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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


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 (18F) leading to a sensitivity of 0.88 cps · Bq⁻¹ · mm² and a mean energy deposition by positrons of 15.1 keV. Simulation in simplified brain-shaped sources modeling a 11C-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, explained in [2], behavior neuroimaging shows applications for the study of addiction in animal models, using 18F-FDG for associating brain metabolism to a particular behavior or 11C-raclopride to study the dynamic changes in the dopaminergic system in real-time.

Achieving such a combination is not straightforward 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 don'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 biocompati-
ible. Their sensor has to be highly sensitive to $\beta^+$ particles and has to present a good transparency to annihilation $\gamma$-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 $\gamma$-rays led on to substantial noise. Moreover, the thickness of the probe, reduced to $200\,\mu m$ to limit annihilation $\gamma$-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 $\beta^+$ 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 $\gamma$-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 charge 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 $500\,\mu m$ 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 $18\,\mu m$ to $40\,\mu m$ 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 $610\,\mu m$ width and a thickness of $200\,\mu m$. The sensor architecture is based on the ALPIDE chip developed for the ALICE experiment at the CERN Large Hadron Collider [13]. The first $10\,\mu m$ in depth receive the CMOS process, then comes the epitaxial layer over a $18\,\mu m$ thickness. The pixel matrix features 16 columns and 128 rows. The pixel dimensions are $50\,\mu m$ along the probe length (longest dimension) and $30\,\mu m$ 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
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 $\gamma$-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 $\gamma$-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).

$$e = \frac{N}{A}$$ (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.

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

$$S = \frac{1}{C_{ref}} \sum_i e_i \times C_i \times v_i$$ (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 $\mu$m, 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 $\mu$m$^2$ pixels. MAPS sensor would allow smaller pixels (20 $\times$ 20 $\mu$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 $\mu$m$^3$ parallelepiped of silicon, simulating the sensor, encapsulating an inner silicon 480 $\times$ 190 $\times$ 6400 $\mu$m$^3$ parallelepiped, simulating the sensitive volume of the sensor (see figure 2). 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 $\mu$m 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 $\beta^+$ 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 $\mu$m 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
simulated a 190 µm thick sensitive area we filtered all recorded interactions occurring below a thickness of 18 µm, 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 equal 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].

In order to model 11C-raclopride experiments, the phantom was based on the simulated 11C source. The activity values were based on the reference time activity curve published in the OSSI-PET 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 µm 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
the sensitivity from equivalent heights
geometry was different from the simulated one, we compared
with the previous PIXSIC probe. As the previous sensor
obtained sensitivity values as a function of the source radius.
of homogeneous cylindrical sources with different radii, we
By adapting the spatial distribution of the source into a set
evaluated for the homogeneous radioactive cylindrical sources.
tom sources.

\[ S_{\text{eq}} = \frac{S_{\text{max}} - S_{\text{min}}}{S_{\text{max}} + S_{\text{min}}} \]  

(4)

Where \( S_{\text{min}} \) is the minimum pixel sensitivity value and
\( S_{\text{max}} \) 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 \(^{18}\text{F}\) 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 \(^{18}\text{F}\), 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\(\mu\)m and located
between two very asymmetrical layers of silicon, of 10\(\mu\)m on
one side and 152\(\mu\)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 \(^{18}\text{F}\) water phantom) is as small as
17.34 mm\(^3\). Other isoefficiency volumes are presented in table
\[III\] 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 \(^{18}\text{F}\) according to \[23\]), the sensitiv-
ity 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 \(^{18}\text{F}\), this direct sensitivity limit was computed at
\((8.83 \pm 0.01) \times 10^{11} \text{cps}\cdot\text{Bq}^{-1}\cdot\text{mm}^3\). The maximum is ob-
tained 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 \(^{11}\text{C}\) and \(^{15}\text{O}\) sources than for \(^{18}\text{F}\)
sources. This difference arises from the positrons larger range
in water for these isotopes.

---

<table>
<thead>
<tr>
<th>Structure</th>
<th>Relative activity concentration</th>
<th>Dimensions (X, Y, Z) (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.O.B.</td>
<td>0.16</td>
<td>(20, 14, 10)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.11</td>
<td>(7, 10, 7)</td>
</tr>
<tr>
<td>L. CPu.</td>
<td>0.64</td>
<td>(3.5, 3.5, 5.5)</td>
</tr>
<tr>
<td>R. CPu.</td>
<td>0.64</td>
<td>(3.5, 3.5, 5.5)</td>
</tr>
<tr>
<td>L. HG.</td>
<td>1.0</td>
<td>(5, 10, 7)</td>
</tr>
<tr>
<td>R. HG.</td>
<td>1.0</td>
<td>(5, 10, 7)</td>
</tr>
</tbody>
</table>

### 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
produced \(\beta\)\(^+\) (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, \(1.60 \times 10^6\) Bq \(\cdot\) mm\(^{-3}\) for the cylindrical \(^{18}\text{F}\) source,
\(0.80 \times 10^6\) Bq \(\cdot\) mm\(^{-3}\) for the cylindrical \(^{15}\text{O}\) source and
\(1.59 \times 10^6\) Bq \(\cdot\) mm\(^{-3}\) for the \(^{11}\text{C}\) cylindrical and brain
phantom sources.

Direct and indirect sensitivities and their ratios were first
examined 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 \(h_{\text{eq}}\). The equivalent
sensitivity \(S_{\text{eq}}\) was computed as the mean sensitivity in a
section of height \(h_{\text{eq}}\), 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 \(h_{\text{eq}} = 500\mu\text{m}\),
as presented in \[10\].

We have also compared the sensitivity of each MAPSSIC
sensor pixel for an array of \(128 \times 16\) 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 :
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.
<table>
<thead>
<tr>
<th>Source</th>
<th>Structure name</th>
<th>Volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹⁸F</td>
<td>V10%</td>
<td>1.49 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>V1%</td>
<td>17.34 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>V0.1%</td>
<td>54.62 ± 0.08</td>
</tr>
<tr>
<td>¹¹C</td>
<td>V10%</td>
<td>2.25 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>V1%</td>
<td>37.52 ± 0.07</td>
</tr>
<tr>
<td></td>
<td>V0.1%</td>
<td>109.05 ± 0.08</td>
</tr>
<tr>
<td>¹⁵O</td>
<td>V10%</td>
<td>3.12 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>V1%</td>
<td>80.13 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>V0.1%</td>
<td>120.68 ± 0.03</td>
</tr>
</tbody>
</table>

**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 contributions: 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 section 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].

Fig. 7 presents the pixel sensitivity over an array of 16 × 128 pixels of a 30 × 50 µm² area. The sensor was placed at the center of a homogeneous ¹⁸F cylindrical source.

![Sensitivity map over the 16 × 128 pixels](image)
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. ($(1.34 \pm 0.01) \text{cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$, 92.35% of the total direct sensitivity), with a small contribution from the R.O.B. ($(1.11 \pm 0.01) \times 10^{-1} \text{cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$, 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 $(1.29 \pm 0.01) \text{cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$ but the direct sensitivity from the R.O.B. is reduced by a factor of 1.91 ($(5.81 \pm 0.03) \times 10^{-2} \text{cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3$).

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 2 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 IV summarizes the deposited energy distribution of direct positrons.
Fig. 8. Deposited energy spectra in an homogeneous \(^{18}\)F solution, for each type of incident particle.

### Table V

<table>
<thead>
<tr>
<th>Isotopes</th>
<th>(^{18})F</th>
<th>(^{11})C</th>
<th>(^{15})O</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E_{\text{peak}} , (\text{keV}))</td>
<td>6.9</td>
<td>7.2</td>
<td>6.1</td>
</tr>
<tr>
<td>(E_{\text{median}} , (\text{keV}))</td>
<td>11.0</td>
<td>9.51</td>
<td>8.72</td>
</tr>
<tr>
<td>(E_{\text{mean}} , (\text{keV}))</td>
<td>15.1</td>
<td>12.9</td>
<td>11.4</td>
</tr>
<tr>
<td>fraction &lt; 1 keV</td>
<td>0.37 %</td>
<td>0.44 %</td>
<td>0.59 %</td>
</tr>
<tr>
<td>fraction &lt; 10 keV</td>
<td>44.3 %</td>
<td>52.9 %</td>
<td>59.0 %</td>
</tr>
</tbody>
</table>

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 30×50 µm\(^2\) 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 µm sensitive thickness to \((1.54 \pm 0.01) \times 10^{-1} \, \text{cps} \cdot \text{Bq}^{-1} \cdot \text{mm}^3\) for the largest sensitive thickness (190 µm). 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 \((2.46 \pm 0.01)\) at 18 µm to \((1.55 \pm 0.01)\) at 190 µm. 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 µm 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
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 ($480 \times 6400 \, \mu m^2$): $16 \times 128$ pixels of $30 \times 50 \, \mu m^2$, as foreseen for our first prototype, $16 \times 256$ smaller pixels, of $30 \times 25 \, \mu m^2$ and $2 \times 16$ larger pixels of $240 \times 400 \, \mu m^2$, comparable to the size of the PIXSIC pixels ($200 \times 500 \, \mu m^2$).

With a $10 \, keV$ energy threshold, the effect of the pixel size on the direct sensitivity remains low,
The ratio between direct and indirect sensitivity decreases with the energy threshold and is always slightly better for larger pixels. At a 10 keV energy threshold, this ratio is $2.14 \pm 0.01$ for the smaller pixels and $2.24 \pm 0.01$ 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 $\beta^+$ 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 20 keV threshold. It also benefits from the larger sensitive region of the MAPSSIC probe (480 µm instead of 200 µm), 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 µm for the PIXSIC sensor, instead of 610 µm on this MAPSSIC model). Thanks to the thin 18 µm 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 [4], 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 $1.34 \times 10^{-1}$cps $\cdot$ Bq$^{-1} \cdot$ 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 kBq $\cdot$ 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 $\beta^+$ 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 $\beta^+$ 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 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 $200 \times 690$ µm$^2$ 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]. 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].

$\beta^-$ sources have been widely used for the study of charged particle sensors using CMOS technology, in particular 2.2 MeV $\beta^-$ from $^{89}$Sr sources. Nonetheless, specific applications of $\beta^+$ or $\beta^-$ detectors remain limited. As of today we have identified only two other CMOS applications of $\beta^+$ and $\beta^-$ sensing [32, 33]. We interpret our results as a confirmation of the relevance of MAPS technology for direct $\beta^+$ 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 on 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 tests 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.

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REFERENCES


