN THE SIMPLIFIED LEFT CAUDATE PUTAMEN REGION.

C. Brain phantom

Sensitivities in the brain phantom, with ^{11}C sources, are summarized in table IV. As anticipated from the cylindrical phantom studies, the direct sensitivity is largely dominated by the activity in the implanted volume, L.CPu. ((1.34 ± 0.01) cps · Bq $^{-1}$ · mm 3 , 92.35 % of the total direct sensitivity), with a small contribution from the R.O.B. ($(1.11 \pm 0.01) \times 10^{-1}$ cps · Bq $^{-1}$ · mm 3 , 7.65 % of the total direct sensitivity) and a marginal contribution from other regions.

The small contribution from the R.O.B. is partly attributable to the 0.9 mm height section of the pixels matrix inside this region. The signal measured only from pixels inside the L.CPu. leads to a direct sensitivity from L.CPu. of (1.29 ± 0.01) cps · Bq $^{-1}$ · mm 3 but the direct sensitivity from the R.O.B. is reduced by a factor of 1.91 ($(5.81 \pm 0.03) \times 10^{-2}$ cps · Bq $^{-1}$ · mm 3).

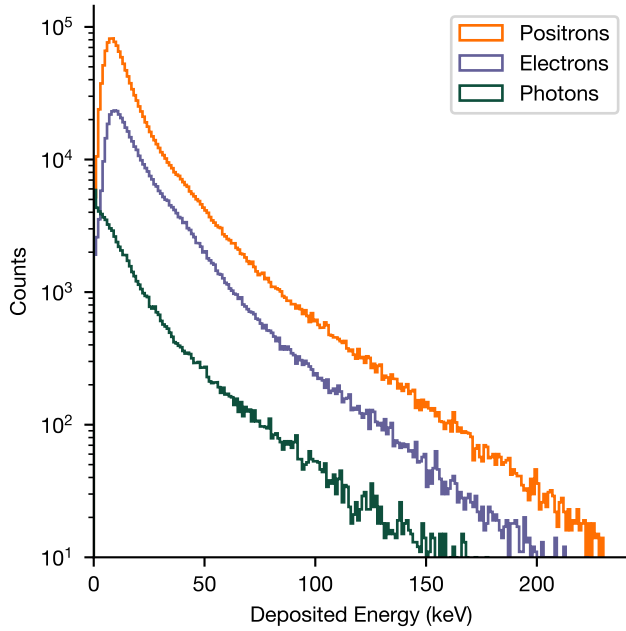
Indirect sensitivity remains low, in particular for remote regions. The direct to indirect sensitivity ratio from the whole phantom is 16.7, but 53.8 % of the indirect sensitivity comes from the implanted volume.

This result confirms our confidence into the ability of the measured signal to reflect the local radioactivity concentration and not to be overtaken by indirect detection of remote hot spots like harderian glands.

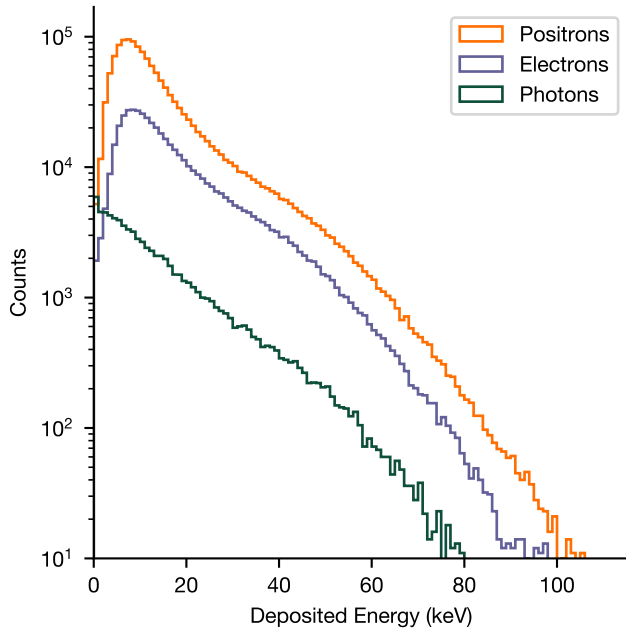
D. Deposited Energy

Figure 8a shows for each type of particle the deposited energy spectrum in the whole sensor, located at the center of the cylindrical ^{18}F source. When we split the sensitive volume into pixels ($30 \times 50 \mu\text{m}^2$ each) and we keep, for each event, the pixel with the highest deposited energy, the spectrum loses its high energy components (see figure 8b), because of the shorter distance limits and consequently shorter particles path in the pixel.

Positron and electron spectra shapes show similarities: peaks are at 6.9 keV and 7.9 keV, respectively. On the other hand, photons present relatively lower energy depositions. The contributions below 4 keV represent 24.3 % of the photons spectrum whereas they account for only 7.15 % of the positrons spectrum. Table V summarizes the deposited energy distribution of direct positrons.



(a) Deposited energy in the entire sensor



(b) Deposited energy spectrum in sensor pixels. In case of multiple pixels hit in the same event, the highest deposited energy in one pixel is kept.

Fig. 8. Deposited energy spectra in an homogeneous ^{18}F solution, for each type of incident particle.

Isotopes	^{18}F	^{11}C	^{15}O
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 %

TABLE V

PEAK, MEDIUM AND MEAN DEPOSITED ENERGY IN THE PIXELS FOR DIRECT DETECTION ONLY, INTO A WATER ^{18}F SOURCE.

As explained in section III-B, for the MAPS sensor model we expect an energy threshold smaller than a few keV to be enough to remove electronic noise. Hence, these spectra confirm that at least one pixel is able to detect the incident particle in most of the cases: in an ^{18}F water solution, with $30 \times 50 \mu\text{m}^2$ pixels, the median energy is estimated to 11.0 keV. If we consider an hypothetical energy threshold value between 1 and 10 keV, we may lose between 0.37% and 44.3% of the signal. This strong effect of the threshold on the sensor sensitivity highlights the need for a low noise sensor, and hence the use of an energy threshold as low as possible. For other isotopes, similar results were found and are presented in table V.

E. Effect of sensitive thickness

Increasing the sensor sensitive thickness leads to an increase of sensitivity for all particles as illustrated in figure 9. For ^{18}F , the direct sensitivity increases from $(8.83 \pm 0.01) \times 10^{-1} \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$ for a $18 \mu\text{m}$ sensitive thickness to $(1.54 \pm 0.01) \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$ for the largest sensitive thickness ($190 \mu\text{m}$). Meanwhile, the indirect sensitivity also increases from $(3.59 \pm 0.01) \times 10^{-1} \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$ to $(9.93 \pm 0.01) \times 10^{-1} \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$.

However, the lower increase of sensitivities to incident electrons and positrons relatively to photons leads to a decrease of the direct to indirect positron sensitivity ratio as the thickness of the probe increases: from (2.46 ± 0.01) at $18 \mu\text{m}$ to (1.55 ± 0.01) at $190 \mu\text{m}$. Consequently a trade-off between the direct sensitivity and direct to indirect sensitivity ratio has to be made. A thin sensitive layer optimizes the direct to indirect sensitivity ratio (by up to a factor of 1.59) while a larger sensitive layer optimizes direct sensitivity (by up to a factor of 1.74).

Hence, when an energy threshold was applied we observed changes in this behavior, the ratio of direct to indirect sensitivity decreases for very low energy thresholds only. As shown in figure 10, the maximum direct to indirect sensitivity ratio achieved for a $18 \mu\text{m}$ probe thickness cannot be reached if the energy threshold is equal or superior to 5 keV. The optimal thickness associated with the maximum direct to indirect sensitivity ratio for a given energy threshold is presented in figure 11.

As the energy threshold increases, the sensitive thickness giving the optimum direct to indirect ratio increases too. A larger sensitive thickness always provide a better direct

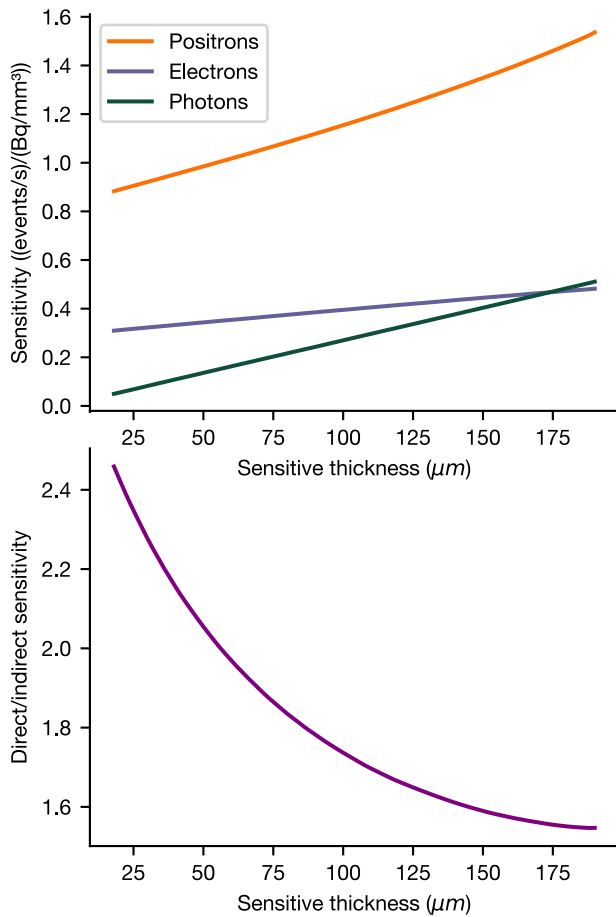


Fig. 9. Evolution of sensitivity and direct to indirect sensitivity ratio with sensitive thickness into a ^{18}F source. Sensitive thickness ranges between $18\mu\text{m}$, epitaxial layer thickness of our first prototype model and $190\mu\text{m}$, the full sensor thickness (excluding the $10\mu\text{m}$ electronic layer)

sensitivity, this demonstrates the interest of thick sensitive thickness in CMOS sensor if a high energy threshold is needed.

F. Pixels size

Without energy threshold, the sensitivities are independent of the pixels dimension. As a matter of fact, smaller pixels lead to smaller energy depositions since only the pixel with the highest deposited energy is recorded.

However, when the energy threshold increases, smaller pixels with smaller energy depositions are more affected and some particles passing through the sensitive volume are not detected.

Figure 12 presents the variations of the direct and indirect sensitivities as a function of energy threshold for three layouts of pixels arrays with the same total sensor area ($480 \times 6400\mu\text{m}^2$): 16×128 pixels of $30 \times 50\mu\text{m}^2$, as foreseen for our first prototype, 16×256 smaller pixels, of $30 \times 25\mu\text{m}^2$ and 2×16 larger pixels of $240 \times 400\mu\text{m}^2$, comparable to the PIXSIC pixels ($200 \times 500\mu\text{m}^2$).

With a 10keV energy threshold, the effect of the pixel size on the direct sensitivity remains low,

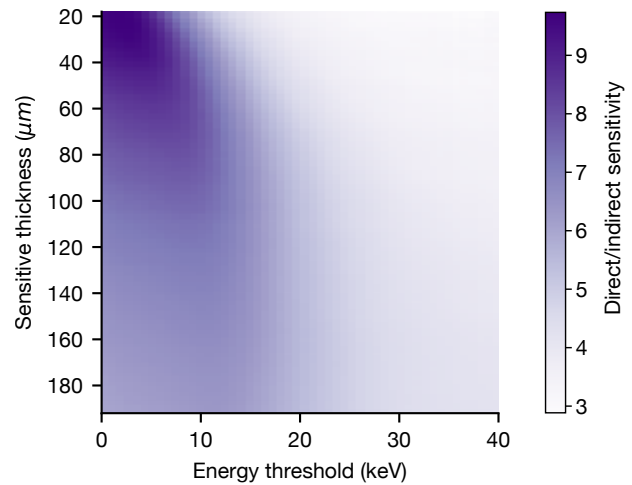


Fig. 10. Direct to indirect sensitivity ratio as a function of energy threshold and sensitive thickness for a ^{18}F source in water.

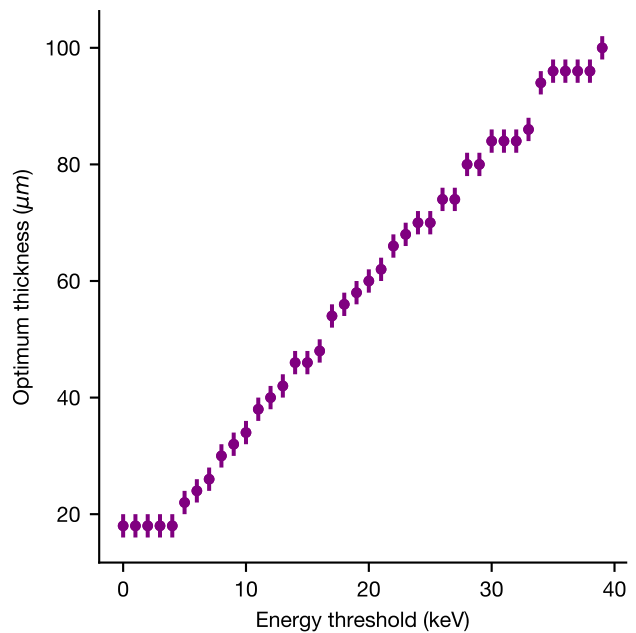


Fig. 11. Optimal thickness in terms of direct to indirect sensitivity ratio as a function of the energy threshold for an homogeneous ^{18}F source in water. The ratios were computed with a $2\mu\text{m}$ step size for the thickness.

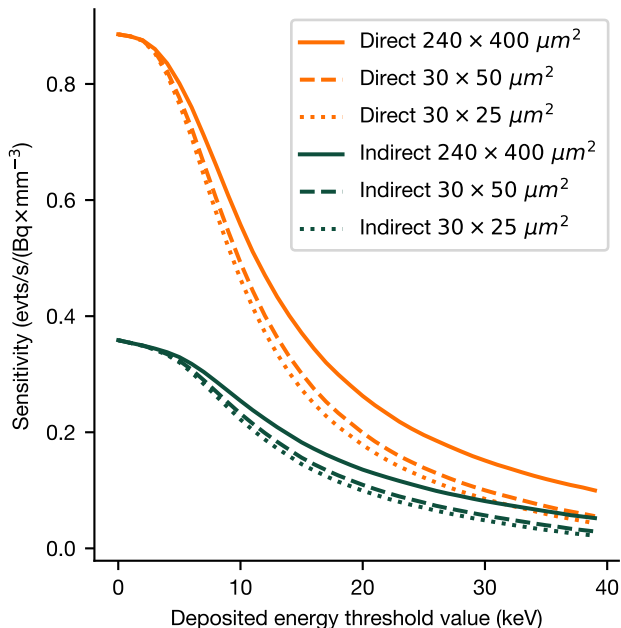


Fig. 12. Evolution of sensitivity of a ^{18}F source in water with deposited energy threshold for three different pixel sizes. Sensitive thickness is $18\mu\text{m}$, pixel sizes are $240 \times 400 \mu\text{m}^2$, $30 \times 50 \mu\text{m}^2$ and $30 \times 25 \mu\text{m}^2$, the total sensitive area remains constant ($480 \times 6400 \mu\text{m}^2$)

$(5.19 \pm 0.01) \times 10^{-1} \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$ for the smaller pixels versus $(6.08 \pm 0.01) \times 10^{-1} \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$ for the larger pixels, $(2.42 \pm 0.01) \times 10^{-1} \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$ and $(2.71 \pm 0.01) \times 10^{-1} \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$ for the indirect sensitivity of the smaller and larger pixels, respectively.

The ratio between direct and indirect sensitivity decreases with the energy threshold and is always slightly better for larger pixels. At a 10keV energy threshold, this ratio is 2.14 ± 0.01 for the smaller pixels and 2.24 ± 0.01 for the larger pixels.

IV. DISCUSSION

We aim to develop a probe suited for the detection of positrons in rodent brain tissues. The instrumental requirements for such a device are of diverse nature and every step is critical : sensitivity, quantification, image quality, biocompatibility, invasiveness and mechanical robustness. In this paper we have presented some expected detection performances in terms of isoefficiency volume, sensitivity and deposited energy. We also have explored how some design parameters impact performances.

This Monte Carlo study sets the MAPSSIC performances above the previous β^+ sensitive implants, notably it predicts a better sensitivity than the PIXSIC sensor. The 22.5% larger equivalent sensitivity is explained firstly by the amplification at the level of the pixel, which allows to set a minimal energy threshold, whereas the sensitivity of the PIXSIC sensor required a 20keV threshold. It also benefits from the larger sensitive region of the MAPSSIC probe ($480\mu\text{m}$ instead of $200\mu\text{m}$), thanks to a strong reduction of the non-sensitive area (guard rings) on the sensor edges (the full sensor width,

including guard rings, was $690\mu\text{m}$ for the PIXSIC sensor, instead of $610\mu\text{m}$ on this MAPSSIC model). Thanks to the thin $18\mu\text{m}$ thick sensitive area, we have also demonstrated a substantial improvement of the direct to indirect sensitivity ratio: 1.58 times larger compared to a similar sensor with a full sensitive thickness. Since the PIXSIC probe has been validated within a pharmacological context, we interpret this result as an evidence of the MAPSSIC sensor ability in terms of sensitivity. Compared to scintillating fibers probes [7], we will get an autonomous device, together with the benefits of a higher two-dimensional number of pixels and less signal from remote sources.

Besides their potential imaging capabilities, the current design of the pixels allows us to tackle issues related to brain radioactivity uptake heterogeneities with regard to the large field of view of the probe. As shown in the simplified brain phantom, when the sensor field of view extends over the volume of interest, the signal suffers from a contribution attributable to tracer concentration in nearby regions where the tracer also binds. However, as the probe position in the brain is known, the pixelated nature of the probes allows us to distinguish the events between their source region.

Since the pixel size does not influence detection performances with low energy thresholds, small pixels can be designed to allow for better spatial resolution. Although other effects related to the pixel sizes must also be investigated. For example, energy consumption and heat emission must be reduced as much as possible in order to increase the system autonomy and limit its invasiveness.

Unlike tomographs systems such as microPET or the wearable RatCAP, MAPSSIC and other intracerebral microprobes won't be able to provide full brain images. However they appear as a complementary tools to study brain local dynamic processes, in particular for behavior neuroimaging or when the anesthesia is a limit.

The simulated sensor shows radiotracers sensitivity comparable to microPET. For the ^{11}C -raclopride model the direct sensitivity from the L.CPu. was evaluated at $1.34 \text{ cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$ in a 67.375 mm^3 volume, thus a 1.99% mean direct efficiency in the L.CPu.. For comparison, the rodent microPET devices presented in [24] perform a peak detection efficiency between 2.06% (microPET R4) and 6.72% (Inveon) (with a 350-650 keV energy window). For the Inveon microPET, the maximum true count rate in a cylindrical rat-sized phantom (60 mm diameter, 96 mm long), was measured to 1020 kcps at an activity of 118 MBq (350-650 keV energy window), thus a mean efficiency of 0.86% in this phantom [25]. The RatCAP wearable tomograph performs a point source efficiency of 0.7% (with an energy threshold of 150 keV) and a peak true counts rate of about 30 kcps at $350 \text{ kBq} \cdot \text{cm}^{-3}$ in a 19 cm^3 phantom filling the field of view, thus a mean efficiency in the phantom of 0.45% [26]. These results confirm that MAPSSIC will benefit of the methodological tools of the microPET for dynamic studies: similar radiotracer doses and comparable time-activity curves.

This study will drive the next sensor design. The Monte Carlo results have already allowed us to refine our β^+ sensor model. The direct to indirect sensitivity, considered as a signal

to noise ratio, will be maximized by a thin sensitive layer. It has driven the first design to use the thinnest epitaxial layer. Nonetheless, the sensitivity also benefits from a deep epitaxial layer, consequently we expect fully depleted CMOS to provide us a substantial improvement.

Sensitivity is depicted as the strongest limit for the use of β^+ probes in biological experiments [27]. It defines how we handle the signal temporal and spatial dynamics and imposes a constraint on the probe surface, hence on its invasiveness. Consequently, we consider the probe sensitivity, *i.e.* its epitaxial thickness, as a parameter to maximize, even to the expense of a slightly lower direct to indirect sensitivity ratio.

Furthermore, the usual parallel between signal to noise ratio and direct to indirect sensitivity could be discussed since the solid angle effect restrains the indirect sensitivity from remote sources. As an example, the simplified brain phantom results showed that 53.8% of the indirect signal originates from the implanted region. Moreover, this ratio allows to better understand and optimize the measurements by taking into account the pixels location inside the brain. In the simplified brain model, the ratio of the signal originating from the L. CPU. to the signal originating from outside of it is 9.18, but if we occult the pixels inside the R.O.B region (where 14% of the sensitive region is implanted), it increases up to of 14.6.

The probe thickness and width, and therefore its invasiveness, is constrained by the sensitivity requirements but also by mechanical and technical constraints. To ensure the robustness of the sensor the thickness was thin down to 200 μm . The width of 610 μm was chosen close to PIXSIC dimensions. PIXSIC probe, with a $200 \times 690 \mu\text{m}^2$ section, produced consistent results compared to microPET in pharmacological studies without uptake modification attributable to tissue damages [28]. Consequently, we are confident that the implantation will not be a major limitation for the measurements.

Moreover, microdialysis cylindrical intracerebral probes with 340 μm outer diameter have shown to not significantly influence ^{11}C -raclopride experiments [29], although inducing a widespread and prolonged decrease in glucose metabolism [30, 31]. More important, Schiffer and colleagues in [31] highlight that the major issue to interpret the effects of probes implantation is the number of experimental variables that limits the relevance of comparison between experiments. As an example, in contrast to Schiffer *et al.* works, Glorie *et al.* in [27] demonstrated the disruptive effect of their 750 μm outer diameter probes on striatal receptors binding and tracer delivery to the implanted region, but it is difficult to distinguish the impact of the larger diameter from other experimental conditions. In one case the measures were done immediately after the 750 μm probe implantation while in the second case the cannulae implantation was performed two days before imaging. As a matter of fact, Benveniste *et al.* have shown that the time between surgery and measurement can influence microdialysis results and suggest a 24 hours recovery time [30].

β^- sources have been widely used for the study of charged particle sensors using CMOS technology, in particular 2.2 MeV β^- from ^{90}Sr sources. Nonetheless, specific applications of β^+ or β^- detectors remain limited. As of today we have identified only two other CMOS applications of β^+ and β^-

sensing [32, 33]. We interpret our results as a confirmation of the relevance of MAPS technology for direct β^+ sensing. As a consequence the first sensor prototype has been manufactured based on this Monte Carlo study and design.

With this first MAPS-based prototype, Monte Carlo simulations will be compared against experimental results in order to evaluate the accuracy of the Monte Carlo model. It will allow studying the effect of several parameters which were not included in our model as charges drift in silicon, exact energy threshold or signal post-processing. Experimental measurements will also assess the sensor counting linearity over activity concentration variations, dark counts rate and sensitivity to visible light.

Beyond electronic and physical testing of the sensor, the future probe developments will focus of the integration of the sensor into a robust and autonomous system. The probe also shall be adapted to be used with stereotaxic surgical tools and we plan to ensure biocompatibility by covering the sensor with a layer parylene C polymer as previously done for PIXSIC [9]. The first *in vivo* testings will aim to validate the surgical implantation procedure, the biocompatibility and the detection performances on anesthetized animals. Once validated, experiments on awake then on freely moving animals will be performed.

The *in vivo* measurements and quantification procedure should follow the well validated one developed for PIXSIC described in [11, 28]. In particular two probes are usually inserted, one in the region of interest and one in a reference tissue (for example the cerebellum for ^{18}F -MPPF or ^{11}C -raclopride studies). In these studies, the specific binding is defined as the difference between the activity in the region of interest and the activity in a reference tissue, accounting for nonspecific binding and free radiotracer activity.

As discussed in [8], the quantification for surface or distant beta sensors is limited by the difficulty to correctly evaluate the distance to the source as well as the attenuation in the non-radioactive medium between them. For intracerebral probes, if we neglect source heterogeneities in the volume of high efficiency, we benefit from Monte-Carlo and experimental sensitivity values obtained with a simpler source geometry. These sensitivity values are easier to use for quantification without correction. Furthermore, the experimental validation of this Monte Carlo model will allow us to use it for more precise predictions within a realistic brain phantom and source distribution. This will allow us to investigate the effects of sources heterogeneities on activity concentration quantification and our ability to extract spatial information.

ACKNOWLEDGMENT

This work was partly founded in 2015 and 2017 by the project *Instrumentation aux limites* from CNRS.

This work was partly funded by France Life Imaging, FLI/ANR-11-INBS- 0006, of the French Investissements d'Avenir program run by the Agence Nationale pour la Recherche.

This work was partly founded by the IN2P3.

REFERENCES

- [1] Simon R Cherry. Functional whole-brain imaging in behaving rodents. *nature methods*, 8(4):301–303, 2011.
- [2] Cameron S Carter and Jeffrey W Dalley. *Brain Imaging in Behavioral Neuroscience*, volume 11. Springer Science & Business Media, 2011.
- [3] Aage Kristian Olsen Alstrup and Donald F Smith. Anaesthesia for positron emission tomography scanning of animal brains. *Laboratory animals*, 47(1):12–18, 2013.
- [4] Vinal D Patel, Dianne E Lee, David L Alexoff, Stephen L Dewey, and Wynne K Schiffer. Imaging dopamine release with positron emission tomography (pet) and 11c-raclopride in freely moving animals. *Neuroimage*, 41(3):1051–1066, 2008.
- [5] Andre Z Kyme, VW Zhou, Steven R Meikle, and Roger R Fulton. Real-time 3d motion tracking for small animal brain pet. *Physics in medicine and biology*, 53(10):2651, 2008.
- [6] Daniela Schulz, Sudeepti Southekal, Sachin S Junnarkar, Jean-François Pratte, Martin L Purschke, Sean P Stoll, Bosky Ravindranath, Sri Harsha Maramraju, Srilalan Krishnamoorthy, Fritz A Henn, et al. Simultaneous assessment of rodent behavior and neurochemistry using a miniature positron emission tomograph. *Nature methods*, 8(4):347–352, 2011.
- [7] Luc Zimmer, Waddad Hassoun, Frederic Pain, Frederic Bonnefoi, Philippe Lanièce, Roland Mastroianni, Laurent Pinot, Jean-François Pujol, and Vincent Leviel. Sic, an intracerebral $\beta+$ -range-sensitive probe for radiopharmacology investigations in small laboratory animals: Binding studies with 11c-raclopride. *Journal of Nuclear Medicine*, 43(2):227–233, 2002.
- [8] Matthias T Wyss, Nicolas M Obrist, Florent Haiss, Rolf Eckert, Ross Stanley, Cyrill Burger, Alfred Buck, and Bruno Weber. A beta-scintillator for surface measurements of radiotracer kinetics in the intact rodent cortex. *NeuroImage*, 48(2):339–347, 2009.
- [9] J Godart, P Weiss, B Chantepie, JC Clemens, P Delpierre, B Dinkespiler, B Janvier, M Jevaud, S Karkar, F Lefebvre, et al. Pixsic: a pixelated beta-microprobe for kinetic measurements of radiotracers on awake and freely moving small animals. *IEEE Transactions on Nuclear Science*, 57(3):998–1007, 2010.
- [10] Julia Maerk, Didier Benoit, Laure Balasse, Mathieu Benoit, Jean-Claude Clémens, Sylvain Fieux, Denis Fougeron, J Graber-Bolis, Batiste Janvier, Michel Jevaud, et al. A wireless beta-microprobe based on pixelated silicon for in vivo brain studies in freely moving rats. *Physics in medicine and biology*, 58(13):4483, 2013.
- [11] Laure Balasse, Julia Maerk, Frédéric Pain, Aurélie Genoux, Sylvain Fieux, Françoise Lefebvre, Christian Morel, Pascale Gisquet-Verrier, Philippe Lanièce, and Luc Zimmer. Pixsic: a wireless intracerebral radiosensitive probe in freely moving rats. *Molecular imaging*, 14(9):7290–2015, 2015.
- [12] Toko Hirono et al. Cmos pixel sensors on high resistive substrate for high-rate, high-radiation environments. *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment*, 831:94–98, 2016.
- [13] Gianluca Aglieri on behalf of the ALICE Collaboration Rinella. The alpine pixel sensor chip for the upgrade of the alice inner tracking system. *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment*, 845:583–587, 2017.
- [14] Adele Lauria, Giovanni Mettivier, MC Montesi, L Aloj, S Lastoria, M Aurilio, and P Russo. Experimental study for an intraoperative probe for 18 f imaging with a silicon pixel detector. *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment*, 576(1):198–203, 2007.
- [15] Serhiy Senyukov, Jerome Baudot, Auguste Besson, Gilles Claus, Loic Cousin, Andrei Dorokhov, Wojciech Dulinski, Mathieu Goffe, Christine Hu-Guo, and Marc Winter. Charged particle detection performances of cmos pixel sensors produced in a process with a high resistivity epitaxial layer. *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment*, 730:115–118, 2013.
- [16] Sébastien Jan, G Santin, D Strul, Steven Staelens, K Assie, D Autret, S Avner, R Barbier, M Bardies, PM Bloomfield, et al. Gate: a simulation toolkit for pet and spect. *Physics in medicine and biology*, 49(19):4543, 2004.
- [17] S Jan, D Benoit, E Becheva, T Carlier, F Cassol, P Descourt, T Frisson, L Grevillot, L Guigues, L Maigne, et al. Gate v6: a major enhancement of the gate simulation platform enabling modelling of ct and radiotherapy. *Physics in medicine and biology*, 56(4):881, 2011.
- [18] George Paxinos, Charles RR Watson, and Piers C Emson. Ache-stained horizontal sections of the rat brain in stereotaxic coordinates. *Journal of neuroscience methods*, 3(2):129–149, 1980.
- [19] Marie-Paule Garcia, Arnaud Charil, Paul Callaghan, Catriona Wimberley, Florian Busso, Marie-Claude Grégoire, Manuel Bardies, and Anthonin Reilhac. Ossi-pet: Open-access database of simulated 11c-raclopride scans for the in vivo preclinical pet scanner: Application to the optimization of reconstruction methods for dynamic studies. *IEEE transactions on medical imaging*, 35(7):1696–1706, 2016.
- [20] National Electrical Manufacturers Association. Performance measurements of gamma cameras (nema nu 1-2012), 2012.
- [21] Yifeng Luo, Zhihong Cao, Dongqing Wang, Liwei Wu, Yuefeng Li, Weibin Sun, and Yan Zhu. Dynamic study of the hippocampal volume by structural mri in a rat model of depression. *Neurological Sciences*, 35(11):1777–1783, 2014.
- [22] Jordan E Wong, Jinyan Cao, David M Dorris, and John Meitzen. Genetic sex and the volumes of the caudate-putamen, nucleus accumbens core and shell: original data and a review. *Brain Structure and Function*, 221(8):4257–4267, 2016.
- [23] Jacobo Cal-González, JL Herraiz, Samuel España, Manuel Desco, Juan José Vaquero, and José Manuel Urdías. Positron range effects in high resolution 3d pet imaging. In *Nuclear Science Symposium Conference Record (NSS/MIC)*, 2009 IEEE, pages 2788–2791. IEEE, 2009.
- [24] Andrew L Goertzen, Qinan Bao, Mélanie Bergeron, Eric Blankemeyer, Stephan Blinder, Mario Canadas, Arion F Chatziioannou, Katherine Dinelle, Esmat Elhami, Hans-Sonke Jans, et al. Nema nu 4-2008 comparison of preclinical pet imaging systems. *Journal of Nuclear Medicine*, 53(8):1300–1309, 2012.
- [25] Brad J Kemp, Carrie B Hruska, Aaron R McFarland, Mark W Lenox, and Val J Lowe. Nema nu 2-2007 performance measurements of the siemens inveon™ preclinical small animal pet system. *Physics in medicine and biology*, 54(8):2359, 2009.
- [26] P Vaska, CL Woody, DJ Schlyer, V Radeka, P O’Connor, J-F Pratte, S Shokouhi, SP Stoll, SS Junnarkar, M Purschke, et al. Initial performance of the ratcap, a pet camera for conscious rat brain imaging. In *Nuclear Science Symposium Conference Record*, 2005 IEEE, volume 5, pages 3040–3044. IEEE, 2005.
- [27] Dorien Glorie, Stijn Servaes, Jeroen Verhaeghe, Tine Wyckhuys, Leonie Wyffels, Olivier Vanderveken, Sigrid Stroobants, and Steven Staelens. Micropet outperforms beta-microprobes in determining neuroreceptor availability under pharmacological restriction for cold mass occupancy. *Frontiers in neuroscience*, 11, 2017.
- [28] Laure Balasse, Julia Maerk, Frédéric Pain, Aurélie Genoux, Sylvain Fieux, Christian Morel, Pascale Gisquet-Verrier, Luc Zimmer, and Philippe Lanièce. Pixsic, a pixelated $\beta+$ -sensitive probe for radiopharmacological investigations in rat brain: Binding studies with [18 f] mppf. *Molecular Imaging and Biology*, 17(2):163–167, 2015.
- [29] Wynne K Schiffer, David L Alexoff, Colleen Shea, Jean Logan, and Stephen L Dewey. Development of a simultaneous pet/microdialysis method to identify the optimal dose of 11c-raclopride for small animal imaging. *Journal of neuroscience methods*, 144(1):25–34, 2005.
- [30] H Benveniste, J Drejer, A Schousboe, and NH Diemer. Regional cerebral glucose phosphorylation and blood flow after insertion of a microdialysis fiber through the dorsal hippocampus in the rat. *Journal of neurochemistry*, 49(3):729–734, 1987.
- [31] Wynne K Schiffer, Martine M Mirrione, Anat Biegon, David L Alexoff, Vinal Patel, and Stephen L Dewey. Serial micropet measures of the metabolic reaction to a microdialysis probe implant. *Journal of neuroscience methods*, 155(2):272–284, 2006.
- [32] Wojciech Dulinski, Jerome Baudot, Cayetano Santos, Marc Winter, Neal Clinthorne, Morand Piert, and Harris Kagan. Beta detection and imaging probe based on optimized cmos monolithic active pixel sensors for open surgical and endoscopic cancer resection applications. *IEEE Nuclear Science Symposium conference record. Nuclear Science Symposium*, 2010.
- [33] Jorge Cabello, Alexis Bailey, Ian Kitchen, Mark Prydderch, Andy Clark, Renato Turchetta, and Kevin Wells. Digital autoradiography using room temperature ccd and cmos imaging technology. *Physics in Medicine and Biology*, 52(16):4993, 2007.