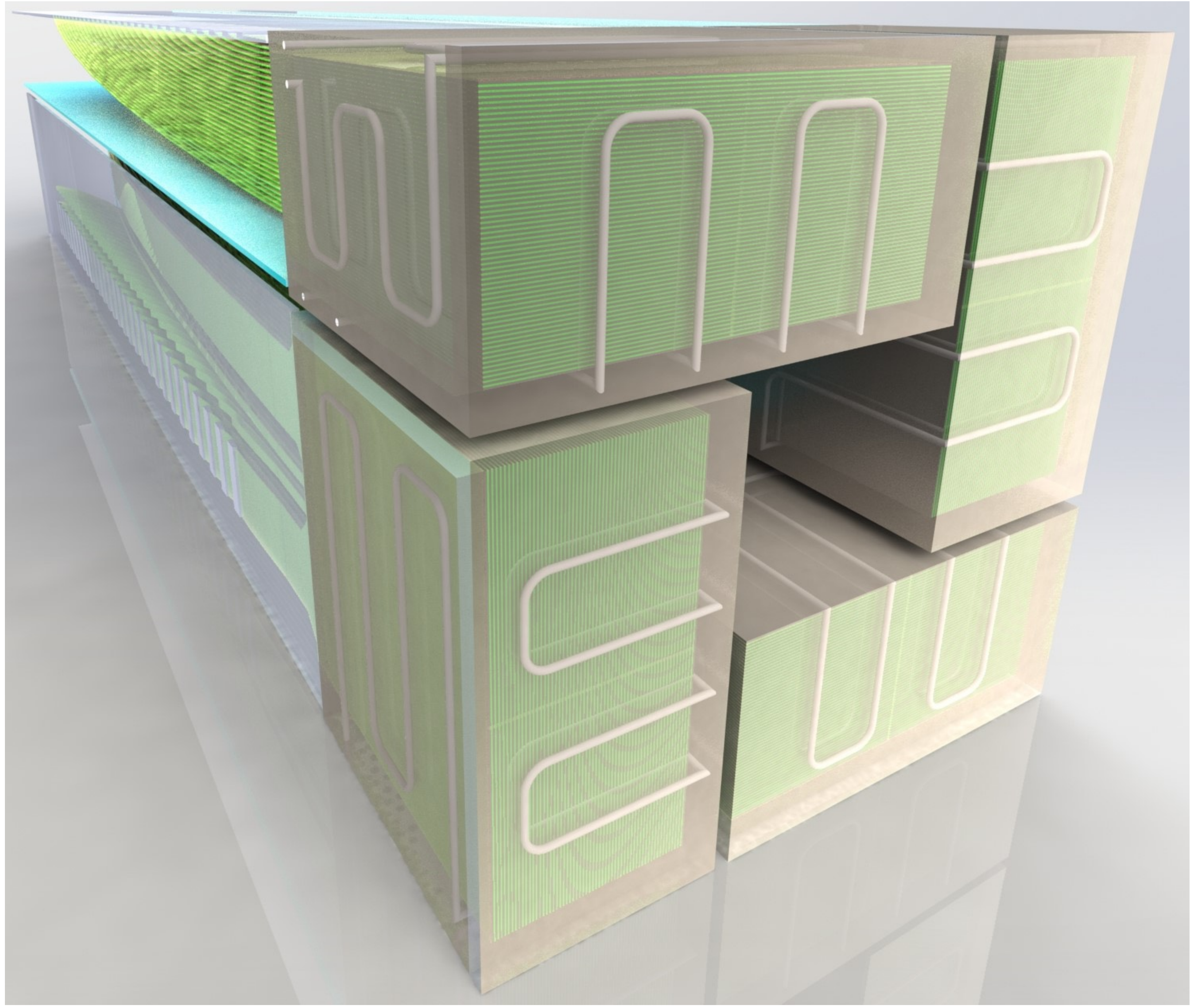
100μPET

ULTRA-HIGH RESOLUTION MOLECULAR IMAGING



Pioneering ultra-high resolution molecular imaging with monolithic silicon pixel detectors

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Foreword

WHAT: Develop and build a **small-animal PET** scanner to **pioneer ultra-high resolution molecular imaging**

HOW: Use multi-layer of **pixelated monolithic silicon sensors** and **advanced reconstruction algorithms**

WHEN: Scanner ready and commissioned in **summer 2025**

Research funded by : Swiss National Science Foundation Sinergia

The 100μPET team

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Giuseppe Iacobucci
- P.I.

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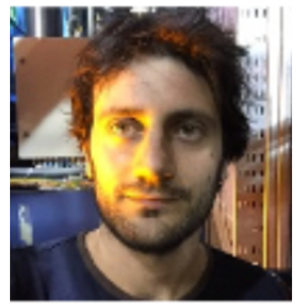
- System integration
- Laboratory test

Jihad Saidi
- System simulation
- Laboratory test

Didier Ferrere
- System integration
- Laboratory test



Lorenzo Paolozzi
- Sensor design
- Analog electronics

Yannick Favre
- Board design
- RO system

Franck Cadoux
- Mechanics
- FEA calculations

EPFL

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- Physical modeling

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- Translational imaging

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- In vivo studies
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Former collaborators

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Emanuele Ripiccini
- Scanner simulation
- Image reconstr.

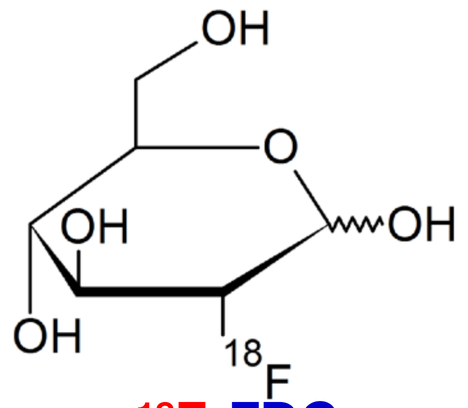
Daiki Hayakawa
- Sensor simulation
- Image reconstr.

Discussions with:
- **Roberto Cardarelli** (INFN Roma Tor Vergata & UNIGE)
- **Marzio Nessi** (CERN & UNIGE)
- **Holger Ruecker** (IHP Mikroelektronik)

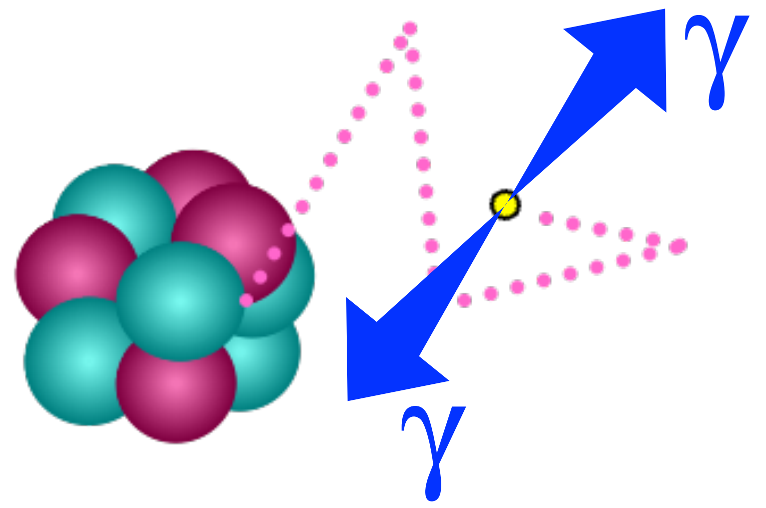
Positron Emission Tomography (PET) imaging

- **PET** is a nuclear medicine method to measure **glucose metabolism in the body**
  - Main application: **oncology** (cancers are eager for sugars), brain studies, cardiac, etc.

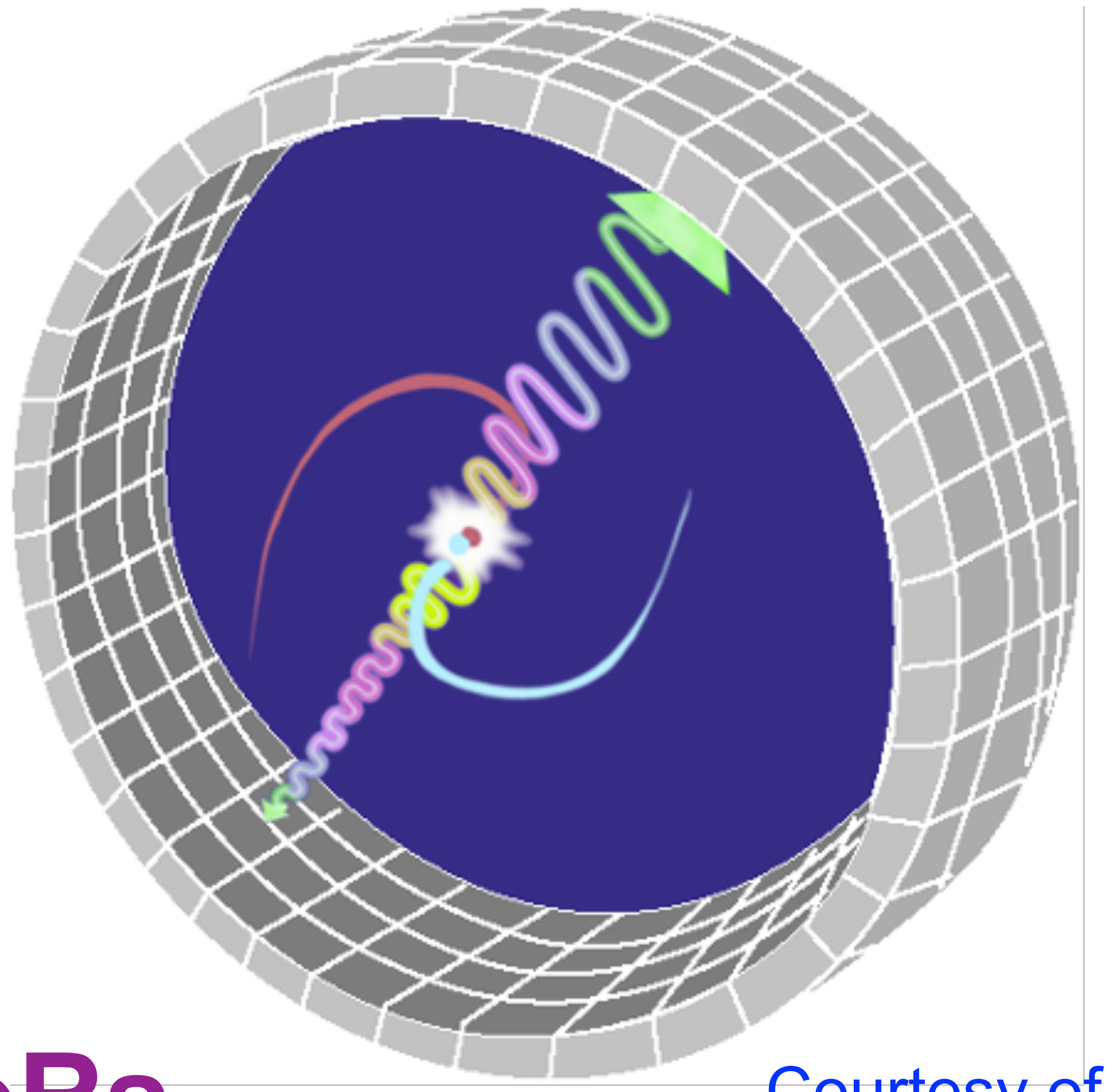
- **Positrons** from a radionuclide injected in a body (typically ^{18}**F fluorodeoxyglucose**, FDG) annihilate with electrons of the nearby tissue, emitting two **back-to-back** 511 keV photons



^{18}**F-FDG**
(fluorodeoxyglucose)



- The two photons are detected in coincidence (within few ns), defining a ***line of response (LoR) VOLUME***

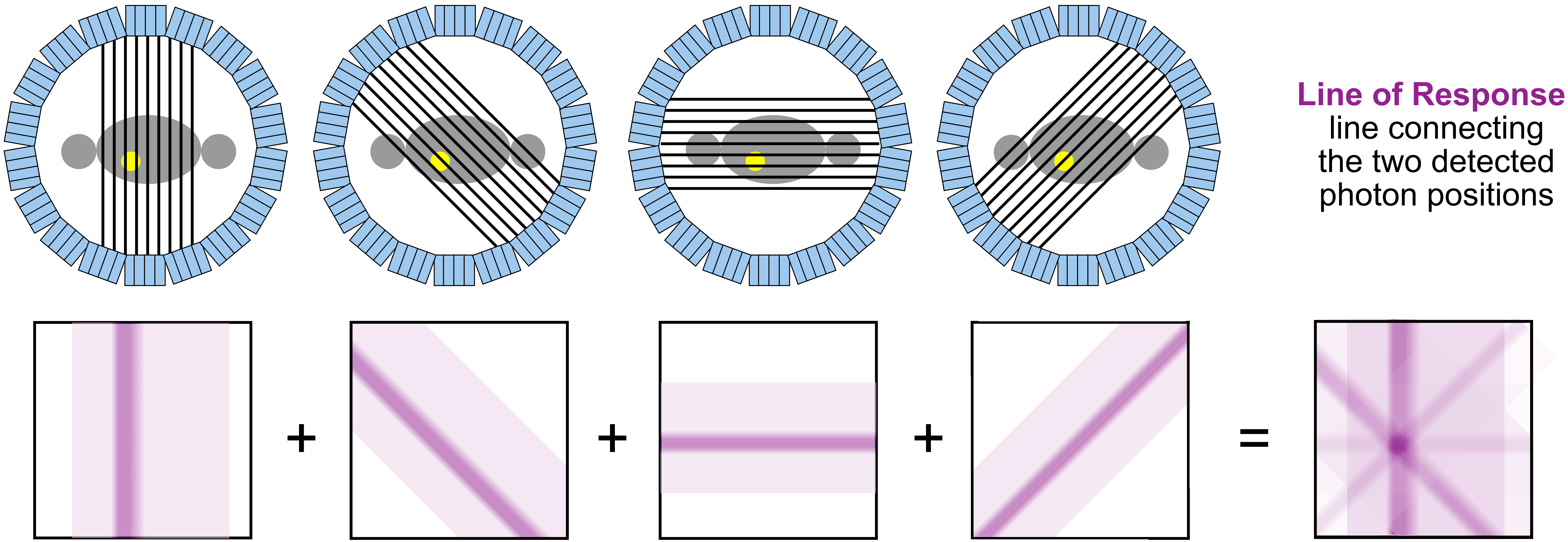


Courtesy of Siemens Healthineers

- PET images are reconstructed from the **projections of the LoRs**

Positron Emission Tomography imaging

PET images are reconstructed from the **projections of the LoRs**



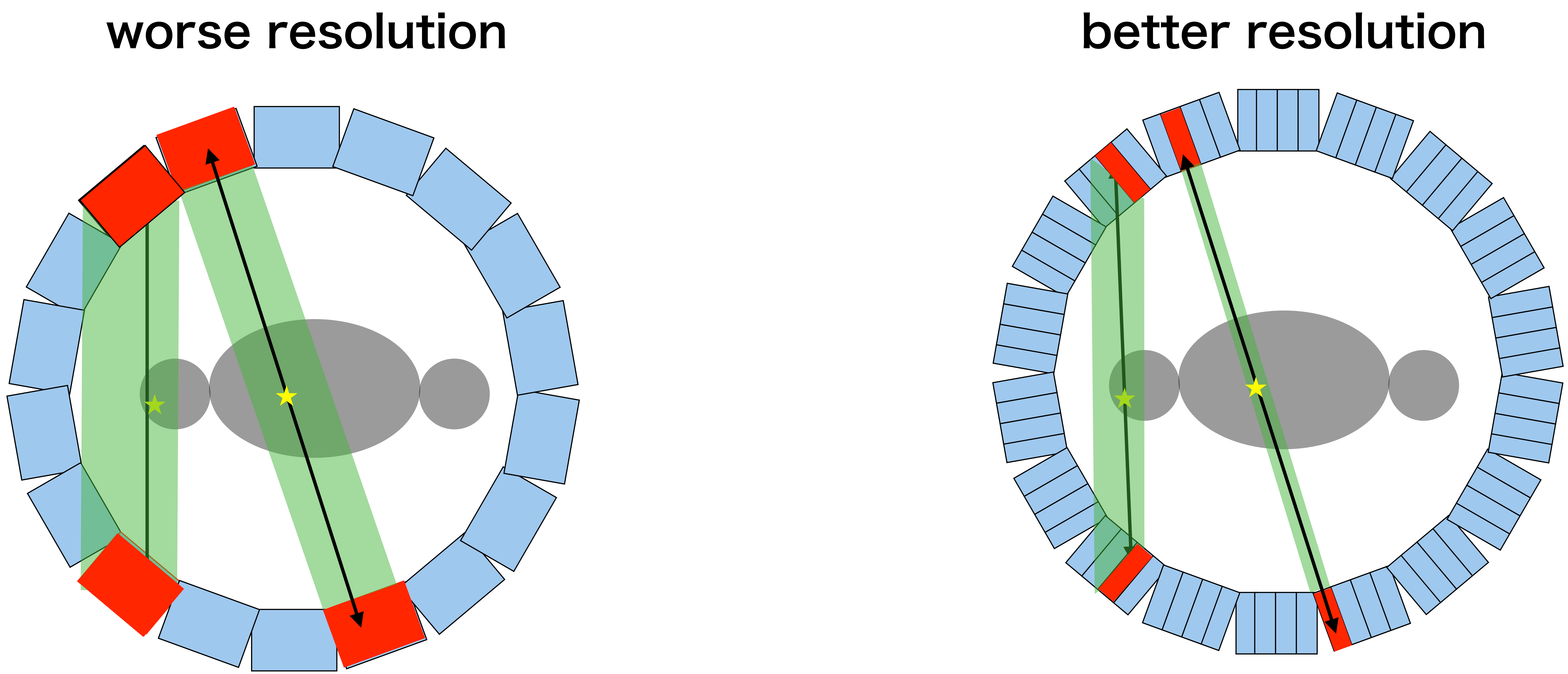
Line of Response:
line connecting
the two detected
photon positions

Important PET scanner parameters:

1. Spatial resolution;
2. Depth of Interaction (DoI);
3. Time of Flight

1. The Detector resolution

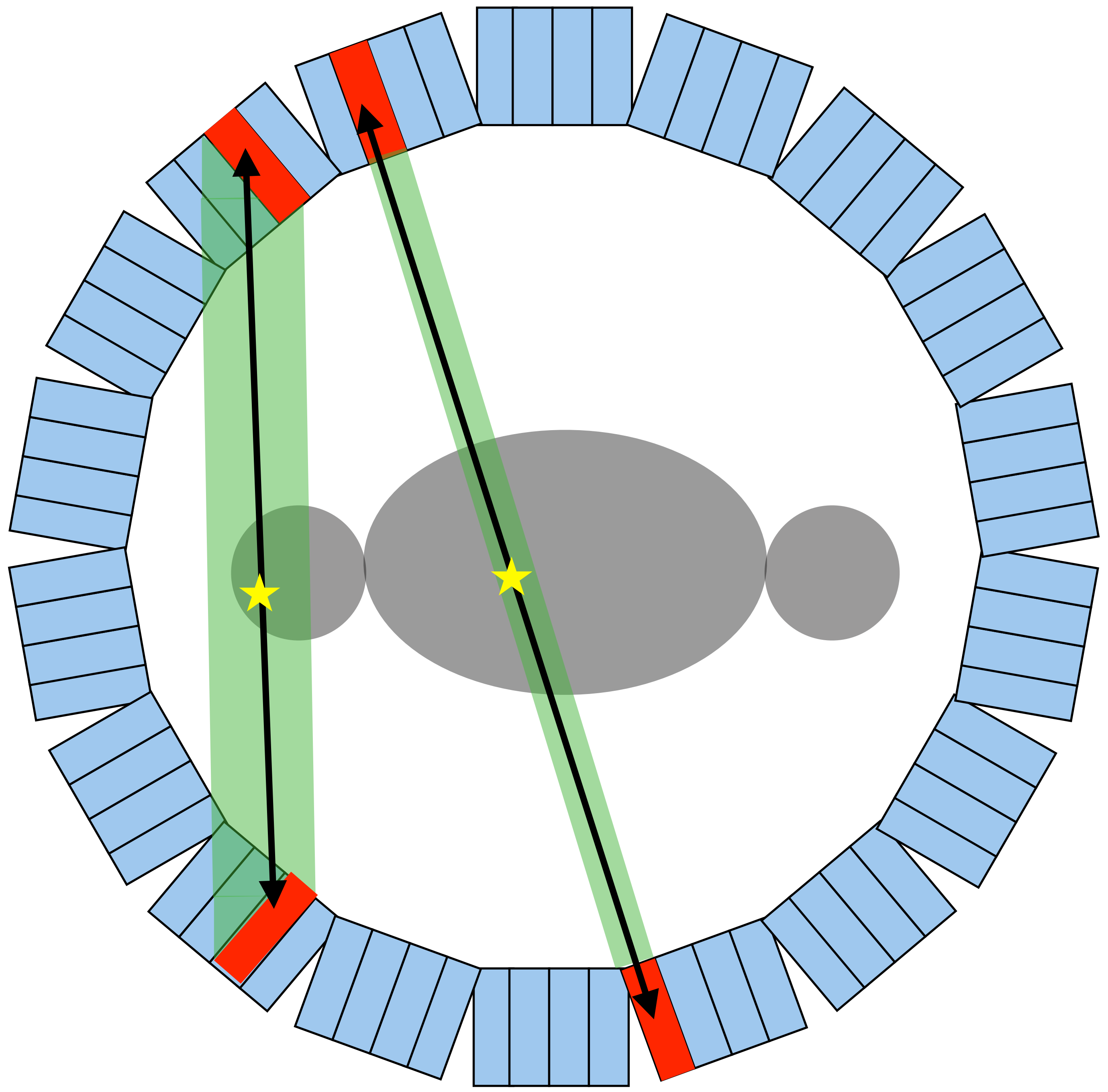
100μPET
Ultra-High Resolution Molecular Imaging



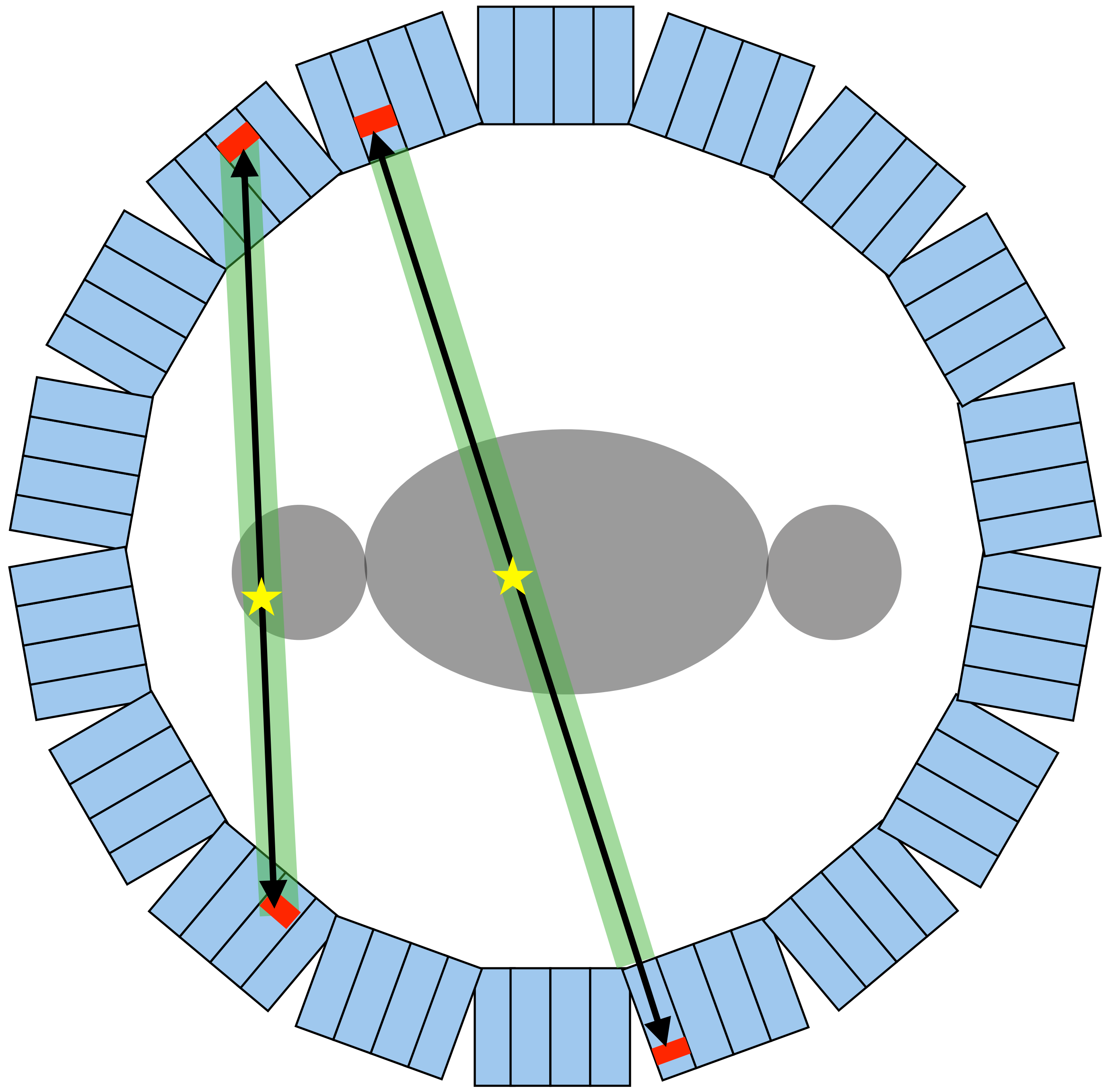
Detector resolution always helps…

The Depth-Of-Interaction (DOI)

without DOI



with DOI

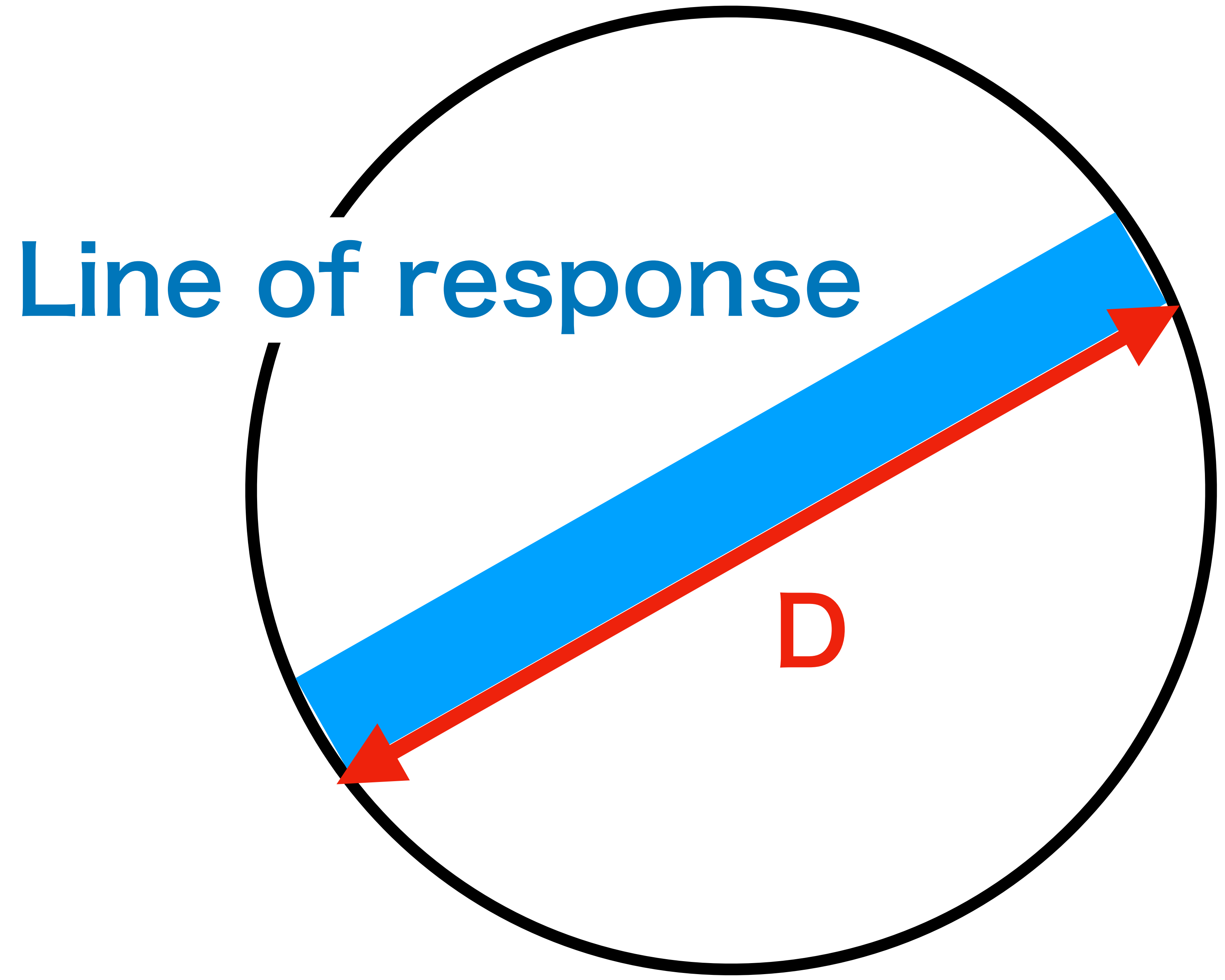


Without DOI measurement
annihilations not in the center
of the scanner produce
LOR volumes much larger
than for annihilations in the centre.

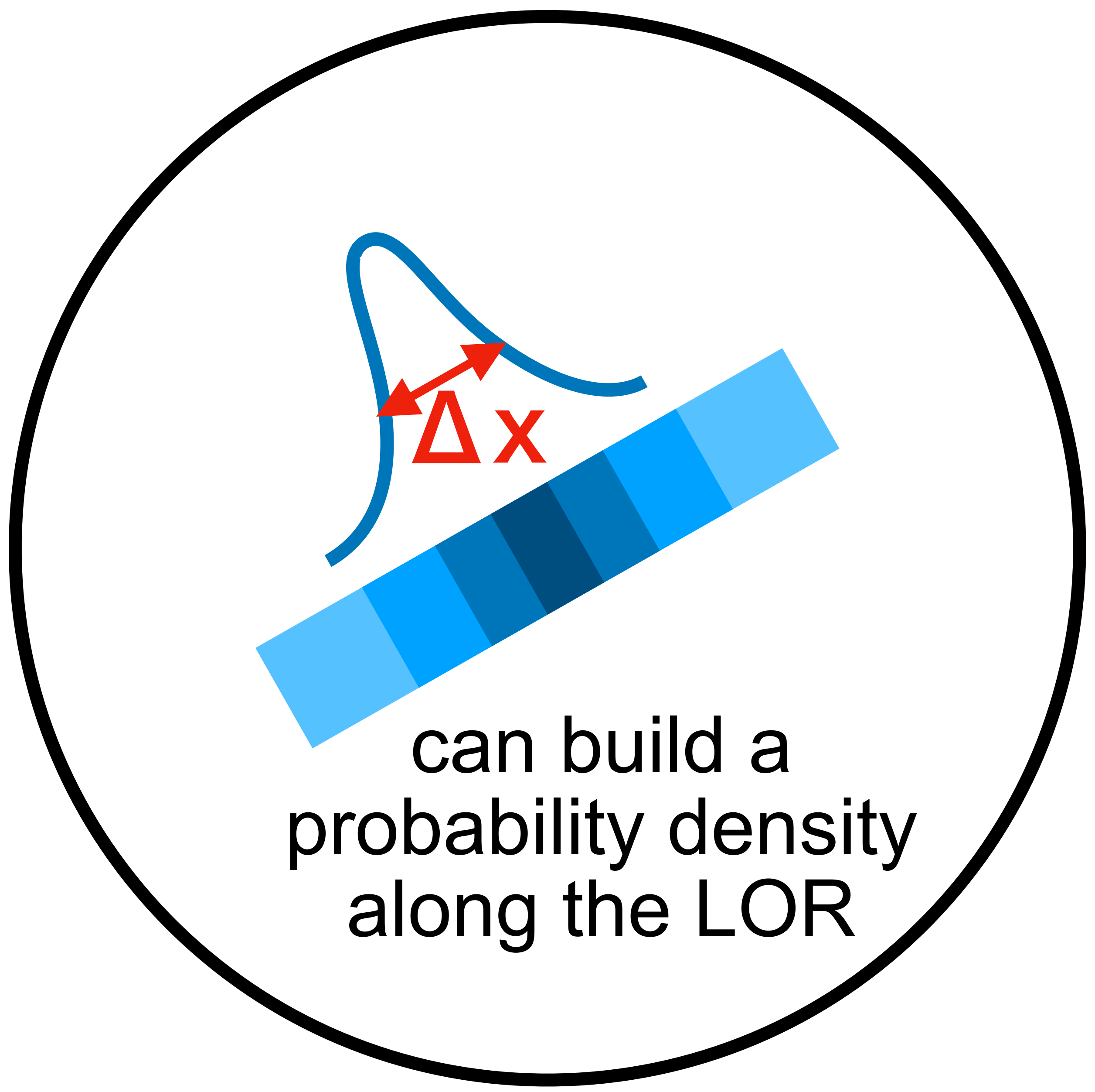
Precise DOI measurement
reduces LOR volumes and therefore
improves spatial resolution
away from the center of the scanner

3. The Time-Of-Flight (TOF)

without TOF



with TOF

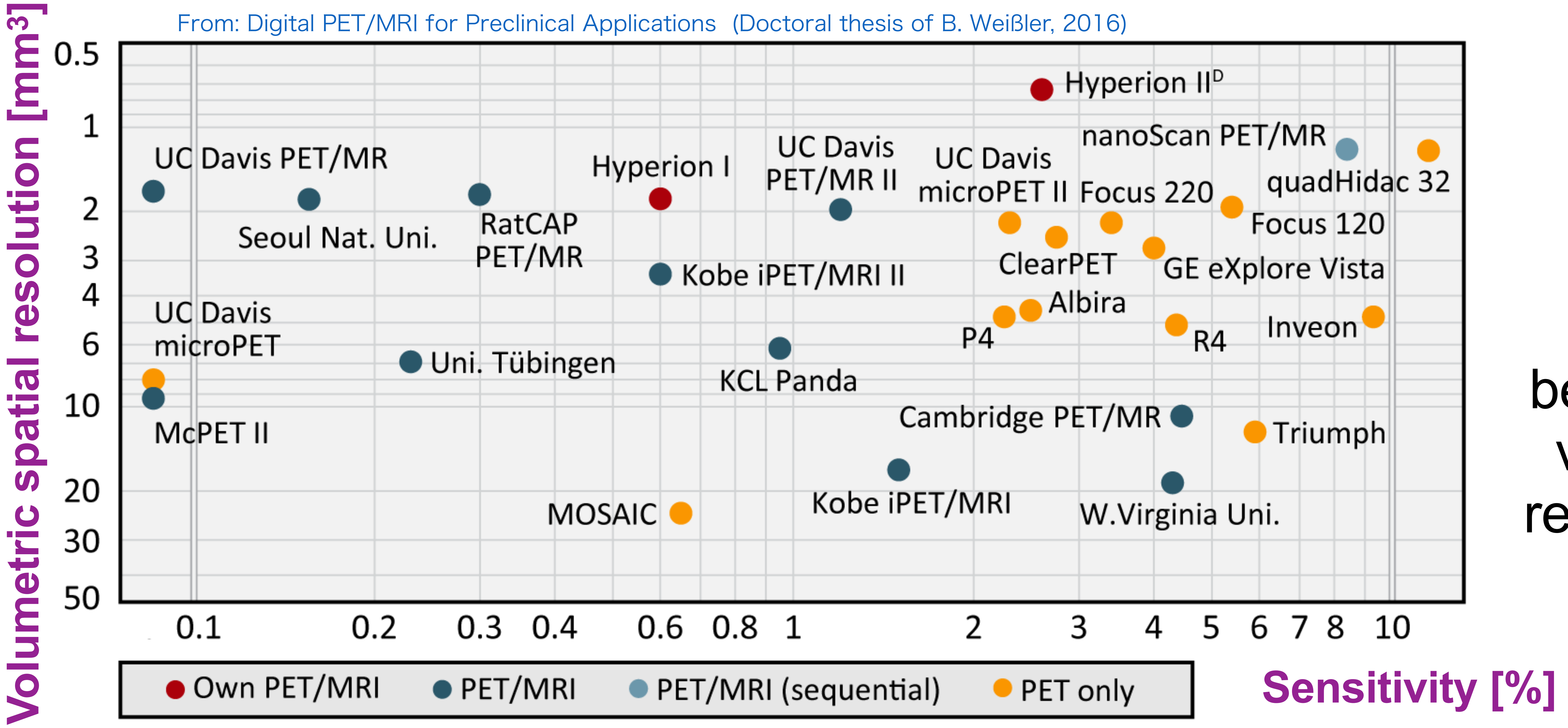


TOF information **reduces the LOR volume** and thus improves the signal-to-noise ratio (SNR) of reconstructed images

$$\frac{SNR_{TOF}}{SNR_{CONVENTIONAL}} \sim \sqrt{\frac{D}{\Delta x}}$$

Conventional small-animal PET scanners

From: Digital PET/MRI for Preclinical Applications (Doctoral thesis of B. Weißler, 2016)



Great progress over the years.

Still, best scanners have volumetric spatial resolution of **≈ 1mm**

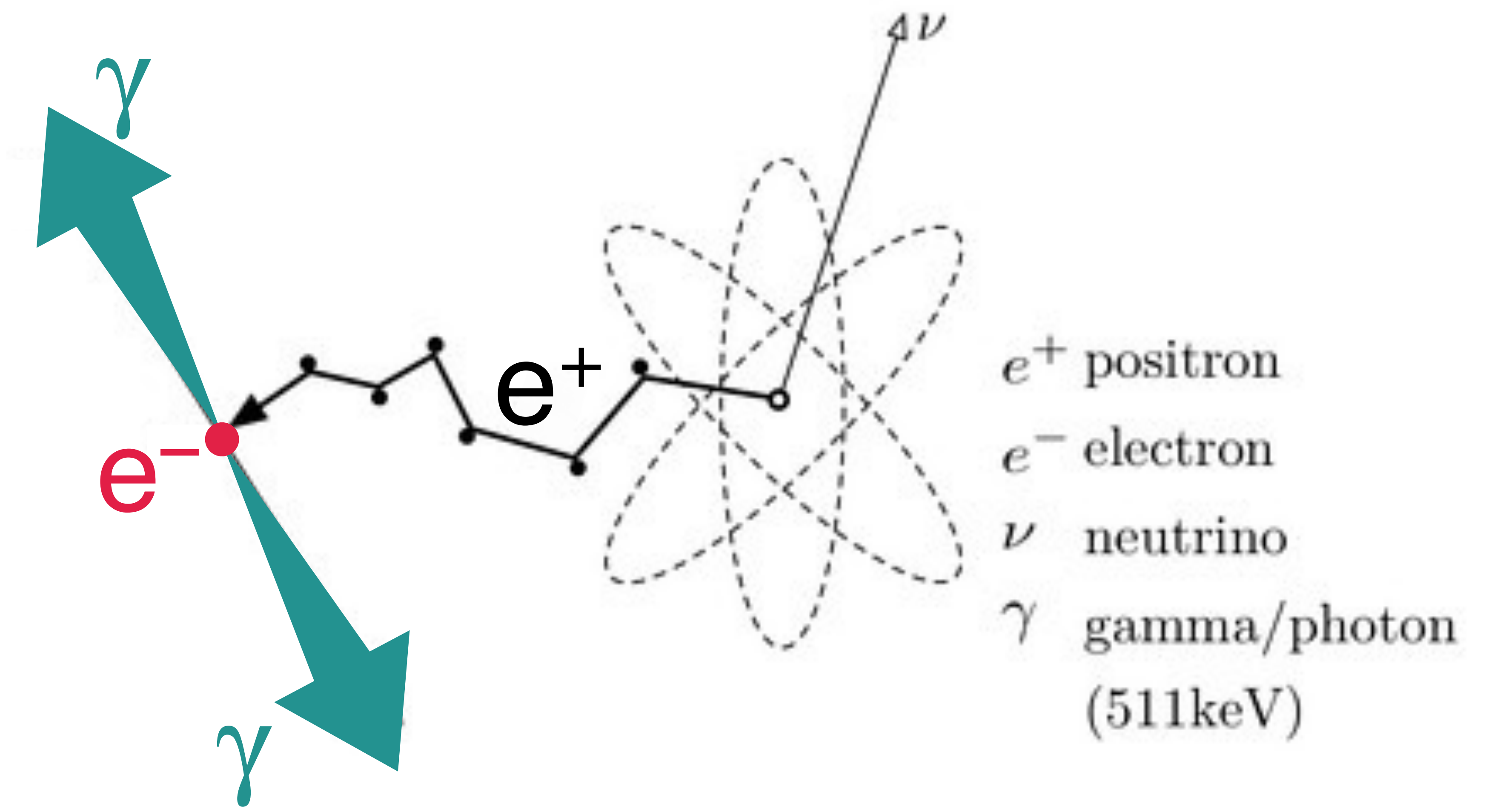
Is it the time for a change of paradigm ?

and to access **ultra-high resolution molecular imaging** ?

We must **reduce the LOR volumes**
by accessing **much improved spatial, DOI and time resolutions**

Can we aim at doing better than 1mm ?

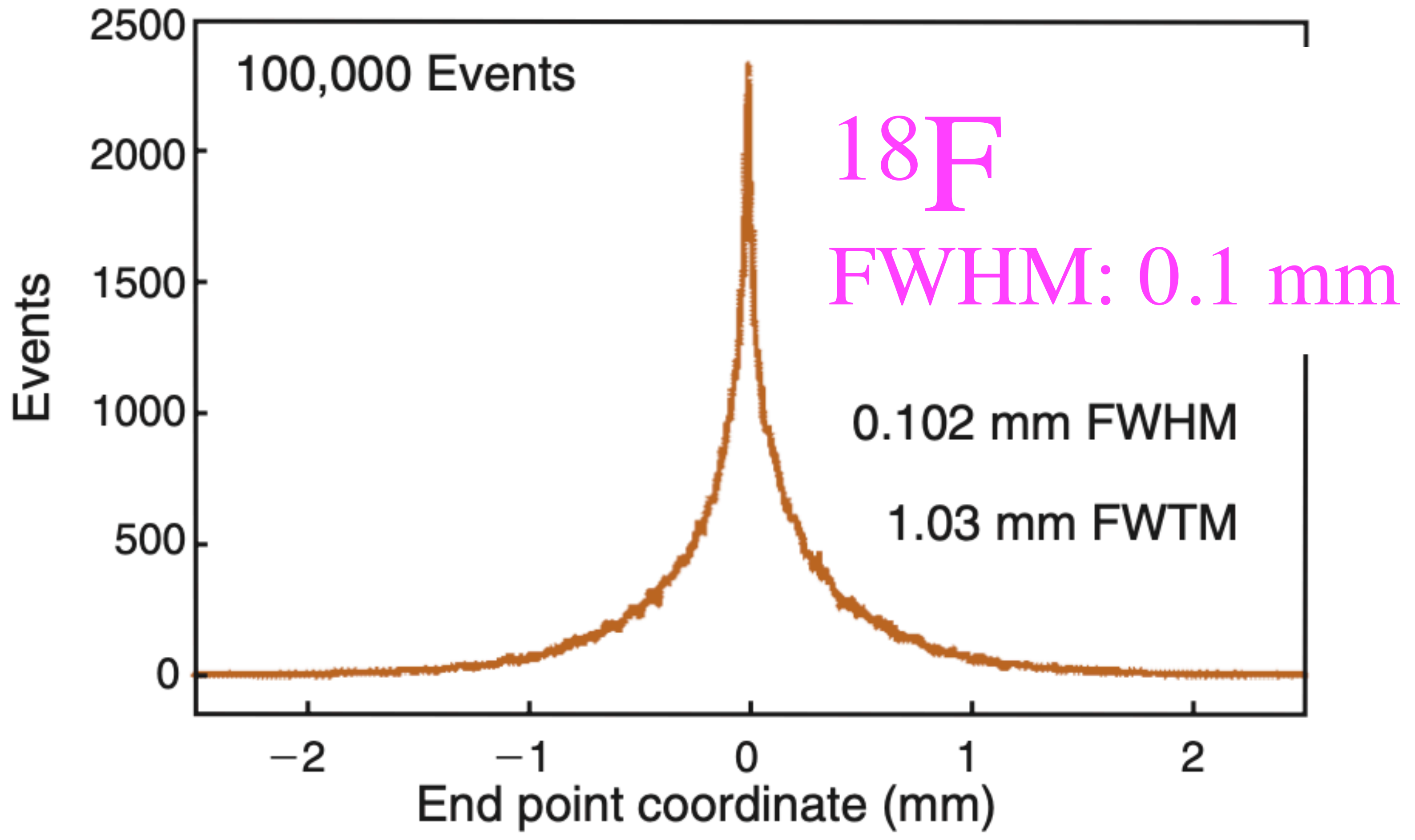
Positrons mean free path in body:

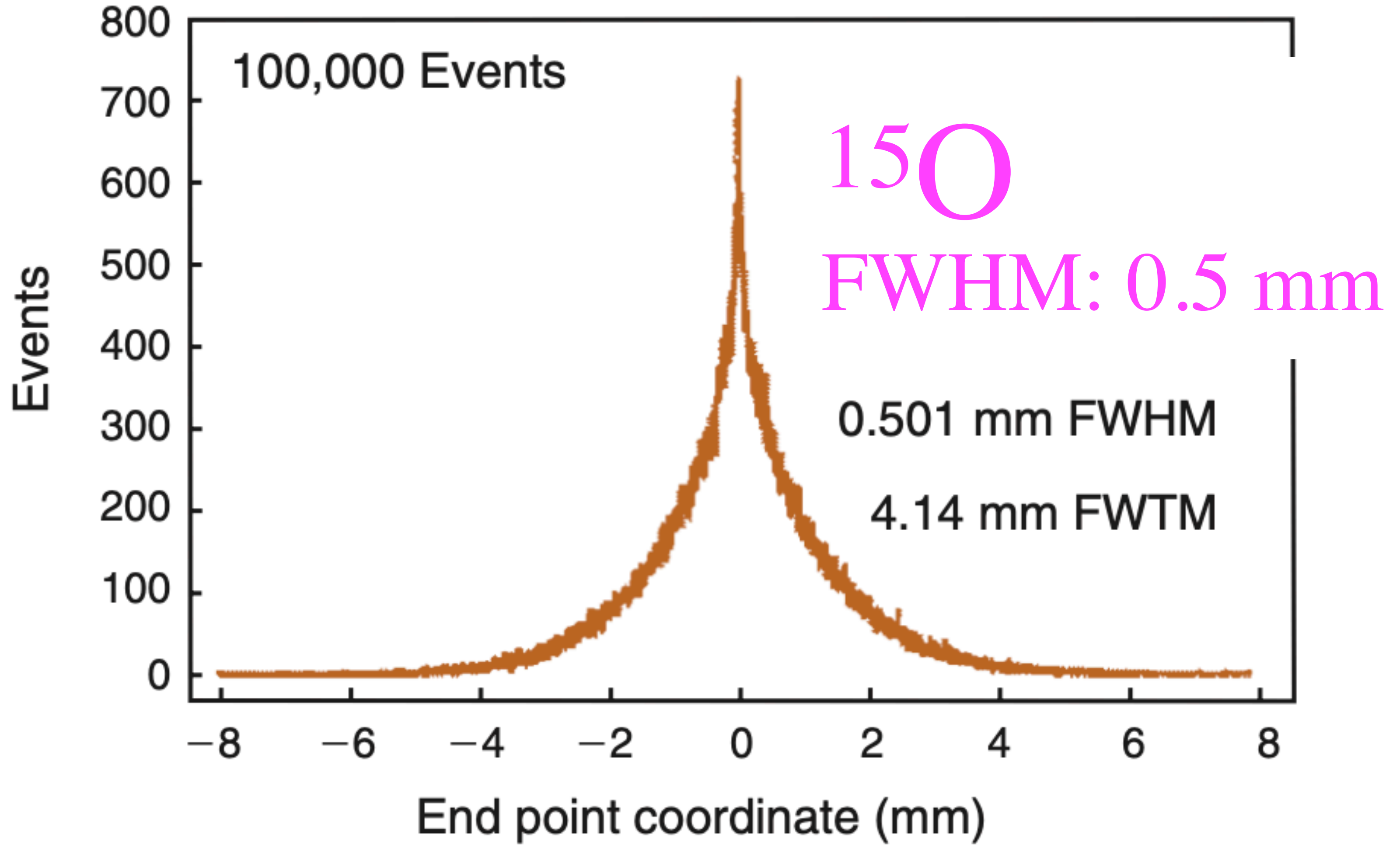


our new target should be a spatial resolution of 0.1 mm FWHM for ^{18}F

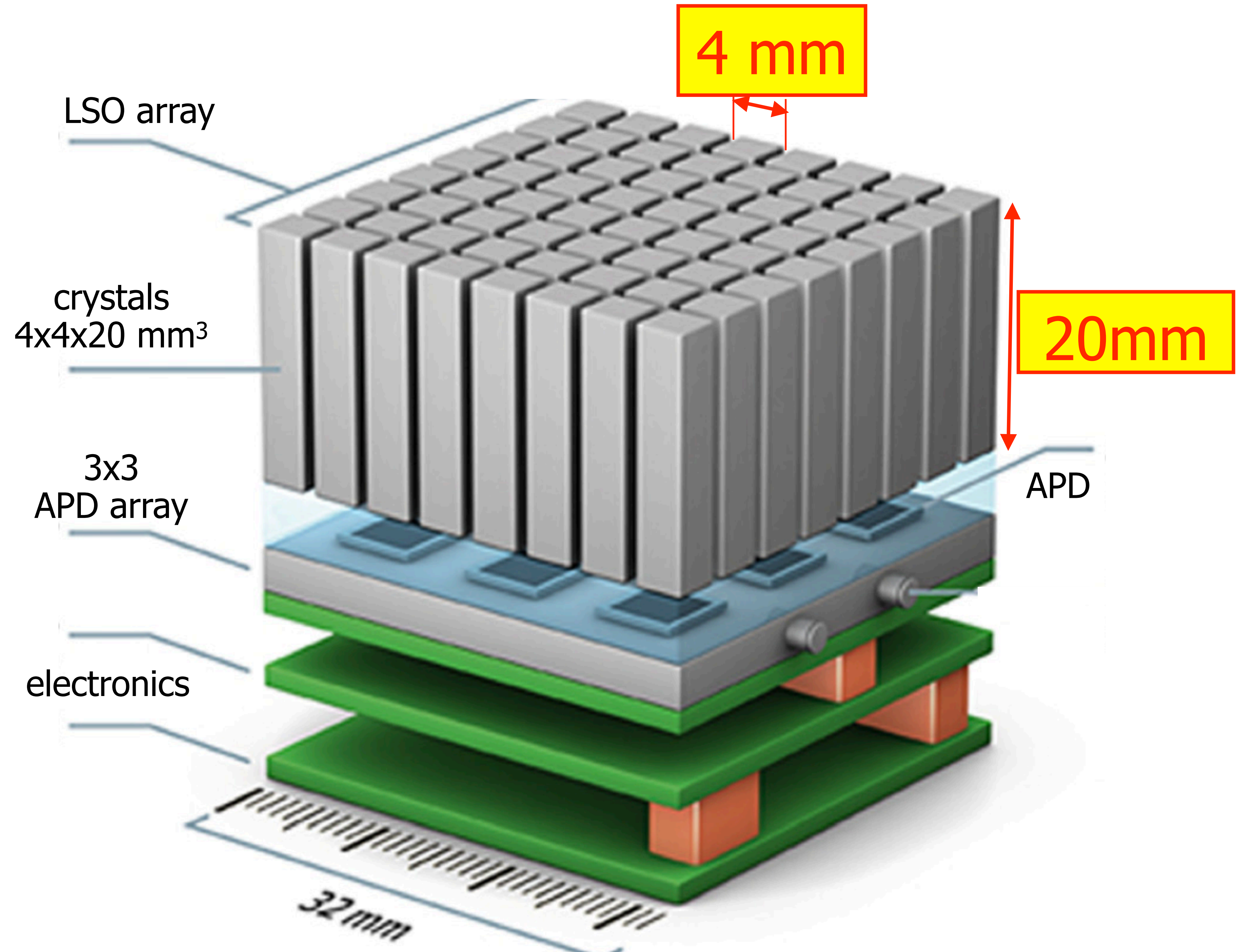
Calculated e^+ annihilation coordinate in H_2O:

Craig S Levin and Edward J Hoffman 1999 *Phys. Med. Biol.* **44** 781

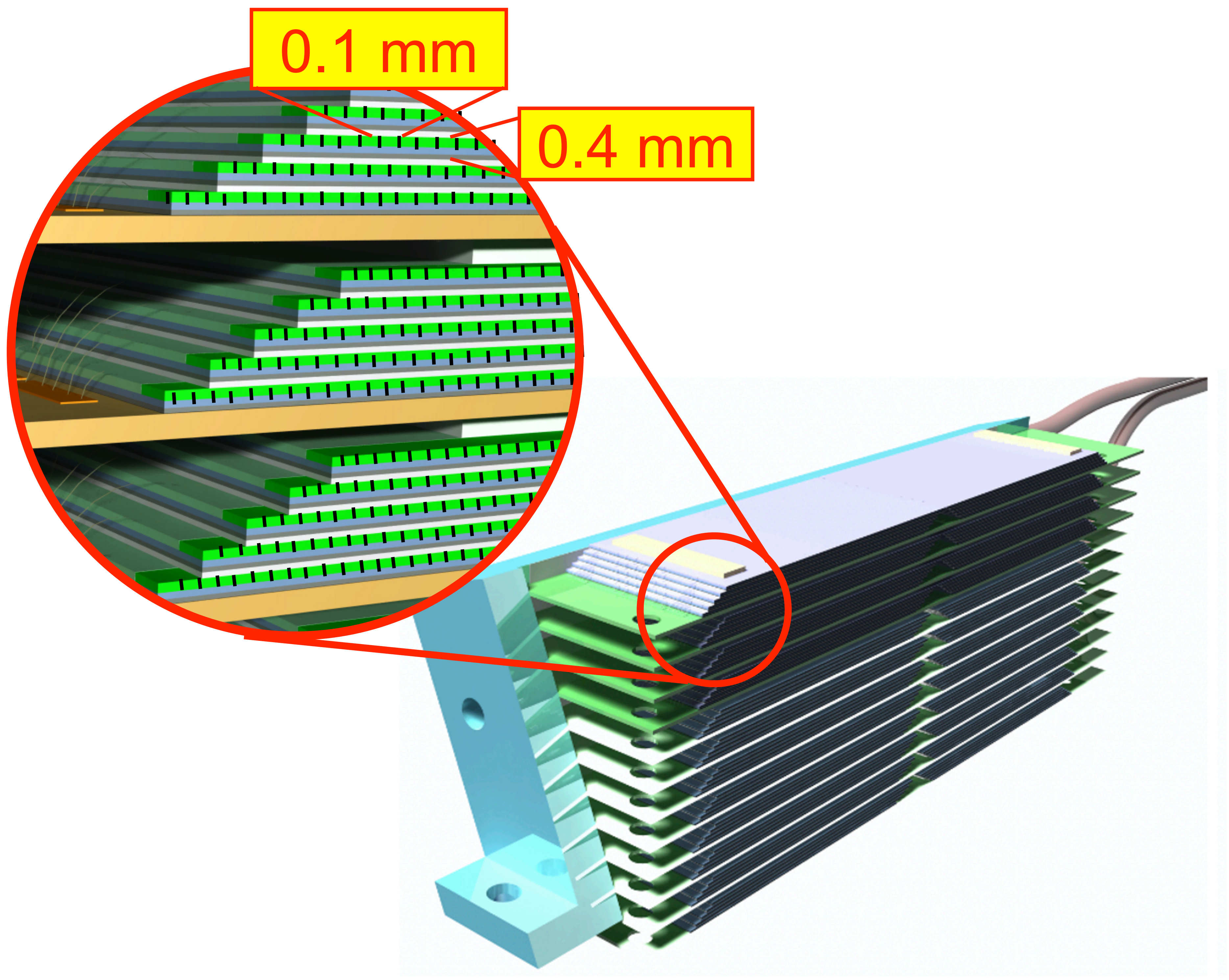




Scanner granularity, LOR volume, DOI



Courtesy of Siemens Healthcare



DOI: 20 mm
Pixel pitch: 4 mm
Scanner granularity: 20x4x4 = **320 mm^3**

DOI: 0.4 mm
Pixel pitch: 0.1 mm
Scanner granularity: 0.4x0.1x0.1 = **0.004 mm^3**

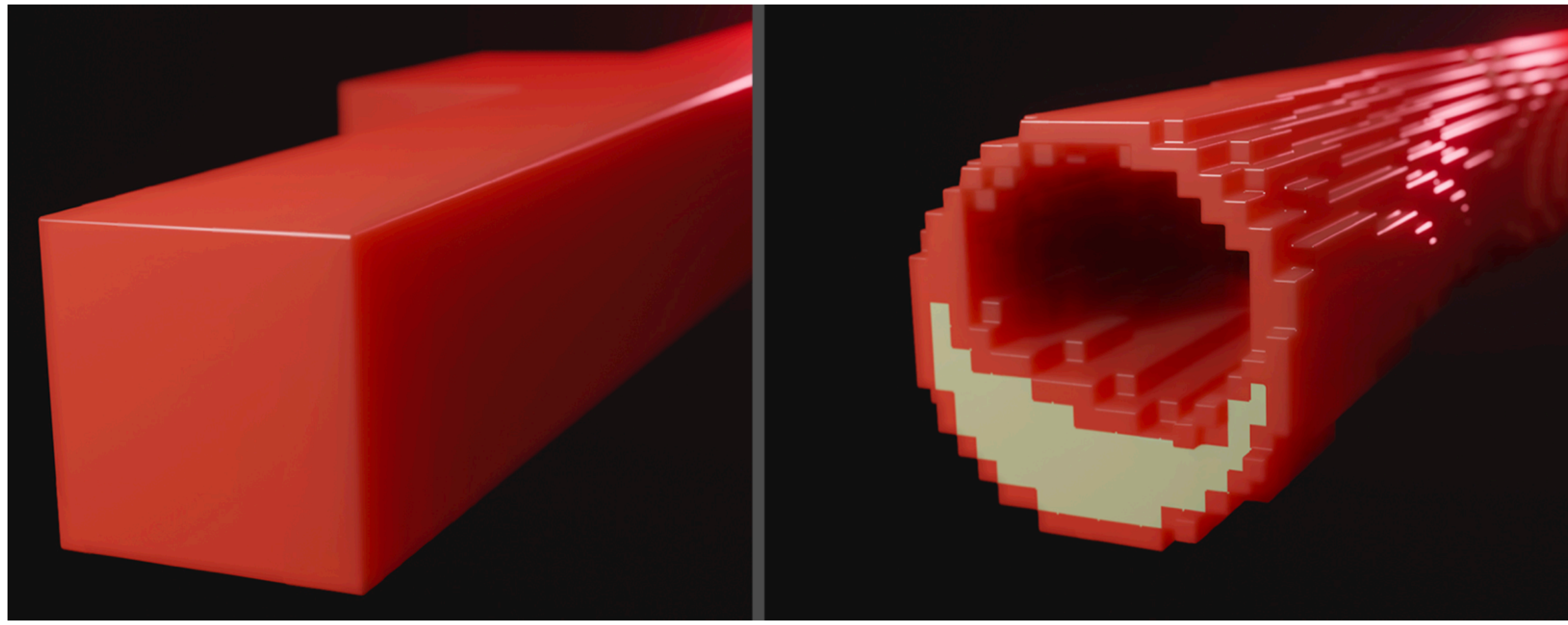
Scanner granularity: ~80'000 times finer with silicon pixel sensors

LOR volume: ~1'600 times smaller **&** **DOI: 50 times** smaller

The SNSF SINERGIA 100μPET Project

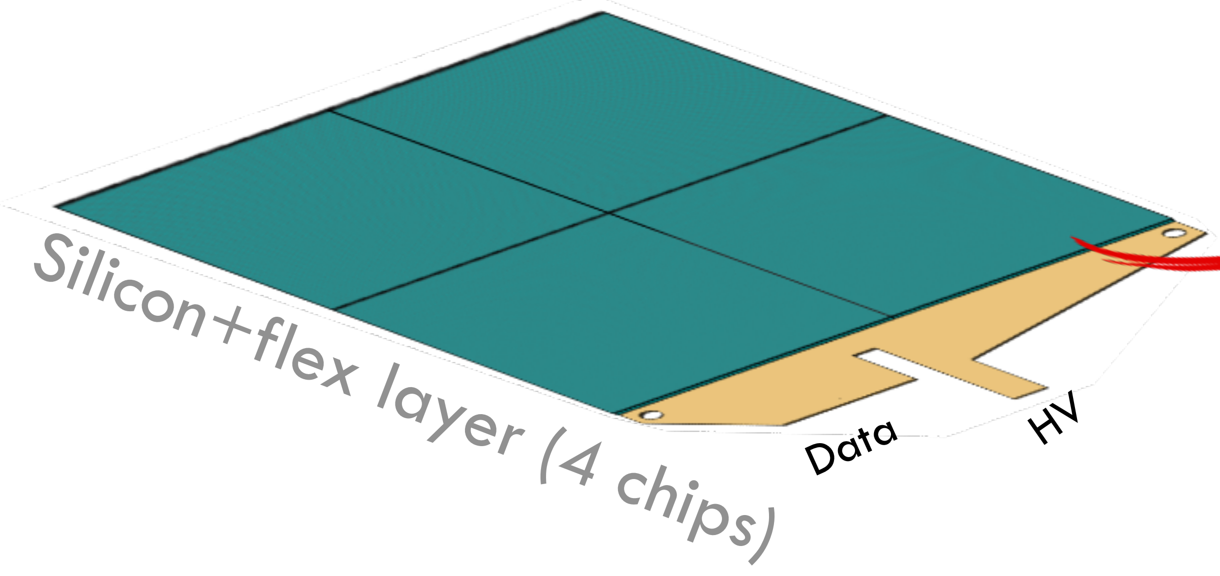
Four Work Packages, four years project:

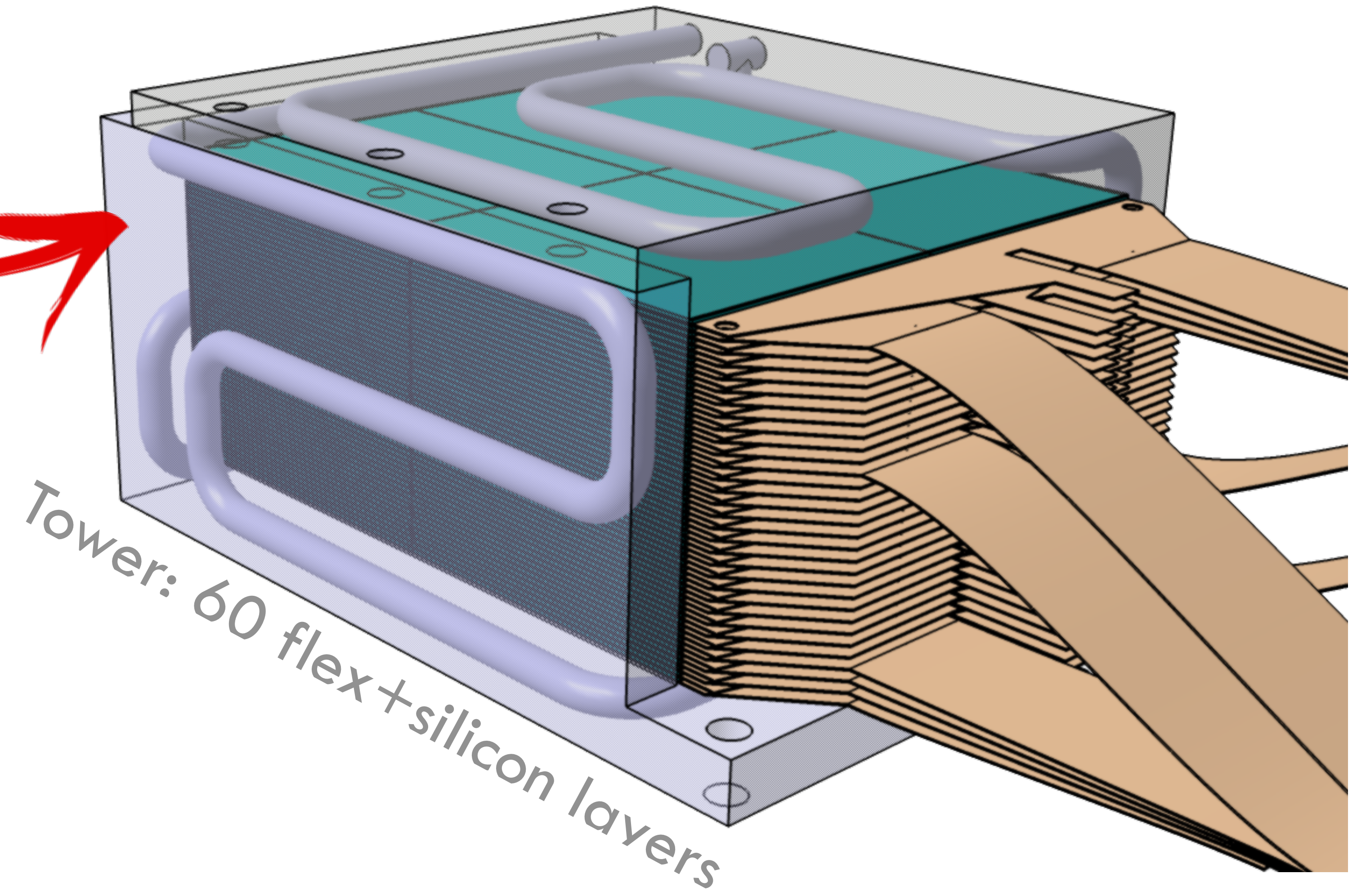
1. **Construction of the 100μPET small-animal scanner** using monolithic silicon detectors
2. **Virtual Animal:**
   virtual ultra-high-resolution PET mouse model produced by autoradiography, to guide the design of the reconstruction software and then become a reference in the field
3. **Image Reconstruction:**
   sophisticated **regularisation schemes and machine learning**, with data reformatting using multidimensional splines in conjunction with **NN** to cope with the **10^{15} LOR**
4. **Molecular Imaging:**
   Study the onset and progression of
   atherosclerotic plaques in aorta of ApoE$^{-/-}$ mice
   to monitor & treat atherosclerosis

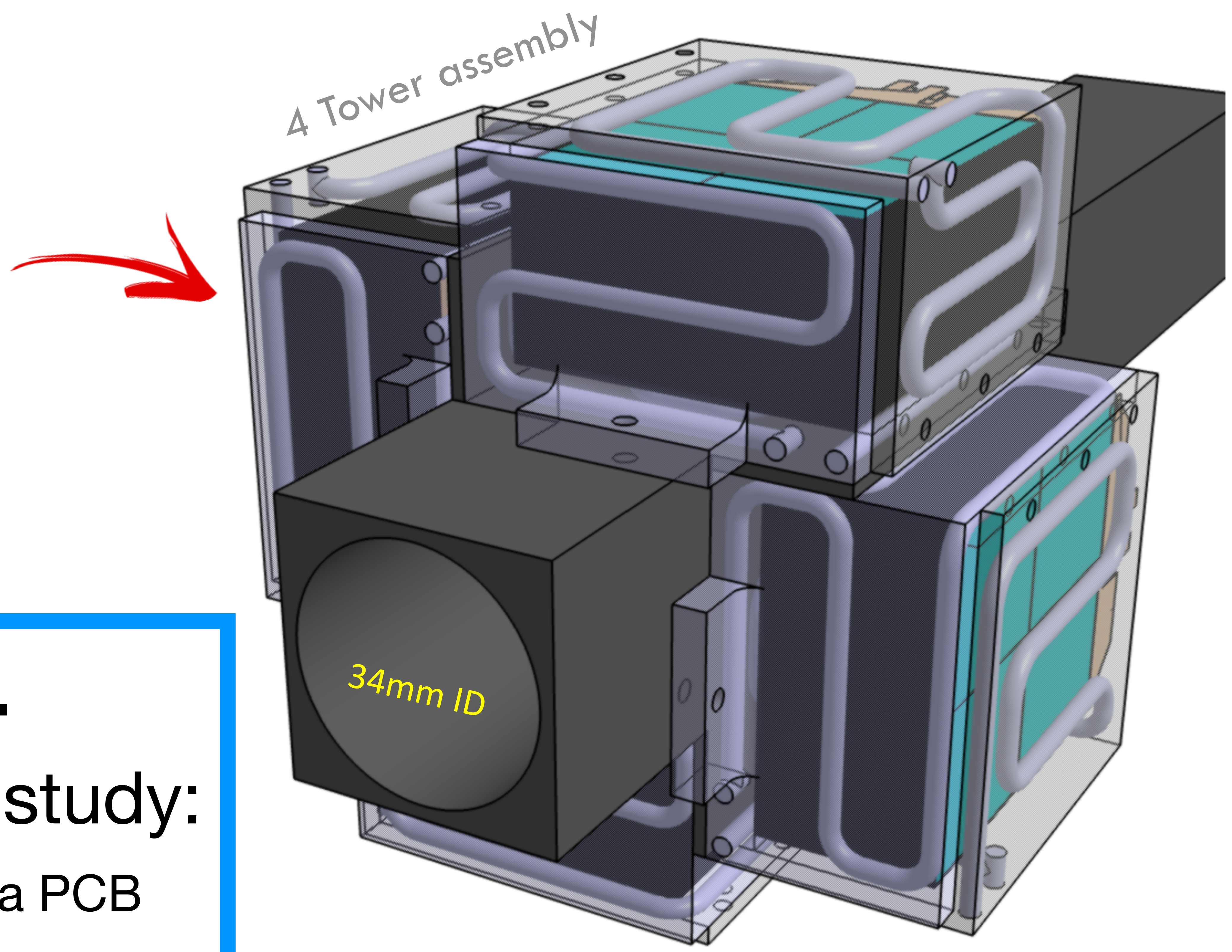


The scanner design

- **Quad modules** of monolithic silicon ASICs 2.5×3.0 cm^2, **100 µm** pitch, **250 µm** thick
- "**Tower**" is a stack of **60 silicon layers**; power consumption: 250 W
- **Four towers** make the scanner, for a total of **960 chips**







Large number of **services and interconnections.**

Requires innovation. Two possible designs under study:

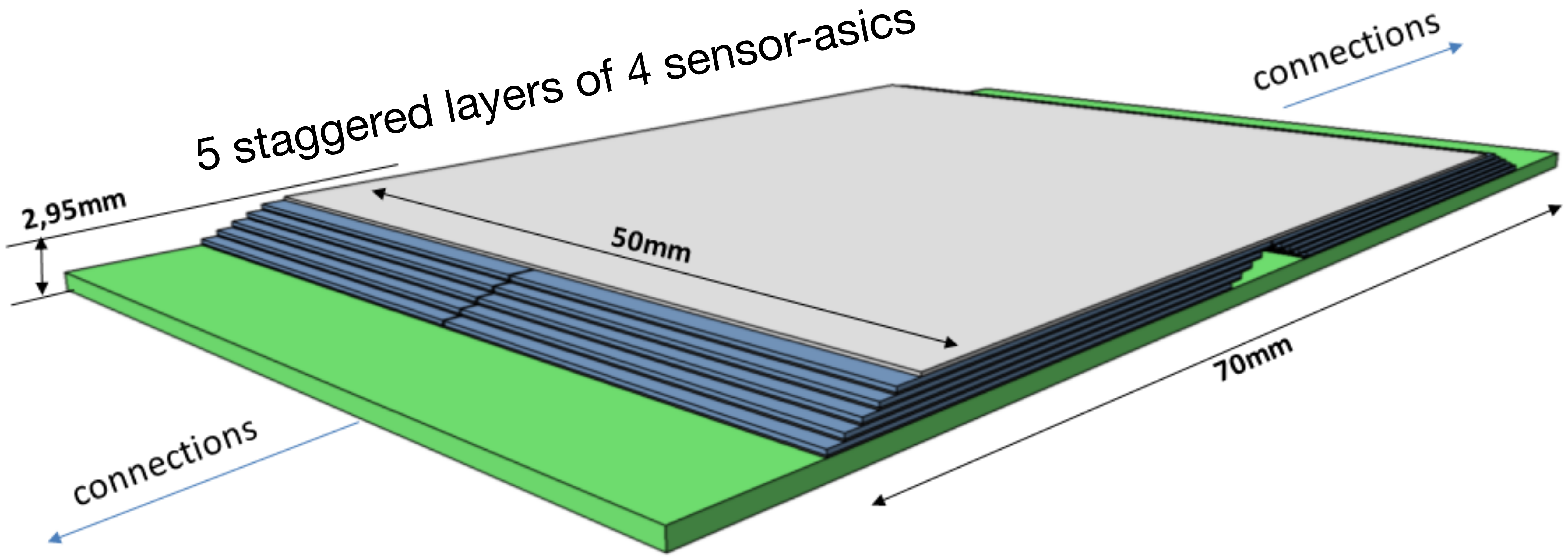
➡ **Option 1:** **staggered wire bonding** of 5 modules (20 chips) on a PCB

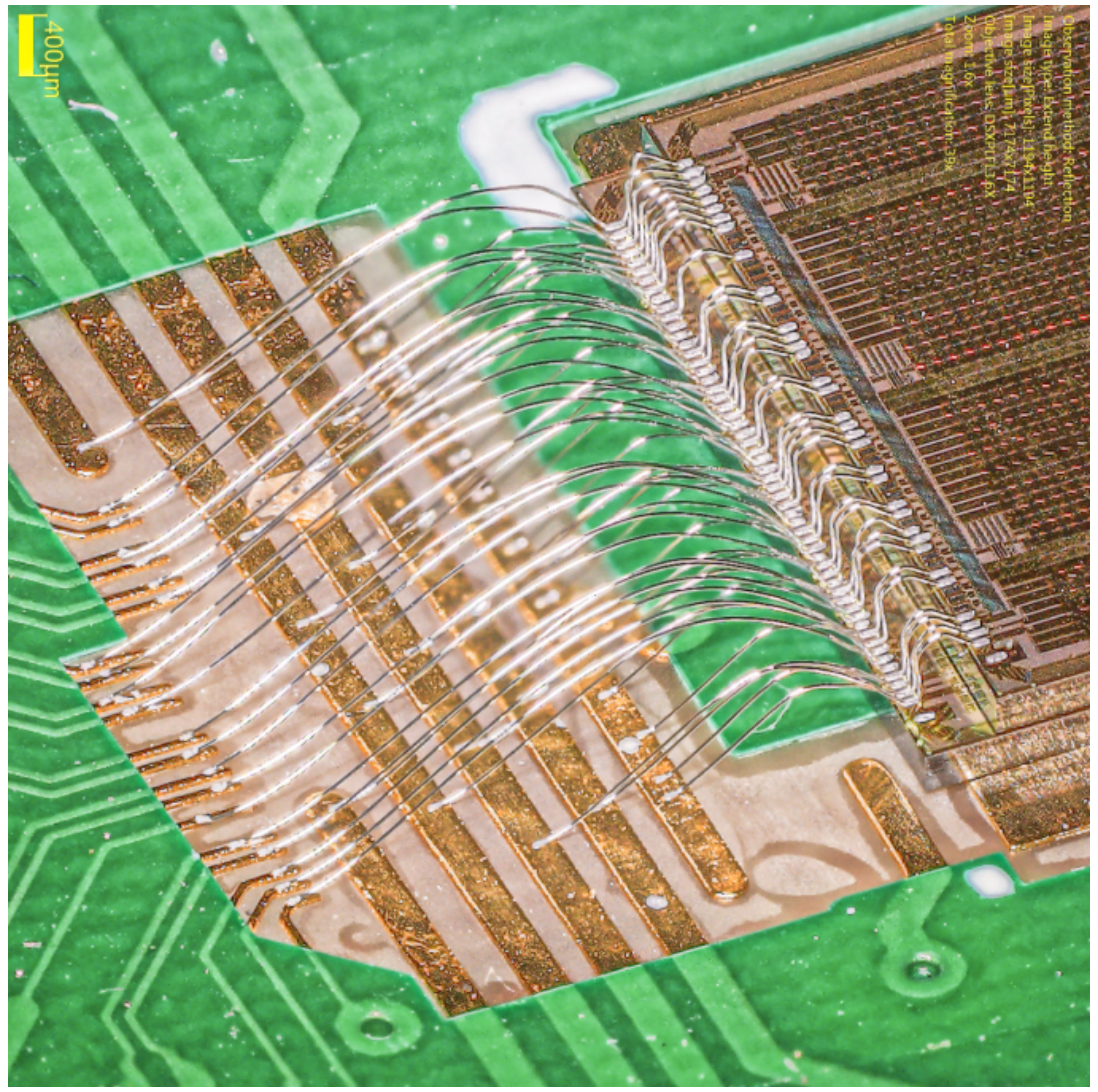
➡ **Option 2:** **ACF glueing** of four ASICs on flex (60 layers)

Module Construction – Option 1

Option 1:

“super-modules” of 5x4 ASICs with wire bonding interconnections



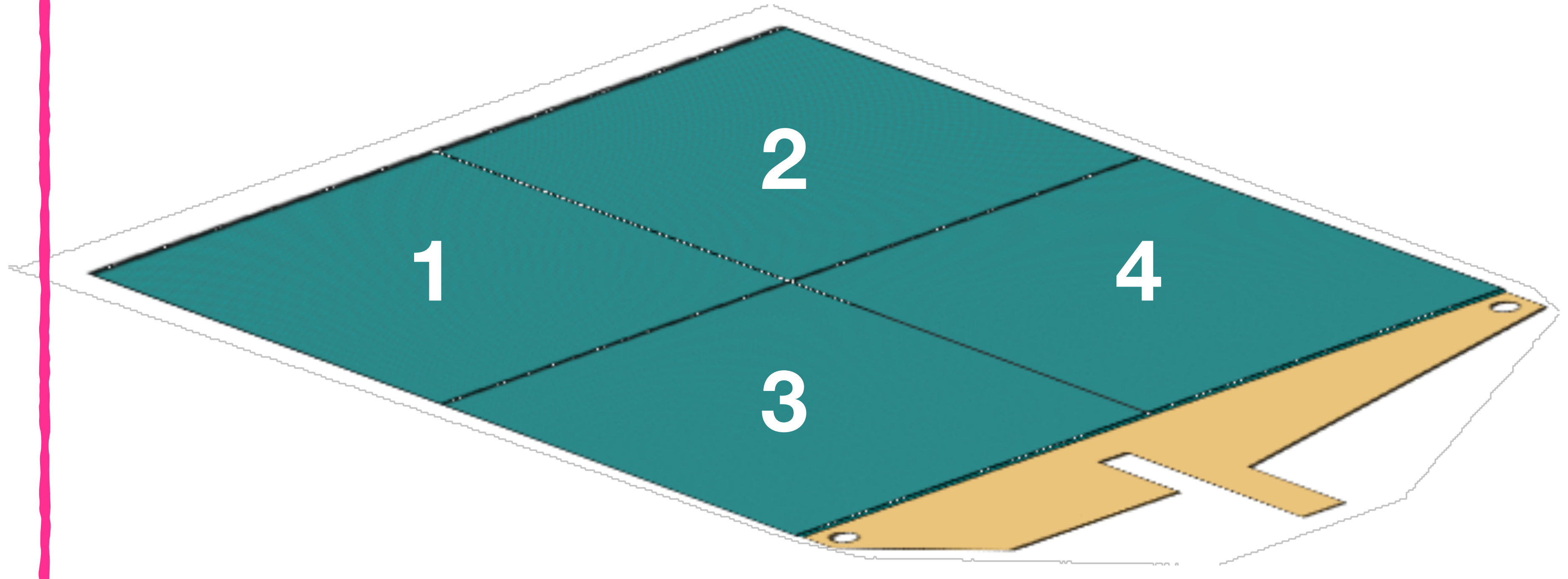


Stitched wire bonding of two FASER preshower chips on PCB.
Tests show that it is electrically operating well

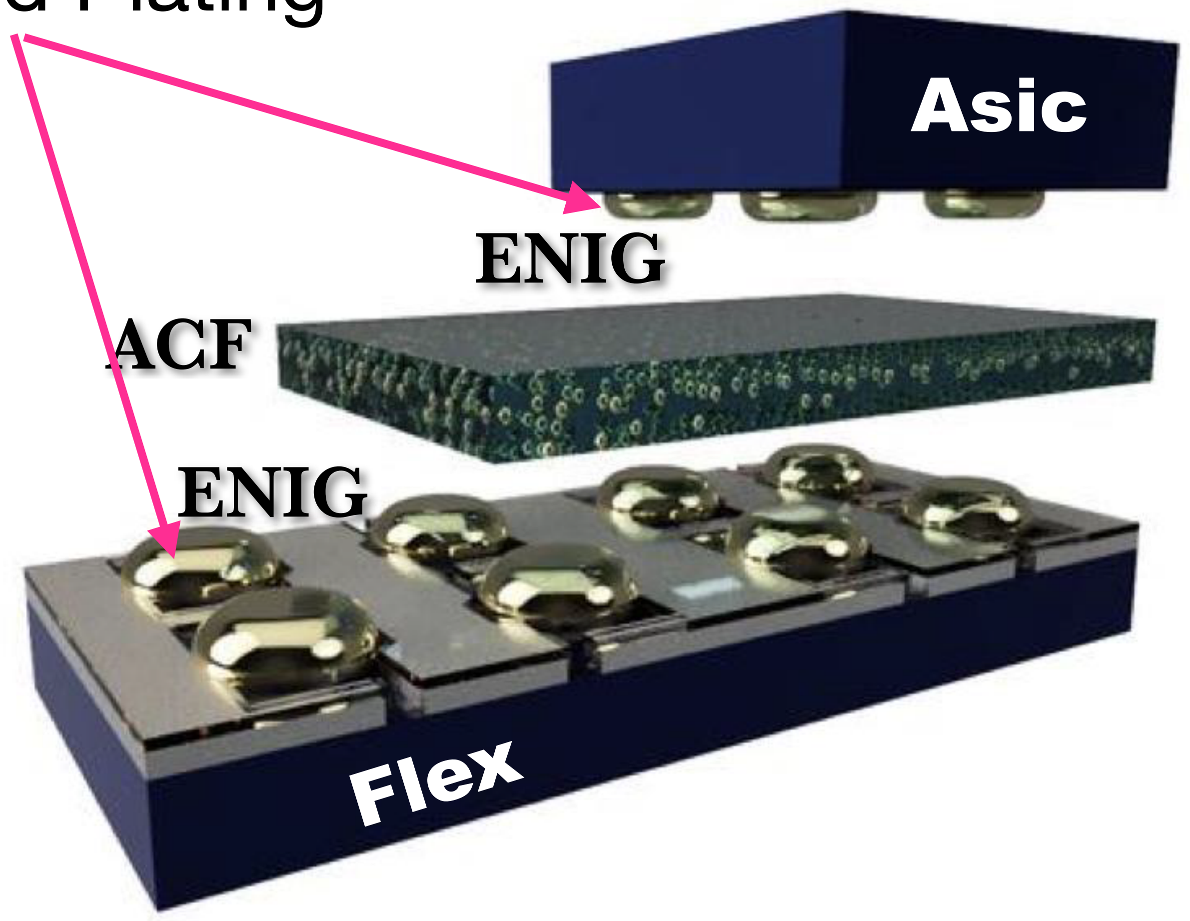
Module Construction – Option 2

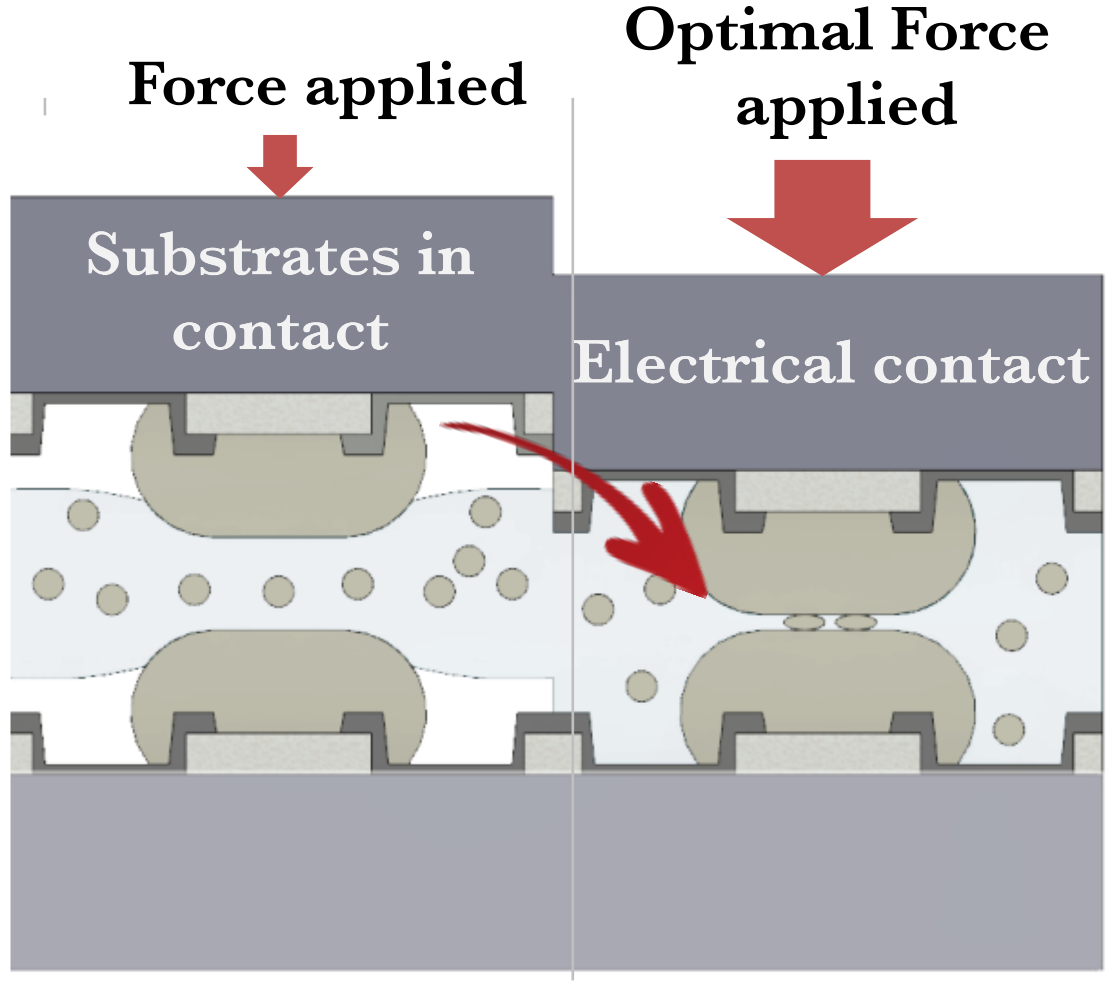
Option 2: Modules interconnected with **ACF (Anisotropic Conductive Film) bonding**

Four chips will be glued to flex
by ACF with UniGe flip-chip machine



Electroless Nickel Immersion Gold (ENIG)
Nickel gold Plating





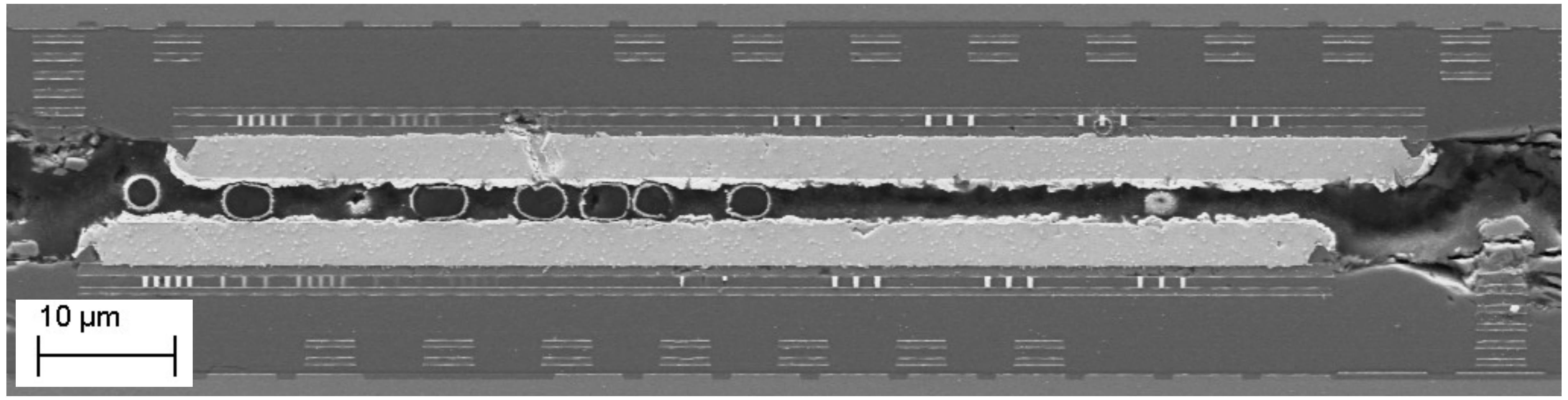
Pad interconnection with ACF on silicon:

- **Thin film (14±2)μm loaded with 3μm conductive particles**
- **Connection** of Ni/Au pads by conductive particles under ≈ 40 MPa

Module Construction – Option 2

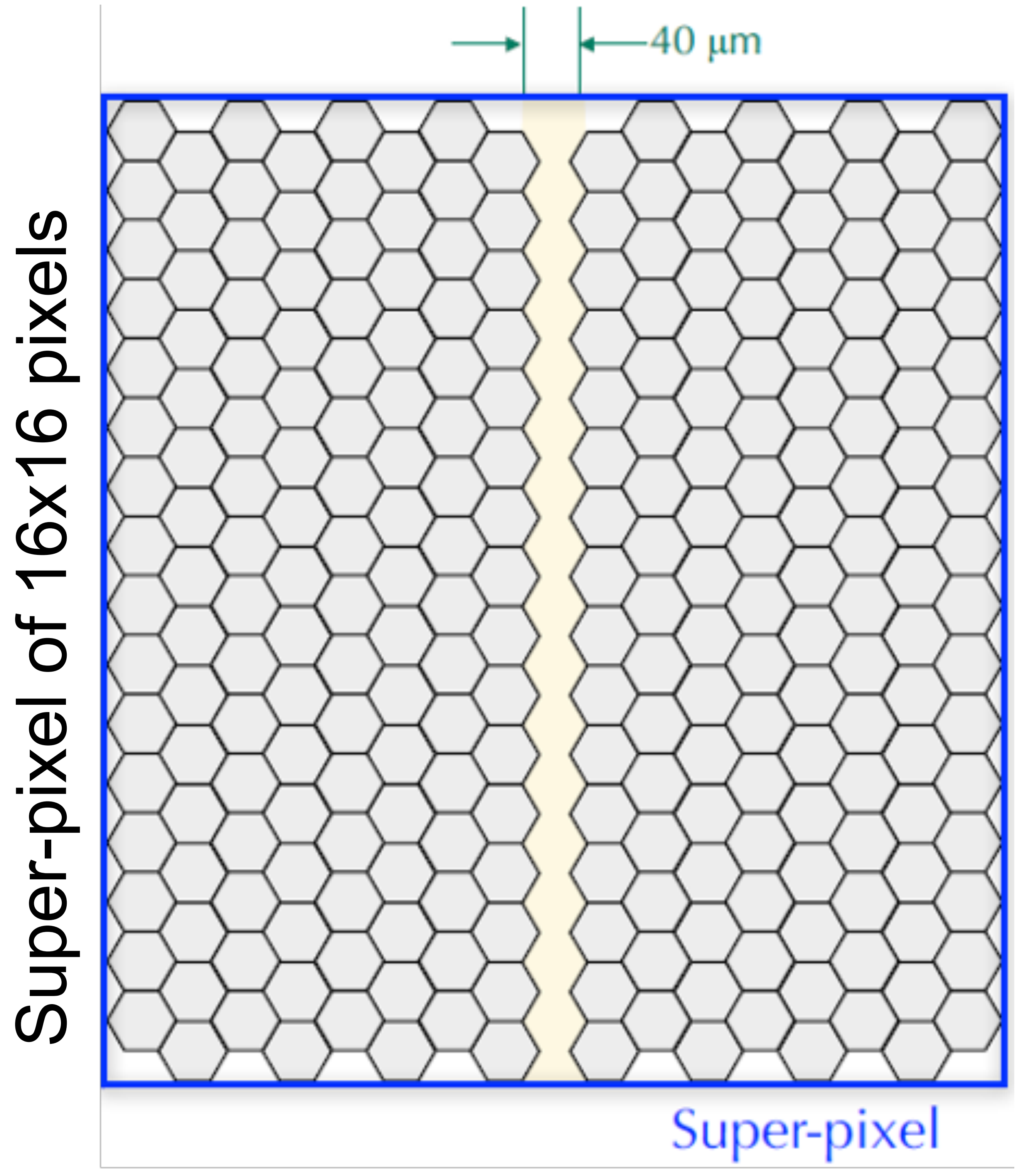
Test performed at UniGe: **pad interconnection with ACF on silicon**

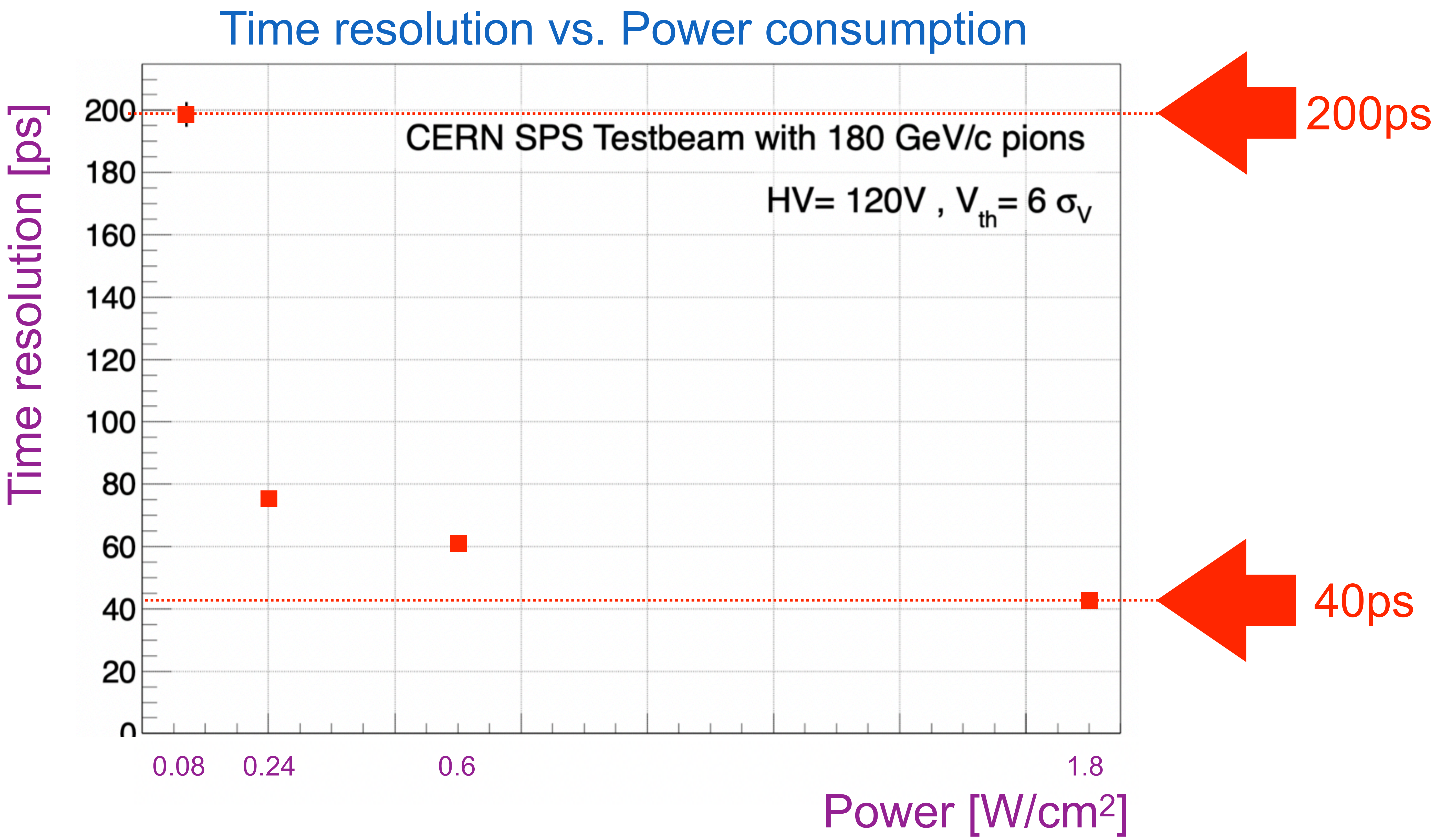
- **Thin film (14±2)μm loaded with 3μm conductive particles**
- **Connection** of Ni/Au pads by conductive particles under high compression force



- **DC resistance** in first tests **~1.7 Ω** (small area)
  (with larger pad area, electrical contact should improve)
- **RF signal transfer** qualitatively tested successful
  (will require more tests and detailed analysis)

Time resolution vs. power



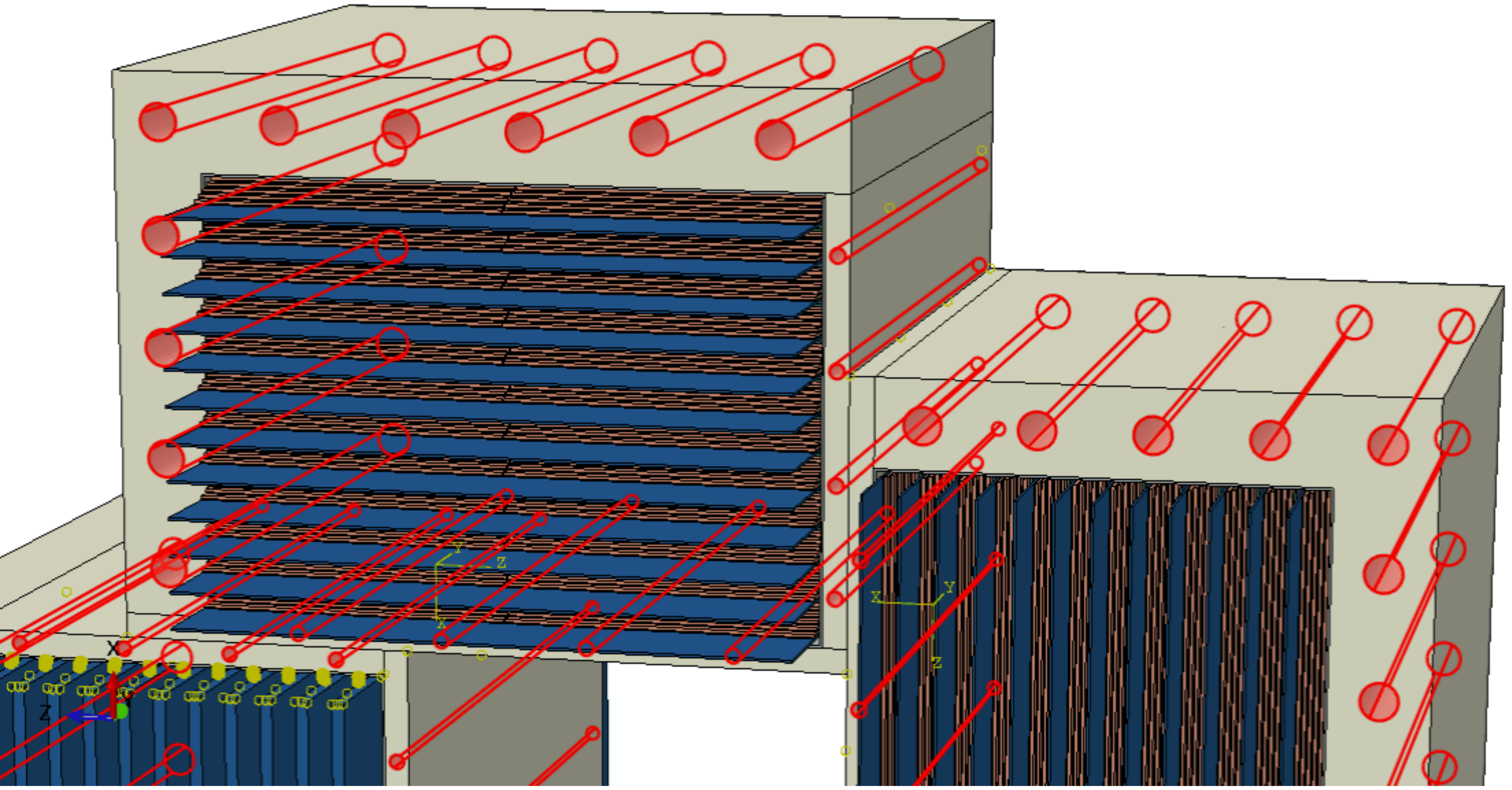


Estimated power 250W/tower to operate the scanner at a time resolution of 200ps

(data above from *JINST* ***17*** *(2022) P02019*; we now have a FE using 4 times less power)

Full-reticle ASIC submission foreseen in Summer 2023

Thermal management – FEA studies

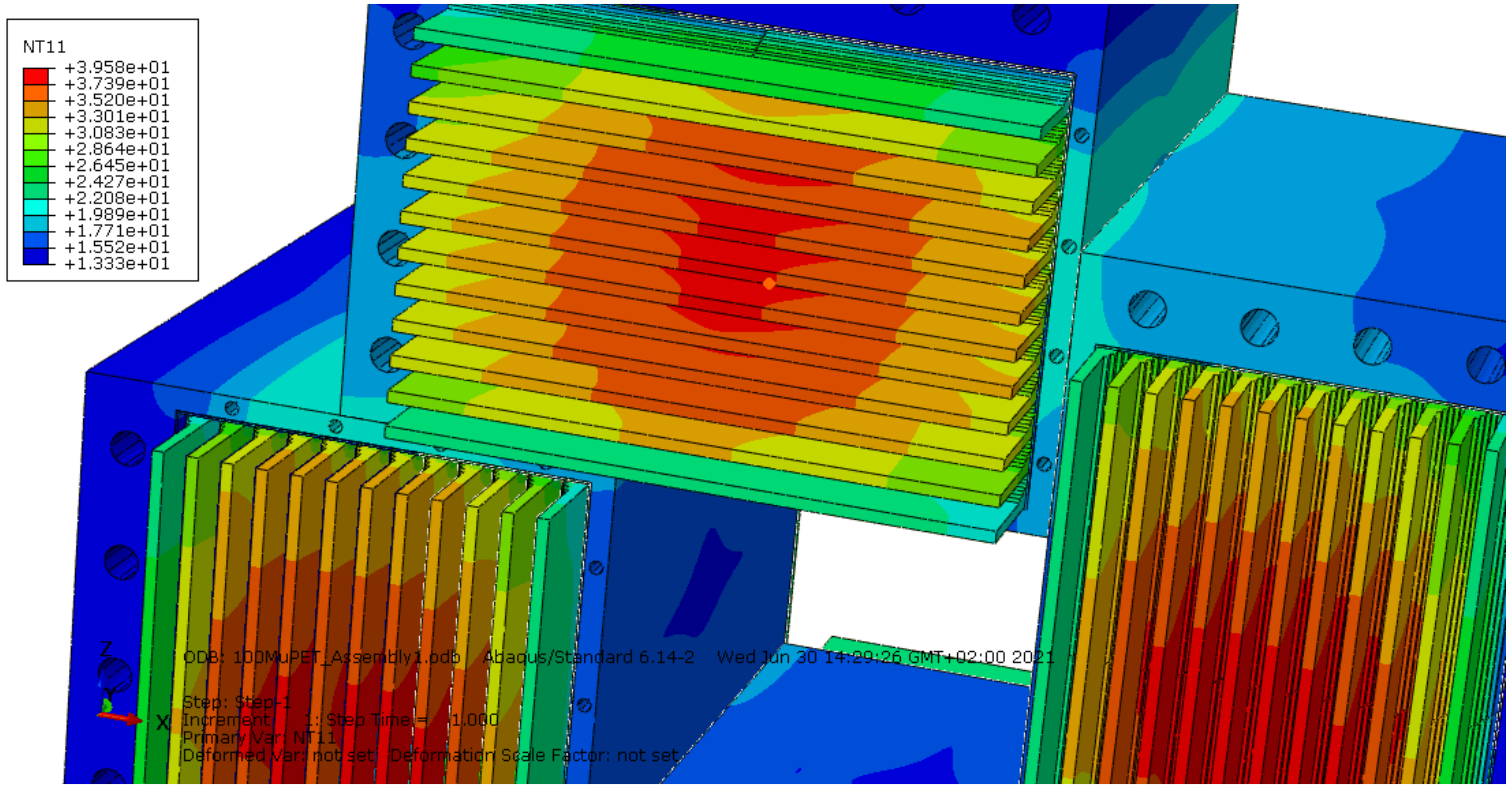


Cooling blocks manufactured
in 3D metal printing
for optimal heat exchange.

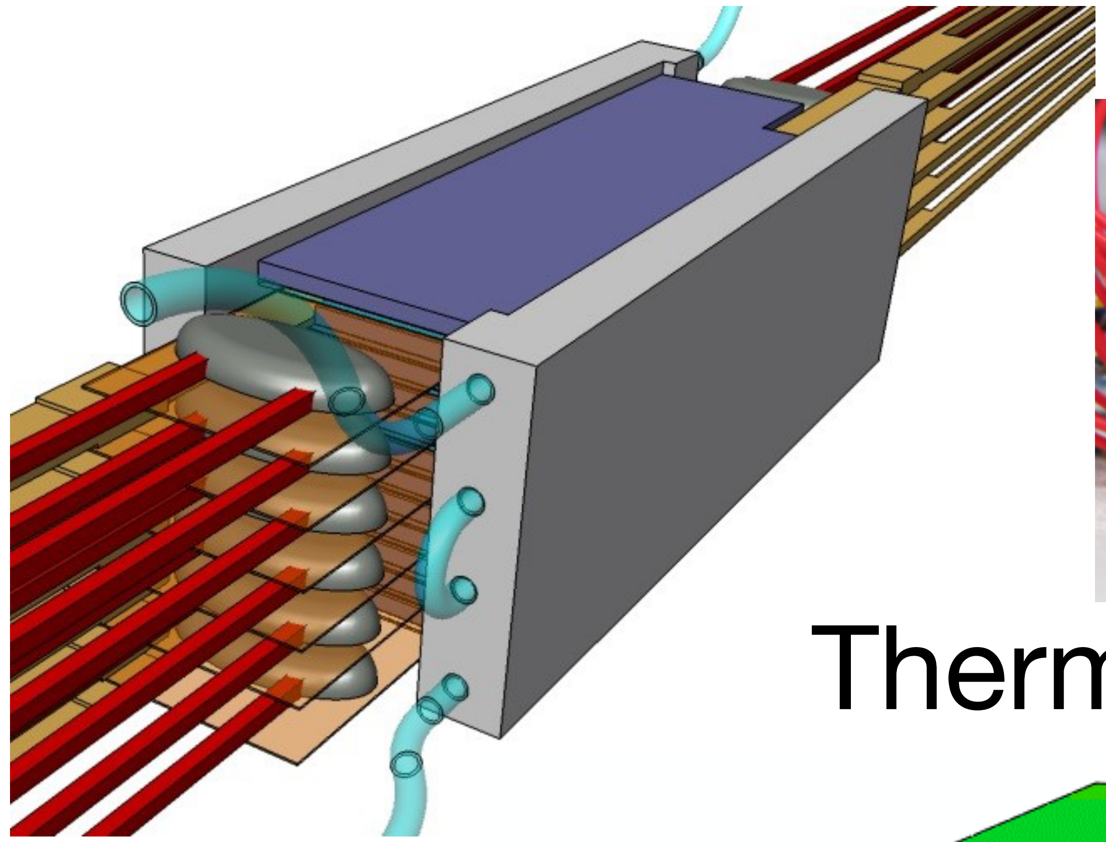
Challenge : 250W heat dissipation within a tower

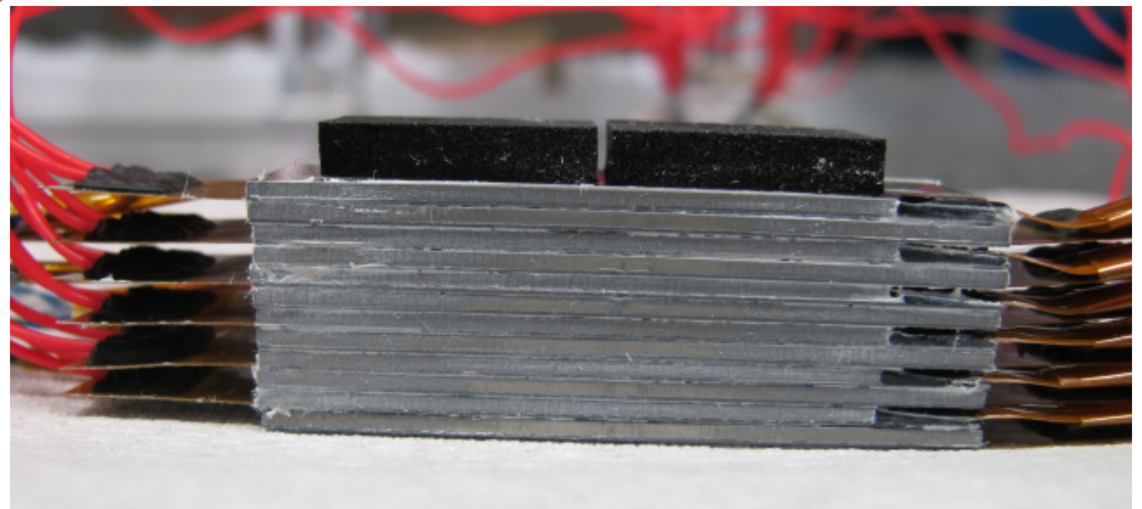
- Cooling water temperature: 12°C
- HTC: 8000 W/m²K

Max temperature of ~39°C achieved

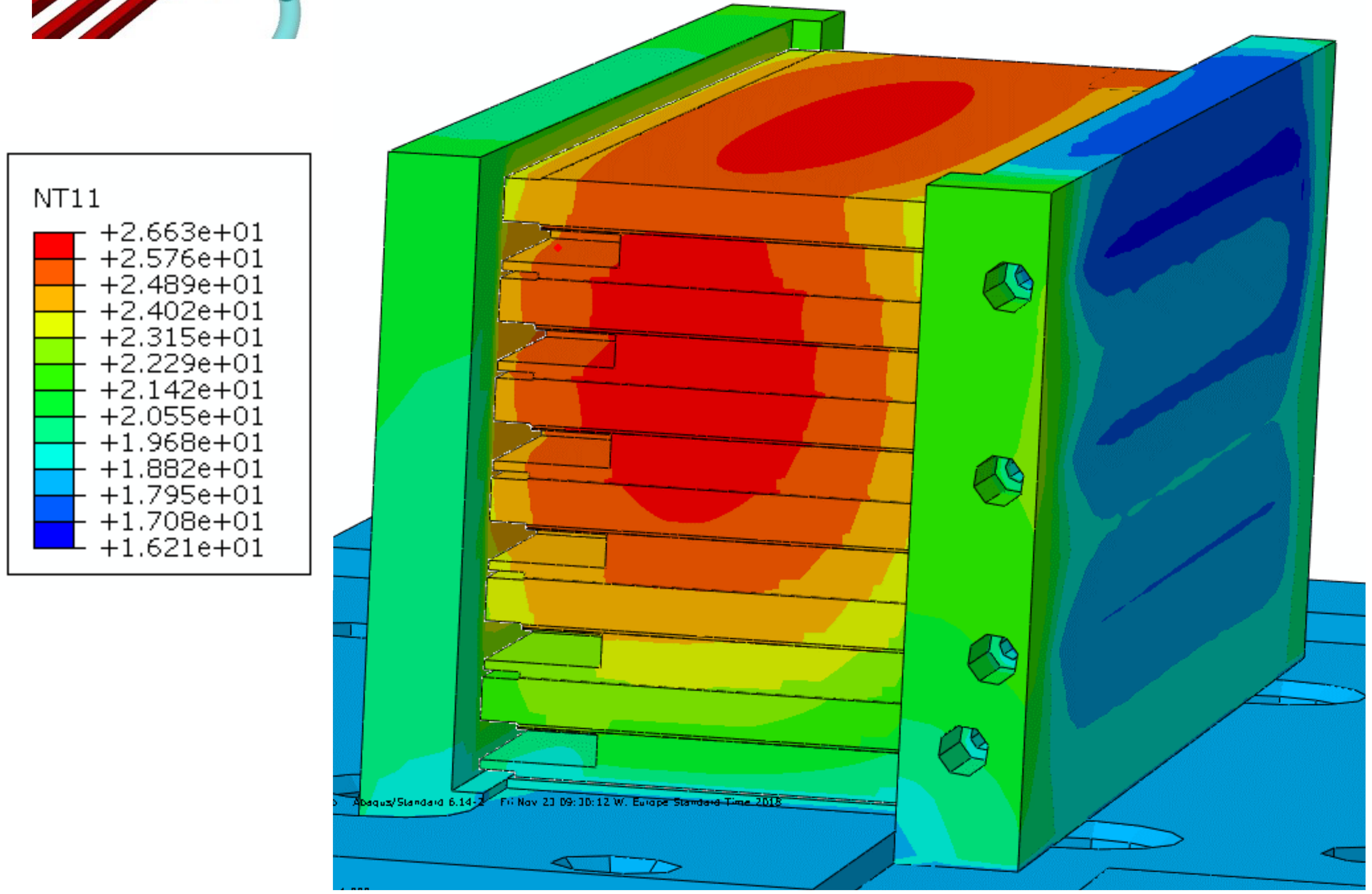


Thermal management – measurement





Thermal mock-up



Test conditions:

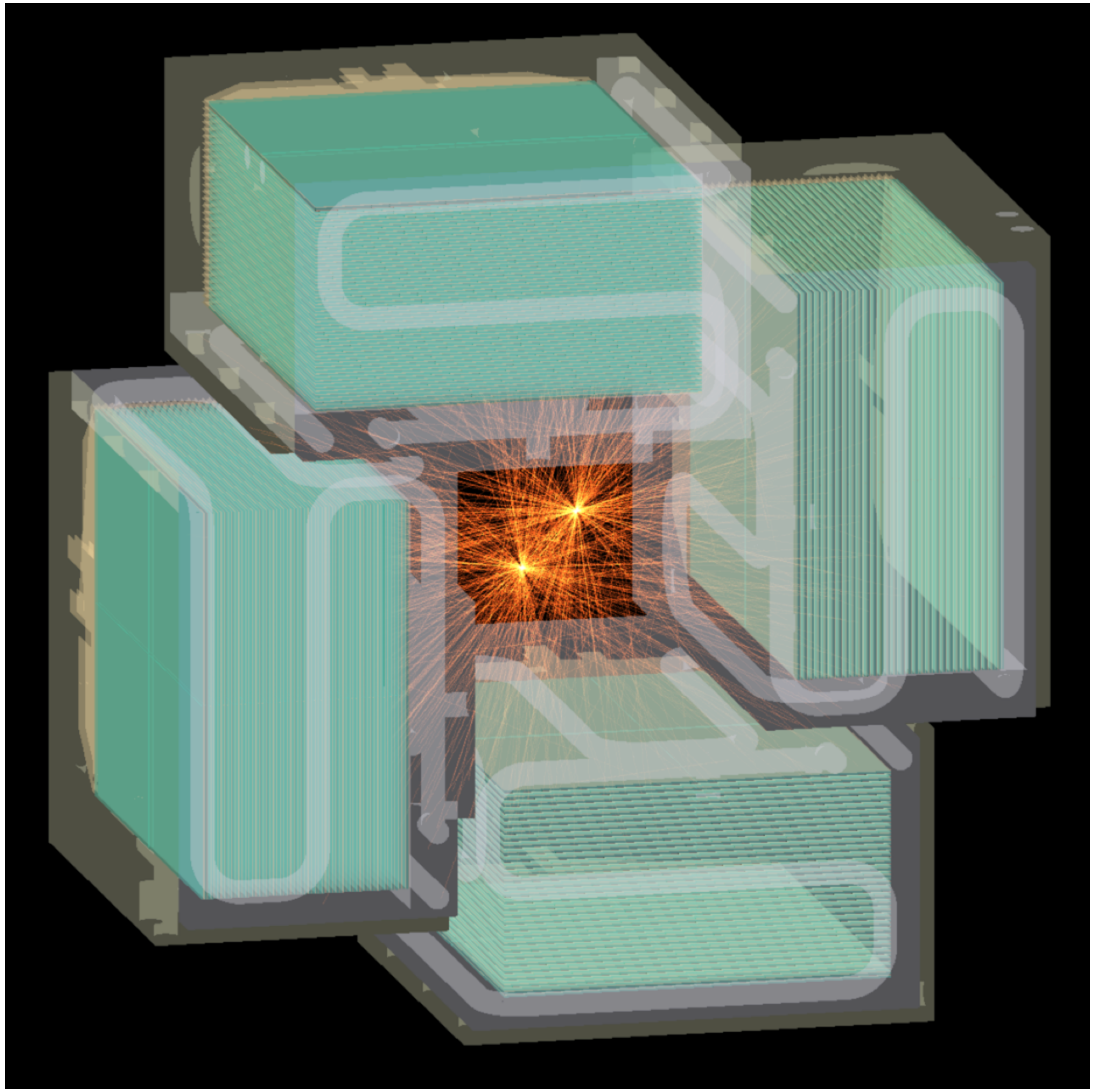
- 36 W injected in total in the tower
- Water cooling set at 10°C
- Environmental temperature: 21°C
- Two parallel cooling blocks with micro channeling of ~0.5 mm ID
- Blocks made of either Aluminum or Al_2O_3 ceramic
- Water inlet and exhaust temperature measured → HTC ≈ 8000Wm^2K^{-1}

Module #	Meas. [°C]	FEA [°C]
1	18.0	19.6
2	20.5	20.6
3	19.3	22.5
4	21.8	22.9
5	21.0	24.0
6	23.6	24.3
7	23.1	24.8
8	24.8	24.8
9	24.6	25.0
10	25.6	24.8
11	24.0	25.0
12	26.0	24.6

Good agreement between FEA and thermo-mechanical mock-up at NTC locations

Performance — Point-Spread Function

Aleix Boquet-Pujadas & Michäel Unser



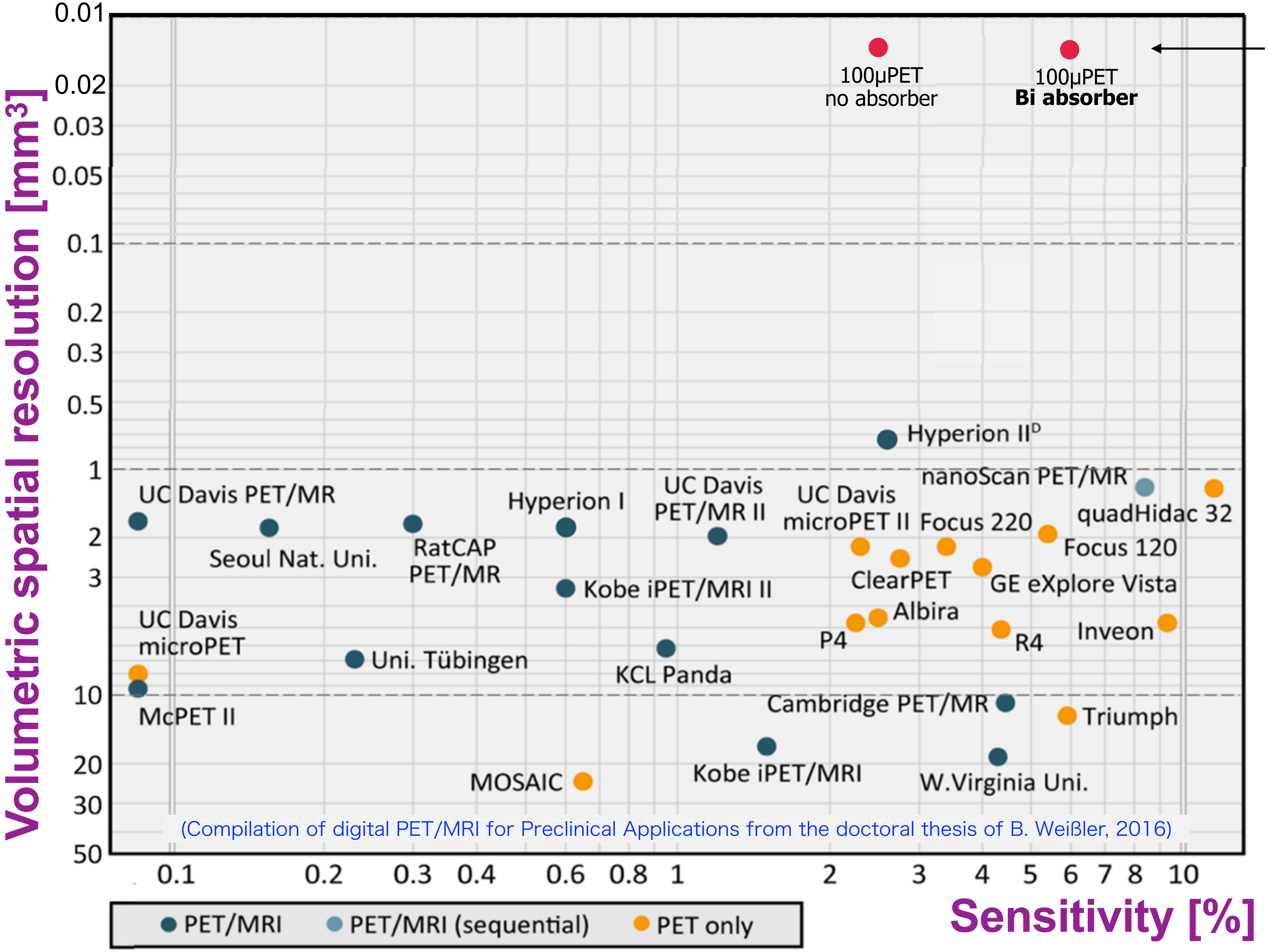
Point Spread Function [mm]
from Filtered Back Projection (FBP)

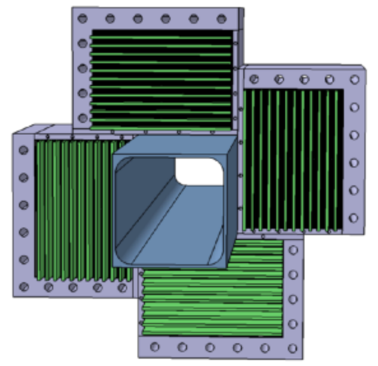
Off-axis [mm]		0	5	10	15
FWHM	No Bi	0.17	0.20	0.20	0.20
	50µm Bi	0.18	0.24	0.27	0.29
FWTM	No Bi	0.49	0.54	0.52	0.52
	50µm Bi	0.69	0.72	0.72	0.73

Excellent PSF down to **170µm,**
not degrading radially due to excellent DoI.
Addition of **50µm Bi converter** for higher efficiency does not degrade much resolution

Notice: *e^+ ^{18}F mean-free path included in the simulation*

The 100μPET Performance





Full simulation results (GEANT + AllPix2):

Volumetric spatial resolution of **0.012 mm³**, Two orders of magnitude better now.

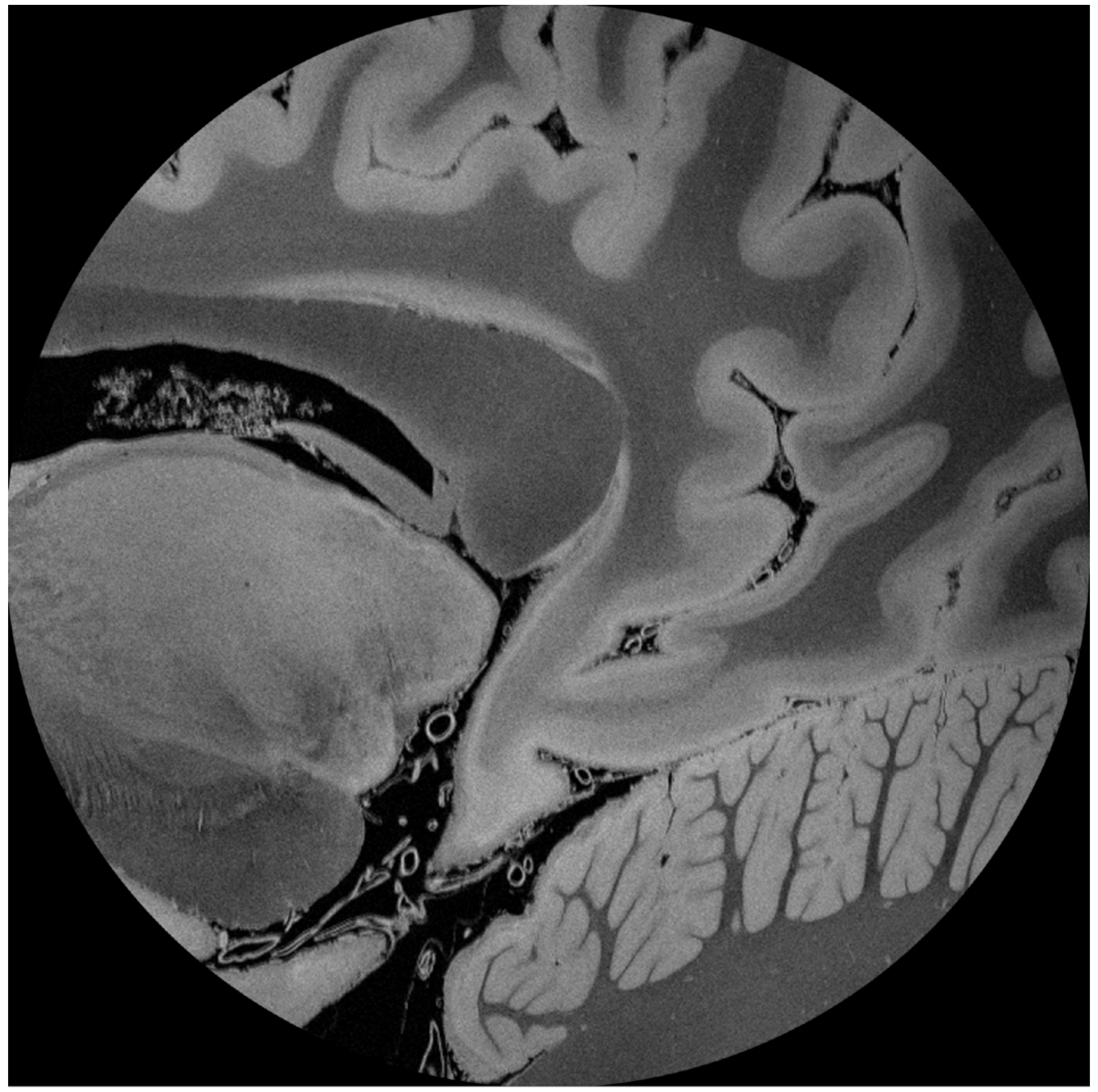
Sensitivity:

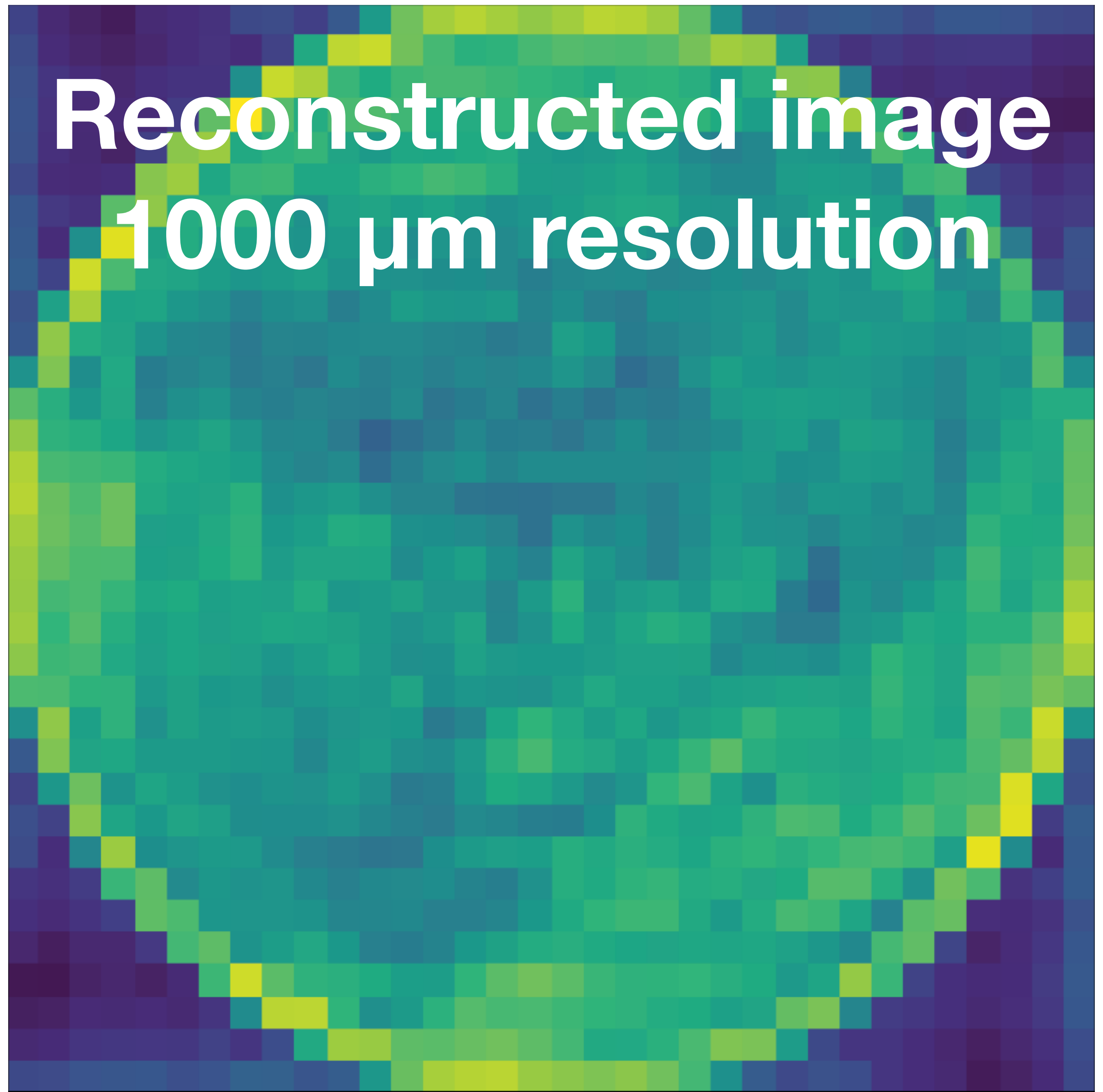
1. no Bi converter: Efficiency: **2.3%**
2. Bi converter: Efficiency: **6%**

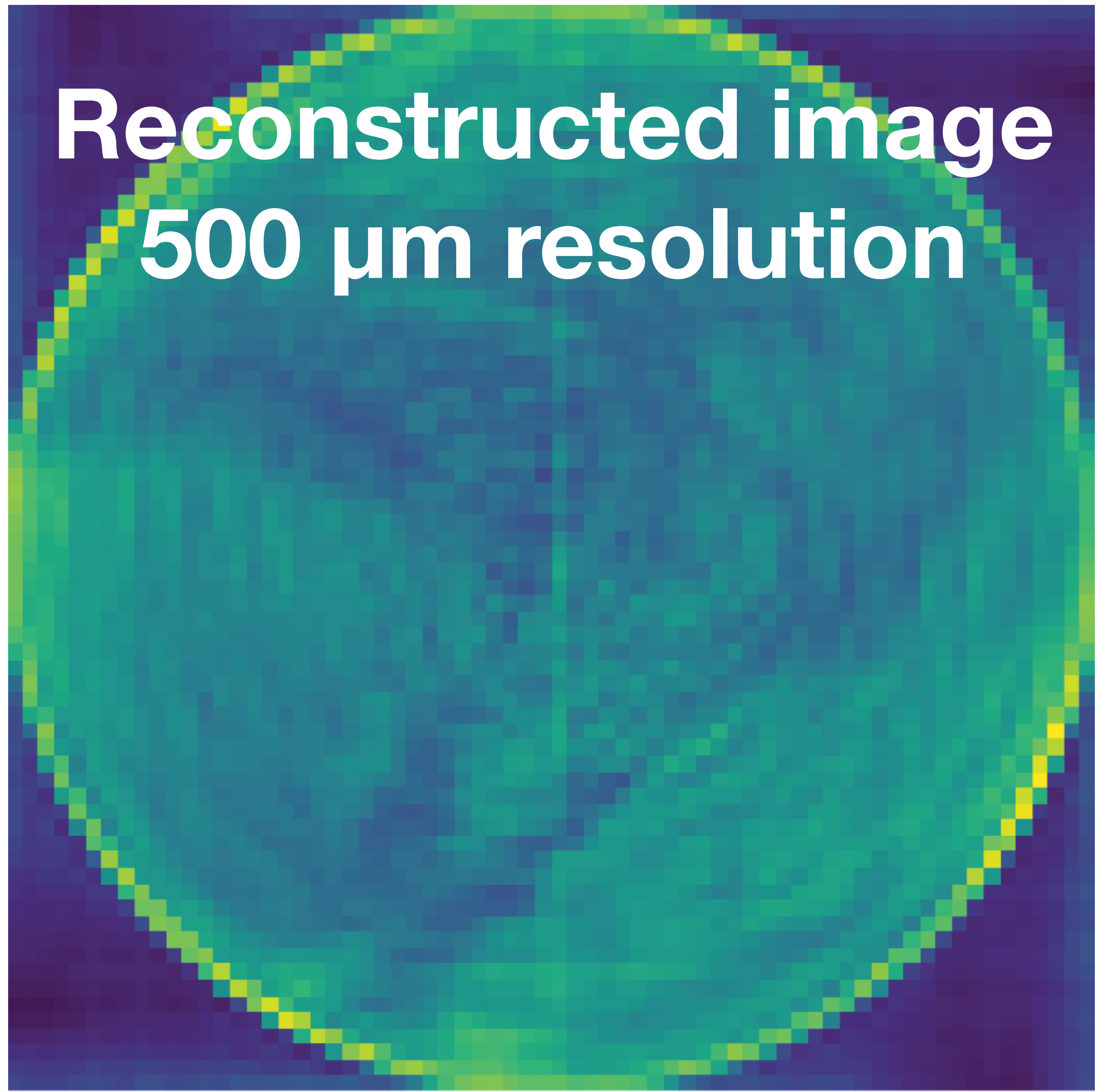
Aleix Boquet-Pujadas & Michäel Unser

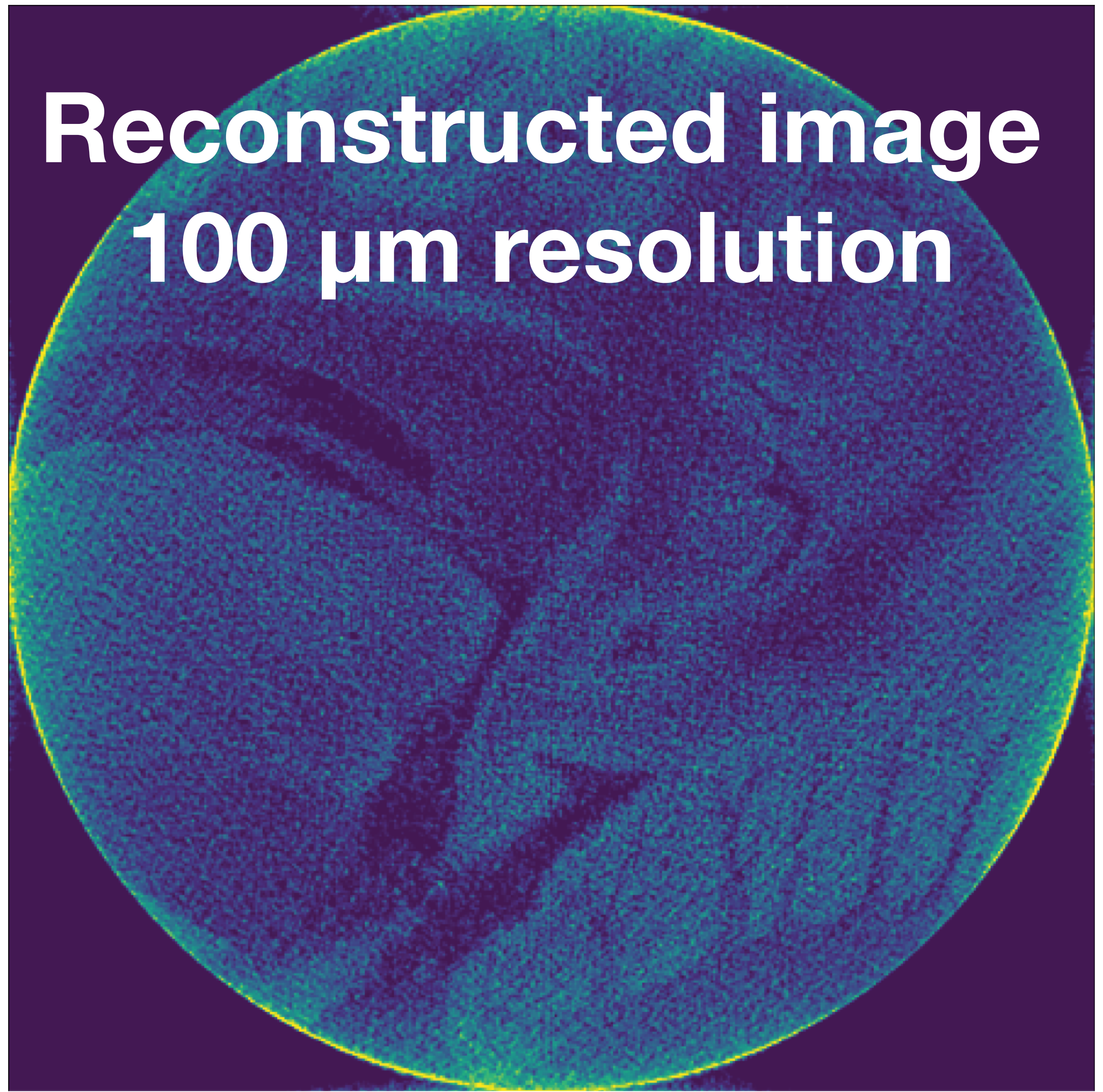
Brain MRI image data set (with 50 μm resolution) from: https://openneuro.org/datasets/ds002179/versions/1.1.0

Template MRI image (68mm diameter)









Conclusions

- **PET scanners** are a very important diagnostic tool with unique capability, but are limited by resolution

- **Monolithic pixelated silicon sensors** have the **enormous potential** to enable **ultra-high-resolution molecular imaging**

- The 100µPET SNSF SINERGIA project aims at delivering in 2025 a small-animal scanner based on silicon technology with expected **almost two orders of magnitude better volumetric spatial resolution**

- Silicon-sensor technology **cost will continue to go down**.
  In the future, scanners larger than those for small animals could be conceived

Articles and Patents:

Articles on monolithic silicon pixel detectors:

Efficiency and time resolution: JINST 17 (2022) P02019, https://iopscience.iop.org/article/10.1088/1748-0221/17/02/P02019
Small-area pixels power consumption: JINST 15 (2020) P11025, https://doi.org/10.1088/1748-0221/15/11/P11025
Hexagonal small-area pixels: JINST 14 (2019) P11008, https://doi.org/10.1088/1748-0221/14/11/P11008
TT-PET demonstrator chip testbeam: JINST 14 (2019) P02009, https://doi.org/10.1088/1748-0221/14/02/P02009
TT-PET demonstrator chip design: JINST 14 (2019) P07013, https://doi.org/10.1088/1748-0221/14/07/P07013
First TT-PET prototype: JINST 13 (2017) P02015, https://doi.org/10.1088/1748-0221/13/04/P04015
Proof-of-concept amplifier: JINST 11 (2016) P03011, https://doi.org/10.1088/1748-0221/11/03/P03011

Patents:

PLL-less TDC & synchronization System: EU Patent EP3591477A1
Picosecond Avalanche Detector (PicoAD): EU Patent EP18207008.6

Preliminary 2D reconstruction

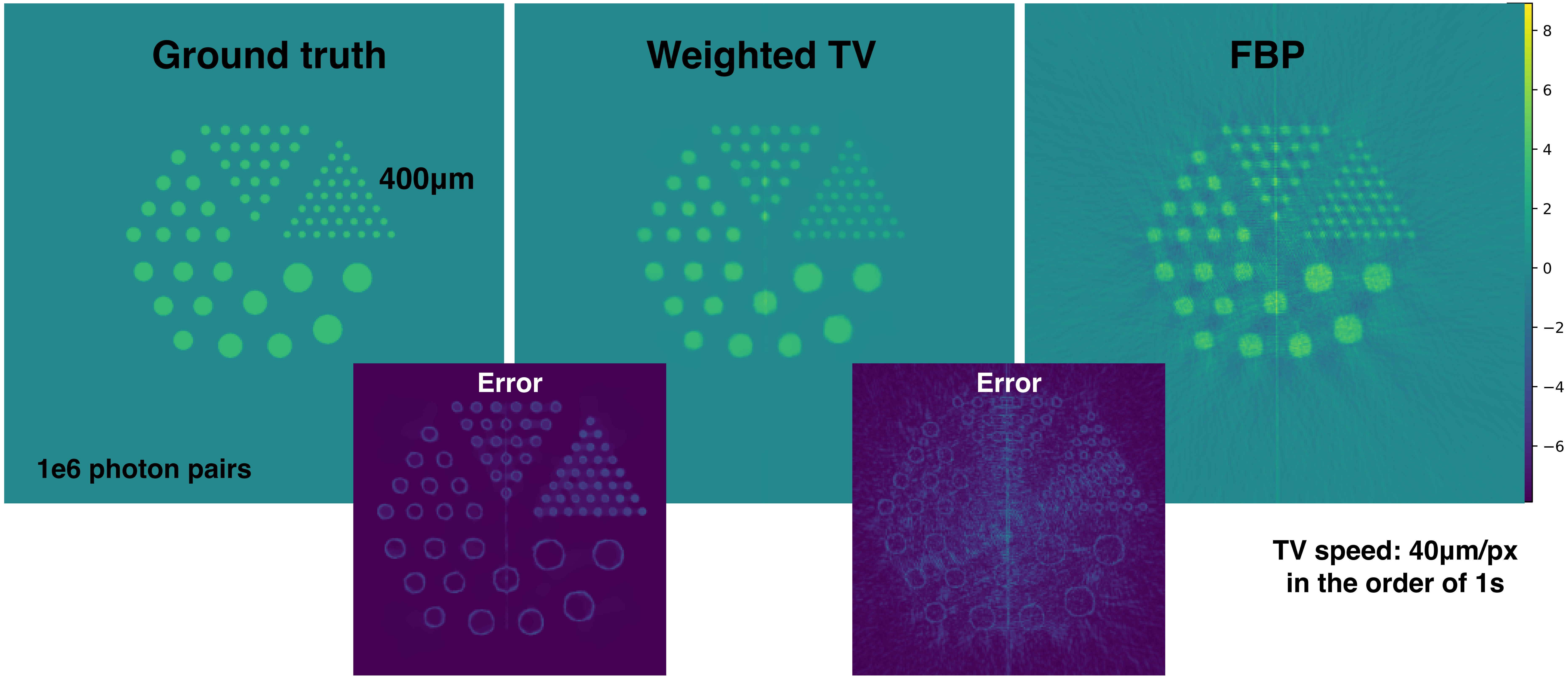
Aleix Boquet-Pujadas & Michäel Unser

Reconstruction

Exploit convolution trick for speed to reconstruct with weighted TV

$$\mathrm{argmin}_{\mathbf{c}} ||P\mathbf{c} - \varsigma_q||^2_{2,A} + ||B_1 * \mathbf{c}||_1 + i_+(B_0 * \mathbf{c})$$

$$\text{with } P^T A P \text{ a convolution}$$



TV speed: 40µm/px in the order of 1s

Weighted TV wins by 9dB even when the number of photons is normalised