erc Advanced Grant

First Results from the 4D-PET Scanner for the Brain Examination

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1. A View to Cure: the coming clinical revolution in Neurology (and Neurosurgery)

- Enemy at the Gates
  - **One in four people worldwide** will suffer from neurological disfunctions or diseases (-1- ECR, March 2019)
  - **New evidence**: Alzheimer´s dementia is one among many **not unrelated** neurodegenerative diseases…
  - …and neurodegenerative diseases are 1/3rd of brain pathologies

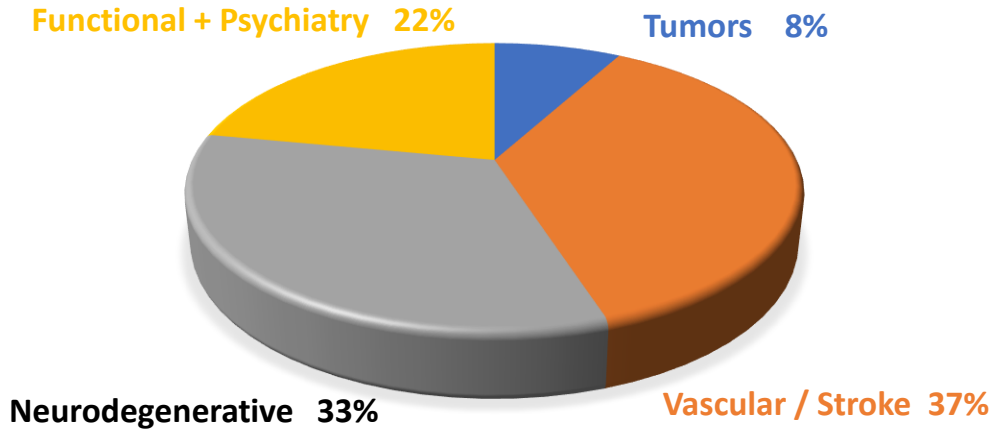
- **Imaging to the rescue**:
  - Brain imaging breakthroughs: From CT to MRI to multimodality with **PET** as decisive
  - **Functional** brain alterations and/vs anatomical changes: earlier / different / predictive
  - The evolving role of brain imaging: from diagnosis to treatment follow up to integrated Imaging-treatment (theranostics, targeted therapies tracer+drug…)

- PET / Positron emission tomography: from "cancer hunter" to pathfinder
  - SEEING brain areas in action, dynamic **quantification of** activity and drug / treatment results
  - The tracer "Big Bang" (see 2)

(1) Including neurophsychiatric conditions and learning disabilities

2. PET tracer "Big Bang": from cancer and Alzheimer´s to the future… now

- **^{18}F-FDG: Keystone / "Jack of all trades"** (cancer, stroke, dementias, aphasias, Multiple Sclerosis, ELA…)
- **Brain Tumors:** ^{18}F-FDG,^{18}F-FDOPA,^{11}C-Metionine, ^{18}F-FET
- Neurodegenerative / cognitive Impairment (Alzheimer´s, FTD…)
  - Neural degeneration: ^{18}F-FDG, new **TAU protein tracers**
  - Amyloid-β deposits: ^{11}C-PIB, ^{18}F-Flutemetamol, ^{18}F- Florbetaben, ^{18}F-Florbetapir
- Parkinsonian syndromes
  - Presynaptic: ^{18}F-FDOPA, ^{11}C-DTBZ, ^{11}C-Metilfenidate
  - Postsynaptic: ^{18}F-FDG, ^{11}C-Raclopride
- Epilepsy:
  - Lesion: ^{18}F-FDG
  - Receptors: ^{11}C-Flumazenil, ^{18}F-Triptofan
- **Post traumatic brain injury:** ^{18}F-FDG, ^{15}O-labeled water ($H_2{}^{15}O$)/ $C^{15}O$ (inhaled)
- **Psychiatric pathologies** (depression, schizophrenia, learning disabilities, substance abuse): ^{18}F-FDG, ^{11}C-Raclopride



Brain disease incidence

3. From whole body (wb) PET to dedicated Brain PET. SEVEN reason

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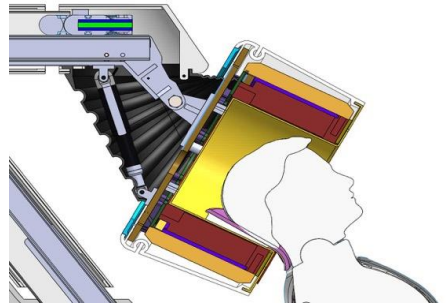
1. wb PET CT use is very often **saturated** by Oncology demand
2. PET in wb PET CT or PET MRI have physical **limitations** for brain imaging
   - eg clinical resolution, 6+ mm wb PET vs CMB´s **<1,5 mm**
3. Brain PET is **optimized** for CNS neurological imaging:
   - Detectors are very near target regions. Unprecedented **resolution** and **sensitivity**
   - Revolutionary **quantification** accuracy at small brain areas / centers, unique **dynamic** capabilities
4. Brain PET **seamless integration** in patient continuum of care
   - Easy **fusion** with anatomical WB studies / atlas, flexible clinical setting / location
5. A new gold standard in **workflow** and **cost-effectiveness**
   - Small footprint, Shorter test time, Controlled investment with fast RoI
   - Easy to use, intuitive interface, full hospital / neurology center systems integration
6. **Patient** comfort / positioning / new options: sitting vs lying down, **“active” PET**
7. Patient safety and **optimum clinical value**: VERY low tracer / RX dose, combined tracers



PERSONALIZED, FUNCTIONAL BRAIN IMAGING: THE SUPREME BRAIN CHALLENGE

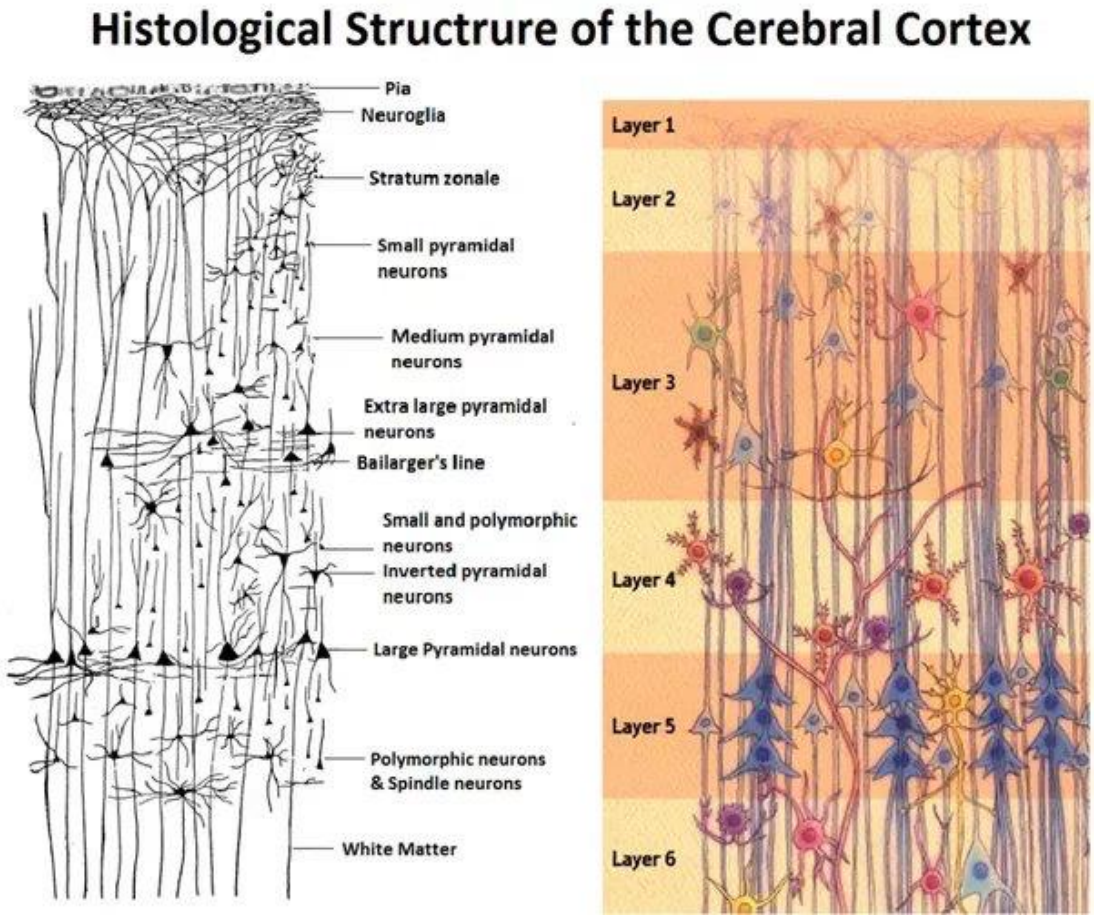
We need to see – and quantify – clinically relevant changes in very small regions vs “normal” by age and condition

Assessing brain functional activity and its alterations at cortex layer /deep nuclei level is a mayor unmet clinical and neurological research need

Multiplying sensitivity and resolution is opening a whole new view of healthy, altered and pathological brain: the critical imapct of heterogeneity

Cortex thickness is 1,5-4,5 mm
SIX layers with different functions and neuro receptors.

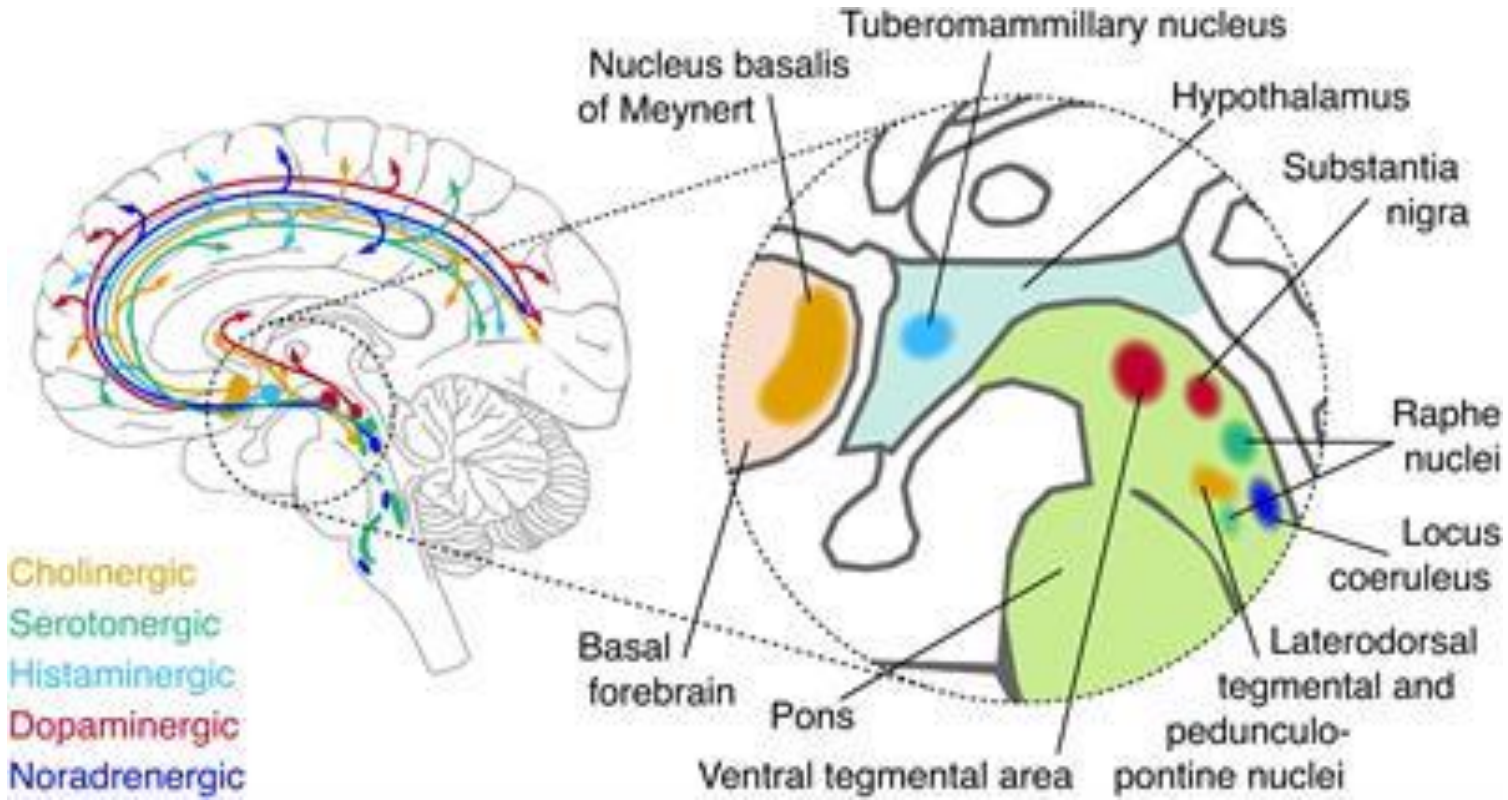
Clinical / practical brain PET resolution HAS TO BE 1,5 mm or better for accurate assessment of cortex changes



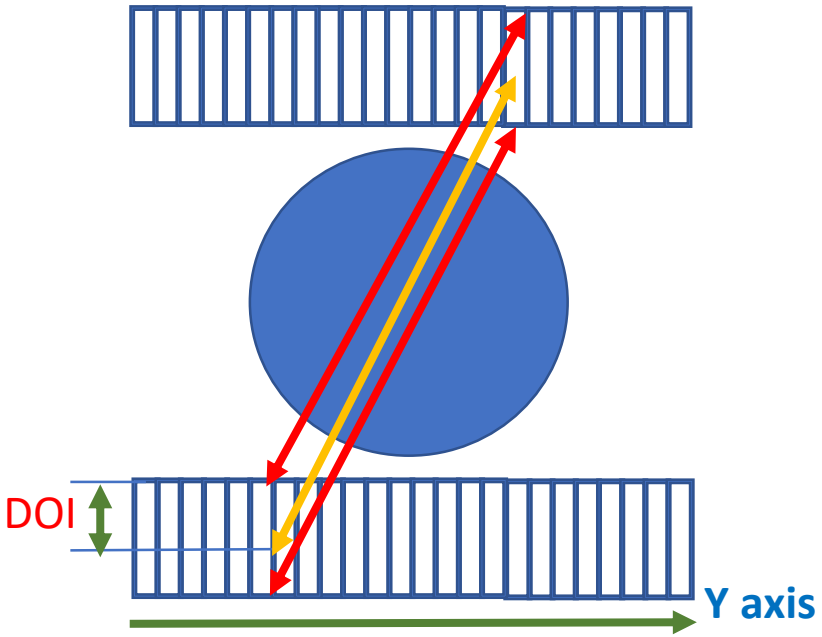
SENSITIVITY & RESOLUTION CHALLENGES: CLINICALLY-RELEVANT CHANGES IN SMALL BRAIN REGIONS

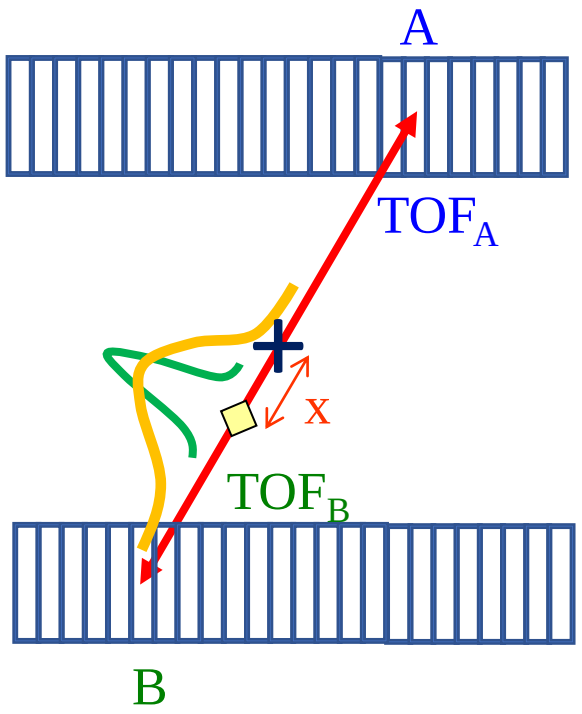
Critical Brain regions (entorrhinal cortex, affected in Braak 1 AD..) and nuclei (Raphe, substantia nigra, locus ceruleus …) are very small, often smaller than 2 cc in volume (grain of rice)

Brain PET requires very high sensitivity, resolution and dyanmic capabilities.



IMPORTANCE OF DOI & TOF





t= 2*x/c

x= c t/2

Uncertainty on this position:

$\Delta x = c\,\Delta t/2$

OBJECTIVE

4D-PET

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4D-PET: Innovative PET scanner for dynamic imaging

To develop a Dedicated Brain PET scanner:

- **Spatial resolution below 1,5 mm.**
- **CTR < 250ps.**
- **SENSITIVITY > 20%.**
- **SCAN ALL HEAD AT ONCE.**
- **AFFORDABLE.**
- **CONFORTABLE TO THE PATIENT.**

THE CHALLENGE

4D-PET

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To develop a detector Module with:

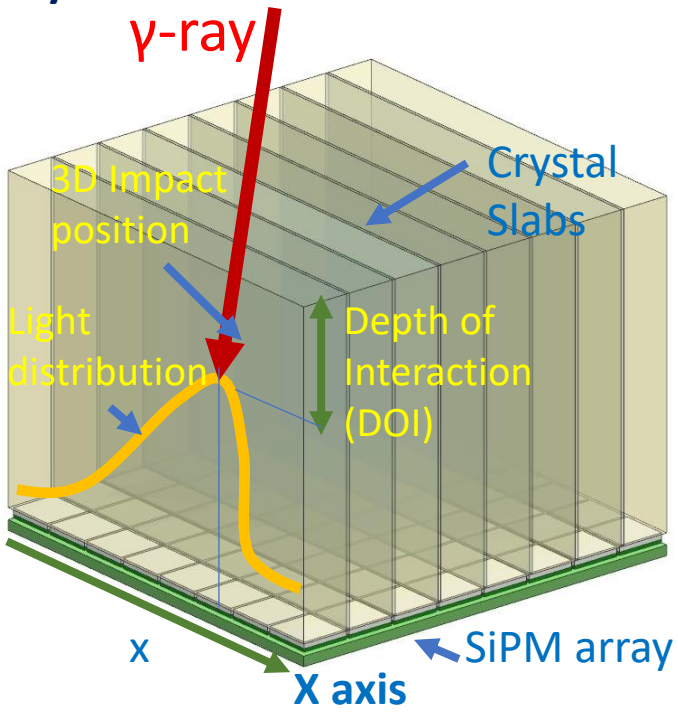
- **Excellent position resolution.**
- **Good DOI (Depth Of Interaction) Information.**
- **Good Timing resolution.**
- **High Efficiency.**

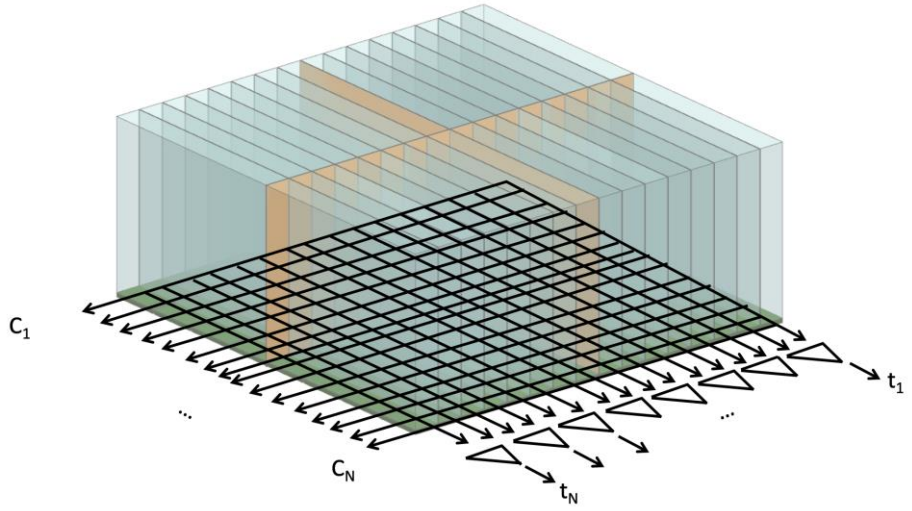
4D-PET DETECTOR MODULE

4D-PET

To develop a detector Module with:

- **Excellent position resolution.**
- **Good DOI (Depth Of Interaction) Information.**
- **Good Timing resolution.**
- **High Efficiency.**



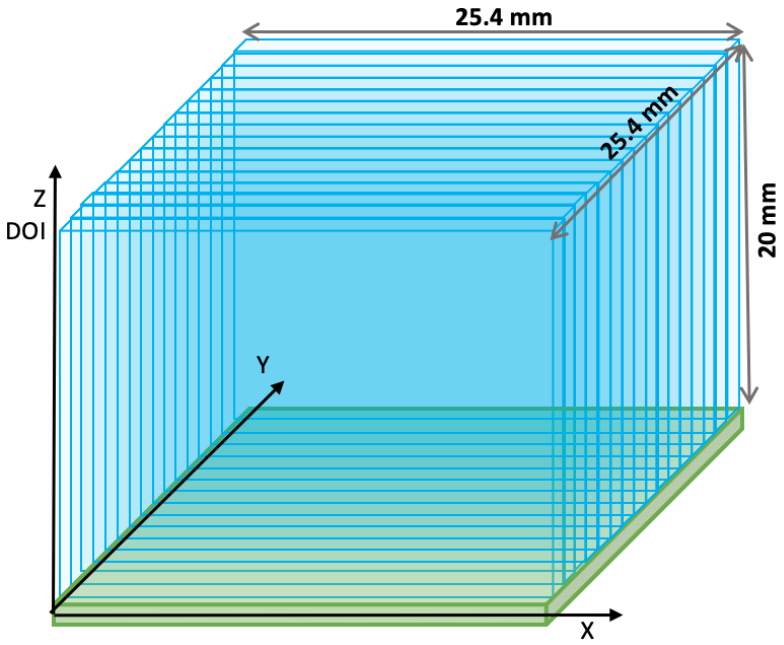


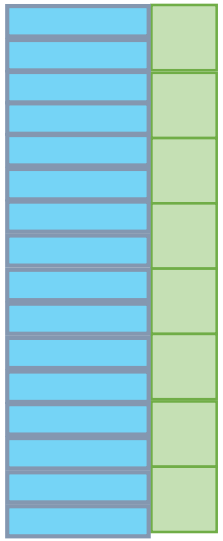
MODULE:

- **LYSO array of 16 slabs:**
  - **Slab dimensions: 25.6x1.5x20 mm³**
  - **all sides polished and separated by**
- **Total dimension: 25.6x25.6x20 mm³**
- **Coupled to 8x8 Hamamatsu SiPM: S13, without light guide**
- **2 slabs per SiPM**

→ 25.6x25.6x20 mm³ , All ESR, 8x8 SiPM S13

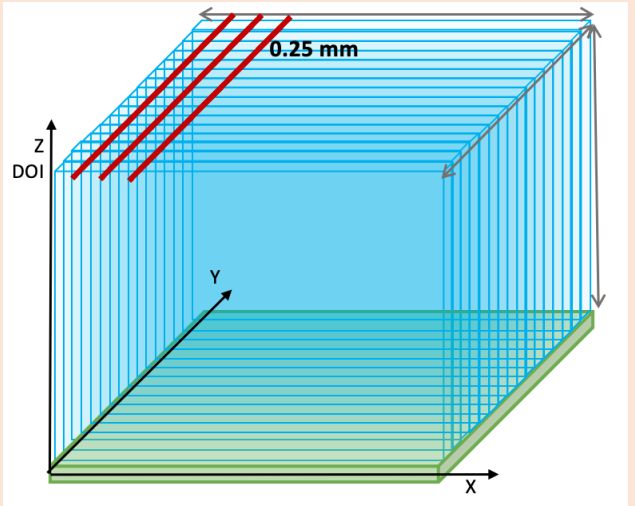
TOTAL : 320 MODULES



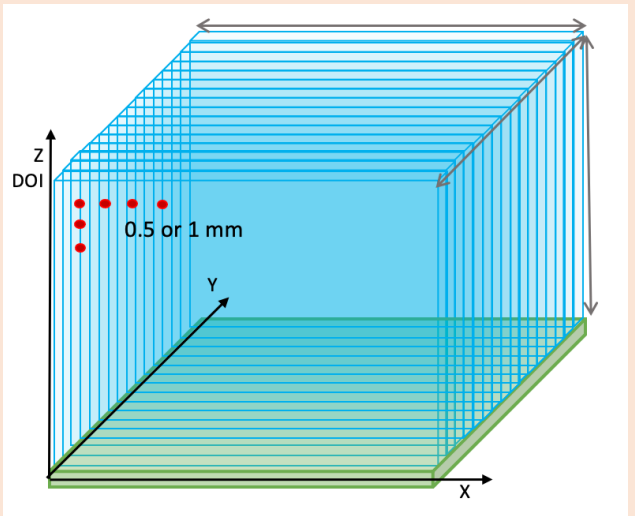


Two types of measurements

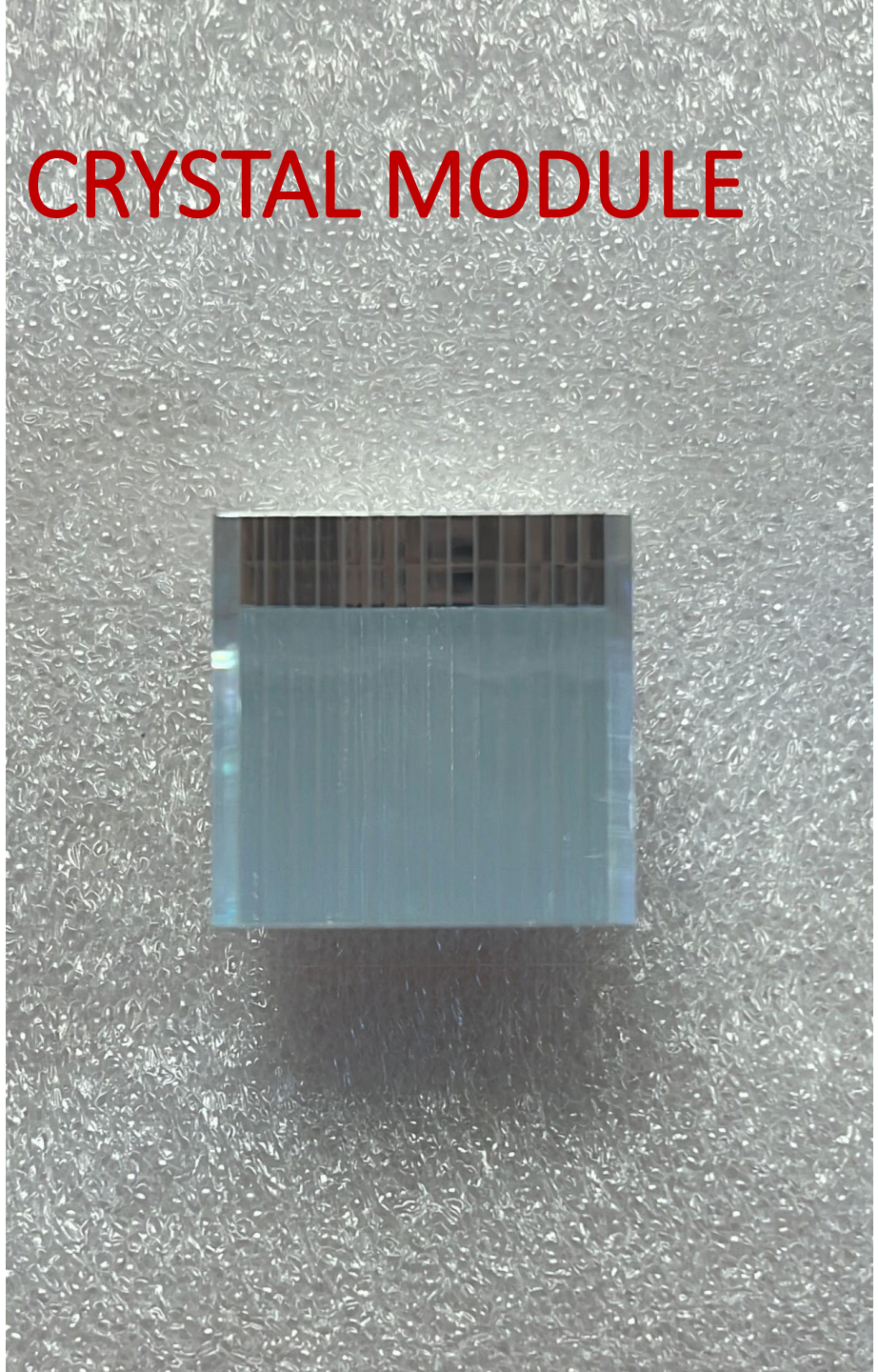
Slit Measurement

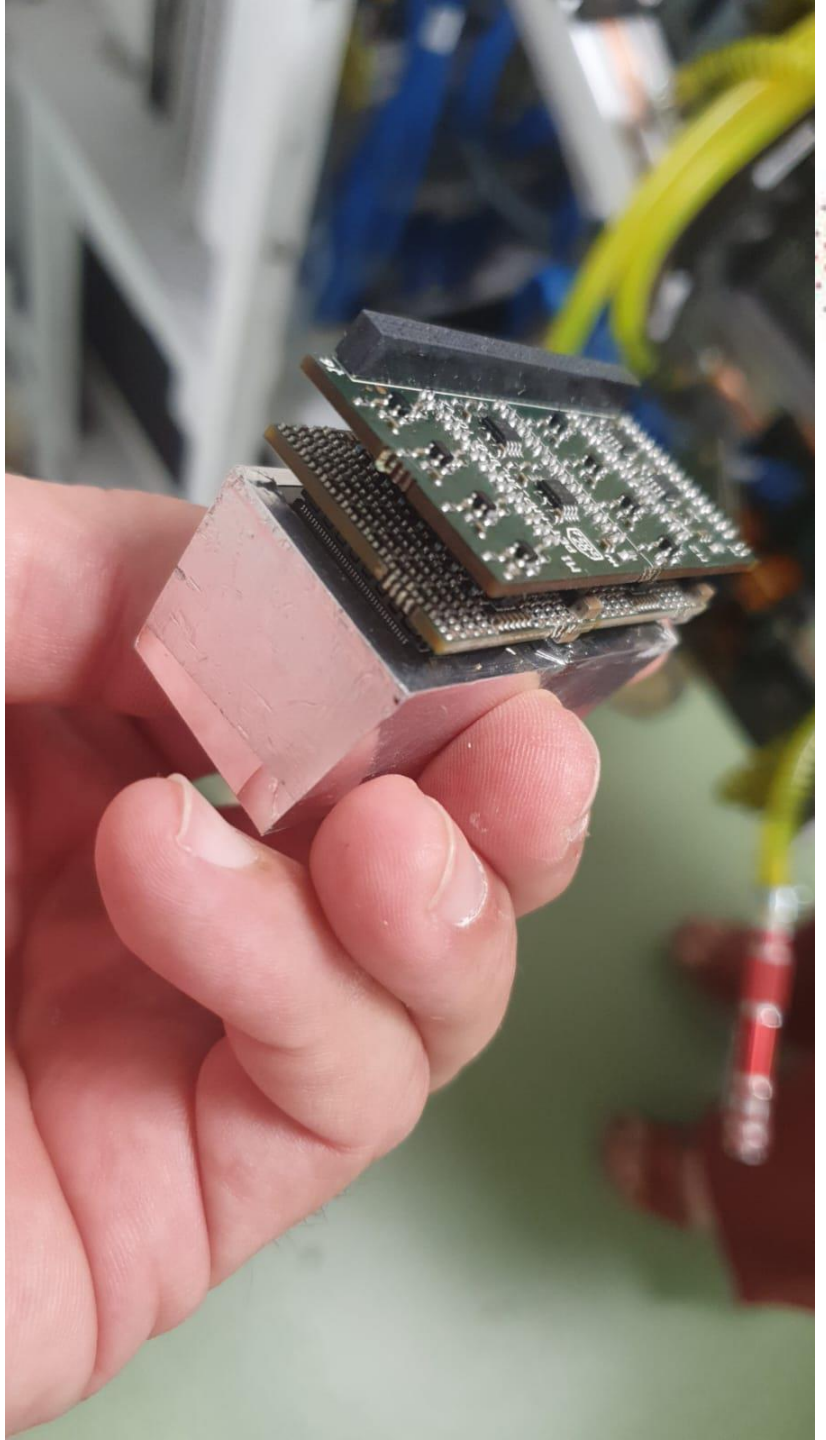


Pinhole Measurement



CRYSTAL MODULE





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DETECTOR ELECTRONICS

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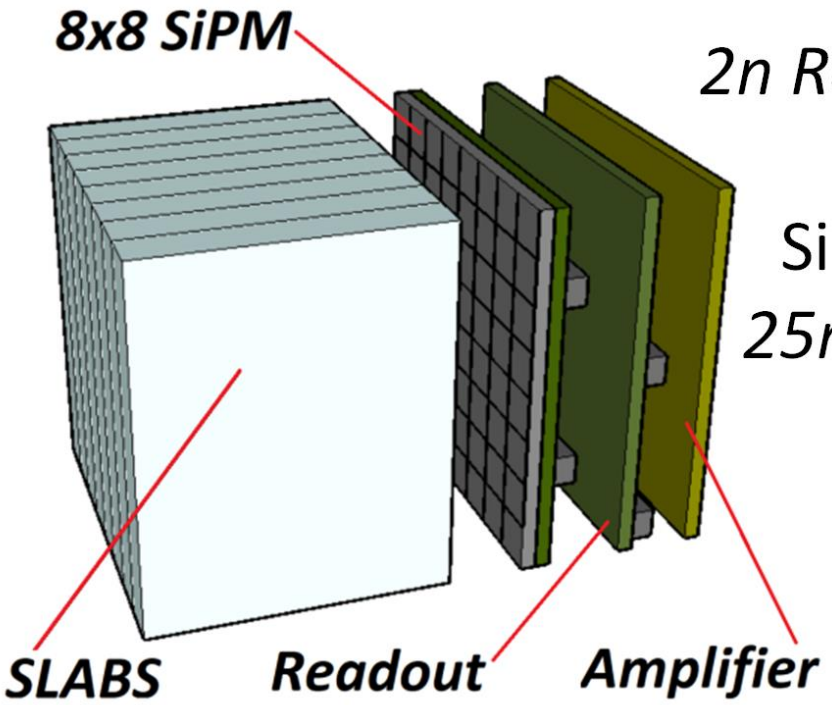
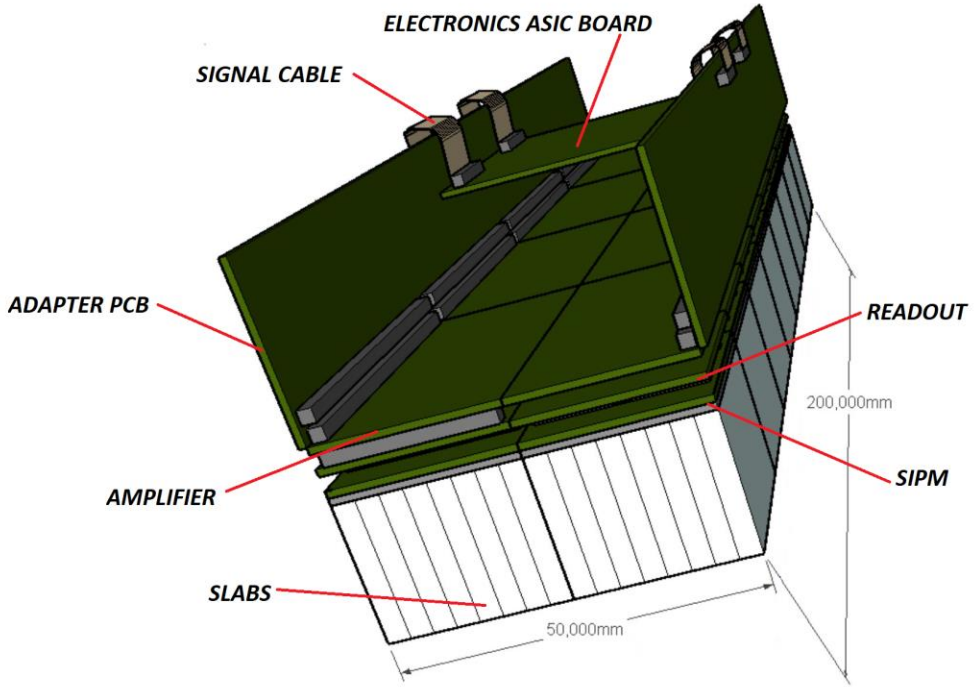
1 ASIC (PETSYS) READS 4 MODULES
SUPERMODULE = 2 x 8 MODULES
SUPERMODULE NEEDS 4 ASICs

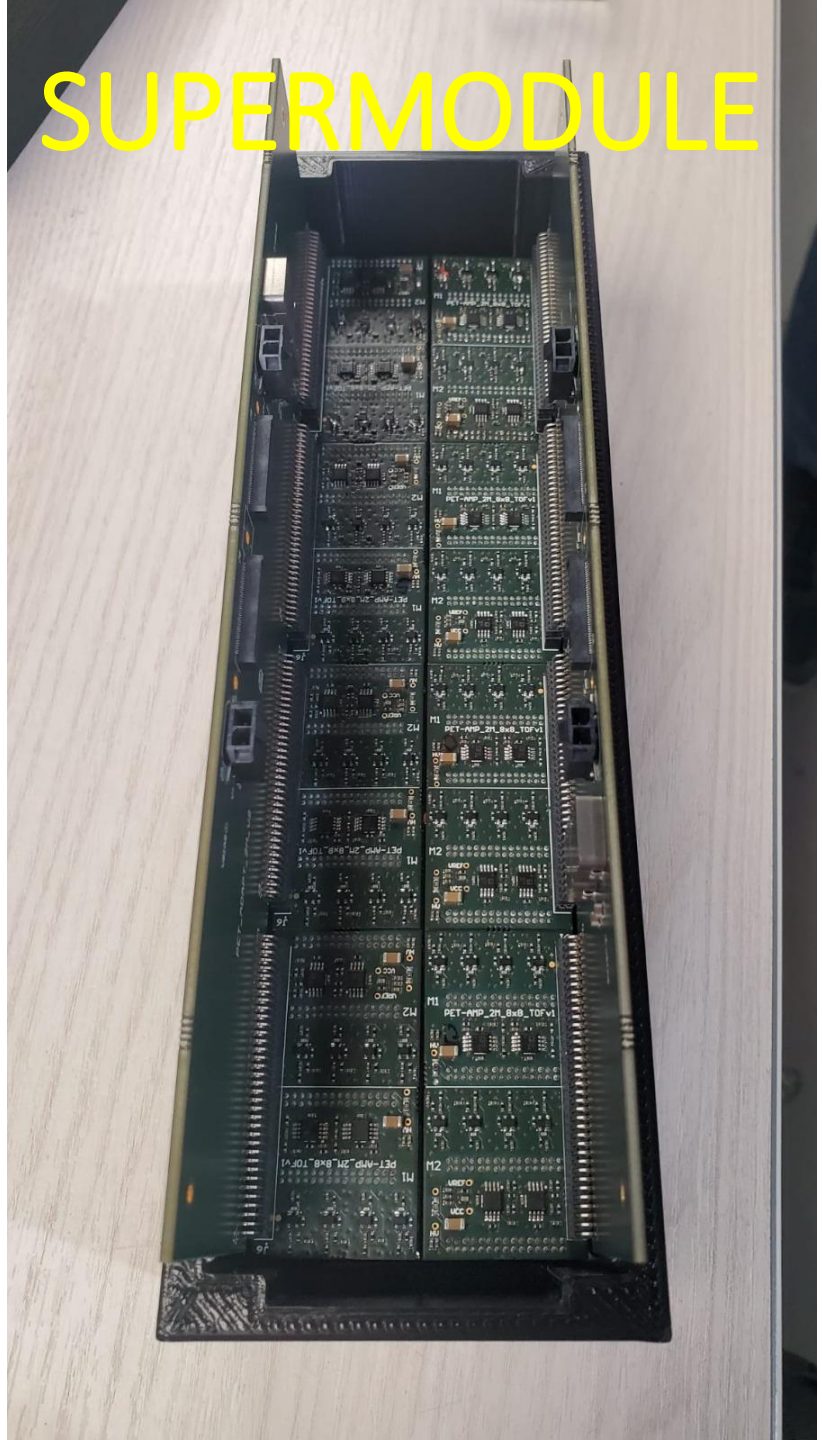


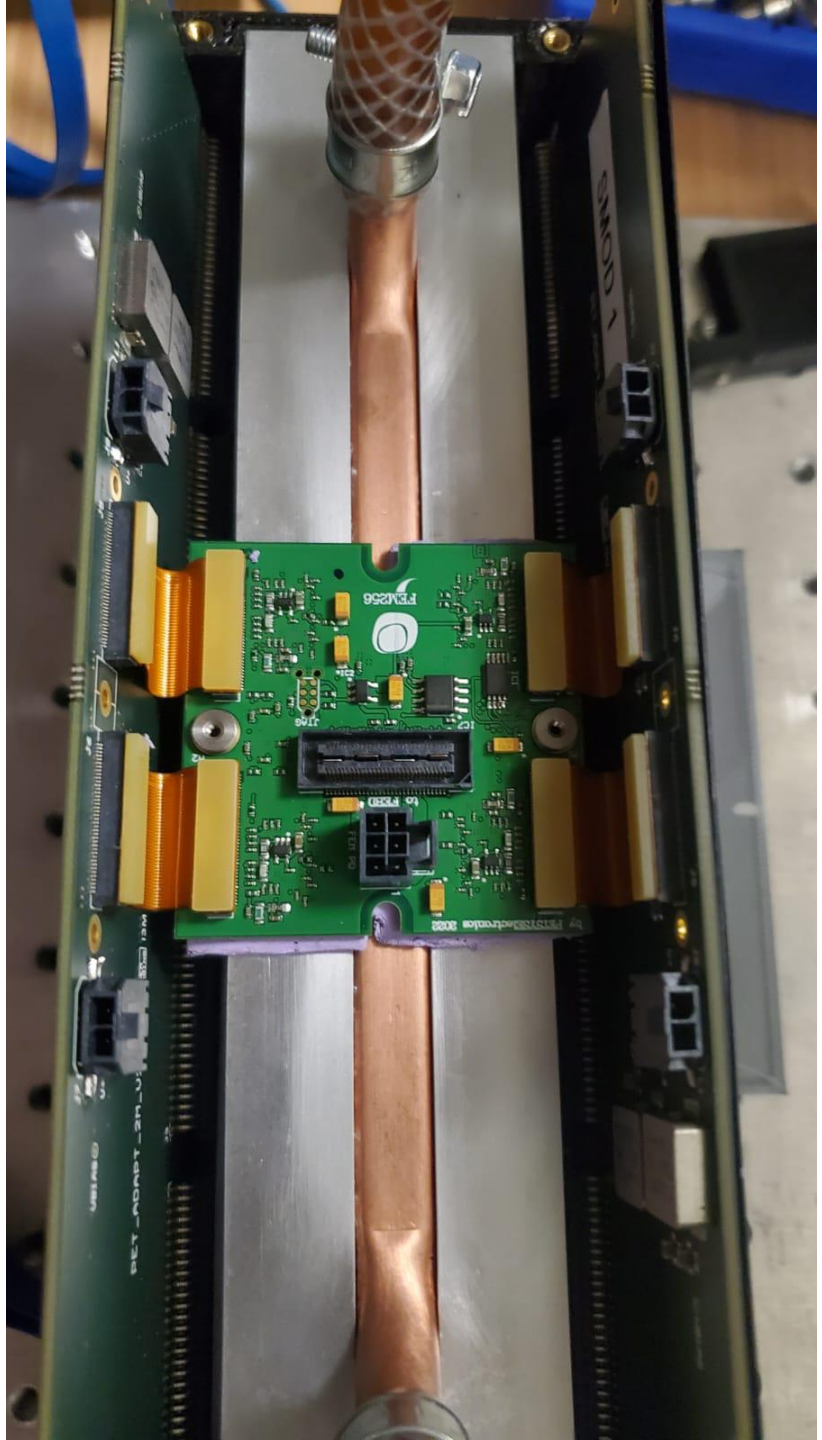
2n Readout (8+8)

SiPM array
25mmx25mm



SUPERMODULE





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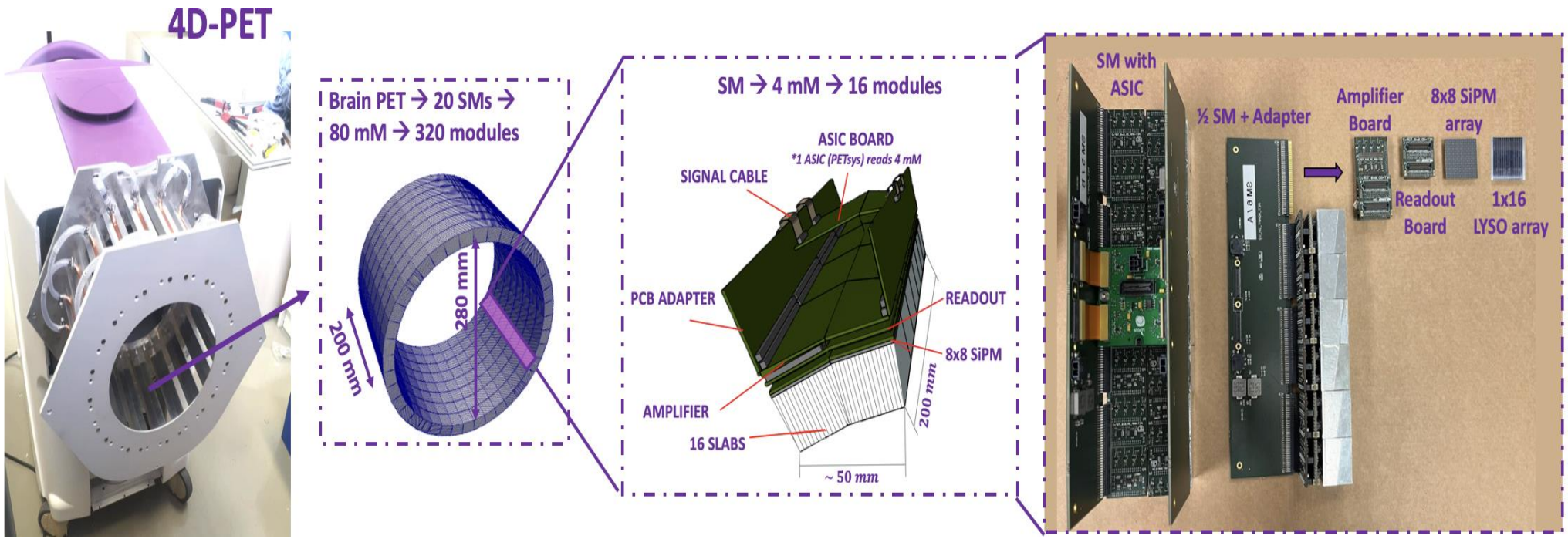
COOLING WITH PLATES

20 SUPERMODULES



SUPERMODULE CALIBRATION

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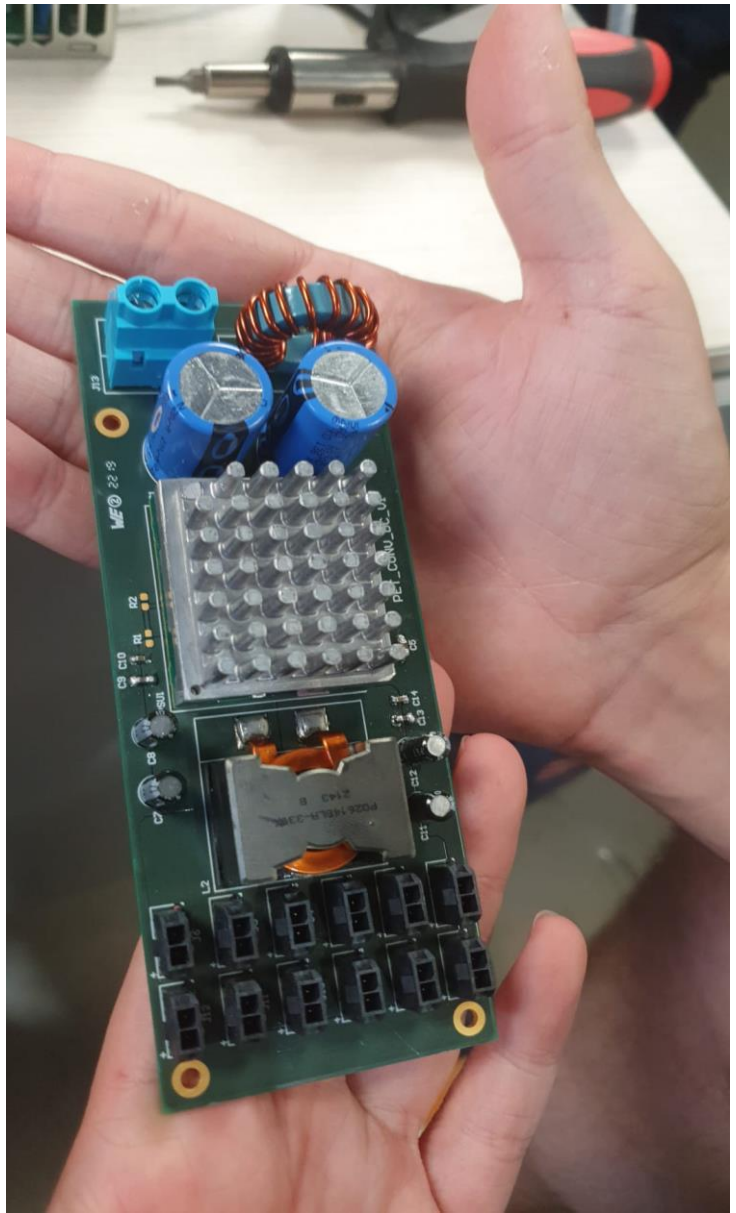
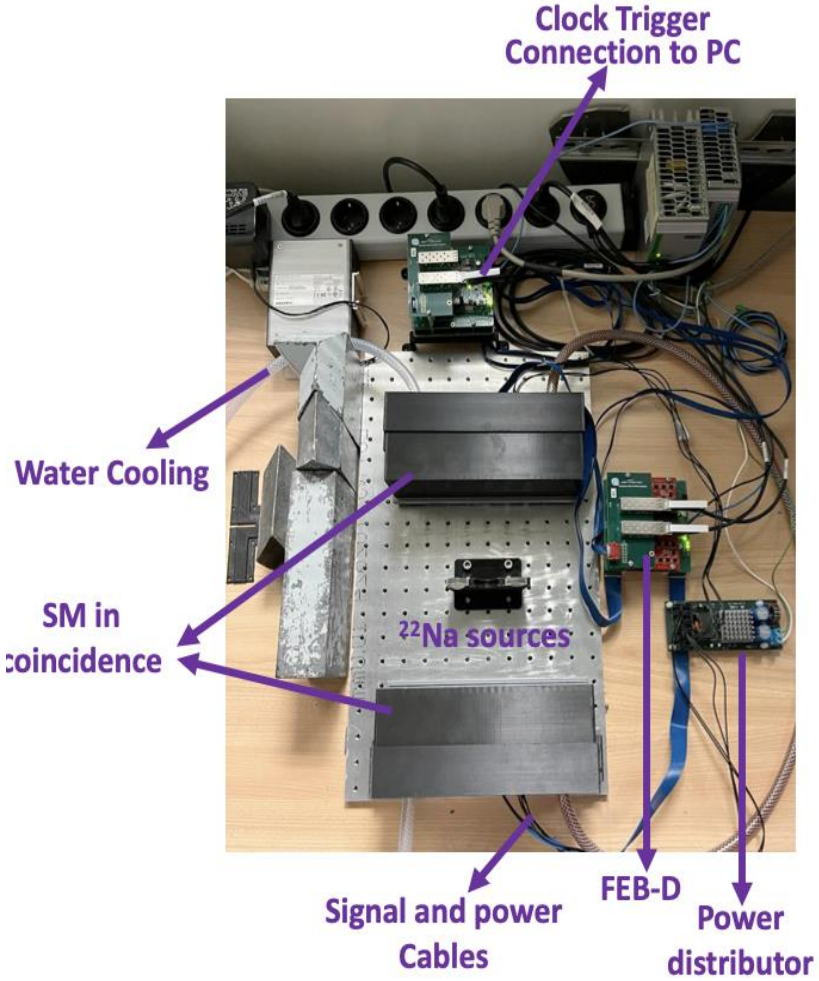
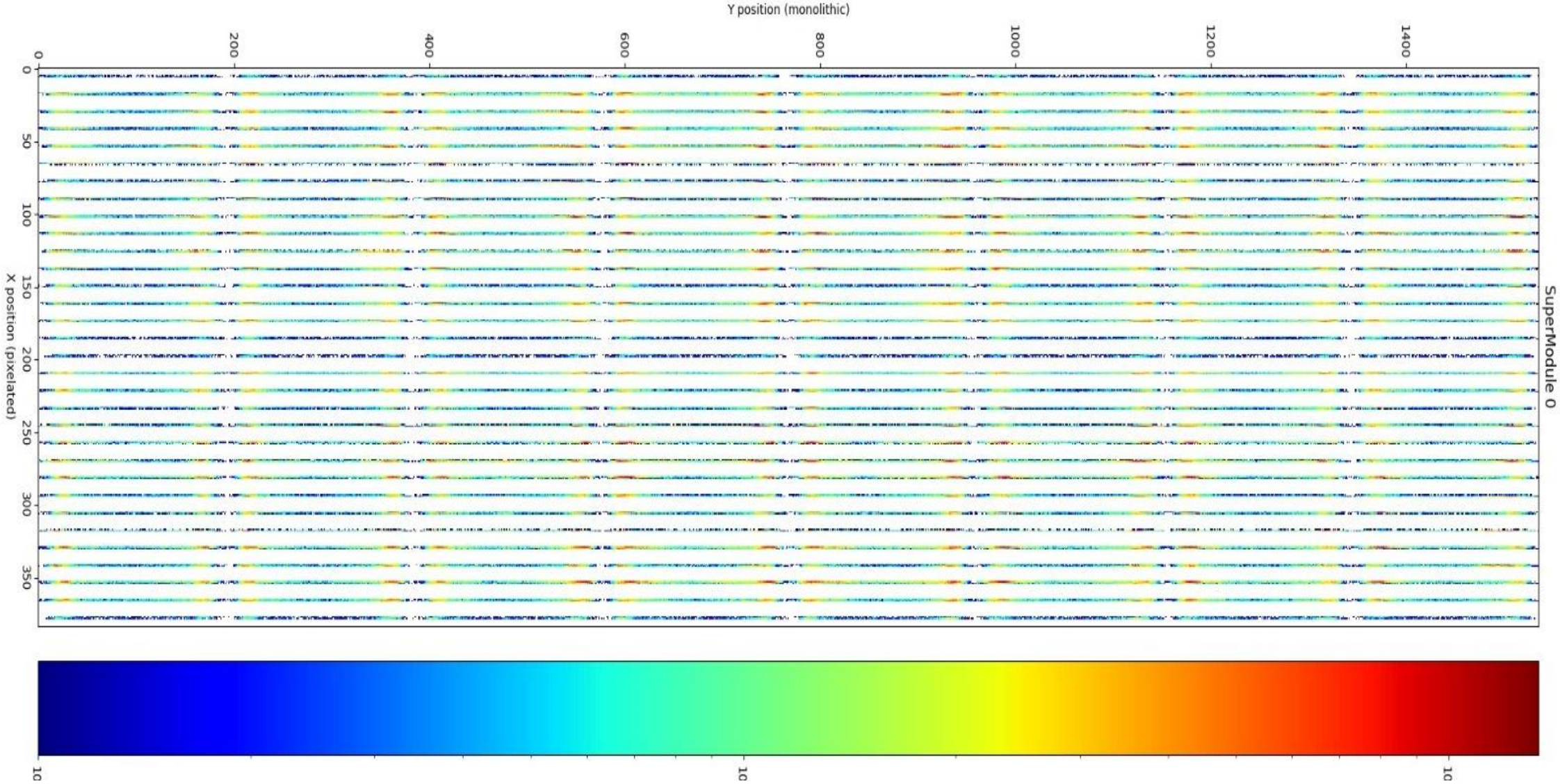
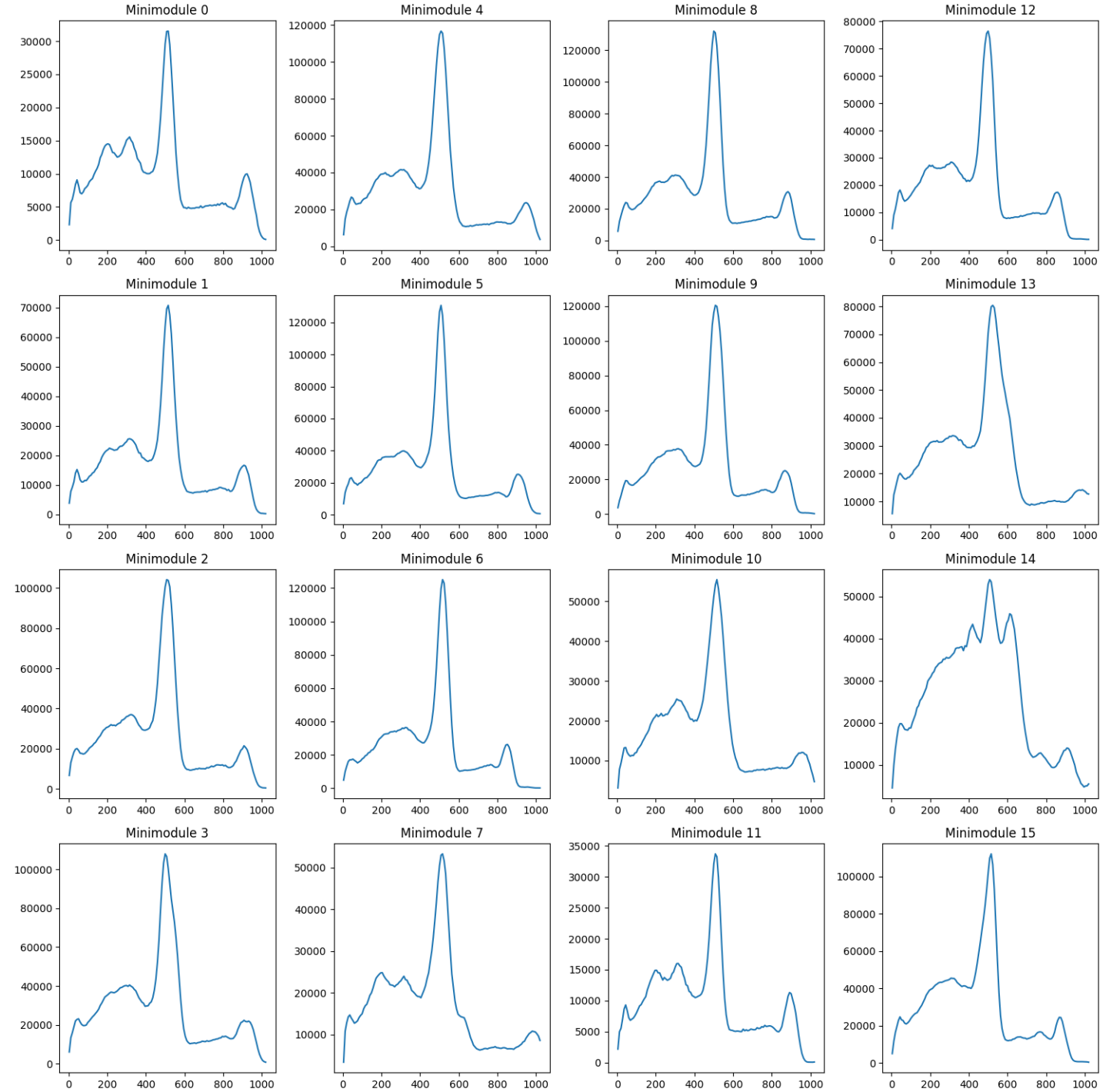
Voltage Control & Temperature Monitor





SUPERMODULE Ø





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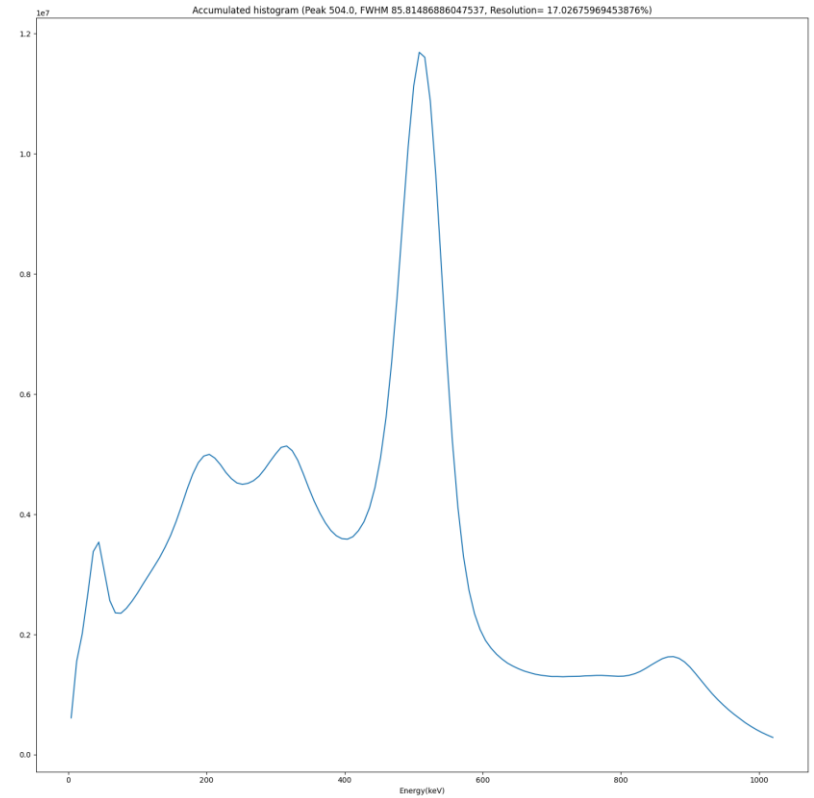
ENERGY RESOLUTION



Detector performance.
Position inside Slab
(Measurement with Pinhole)

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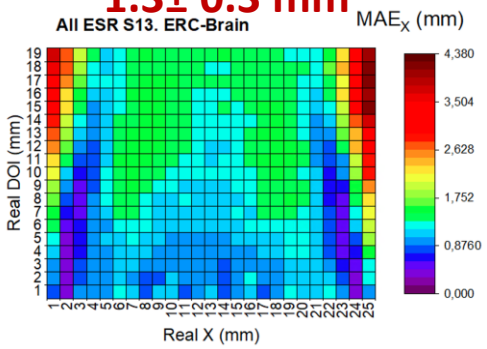
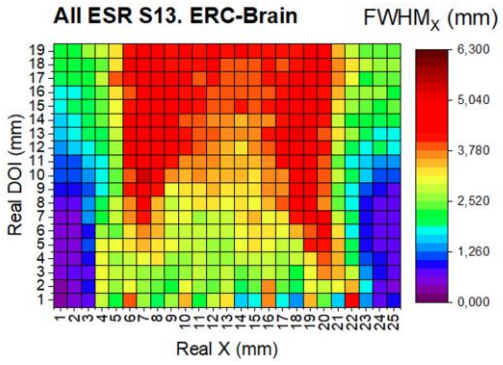
Neural Network Prediction (Slab 3)

Monolithic direction

1.3± 0.3 mm

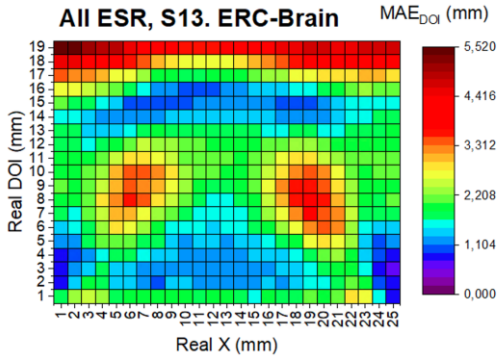


3.0± 0.5 mm

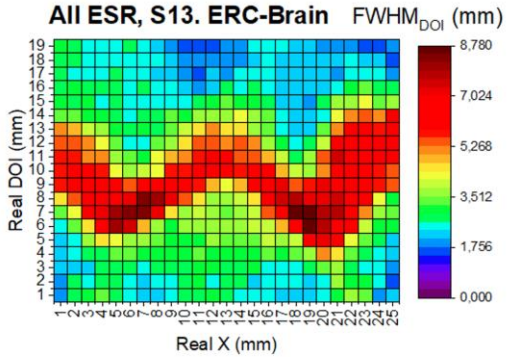


DOI direction

2.1± 0.8 mm



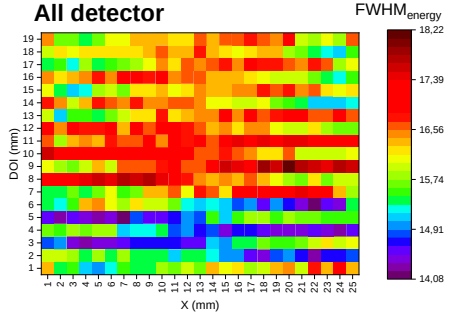
3.8± 1.4 mm



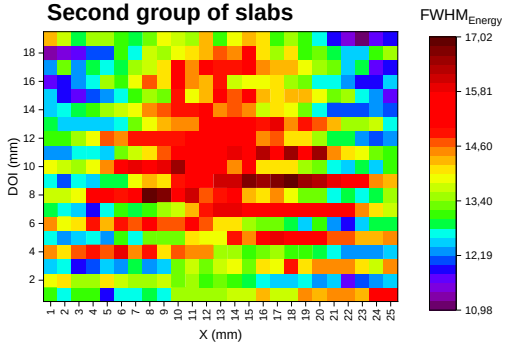
*Pinhole Measurement. 2 mm pinhole diameter

Energy

16.1 ± 0.8%

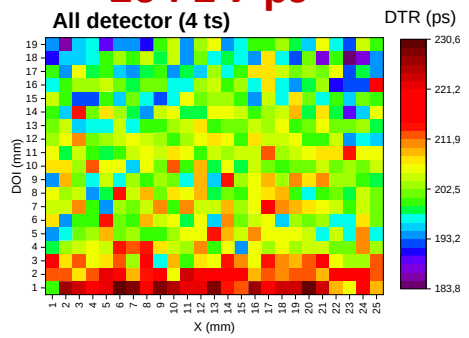


13.8 ± 1.2%

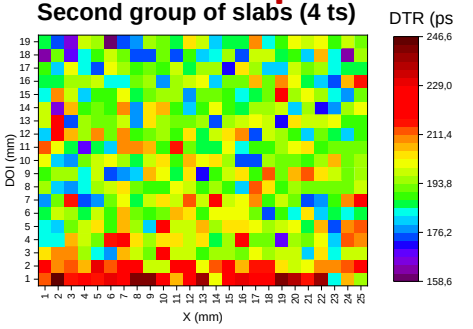


Timing DTR

204 ± 7 ps

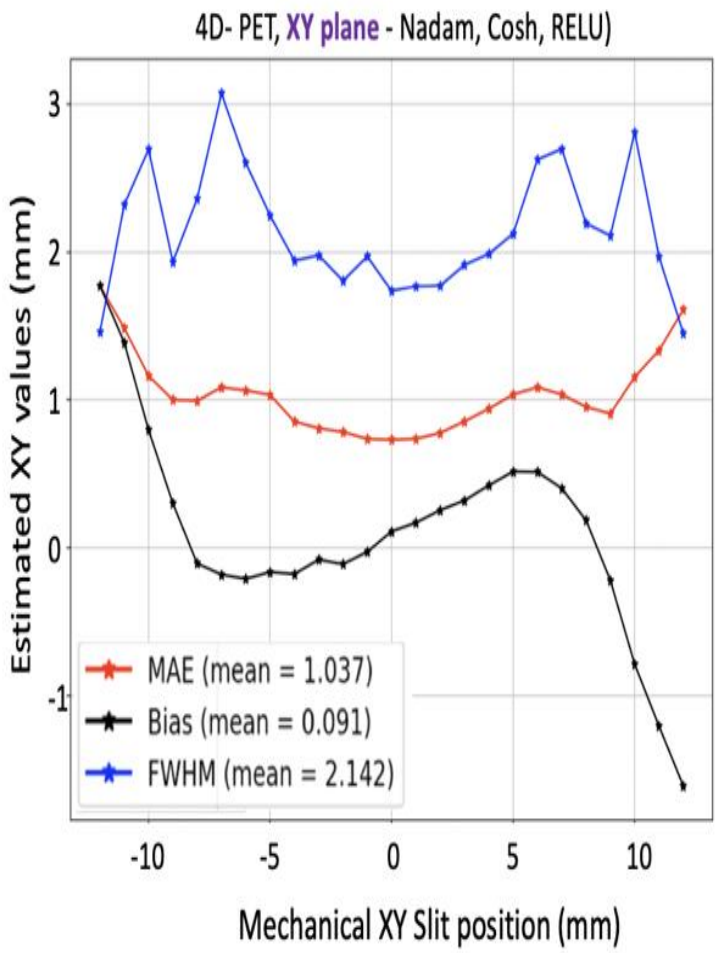


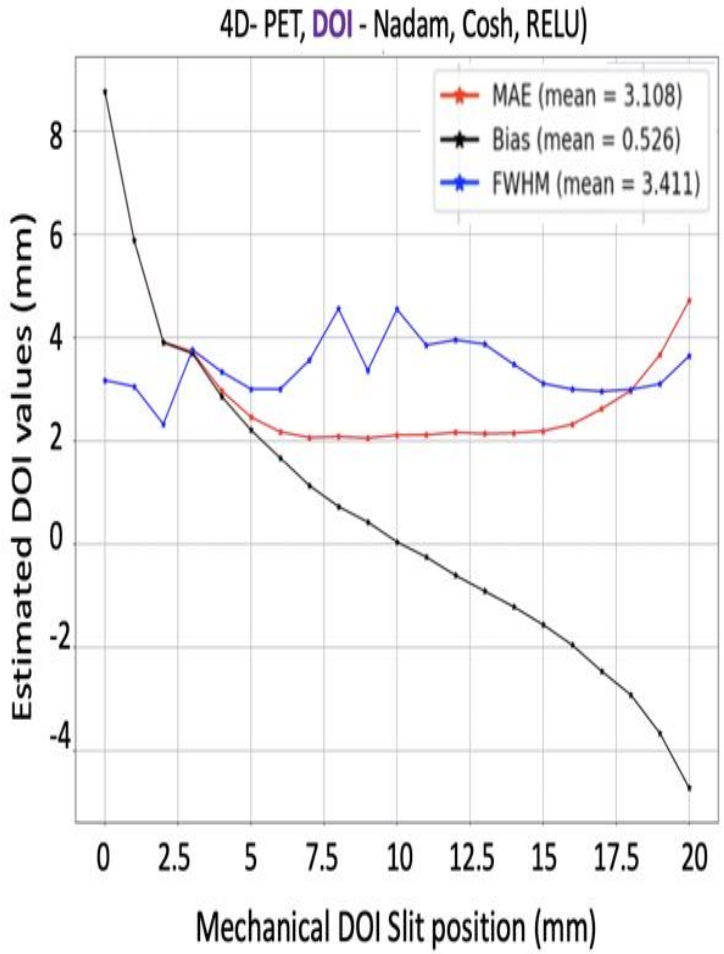
196 ± 13 ps



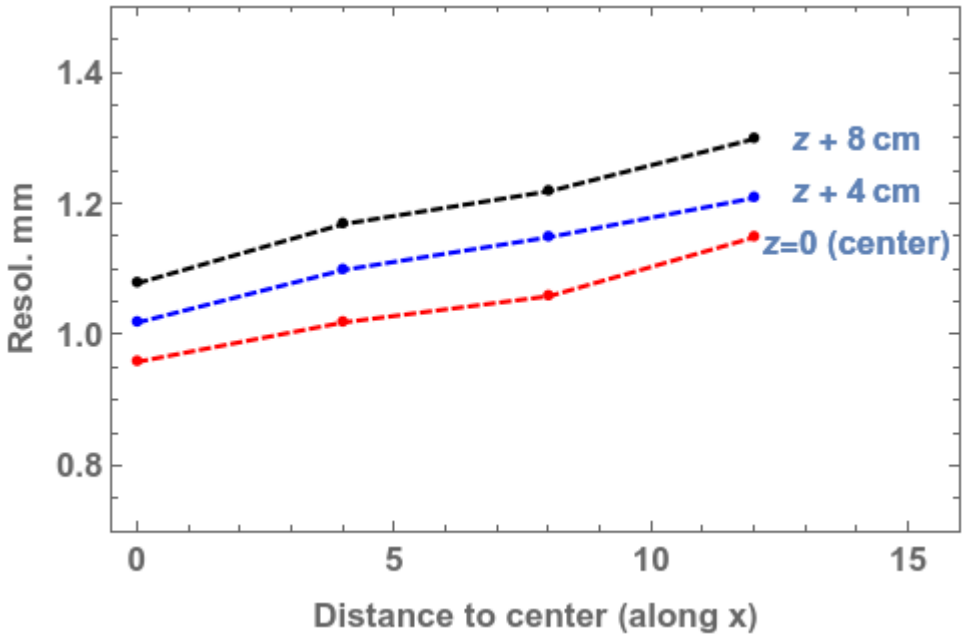
*No energy calibration

SPATIAL RESOLUTION ALONG SLAB





SPATIAL RESOLUTION



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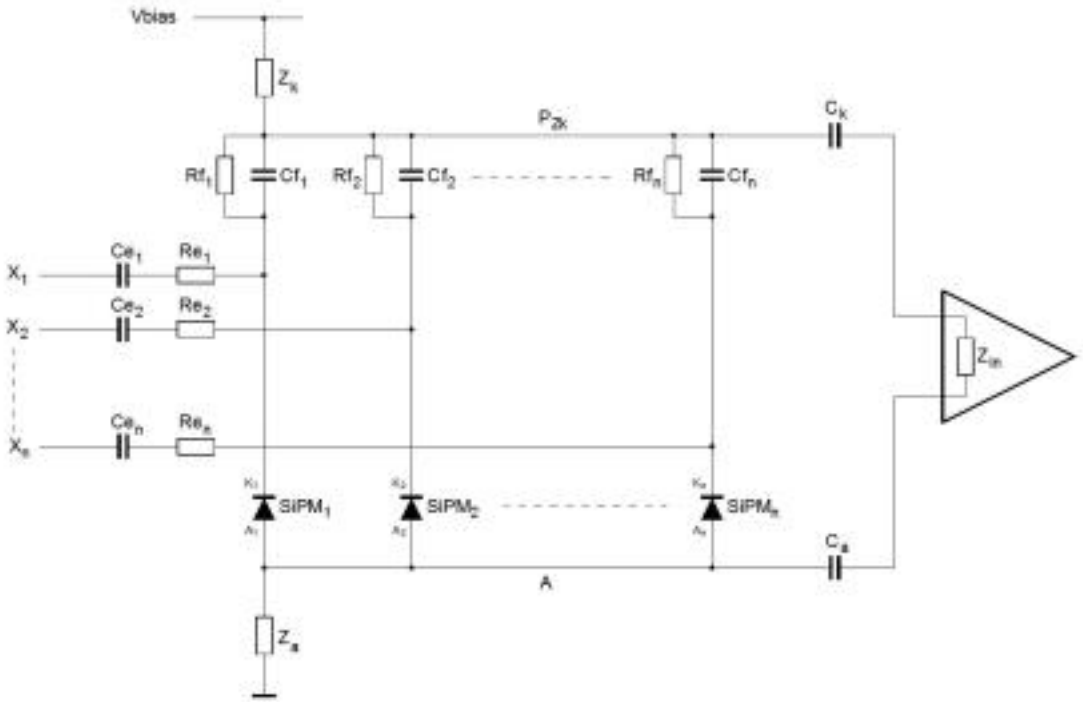
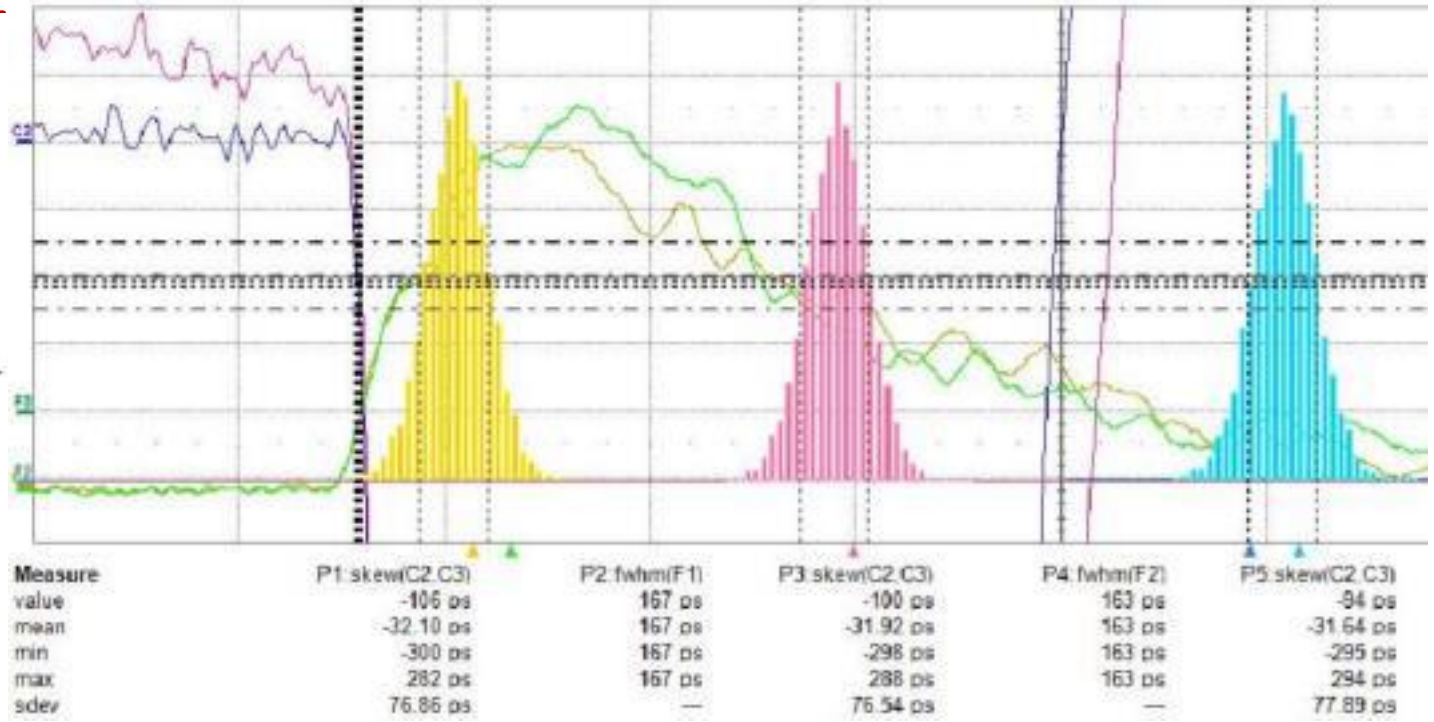


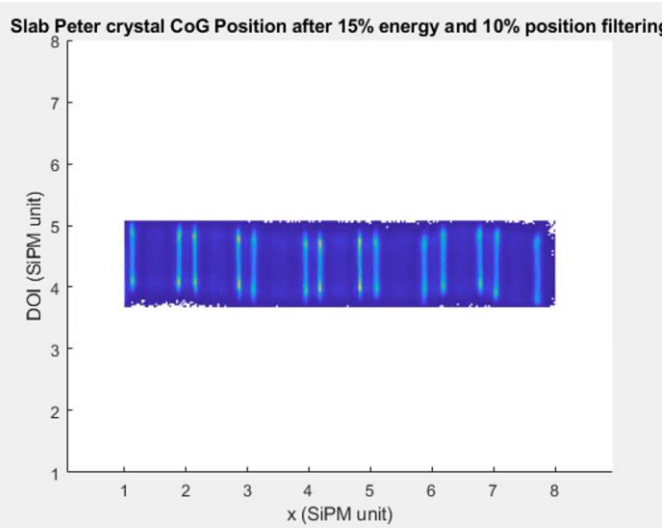


Measure	P1:skew(C2,C3)	P2:fwhm(F1)	P3:skew(C2,C3)	P4:fwhm(F2)	P5:skew(C2,C3)
value	-106 ps	167 ps	-100 ps	163 ps	-94 ps
mean	-32.10 ps	167 ps	-31.92 ps	163 ps	-31.64 ps
min	-300 ps	167 ps	-298 ps	163 ps	-295 ps
max	282 ps	167 ps	288 ps	163 ps	294 ps
sdev	76.86 ps	—	76.54 ps	—	77.89 ps

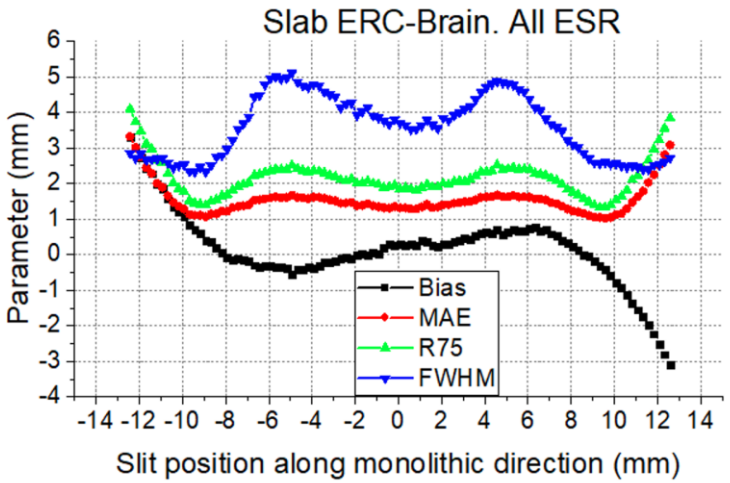
Detector performance. Slit measurement

4D-PET

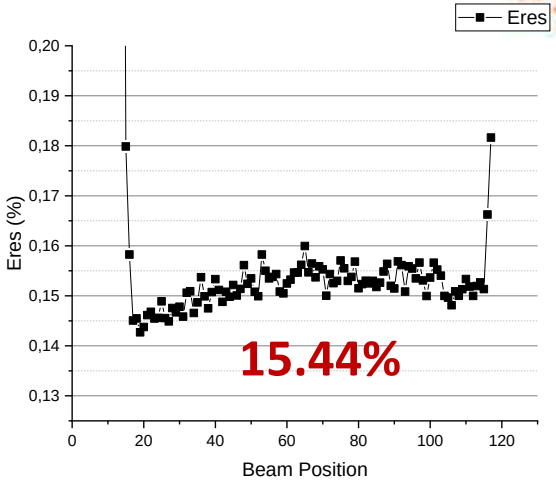
Slab Identification



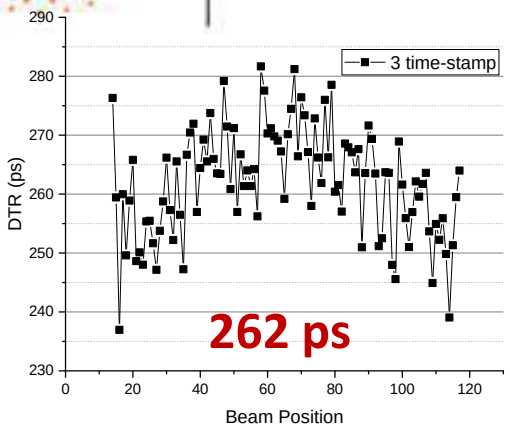
Neural Network Prediction

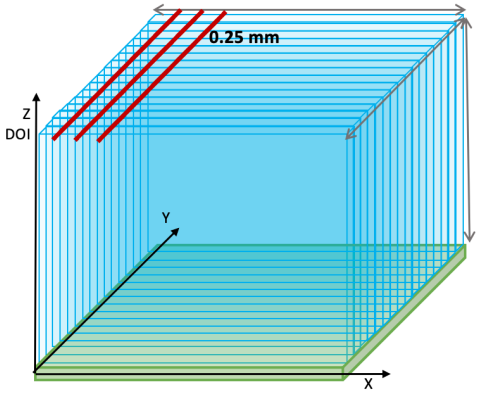


Energy

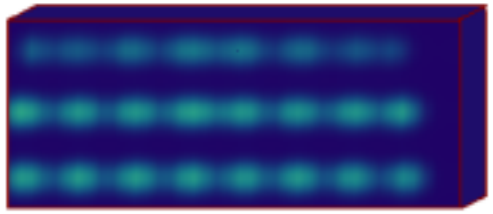


Timing

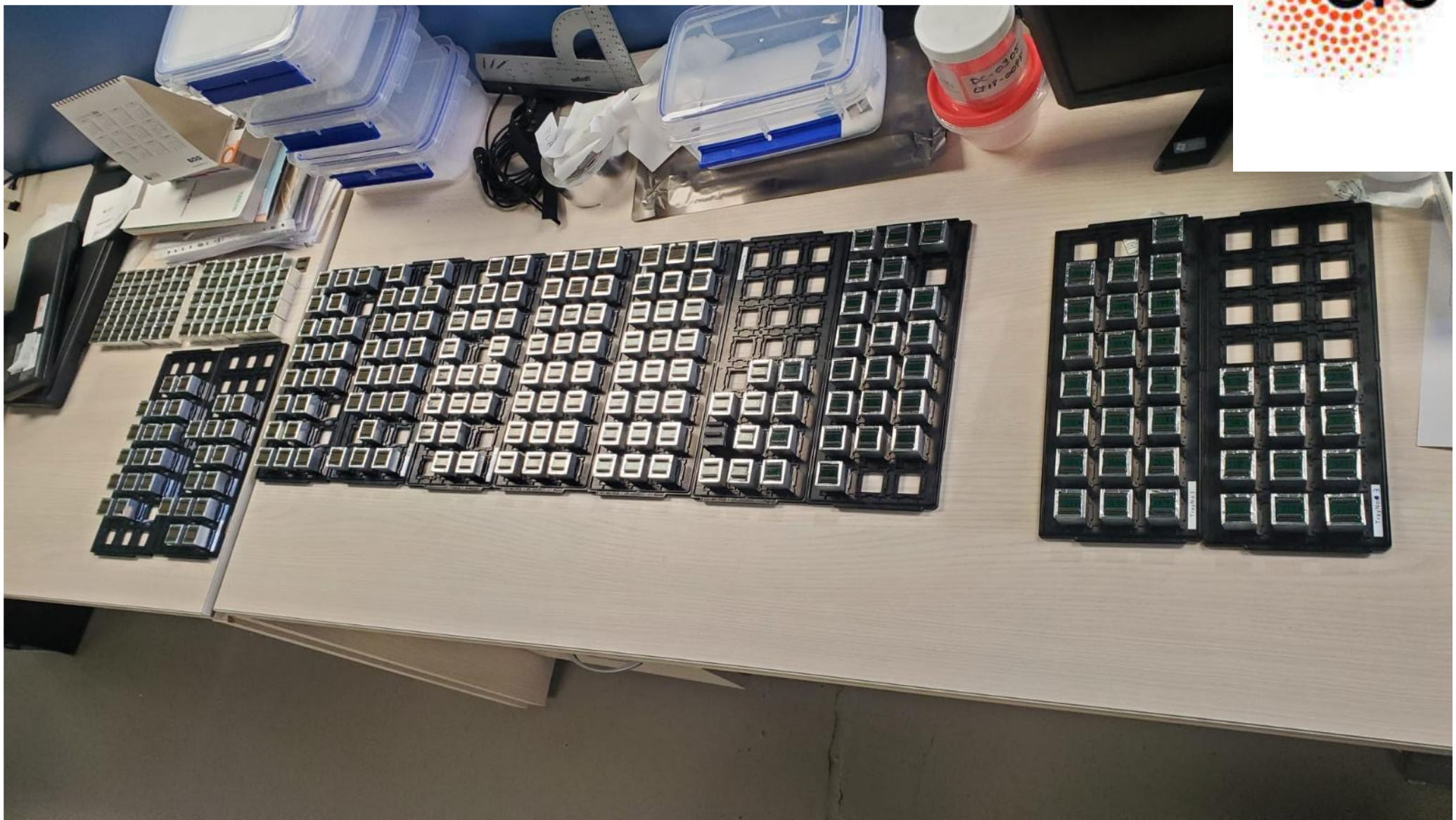


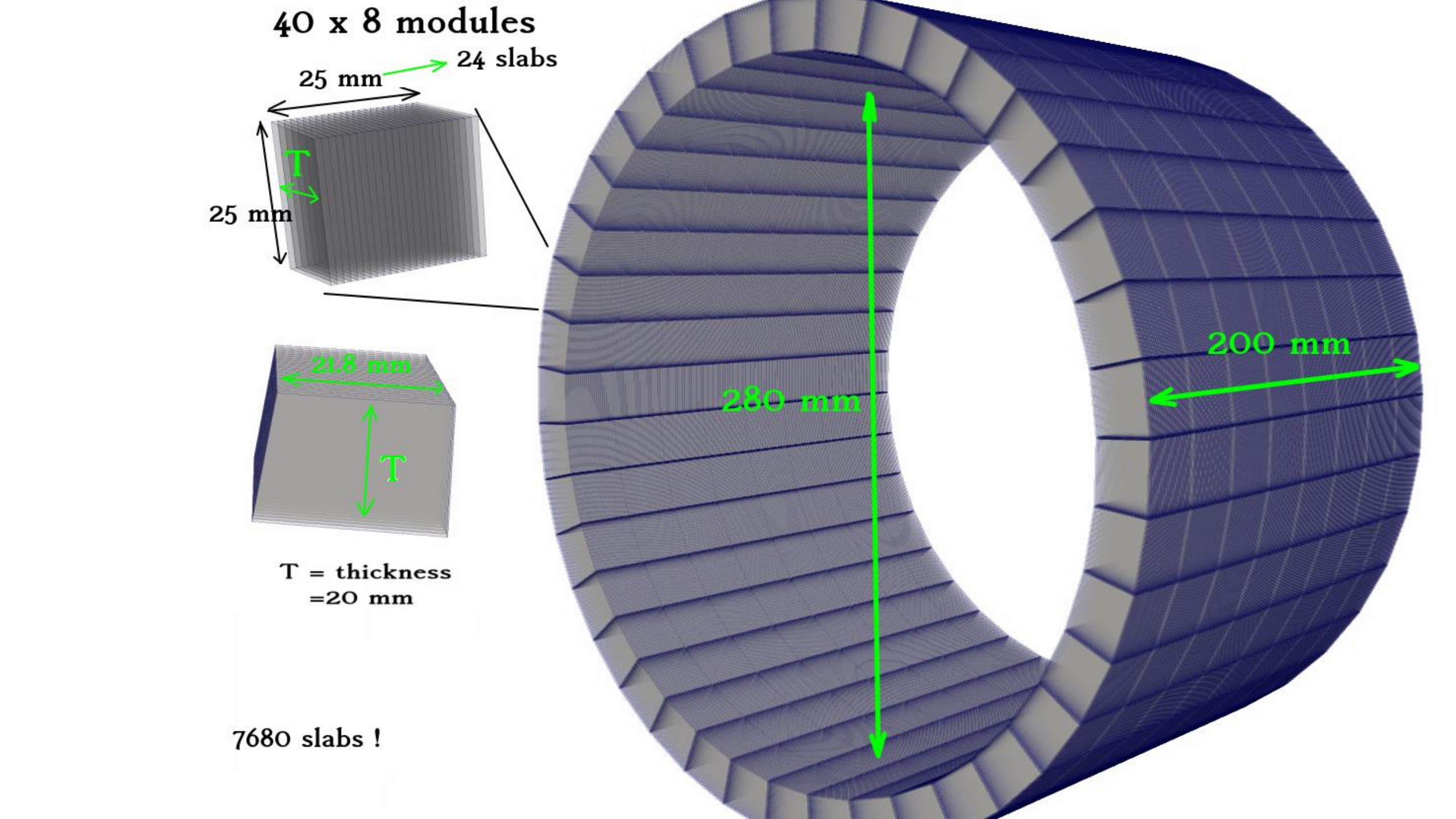


MAE (mm)	R75 (mm)	FWHM (mm)
1.5±0.4	2.1±0.5	3.5±0.9



MOUNTING ALL CRYSTAL MODULES




40 x 8 modules
24 slabs
25 mm
T
25 mm
21.8 mm
T
T = thickness
=20 mm
7680 slabs !
280 mm
200 mm

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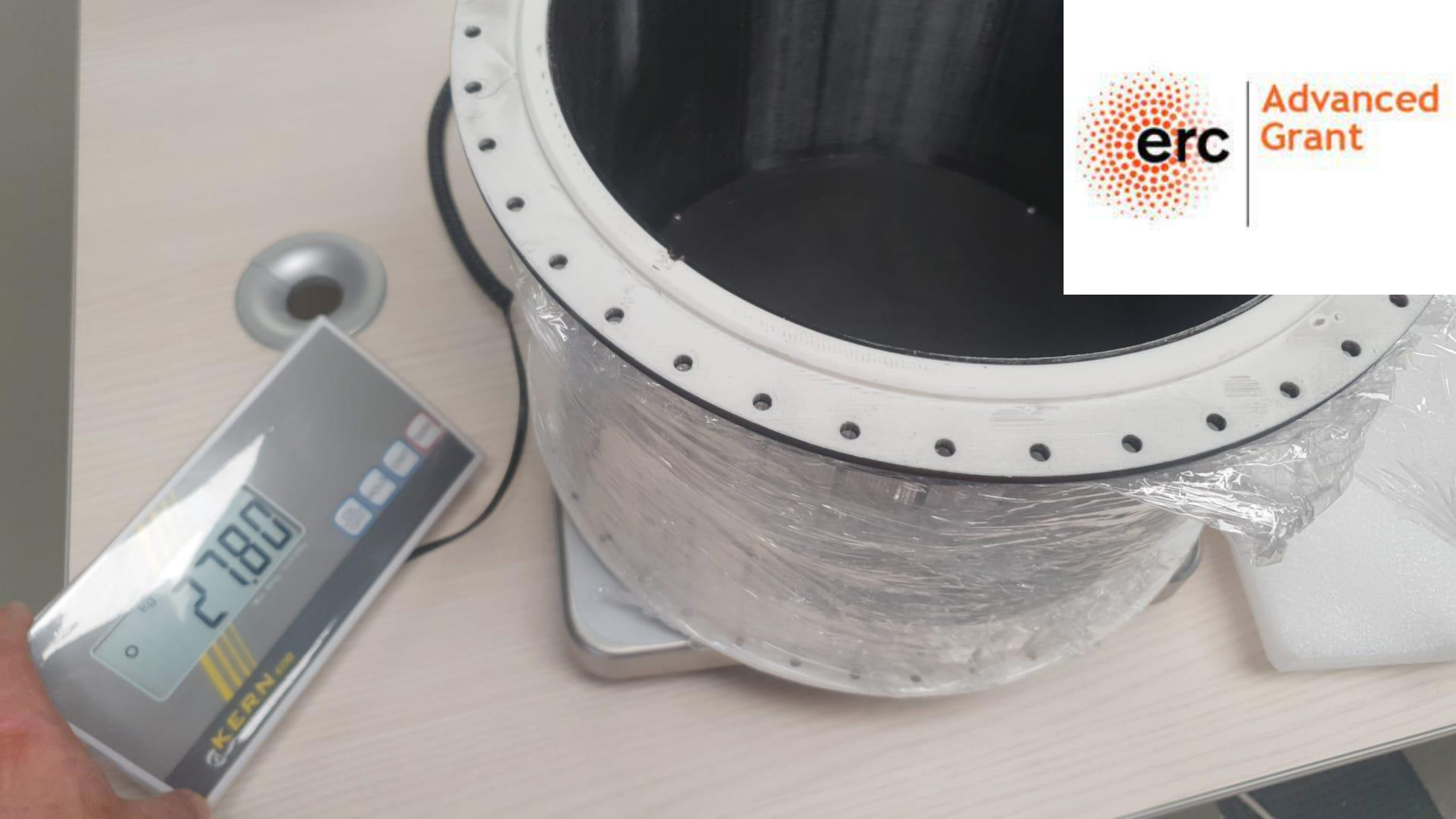

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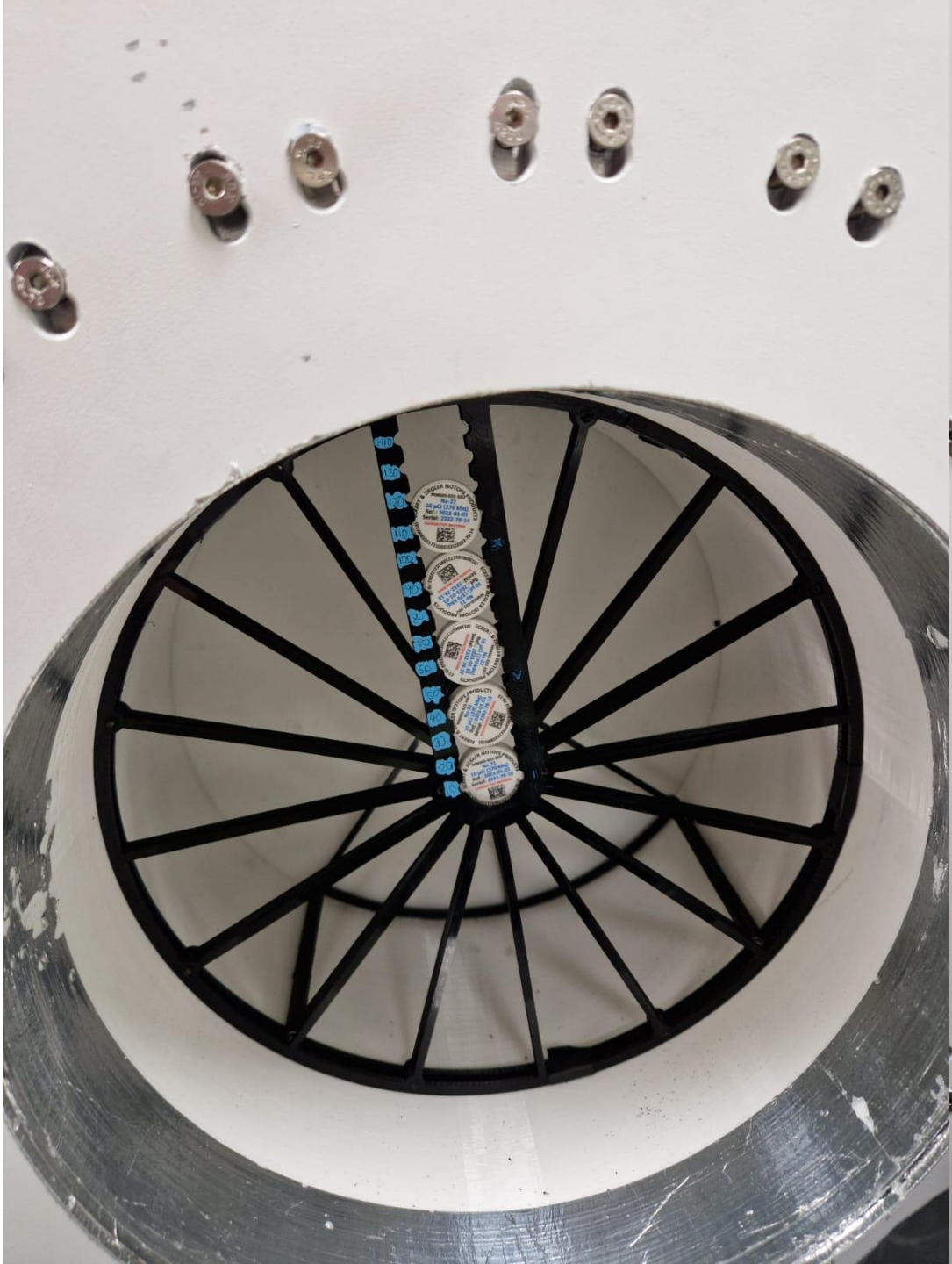
DATA PROCESSING UNIT



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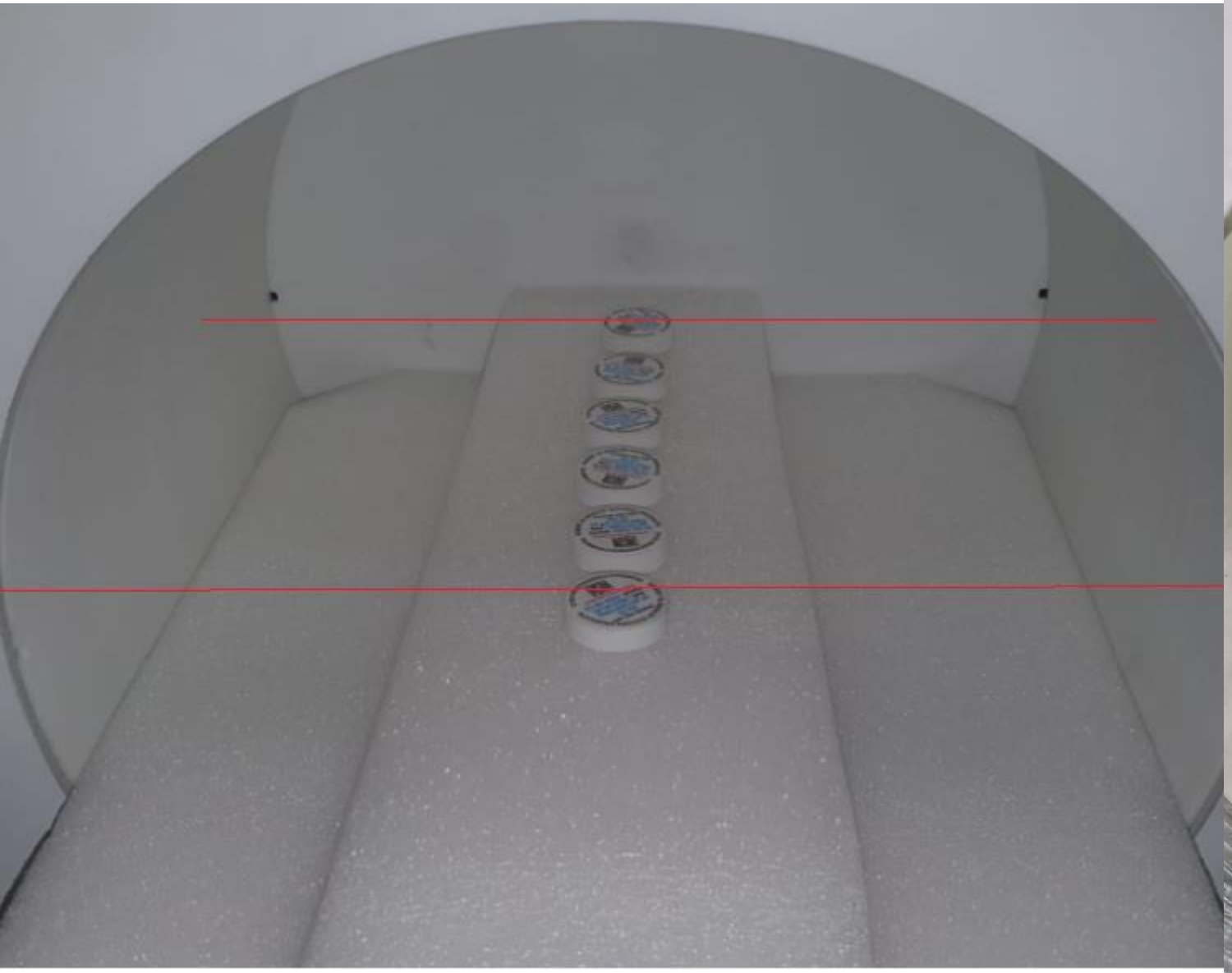
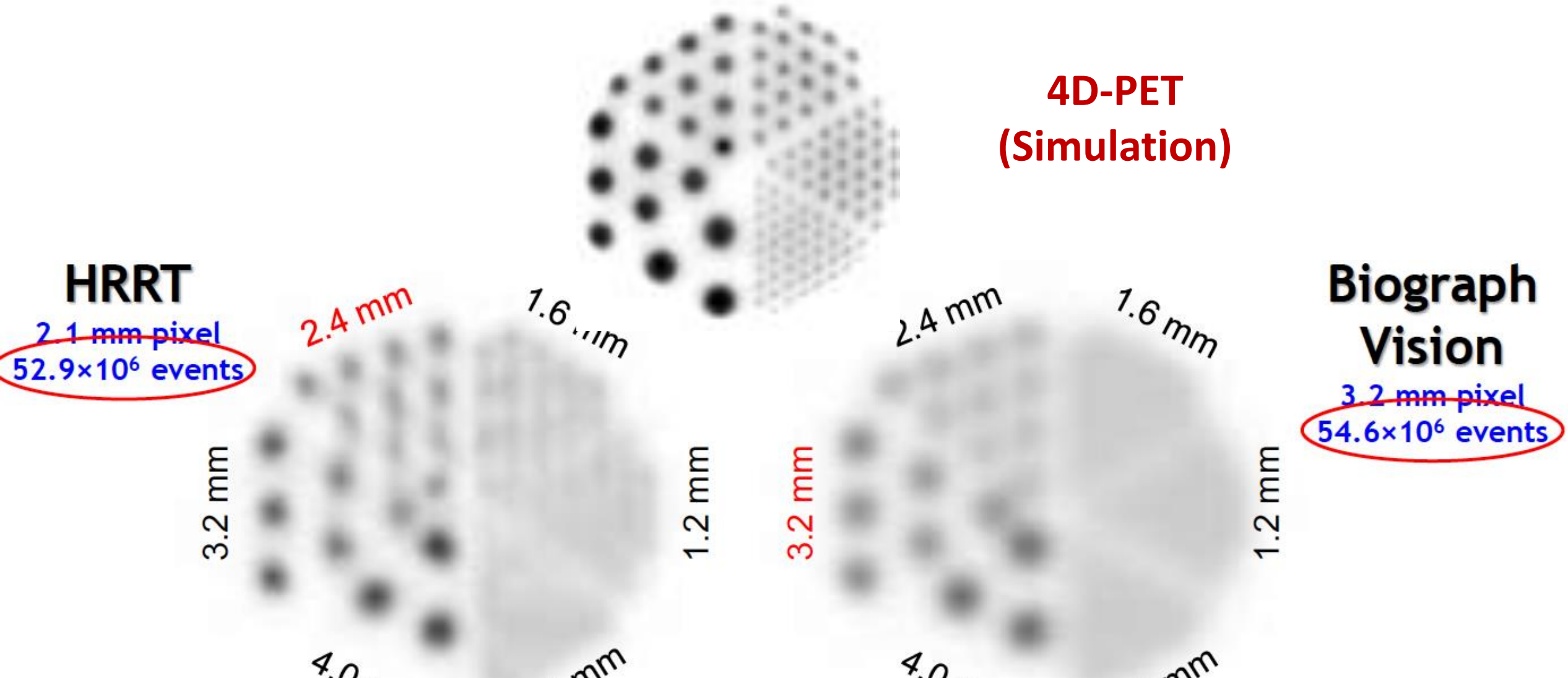


IMAGING PERFORMANCE: DERENZO PHANTOM



4D-PET

4D-PET (simulation)

Siemens Biograph MCT (simulation)

Siemens Biograph MCT (real data, paper)

Now

4D-PET (simulation 205 ps TOF)

Siemens Biograph Vision 205 ps TOF (simulation)

Next generation

Seeking an objective comparison:
HOFFMANN PHANTOM SIMULATIONS

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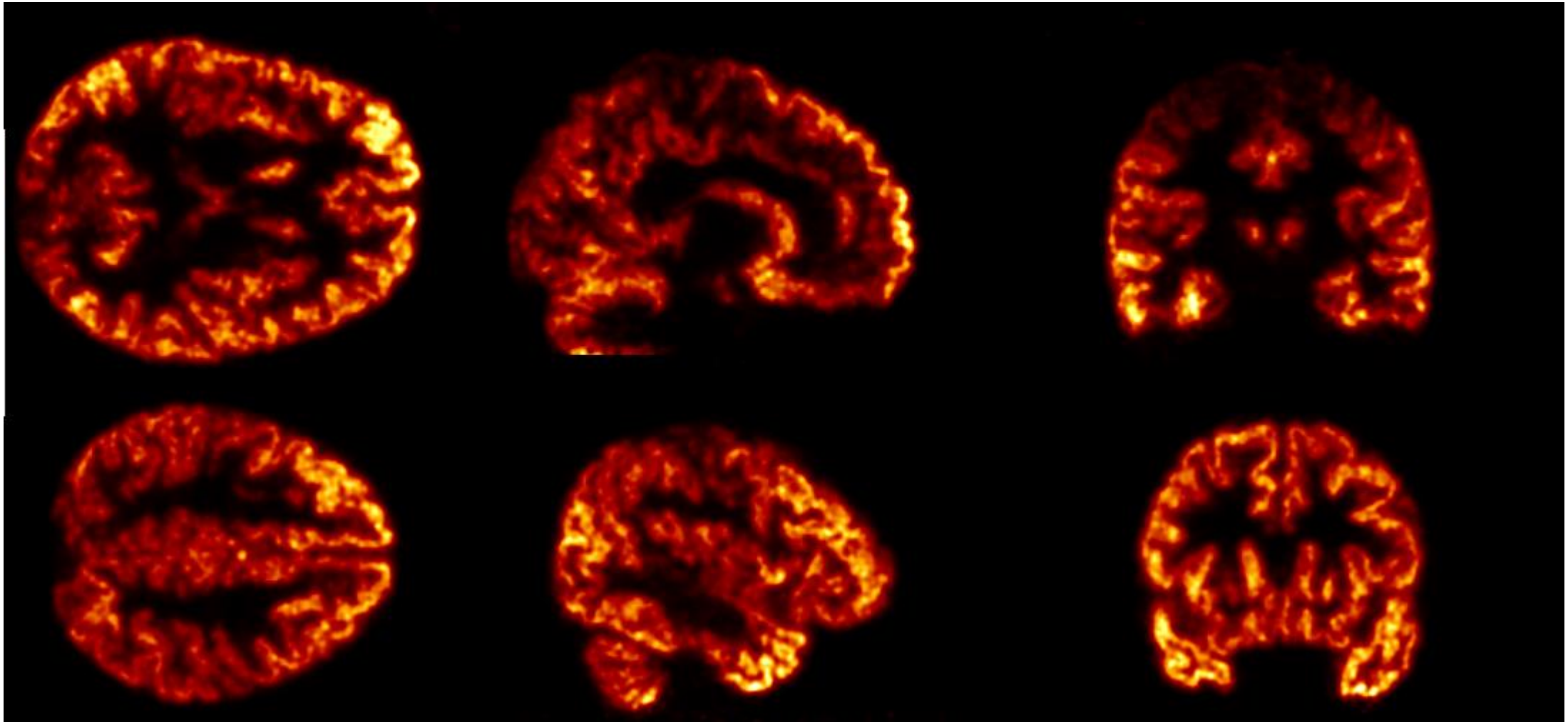
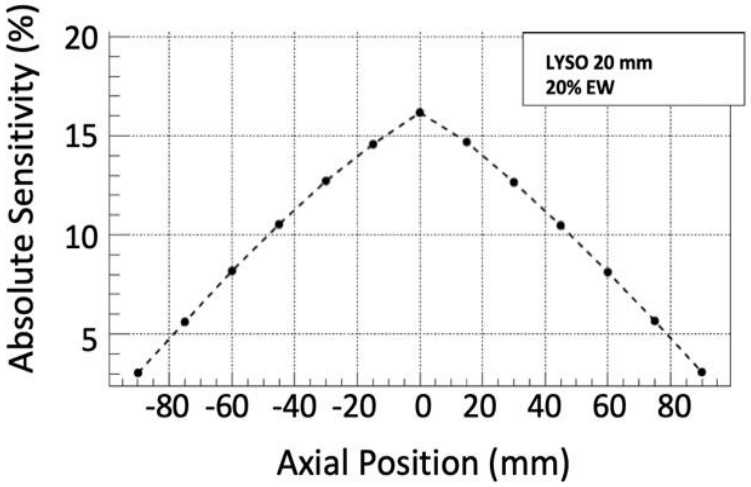
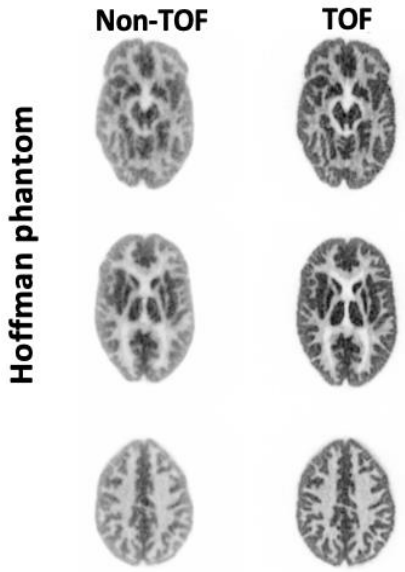
i3M
Instituto de Instrumentación para Imagen Molecular

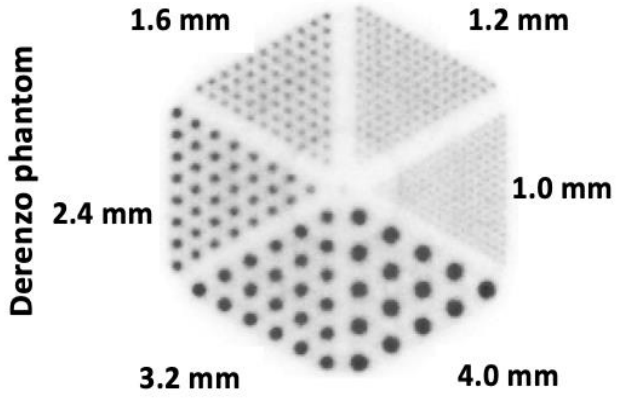
NEW PET PHANTOM

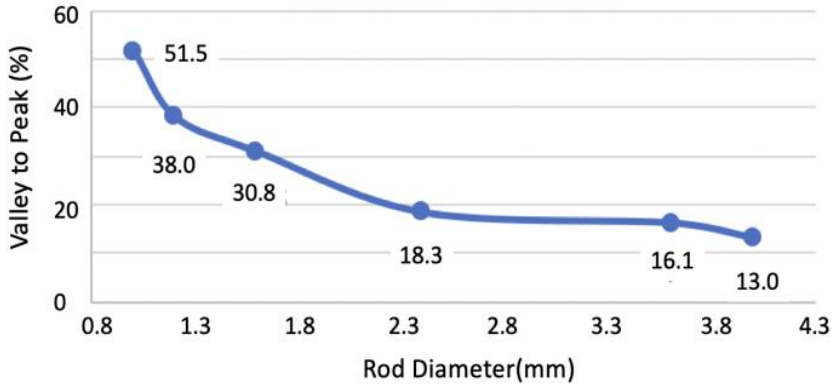


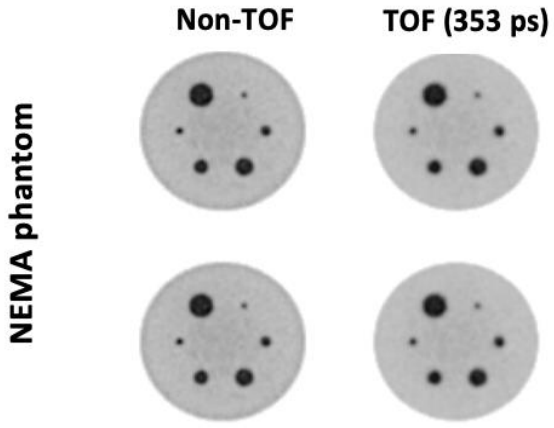
SUMMARY: EXPECTED PERFORMANCE

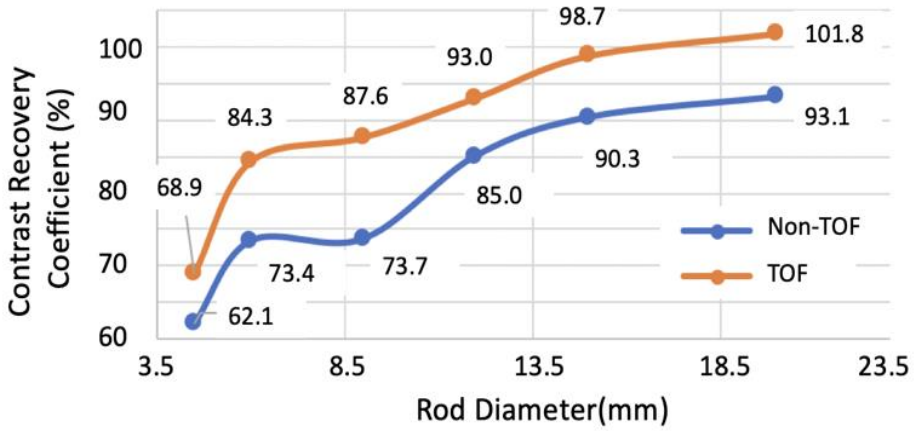












SENSITIVITY and RESOLUTION of Brain PET, existing and under development

4D-PET

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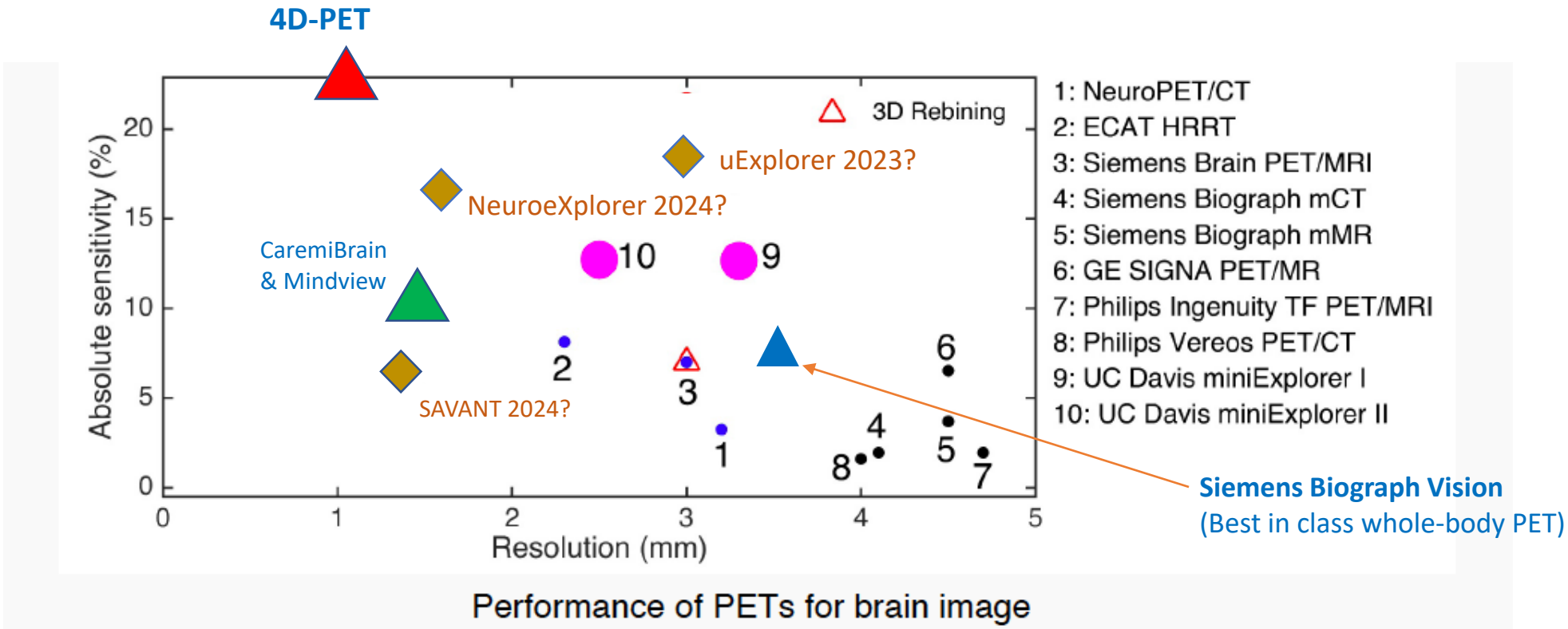
- Estimated sensitivity and resolution
  - Performance of current available PETs (1-8) are poor for imaging human brains.
  - The sensitivity is estimated for 25 cm length line source using data measured using 70 cm length source by following NEMA NU 2-2012 standard.



Performance of PETs for brain image

(Initial plot courtesy of Dr. Junwei Du, UC Davis)

CONCLUSIONS: PROJECT PLAN FOR REAL DATA

4D-PET

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SCANNER CALIBRATION & PHANTOM MEASUREMENTS ONGOING

First 3 human patients in July

Dr. John Prior

Compare Images with SIEMENS PET BIOGRAPH VISION

ETHICAL COMMITTEE DOCUMENTATION in Preparation

Centre hospitalier universitaire vaudois