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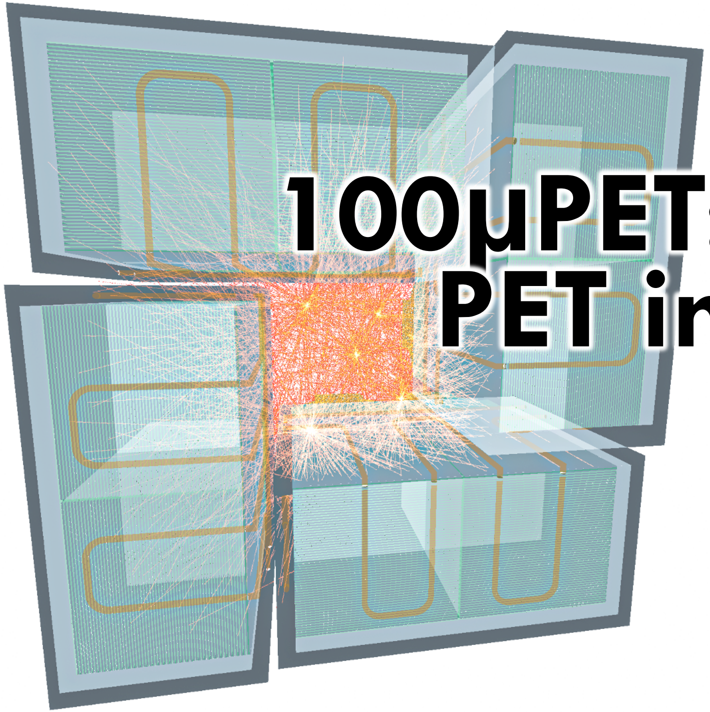


100μPET: Ultra-high-resolution PET imaging with MAPS

18th Trento workshop
28 Feb - 2 Mar 2023

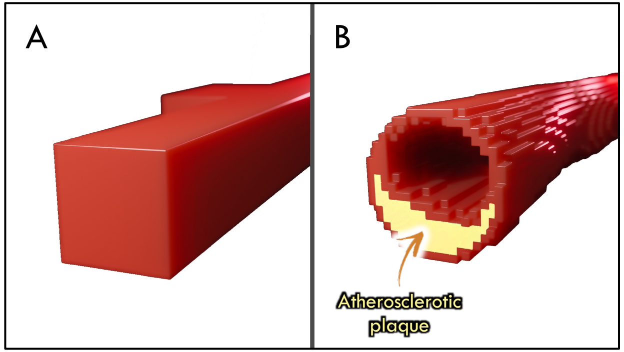
Mateus Vicente
on behalf of the 100μPET collaborators

Introduction

mvicente@cern.ch

- The **100μPET** project: molecular imaging with ultra-high resolution
  - **SNSF SINERGIA** grant among **UNIGE** (scanner production) **EPFL** (imaging) and **UNILU** (medical application studying atherosclerosis in ApoE$^{+/-}$ mice)
    - Deliverable: Small-animal PET scanner with monolithic silicon pixel detectors

- Talk outline
  - Introduction to PET and spatial resolution overview
  - How ultra-high resolution is aimed
  - The 100μPET scanner
    - Flip-chip prototyping and reliability tests
    - Monte-Carlo performance simulations
    - Imaging capabilities
  - Summary and Conclusions



Images: © Xavier Ravinet - UNIGE

With today's PET technology, small blood vessels can only be visualized in their entirety (A). The proposed new PET technology will allow the study of changes in the walls of small blood vessels, such as atherosclerotic plaques (B).

The team and other collaborators

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100µPET
MOLECULAR IMAGING AT ULTRA-HIGH RESOLUTION

The 100µPET project

Giuseppe Iacobucci
- project P.I.
- System design

Lorenzo Paolozzi
- Sensor design
- Analog electronics

Didier Ferrere
- System integration
- Laboratory test

Sergio Gonzalez-Sevilla
- System integration
- Laboratory test

Martin Walter
- P. I.

Michäel Unser
- P. I.

Yannick Favre
- Board design
- RO system

Stéphane Débieux
- Board design
- RO system

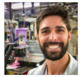
Franck Cadoux
- Mechanical design

Thanushan Kugathasan
- Lead chip design
- Digital electronics

Pablo Jané
- Nuclear Medicine
- PET imaging
- Translational imaging

Pol del Aguila Pla
- Statistical signal processing

Roberto Cardella
- Sensor design
- Laboratory test



Mateus Vicente
- System integration
- Laboratory test

Jihad Saidi
- Detector simulation
- Data analysis

Luca Iodice
- Chip design
- Firmware

Vincent Taelman
- Molecular biology
- Radiopharmacy

Aleix Boquet-Pujadas
- Signal/image processing
- Physical modeling

Antonio Picardi
- Chip design
- Firmware

Stefano Zambito
- Laboratory test
- Data analysis

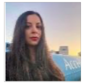
Matteo Milanesio
- Laboratory test
- Data analysis

Théo Moretti
- Laboratory test
- Data analysis

Carlo A. Fenoglio
- Chip design
- Firmware

Chiara Magliocca
- Laboratory test
- Data analysis

Jordi Sabater
- Detector simulation
- Laboratory test



Rafaella Kotitsa
- Sensor simulation

Andrea Pizarro
- Laboratory test
- Data analysis

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UNIVERSITY OF LUCERNE

EPFL

Main research partners:

Roberto Cardarelli
INFN Rome2 & UNIGE

Holger Rücker
IHP Mikroelektronik

Marzio Nessi
CERN & UNIGE

Matteo Elviretti
IHP Mikroelektronik

Funded by:

Swiss National Science Foundation

erc European Research Council
Established by the European Commission

Sinergia

ATTRACT

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Positron Emission Tomography (PET)

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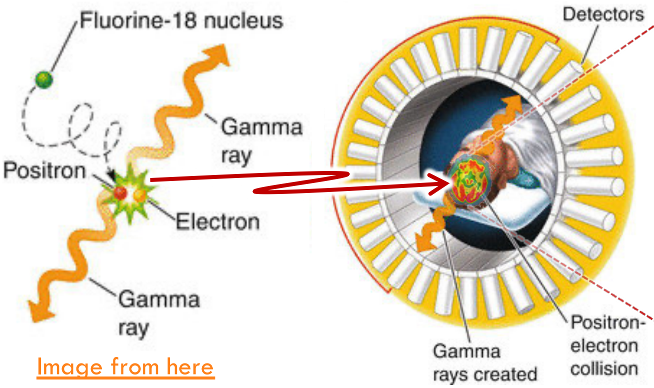
- PET is a nuclear medicine method to study metabolic processes in the body
  - Radiotracer is injected in a body; Positrons from the radionuclide annihilates with electrons of the nearby tissue Two **back-to-back** 511 KeV photons are emitted and detected in **coincidence**
    - **Lines-of-Response (LoR)** are defined by the volume between the **sensitive elements** detecting the two photons
  - Lines-of-response are processed to generate density maps of the detected annihilations



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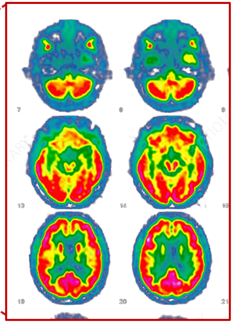

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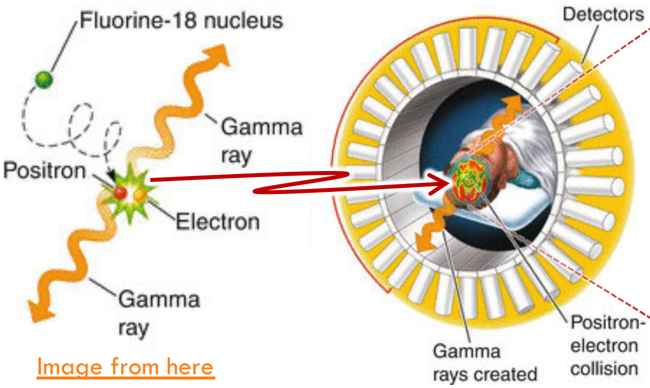
    - Today, due to the lack of spatial resolution, PET imaging must be done in hybrid mode (combining MRI or CT measurements)



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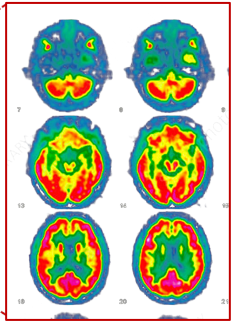

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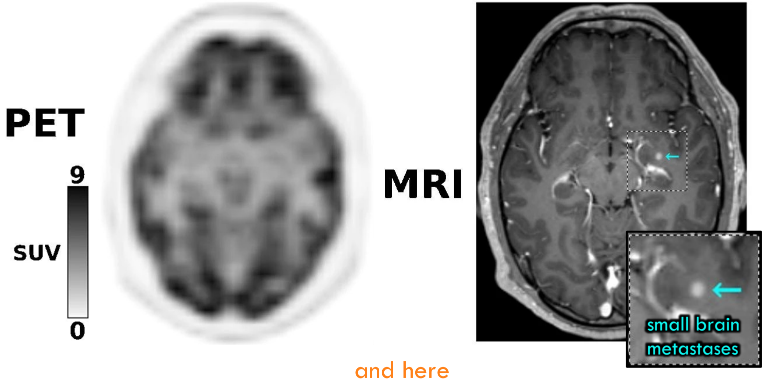

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Positron Emission Tomography (PET)

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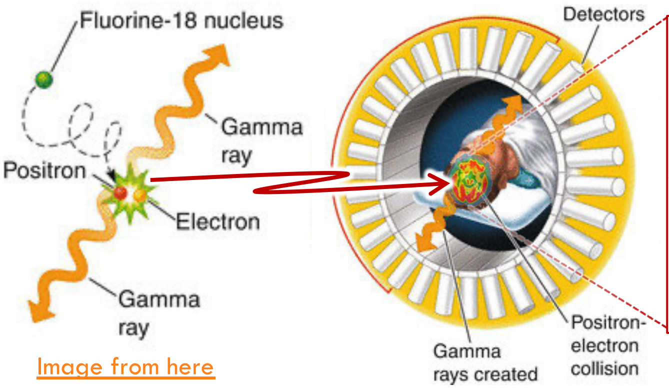
  - Lines-of-response are processed to generate density maps of the detected annihilations
    - Today, due to the lack of spatial resolution, PET imaging must be done in hybrid mode (combining MRI or CT measurements)
      - Typical resolution is in the arrange of **1-2 mm³**



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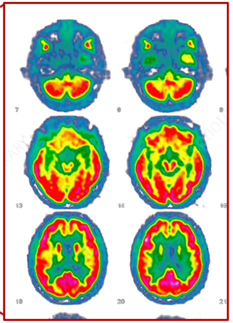

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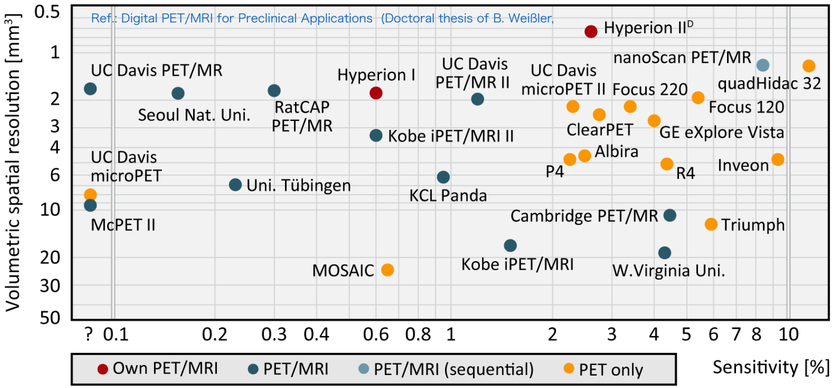
Overview of current small animal PET scanners



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PET imaging using MAPS

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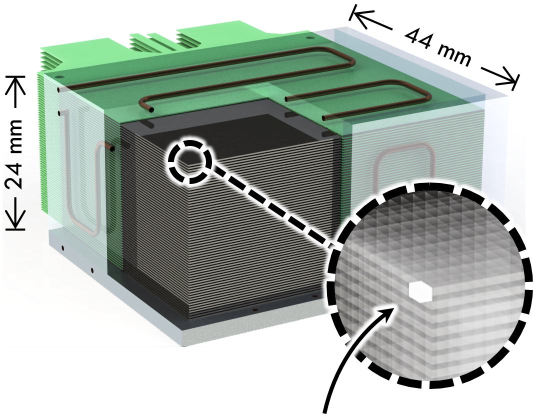
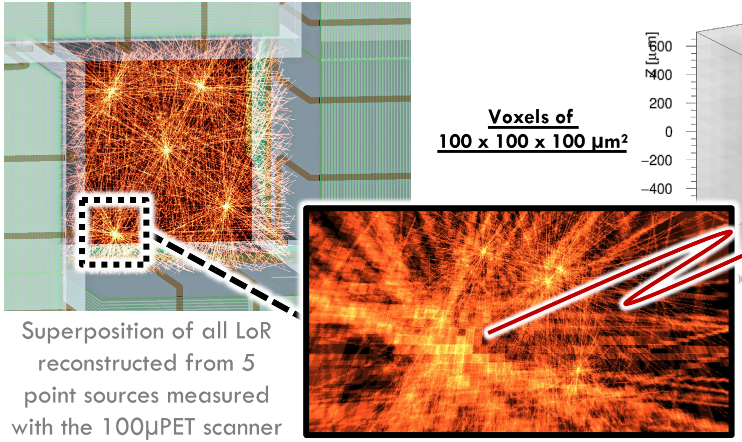
- Ultra-high resolution can be achieved increasing the detection volume granularity,
  - **Multi-layers of monolithic pixel detectors**, reducing the volume-of-response by **80'000** (w.r.t. 4 x 4 x 20 mm^3 scintillators)
    - Allowing fast LoR 3D histogramming for online monitoring, without standard PET reconstruction, for example

Render of 60 layers of MAPS stacked

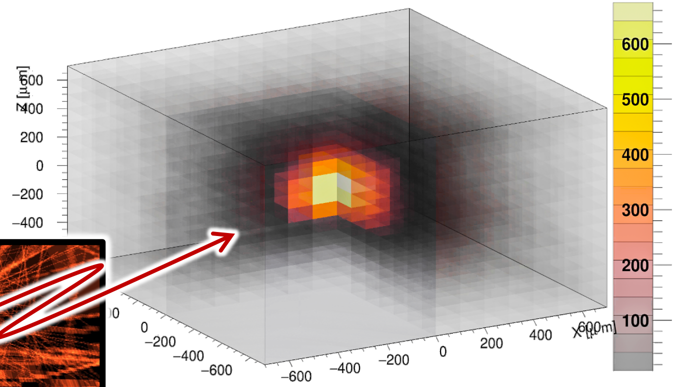


Pixel pitch: 100 µm | DOI: 400 µm
Sensor granularity: **0.004 mm^3**



Superposition of all LoR reconstructed from 5 point sources measured with the 100µPET scanner

Voxels of 100 x 100 x 100 µm²



3D histogram centered at a given source position, counting LoR at each space

Limit in spatial resolution in PET imaging

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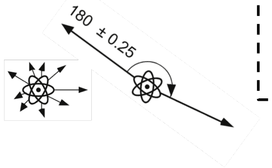
- How good can PET spatial resolution be?
  What are the limitations to pinpoint the positron source?

Fundamental

Positron range: 102µm FWHM for F18

Acolinearity: $90\mu m \approx 4 \cdot 10^{-3} R$



detector = detection channel pitch
o = Offset from the center
h = Depth-of-interaction
R = Radius of the FOV

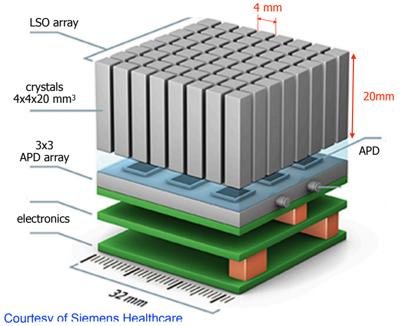
Design-induced

	Conventional PET		100µPET
Parallax error:	$\frac{1}{4R^2}\left((\text{detector})\sqrt{R^2 - o^2} + ho\right)^2$	→	$\approx (\text{detector})/2$
Non-uniform sampling:	$1.25*$	→	$\approx 1*$
Detector size:	$1000\mu m$	→	$100\mu m$

$$(\text{sampling})\sqrt{\frac{1}{4R^2}\left((\text{detector})\sqrt{R^2 - o^2} + ho\right)^2 + \text{range}^2 + (4 \cdot 10^{-3} R)^2 + \text{decode}^2}$$

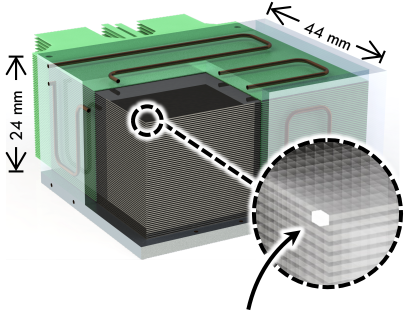
$$\sqrt{(\text{detector}/2)^2 + \text{range}^2 + (4 \cdot 10^{-3} R)^2}$$
$$\approx \sqrt{2} \cdot 100\mu m$$

Conventional PET scanner module



Crystal pitch: 4000 µm | DOI: 20000 µm

100µPET detection tower



Pixel pitch: 100 µm | DOI: 400 µm

Credit: Aleix Boquet I Pujadas (EPFL)

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100µPET
Molecular Imaging at Ultra-High Resolution

The 100μPET

ASIC, module/layer, tower and scanner

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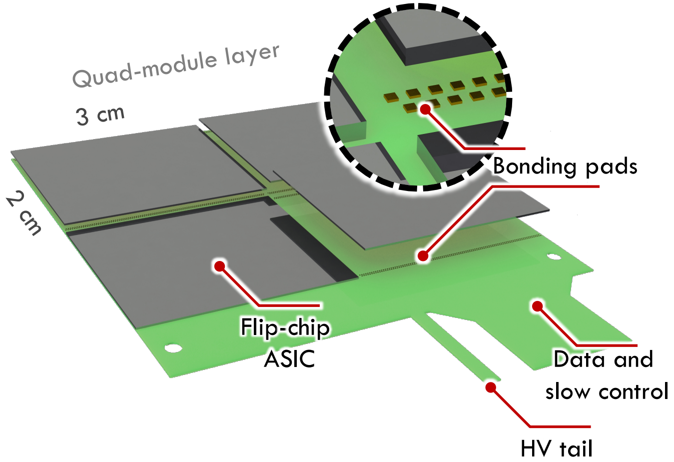
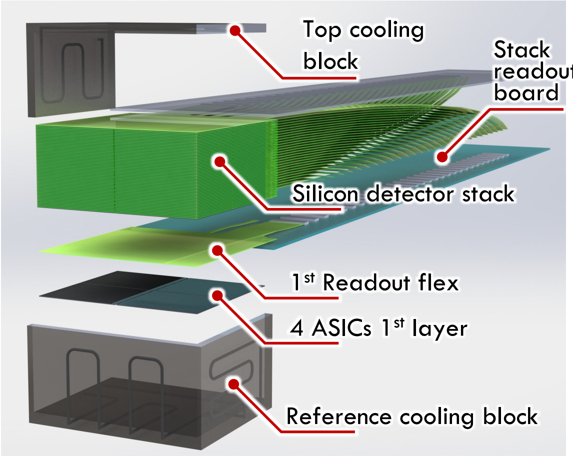
*check talks from Stefano Z. and Matteo M.

- Multi-layer stack of CMOS imaging sensors based on silicon pixel detectors used in HEP
  - Monolithic **100μPET** ASIC: **130 nm** SiGe BiCMOS*; **2.2 x 3 cm^2**; **100 μm** pixel pitch; **270 μm** thick; **~1W** power
  - Single silicon detection layer composed by **2x2 ASICs** flip-chip to a flex printed circuit, covering ~**30 cm^2**
    - Optional **50 μm thick Bismuth** layer to increase the photon conversion efficiency (w.r.t. only silicon)
  - **60** detection layers compose each scanner **tower,** with 4 towers per scanner (for a grand total of **960 chips!)**





Module assembly

Flip-chip bonding with a pad-wafer

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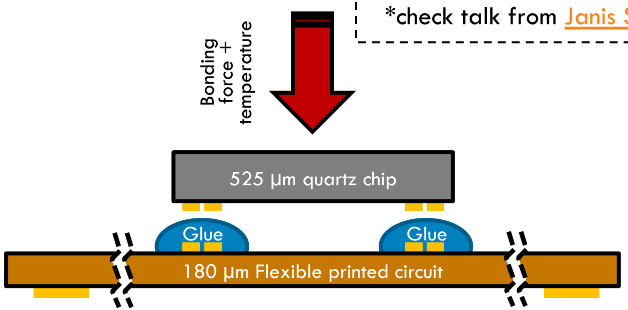
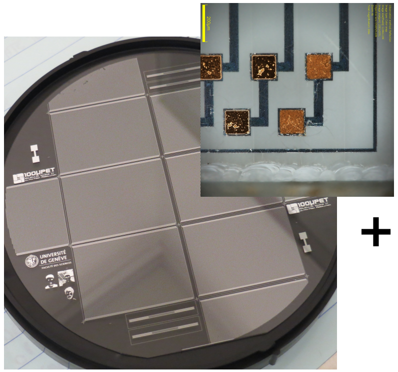
- Pad-wafer produced at CMi (EPFL) with flip-chip pad-chain structure
  - 525 µm thick. Single layer Ti/Al metal patterning + ENIG plating (CERN)
- Flex designed to measure flip-chip bonding yield
  - 4 layers, ~180 µm total thickness. ENIG pad finishing
- Chip's IO pad design driven by chosen (standard) FPC technology
  - Pads 125 µm wide, 250 µm pitch, 2 rows (**238 IO pads** over one 30 mm edge)

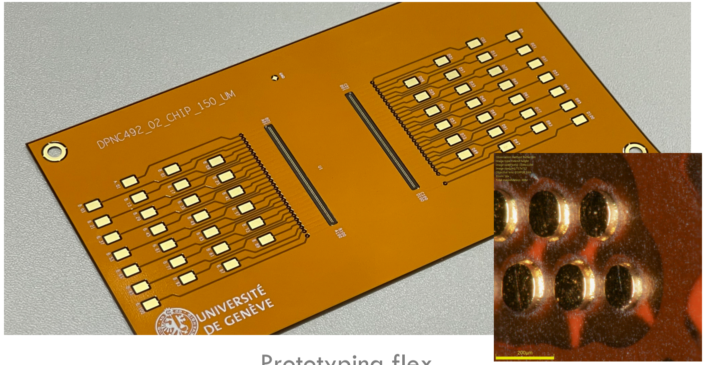
*check talk from Janis S.





Pad wafer with 6 full chain dies

+



Prototyping flex

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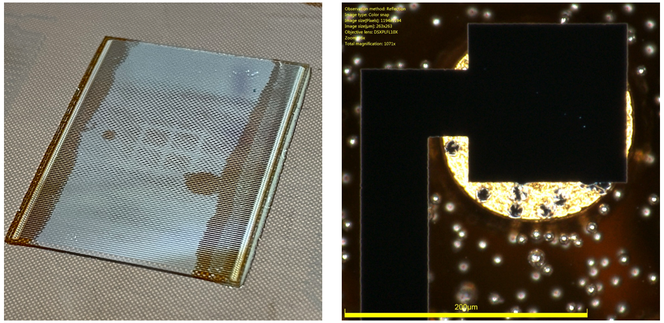

Flip-chip bonded test assembly

Module assembly

First reliability tests

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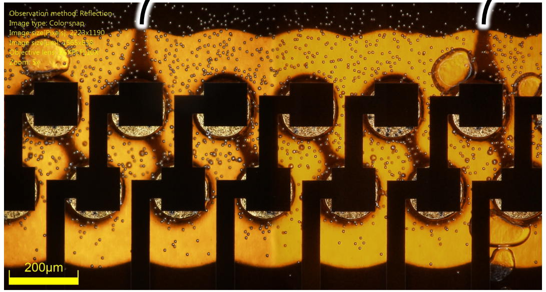
- 2-wire measurements of the full chain, or individual segments with <u>8 pads</u>
  - Quantitative measurement limited to check <u>open or closed connection</u>
    - Bonding tool smaller than test chip → Lower bonding force in chip edges
- Reliability tests with up to 100 temperature cycles from +5 to +60 °C

Flex probing pad N

pad N+1



Chain segment with 8 pads connection

3 Samples in the climate chamber

Module assembly

First reliability tests

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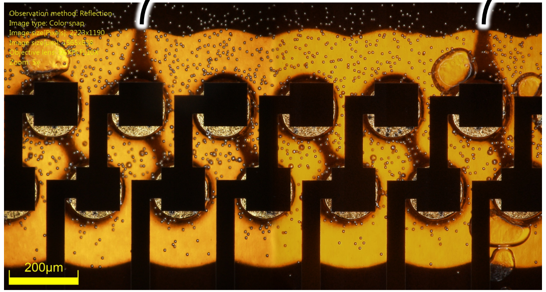
- 2-wire measurements of the full chain, or individual segments with 8 pads
  - Quantitative measurement limited to check open or closed connection
    - Bonding tool smaller than test chip → Lower bonding force in chip edges
- Reliability tests with up to 100 temperature cycles from +5 to +60 °C
  - Very promising results with first samples produced…



Chain segment with 8 pads connection

3 Samples in the climate chamber

Resistance measurements for top and bottom edges (systematic flex/probing resistance not corrected)

Top edge [#chain segment]	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Initial	2,3	2,4	2,2	2,2	2,2	Disconnected by accident		2,1	2,2	2,2	2,1	1,8	2	2,1	1,9	1,8	1,9	2	2	1,8	2,1	2	2,2
After 40°C	2,2	2,2	2,2	2,2	2,2			1,9	2,3	2,2	2,1	1,8	2	2,1	2	1,9	1,9	2,1	2,1	1,9	2,1	2,2	2,3
1 cycle	2,4	2,5	2,4	2,4	2,4			2,2	2,5	2,4	2,2	2	2,2	2,4	2,2	1,9	2	2,2	2,2	2	2,2	2,3	2,4
3 cycles	2,5	2,5	2,5	2,4	2,4			2,1	2,7	2,3	2,2	2	2,2	2,2	2,1	2	2,1	2,3	2,2	2,1	2,3	2,4	2,5
5 cycles	2,6	2,5	2,5	2,4	2,4			2,1	2,7	2,3	2,3	2	2,2	2,3	2,2	2	2,1	2,3	2,2	2,1	2,3	2,4	2,5
11 cycles	19,3	2,4	2,3	2,3	2,2			2	2,5	2,2	2,1	1,9	2,1	2,2	2	1,9	2	2,2	2,1	2	2,2	2,3	2,4
35 cycles			21,2	2,3	2,2			2	2,6	2,2	2,1	1,9	2,1	2,2	2	1,9	2	2,2	2,1	2	2,2	2,3	2,4

Bottom edge [#chain segment]	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Initial	2,4	2,4	2,4	4,5	2,4	2,2	1,9	1,8	2	2,1	2	1,9	2	2,1	2	2	2,3	2,2	2,2	1,9	1,9	2,3	2,4
After 40°C	2,4	2,4	2,5	6,1	2,5	2,3	2	1,8	2	2,1	2	1,9	2,1	2	2	2	3,3	2,1	2,1	1,9	2	2,3	2,5
1 cycle	7,4	7,4	7,5	10,4	7,6	7,4	7,5	2,4	2,6	2,7	2,6	2,5	2,6	2,7	2,5	2,6	3,2	2,9	2,9	3,1	3	3,3	3,4
3 cycles	2,6	2,6	2,8	6,6	2,9	2,5	2,2	2	2,2	2,3	2,2	2,1	2,1	2,2	2,1	2,1	2,5	2,5	2,6	2,3	2,3	2,7	2,7
5 cycles	2,7	2,6	2,8	6,5	2,9	2,5	2,2	2	2,2	2,3	2,2	2	2,1	2,2	2,1	2,1	2,4	2,3	2,3	2	2,1	2,1	2,6
11 cycles	2,7	2,5	2,6	5,8	2,7	2,4	2,1	1,9	2,1	2,2	2,1	1,9	2	2,3	2	2,1	2,4	2,2	2,3	2	2	2,4	4,2
35 cycles	2,7	2,7	2,8	4,9	2,7	2,4	2,1	1,9	2,1	2,2	2,1	1,9	2	2,1	2	2	2,3	2,3	2,3	2	2	2,5	17,4

Module assembly

First reliability tests

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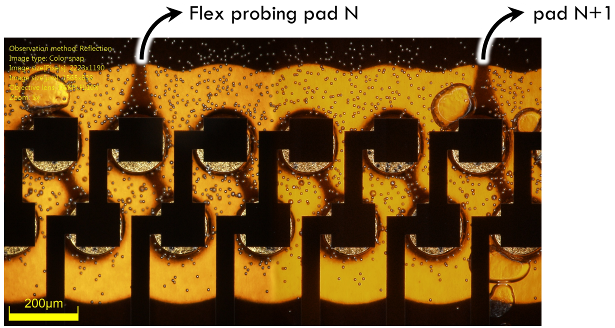
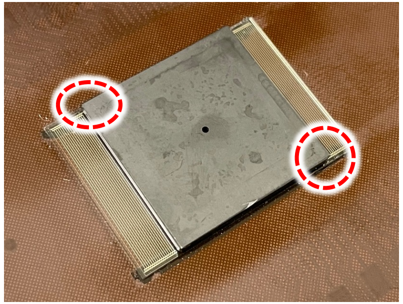
- 2-wire measurements of the full chain, or individual segments with 8 pads
  - Quantitative measurement limited to check open or closed connection
    - Bonding tool smaller than test chip → Lower bonding force in chip edges
- Reliability tests with up to 100 temperature cycles from +5 to +60 °C
  - Very promising results with first samples produced…
    - On-going tests with new samples implementing new bonding features
      - e.g.: Larger glue underfill for mechanical reinforcement at at the extreme edges



Chain segment with 8 pads connection

Sample with SiC bonding tool on top



Resistance measurements for top and bottom edges (systematic flex/probing resistance not corrected)

	Top edge [#chain segment]																						
	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Initial	2,3	2,4	2,2	2,2	2,2	*Disconnected by accident*		2,1	2,2	2,2	2,1	1,8	2	2,1	1,9	1,8	1,9	2	2	1,8	2,1	2	2,2
After 40°C	2,2	2,2	2,2	2,2	2,2			1,9	2,3	2,2	2,1	1,8	2	2,1	2	1,9	1,9	2,1	2,1	1,9	2,1	2,2	2,3
1 cycle	2,4	2,5	2,4	2,4	2,4			2,2	2,5	2,4	2,2	2	2,2	2,4	2,2	1,9	2	2,2	2,2	2	2,2	2,3	2,4
3 cycles	2,5	2,5	2,5	2,4	2,4			2,1	2,7	2,3	2,2	2	2,2	2,2	2,1	2	2,1	2,3	2,2	2,1	2,3	2,4	2,5
5 cycles	[illegible]	[illegible]	[illegible]	2,4	2,4			2,1	2,7	2,3	2,3	2	2,2	2,3	2,2	2	2,1	2,3	2,2	2,1	2,3	2,4	2,5
11 cycles	19,3	2,4	2,3	[illegible]	2,2			2	2,5	2,2	2,1	1,9	2,1	2,2	2	1,9	2	2,2	2,1	2	2,2	2,3	2,4
35 cycles			21,2	[illegible]	2,2			2	2,6	2,2	2,1	1,9	2,1	2,2	2	1,9	2	2,2	2,1	2	2,2	2,3	2,4

	Bottom edge [#chain segment]																						
	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Initial	2,4	2,4	2,4	4,5	2,4	2,2	1,9	1,8	2	2,1	2	1,9	2	2,1	2	2	2,3	2,2	2,2	1,9	1,9	2,3	2,4
After 40°C	2,4	2,4	2,5	6,1	2,5	2,3	2	1,8	2	2,1	2	1,9	2,1	2	2	2	3,3	2,1	2,1	1,9	2	2,3	2,5
1 cycle	7,4	7,4	7,5	10,4	7,6	7,4	7,5	2,4	2,6	2,7	2,6	2,5	2,6	2,7	2,5	2,6	3,2	2,9	2,9	3,1	3	3,3	3,4
3 cycles	2,6	2,6	2,8	6,6	2,9	2,5	2,2	2	2,2	2,3	2,2	2,1	2,1	2,2	2,1	2,1	2,5	2,5	2,6	2,3	2,3	2,7	2,7
5 cycles	2,7	2,6	2,8	6,5	2,9	2,5	2,2	2	2,2	2,3	2,2	2	2,1	2,2	2,1	2,1	2,4	2,3	2,3	2	2,1	2,1	2,6
11 cycles	2,7	2,5	2,6	5,8	2,7	2,4	2,1	1,9	2,1	2,2	2,1	1,9	2	2,3	2	2,1	2,4	2,2	2,3	2	2	[illegible]	4,2
35 cycles	2,7	2,7	2,8	4,9	2,7	2,4	2,1	1,9	2,1	2,2	2,1	1,9	2	2,1	2	2	2,3	2,3	2,3	2	2	[illegible]	17,4

NB: Start of disconnection at the far edges where the maximum stress is concentrated

Performance simulations

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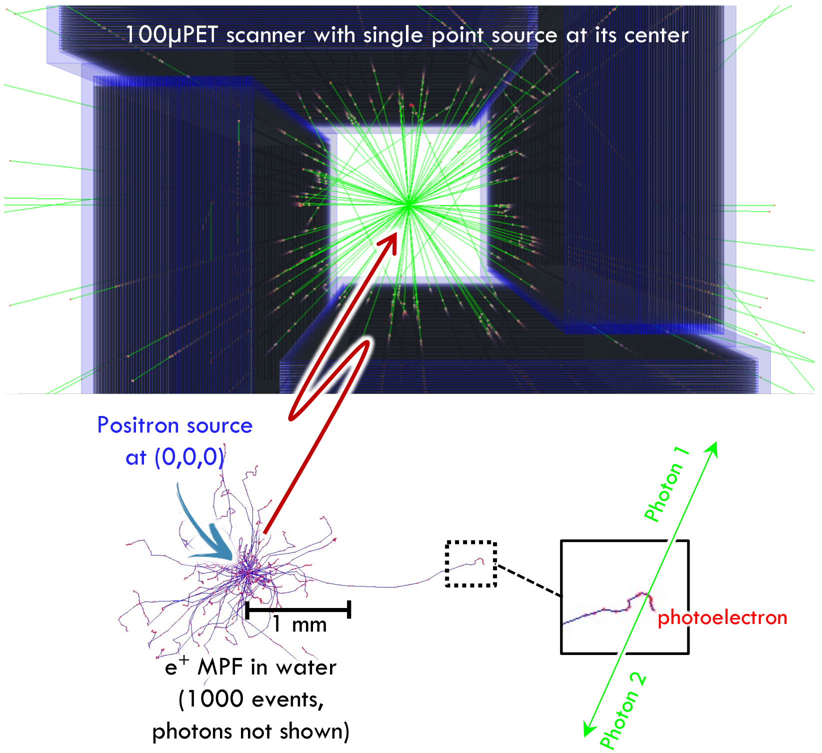
- **Full Monte Carlo** (Geant4 + AllPix^2) simulations
  - Full scanner geometry (w/ or w/o Bi layers) + water volume
  - Positron mean free path and annihilation from [^{18}F]FDG
  - Photon interactions (scattering and photoelectric effect)
  - Sensor/ASIC response + pixel clustering
- Single positron annihilation per event (**no time information**)
  - Event filtering for **unambiguous** line-of-response acceptance
    - Only events with two scanner towers having each a single cluster
  - No energy window for discriminating signals form Compton or photoelectric interactions
- Positron sources:
  - Single point; Derenzo phantom; High resolution medical images



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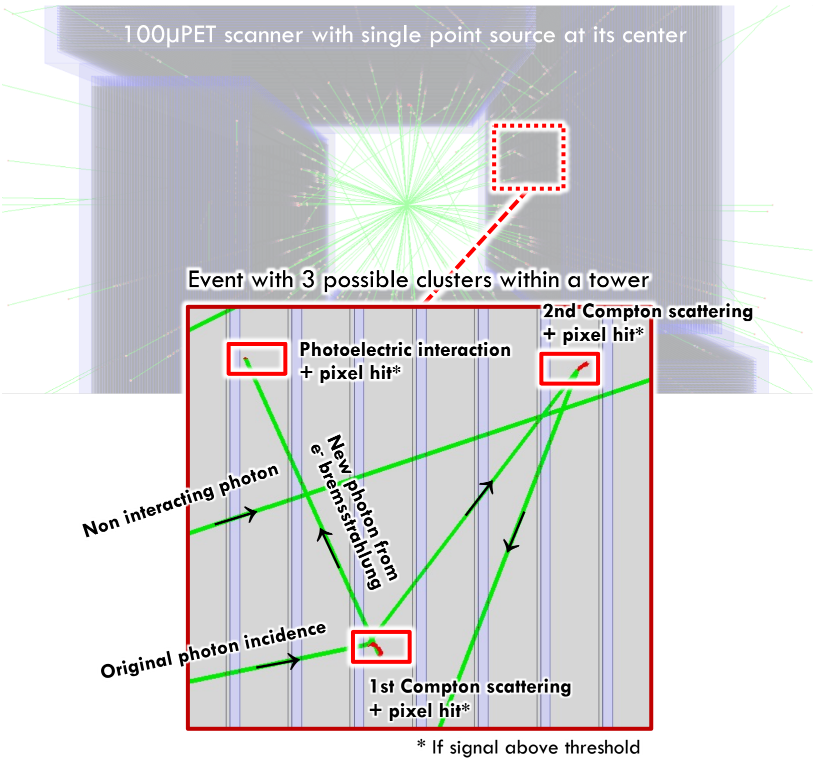

Performance simulations

Single point source: Sensitivity and resolution

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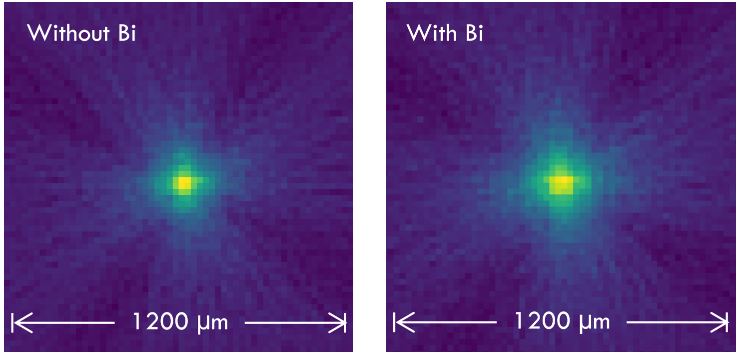
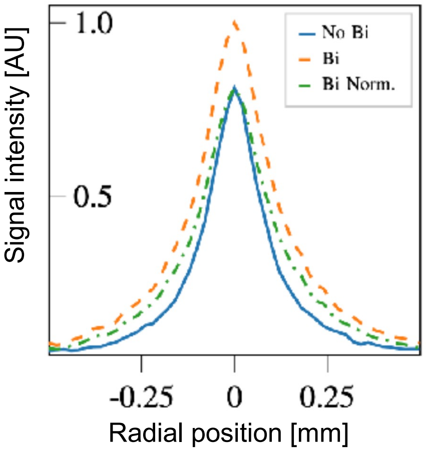
- **<u>Sensitivity:</u>** amount of <u>unambiguous LoR</u> measured as a function of the total number of positrons
  - **<u>3.3%</u>** and **<u>4.8%</u>** <u>detection efficiency</u>, with and without Bi respectively
- **<u>Spatial resolution:</u>** <u>Point Spread Function</u> with FBP (Filtered Back Projection)
  - **<u>0.13 mm</u>**, lowered to **<u>0.17 with Bi</u>** absorber layer (±0.014 mm)

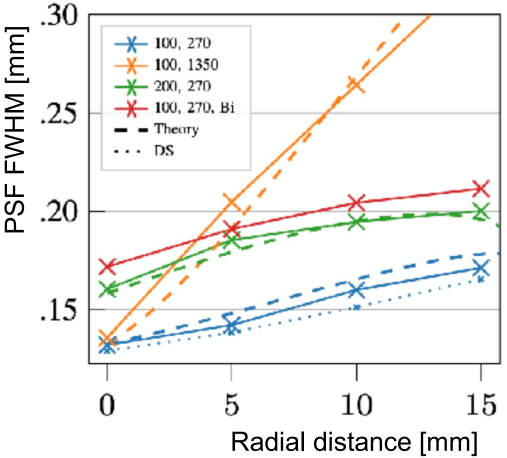
⇨ <u>Very small parallax distortion!</u> Investigating effect of 50 µm Bi with 200 µm pixel pitch

  - Higher sensitivity; slight lower spatial resolution; 1/4th of the number of channels (<u>lower power!</u>)



Reconstructed point source
<u>Bin size: 20 µm</u>





UNIVERSITÉ DE GENÈVE
FACULTÉ DES SCIENCES

Performance simulations

Derenzo phantom for imaging reconstruction

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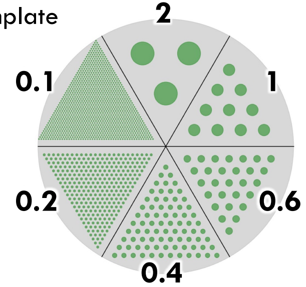
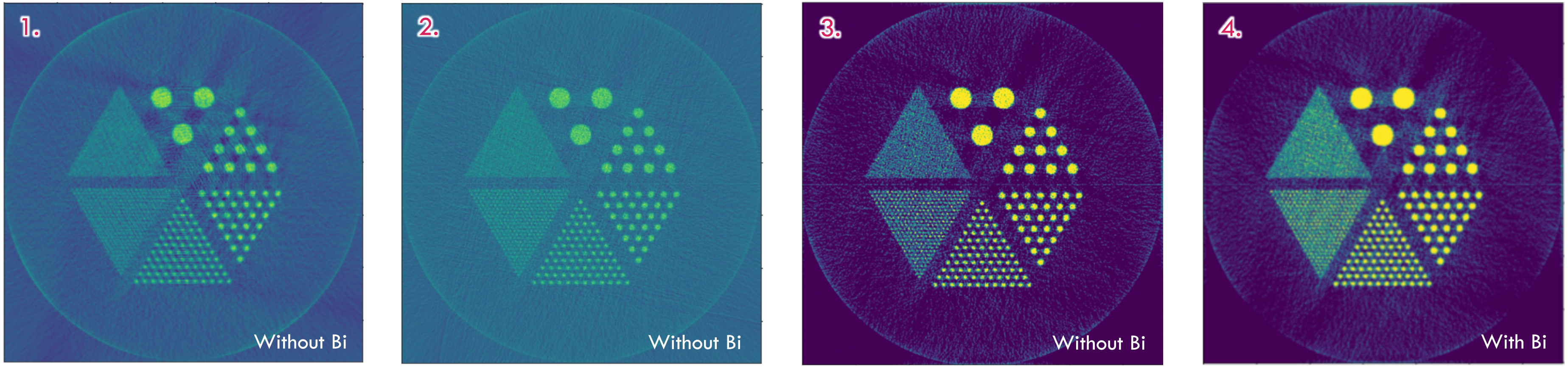
- Derenzo phantom to test reconstruction down to given feature size
  - 2.0, 1.0, 0.6, 0.4, 0.2, 0.1 mm rods (no positron mean free path)
    1. Filtered back projection (FBP)
    2. FBP + sensitivity correction
    3. Iterative TV + sensitivity correction
    4. Iterative TV + sensitivity correction

Derenzo template (sizes in mm)





Performance simulations

Hi-res MRI/CT image templates

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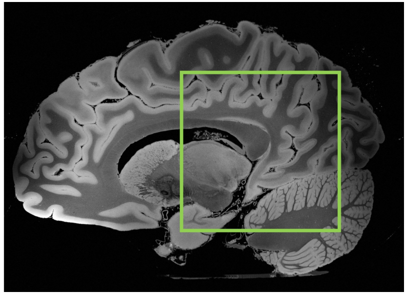
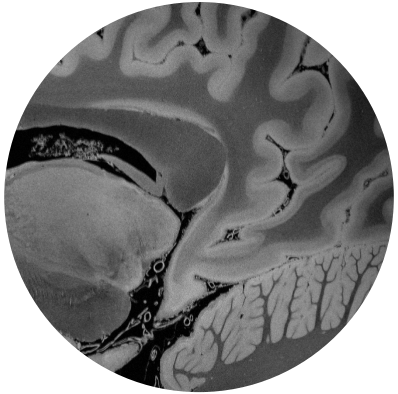
Extension of Derenzo template to real medical images

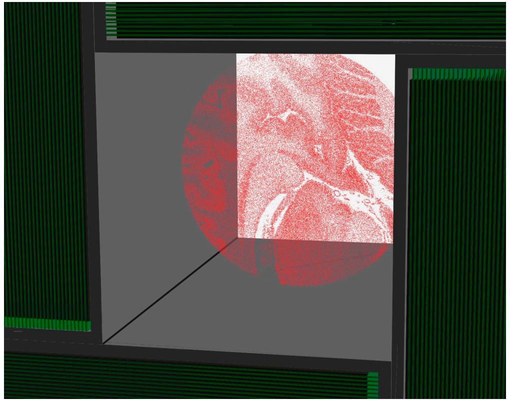
- 7 Tesla MRI of the ex *vivo* human brain at 100 micron resolution
  doi:10.18112/openneuro.ds002179.v1.1.0
  - 68 x 68 mm^2 (680 x 680 pixels) resized to 34 x 34 mm^2 (scaling pixel resolution to 50 x 50 µm^2)
  - Each 50 x 50 µm^2 pixel is used as a plane source, with activity proportional to pixel's grey scale



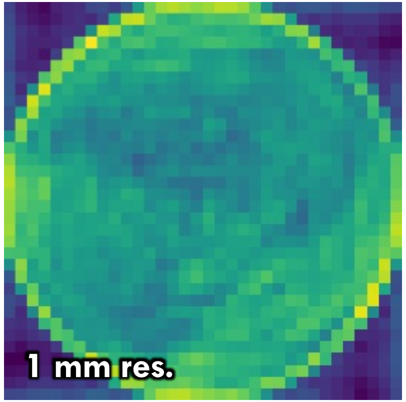
MRI (TIFF) image used



"Image source" placed in the scanner



Reconstruction with typical 1mm res.



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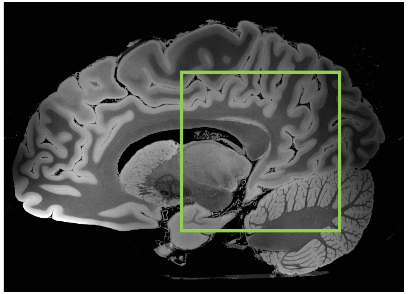
  - Each 50 x 50 µm^2 pixel is used as a plane source, with activity proportional to pixel's grey scale
- Results shows that unprecedented details can be reconstructed



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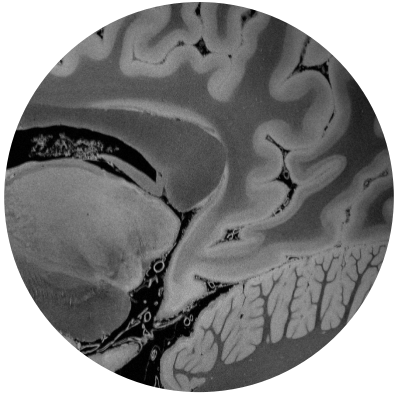

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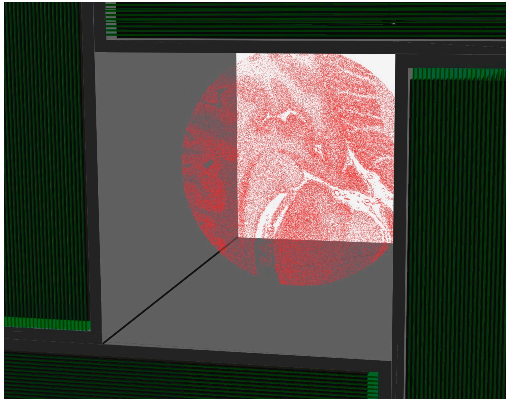

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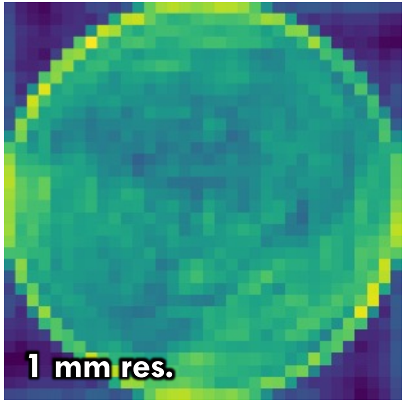
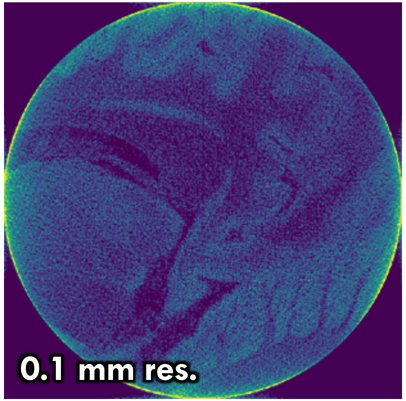


Reconstruction with 100 µm res.



Summary and conclusions

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- **PET scanners** are an important diagnostic tool for metabolic process imaging
  - Continuous improvements over the years (e.g. Time-of-Flight PET with tens of ps; Depth-of-Interaction encoding)
- Potential ultra-high-resolution molecular imaging using **MAPS**
  - ASIC designed within the UniGE DPNC group (Together with the FASER and MONOLITH projects)
  - Development of module construction technique based on flip-chip bonding for minimal packaging

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- Potential ultra-high-resolution molecular imaging using **MAPS**
  - ASIC designed within the UniGE DPNC group (Together with the FASER and MONOLITH projects)
  - Development of module construction technique based on flip-chip bonding for minimal packaging
- **4.8%** and **3.3% scanner sensitivity** (w/ or w/o Bismuth layer)
- **0.13-0.21 mm PSF → 0.006-0.017 mm³ volumetric resolution**
  - ❖ In the whish-list: TOF ≲ 10ps, when delivered by the MONOLITH project
- Delivery of a proof-of-concept scanner for small animals in 2025
  - With silicon-sensor technology advances, its cost will go down and larger scanners can be envisaged in the near future