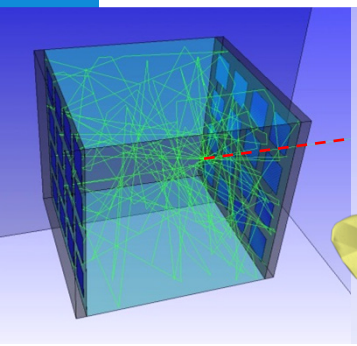
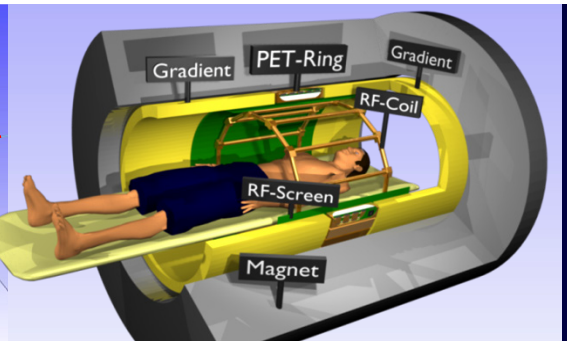
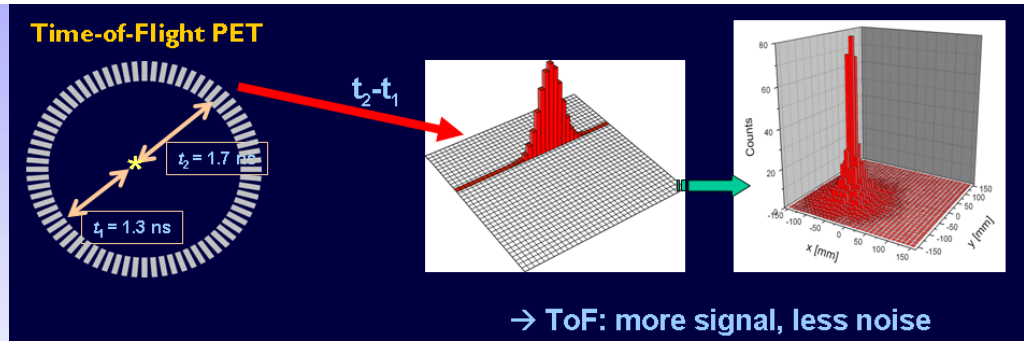






HYPMED

FAST
Fast Advanced Scintillator Timing

Programme co-funded by the
EUROPEAN UNION

SUBLIMA

A cost-effective, scalable approach to high-resolution, sub-100 ps TOF-PET

EUREKA

cost
EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

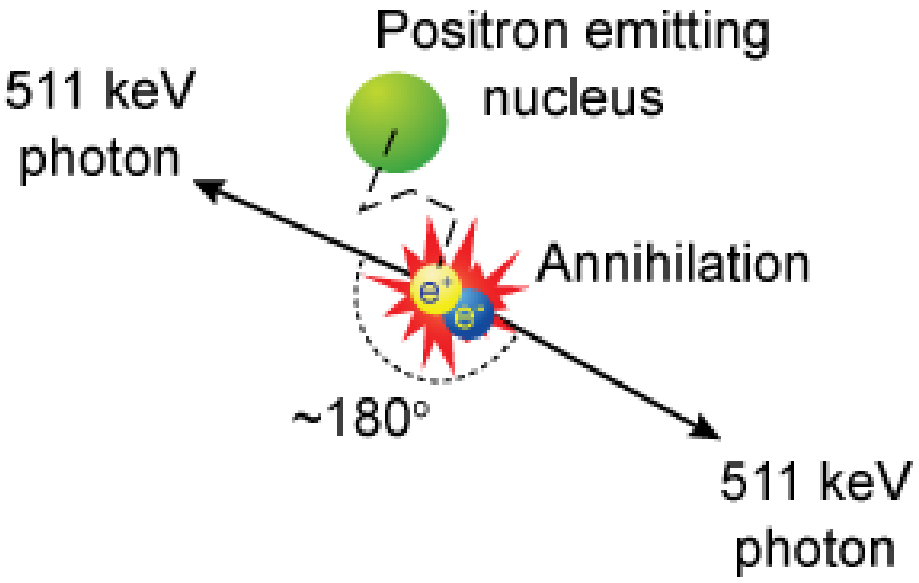
SEVENTH FRAMEWORK
PROGRAMME

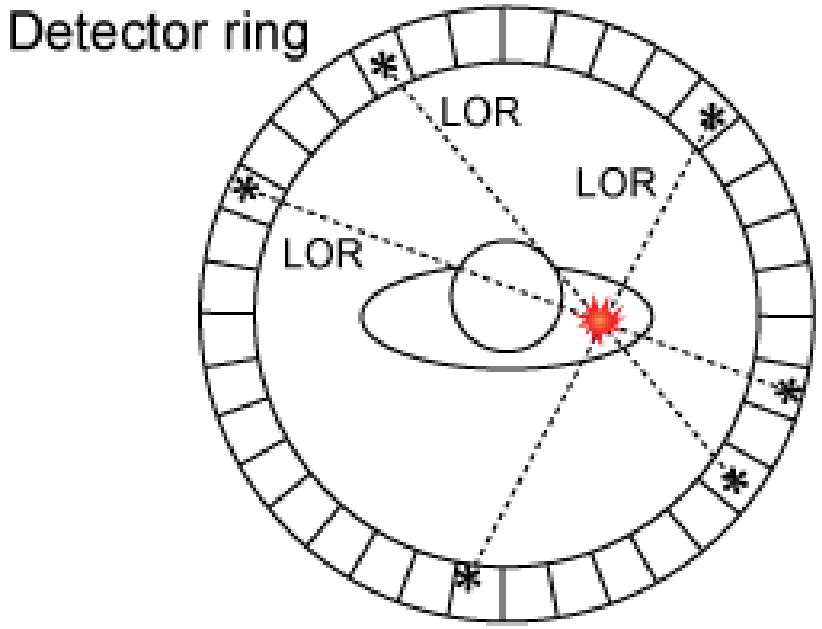
THE FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION
HORIZON 2020

MEDAMI 2016, May 1-5, 2016, Ajaccio, Corsica

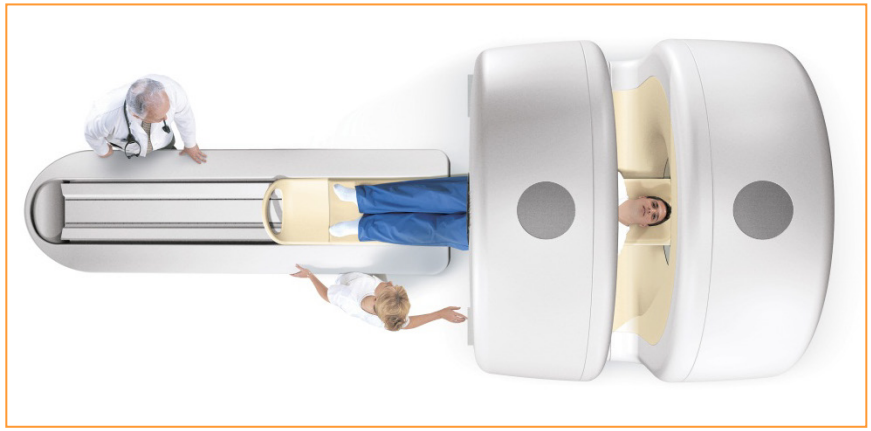
TU Delft
Dennis R. Schaart
Delft University of Technology
d.r.schaart@tudelft.nl

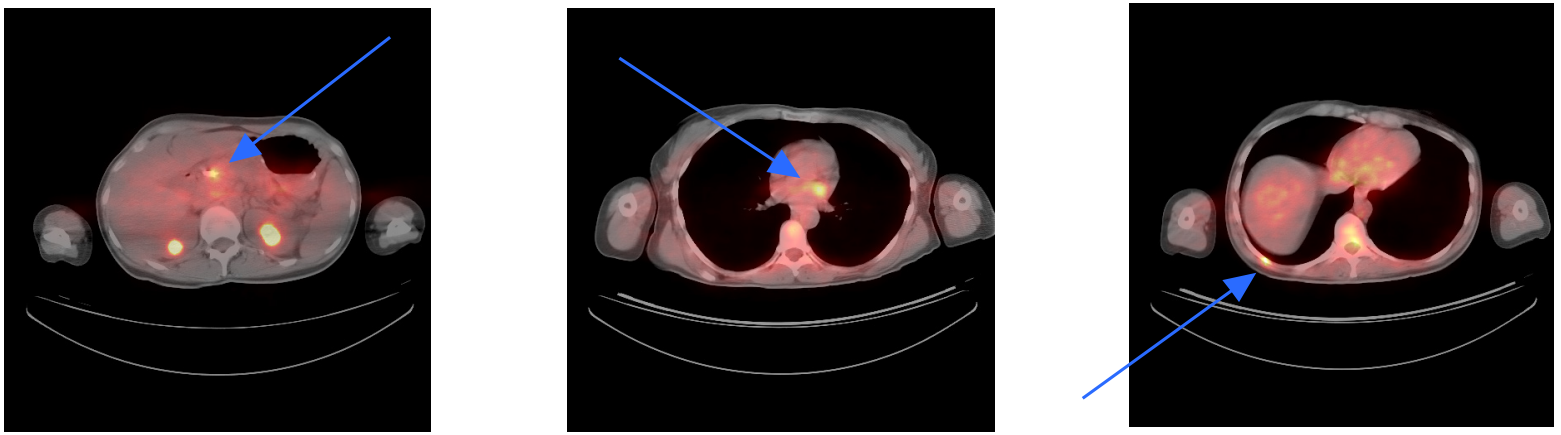
Positron Emission Tomography





PET/CT





PET/CT (fused images): primary pancreatic cancer with suspicious chest wall and mediastinum lesions

Courtesy of A.A. Lammertsma, VUmc PET Centre, and Philips

In vivo molecular imaging

PET provides 4D in vivo molecular imaging with:

- the best spatial resolution
- the highest molecular sensitivity (~10^6 times better than MRI)
- and the most accurate quantitation

available clinical practice today

Use of PET

PET is e.g. used in **oncology** for:

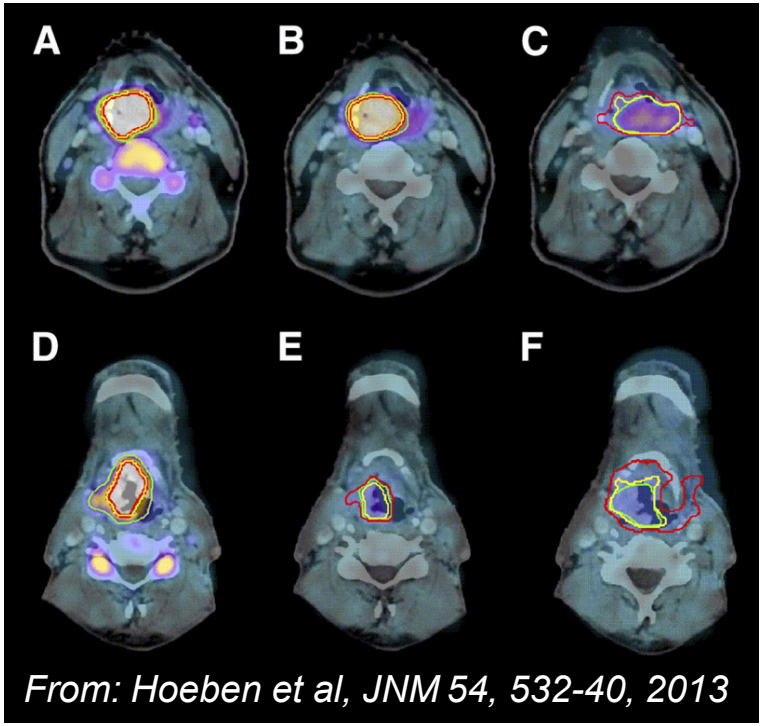
- Preclinical research
- Clinical research
- Cancer diagnosis
- Cancer staging
- Treatment planning
- (Early) monitoring of response to treatment
- Follow-up

⇒ PET is a truly **translational modality** as well as a proven and widely used tool in **personalized medicine**

^{18}FLT-PET/CT before therapy (A,D), in 2nd week of therapy (B,E) and in 4th week (C,F)

Top row shows slow decrease in FLT uptake in patient treated for supraglottic laryngeal carcinoma

Bottom row shows a patient with fast decrease of FLT uptake, associated with better survival probability



From: Hoeben et al, JNM 54, 532-40, 2013

Why is PET not yet used as often as e.g. CT or MRI?

What is still missing?

In vivo molecular imaging needs:

- More and more specific tracers, readily available, and affordable
- Lower dose (currently 5-25 mSv, should be << 1 mSv)
- Shorter scan time (currently > 10 minutes, should be < 1 minute)
- More flexibility (combination with imaging and therapeutic modalities)
- Lower costs (currently > 1000 € per scan, must be value-based)

Technologically, this necessitates:

- Order-of-magnitude increase in molecular sensitivity (**=> TOF!**)
- High spatial resolution and DOI recovery
- Quantitative accuracy (< 5%)
- Compact, flexible, scalable, and affordable solutions

The importance of spatial resolution

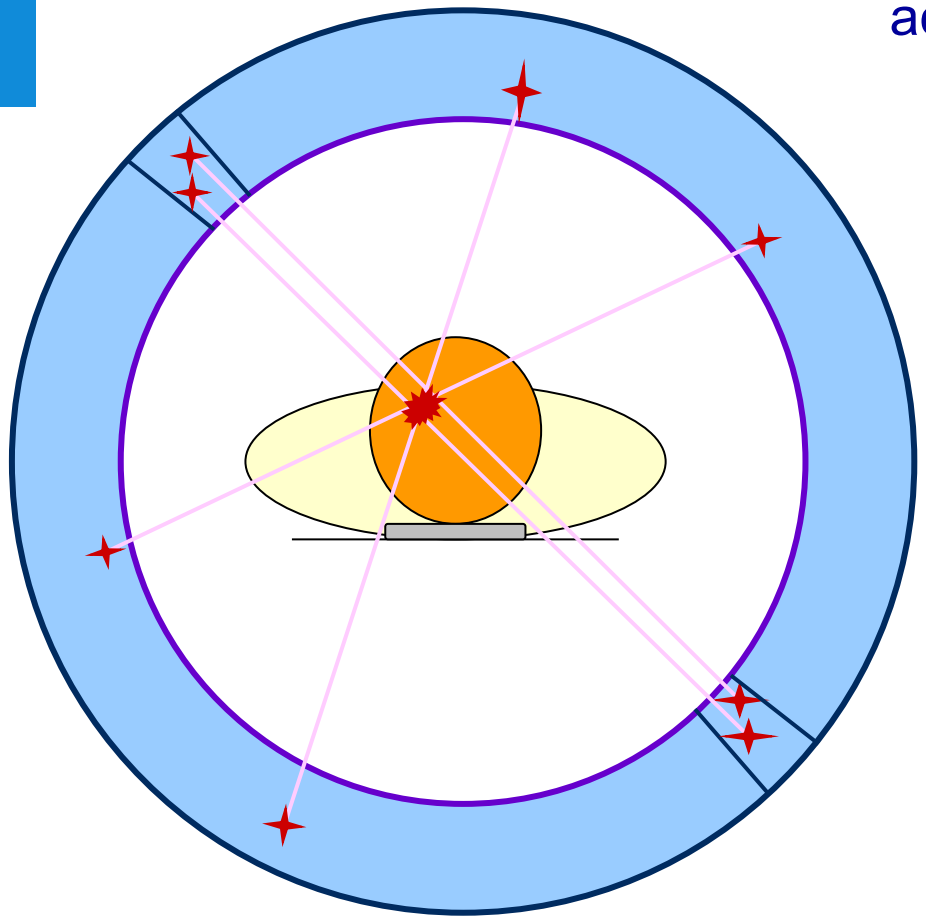
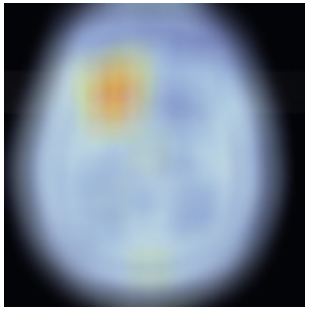


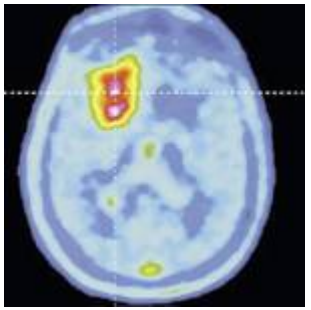
Image resolution is determined by the accuracy with which we can determine the interaction position of the gamma photon in the detector

Clinical PET today: ~ 4-5 mm

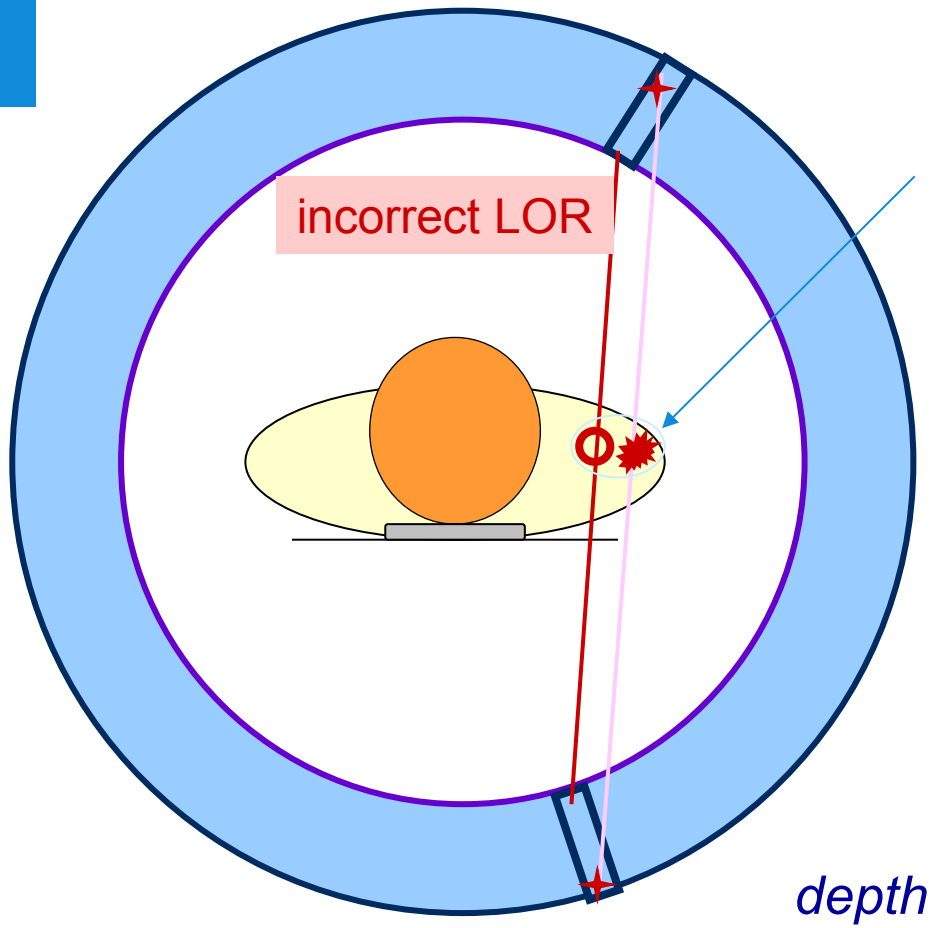
low spatial resolution:



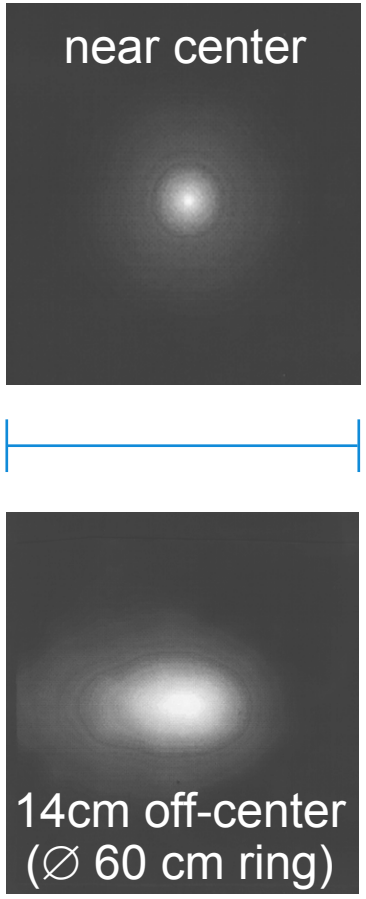
high spatial resolution:



Depth of interaction errors



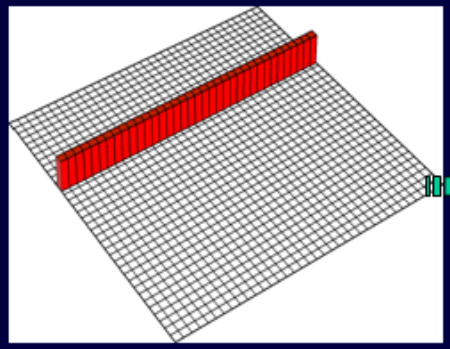
parallax error or
radial elongation
(at off-centre
positions only)

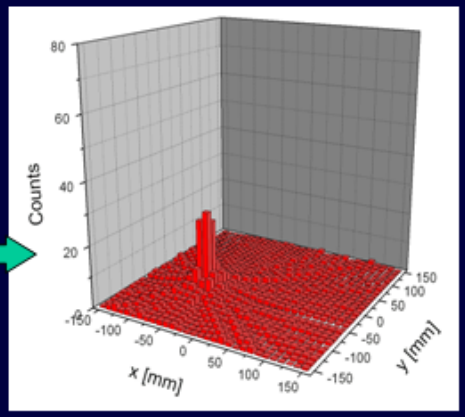


Parallax errors can be
avoided by correcting for the
depth of interaction (DOI) in the scintillator

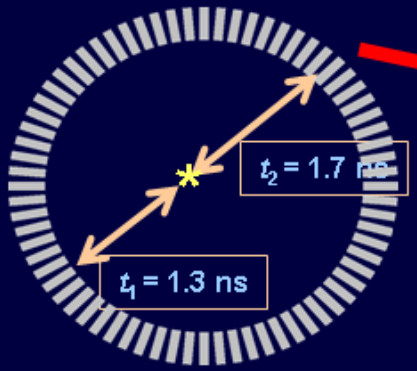
Time of Flight PET Systems

Conventional PET/ ToF off

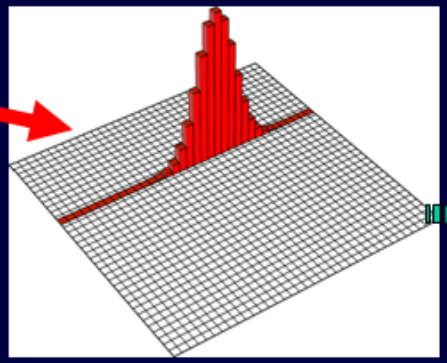


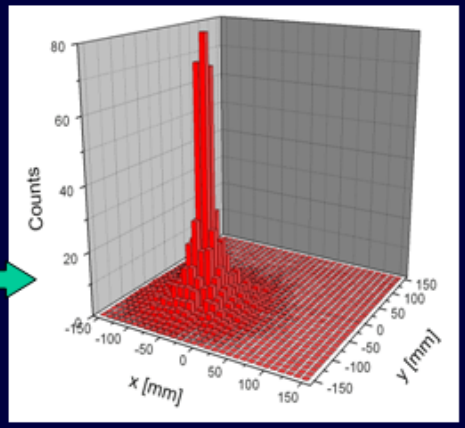


Time-of-Flight PET



t_2-t_1



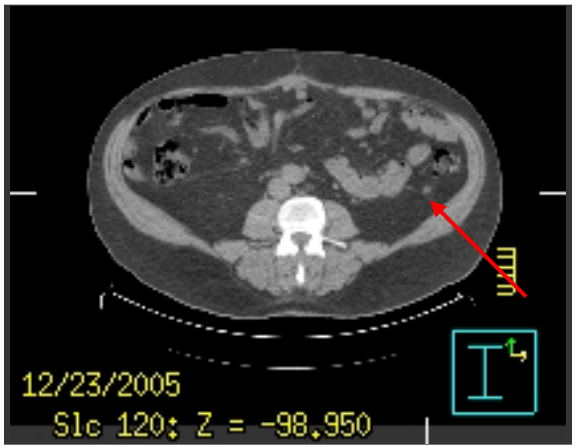


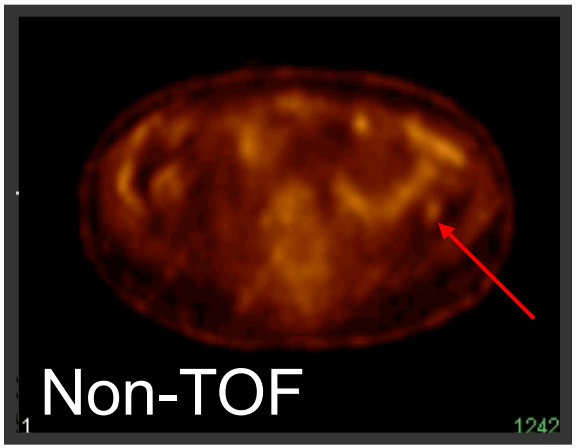
→ ToF: more signal, less noise

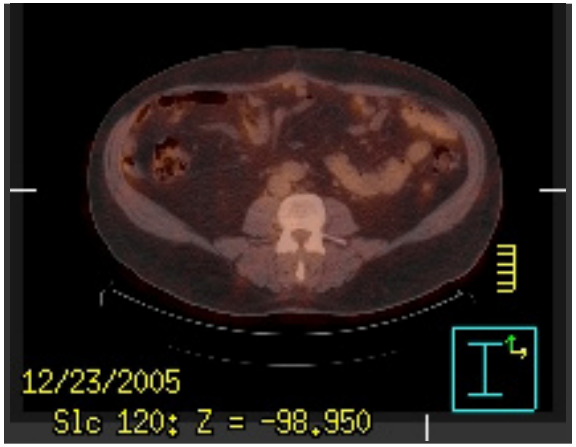
Time-of-flight PET

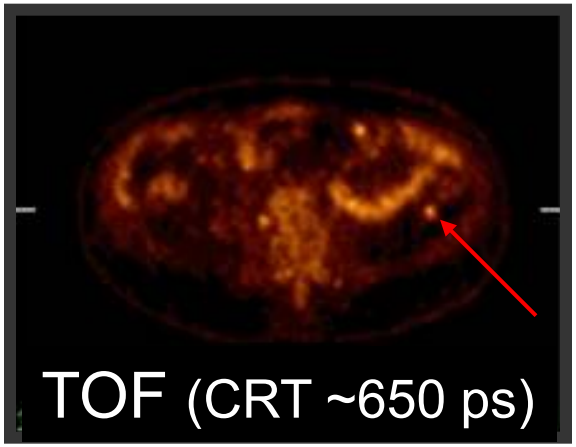
Colon cancer, left upper quadrant peritoneal node

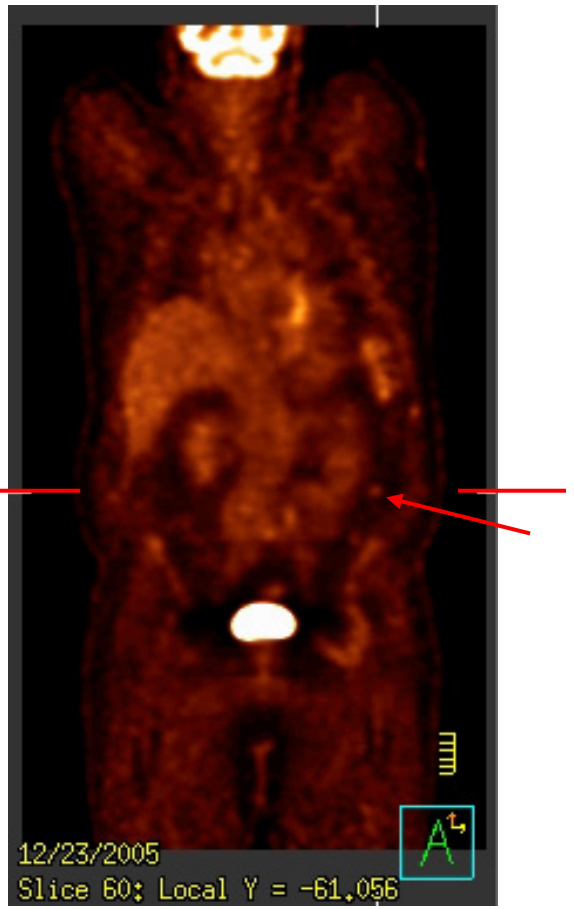
114 kg; BMI = 32.2
13.4 mCi; 2 hr post-inj









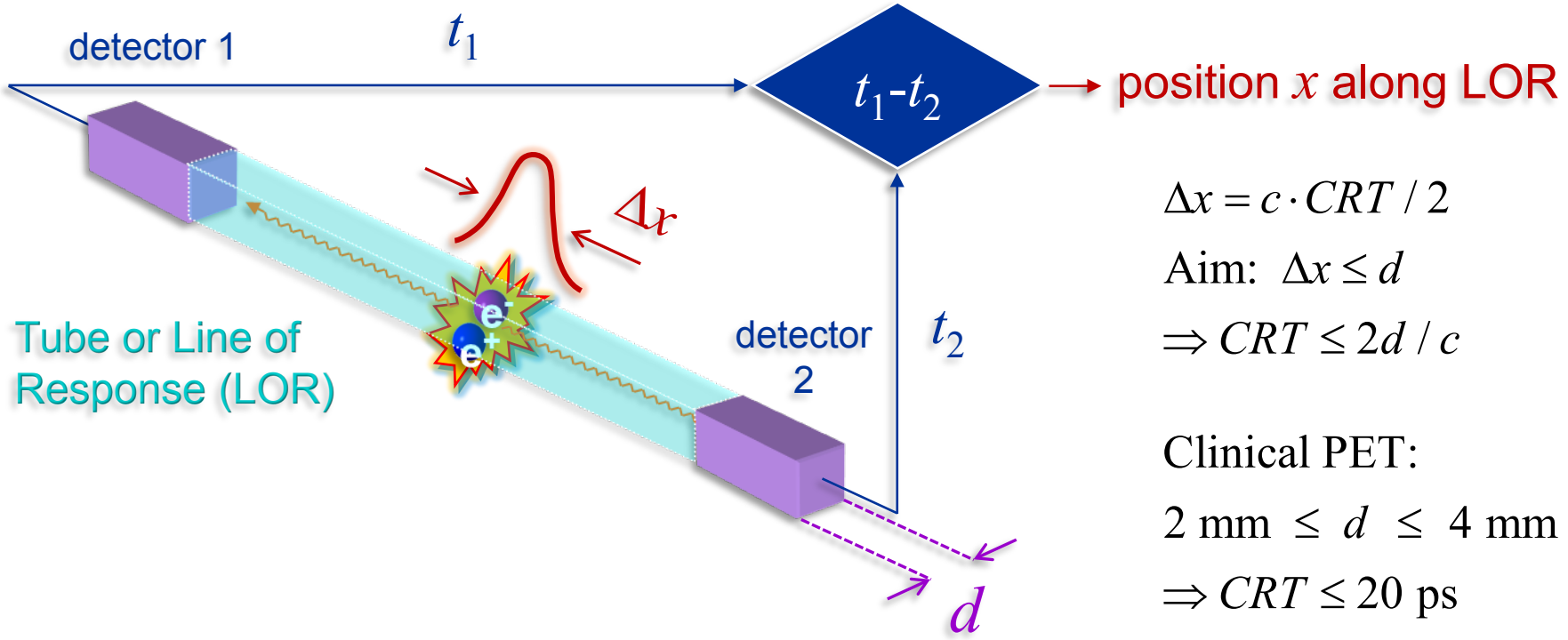


Images: J. Karp, University of Pennsylvania

The holy grail: “10-picosecond PET”

With a CRT of ~10 ps events an be localized directly:

- Image reconstruction no longer needed => real-time image formation
- Extreme sensitivity => new applications (e.g. single cell tracking?)



$$\Delta x = c \cdot CRT / 2$$

Aim: $\Delta x \leq d$

$$\Rightarrow CRT \leq 2d / c$$

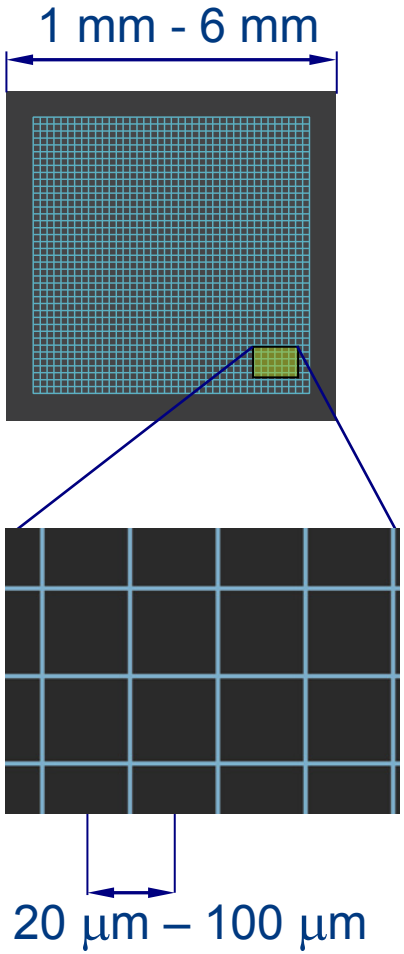
Clinical PET:

$2\ \text{mm} \leq d \leq 4\ \text{mm}$

$$\Rightarrow CRT \leq 20\ \text{ps}$$

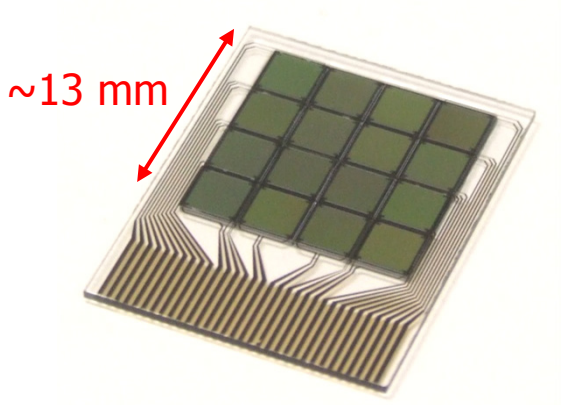
The silicon photomultiplier (SiPM)

- a disruptive photosensor technology



- Array of many self-quenched Geiger-mode APDs (microcells) connected in parallel
- Increasingly interesting as replacement for PMTs:
  - high gain (~10^6)
  - high PDE
  - compact and rugged
  - transparent to γ-photons
  - fast response (ns)
  - insensitive to magnetic fields

First SiPM array based PET detectors (2008)



IOP Publishing
Phys. Med. Biol. 54 (2009) 3501–3512
Physics in Medicine and Biology
doi:10.1088/0031-9155/54/11/015

A novel, SiPM-array-based, monolithic scintillator detector for PET

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Abstract

Silicon photomultipliers (SiPMs) are of great interest to positron emission tomography (PET), as they enable new detector geometries, for e.g., depth-of-interaction (DOI) determination, are MR compatible, and offer faster response and higher gain than other solid-state photosensors such as avalanche photodiodes. Here we present a novel detector design with DOI correction, in which a position-sensitive SiPM array is used to read out a monolithic scintillator. Initial characterization of a prototype detector consisting of a 4×4 SiPM array coupled to either the front or back surface of a 13.2 mm $\times$ 13.2 mm $\times$ 10 mm LYSO:Ce^{3+} crystal shows that front-side readout results in significantly better performance than conventional back-side readout. Spatial resolutions <1.6 mm full-width-at-half-maximum (FWHM) were measured at the detector centre in response to an ~0.54 mm FWHM diameter test beam. Hardly any resolution losses were observed at angles of incidence up to 45°, demonstrating excellent DOI correction. About 14% FWHM energy resolution was obtained. The timing resolution, measured in coincidence with a BaF_2 detector, equals 960 ps FWHM.

(Some figures in this article are in colour only in the electronic version)

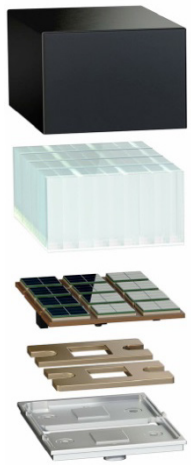
SciSiLiA Project (2006-2010)

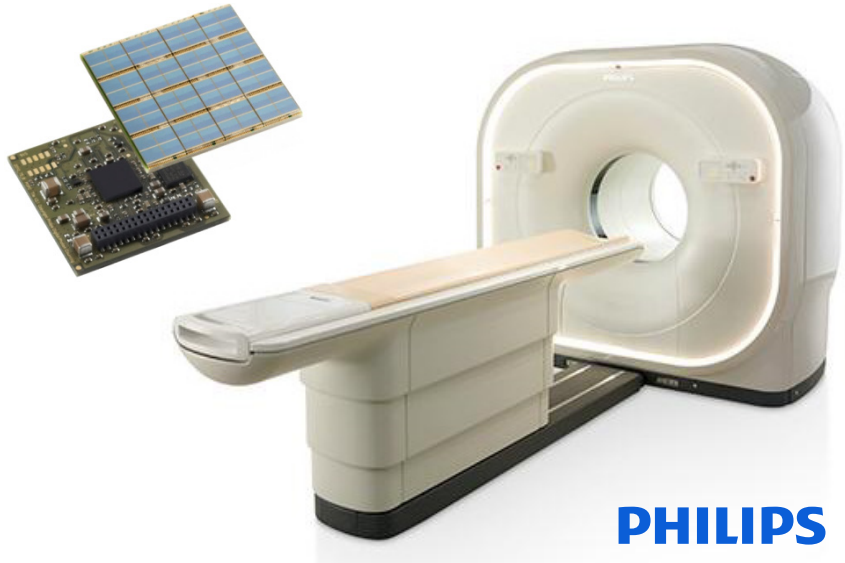
One of the first SiPM arrays: SensL SPMarray 3035G16 (Dec 2007), containing 4 x 4 SiPMs of ~3 x 3 mm^2 each

D.R. Schaart et al, Phys Med Biol 54, 3501-3512 (2009)

SiPMs have arrived in nuclear medicine

TOF-PET/MRI and TOF-PET/CT system based on Silicon Photomultipliers



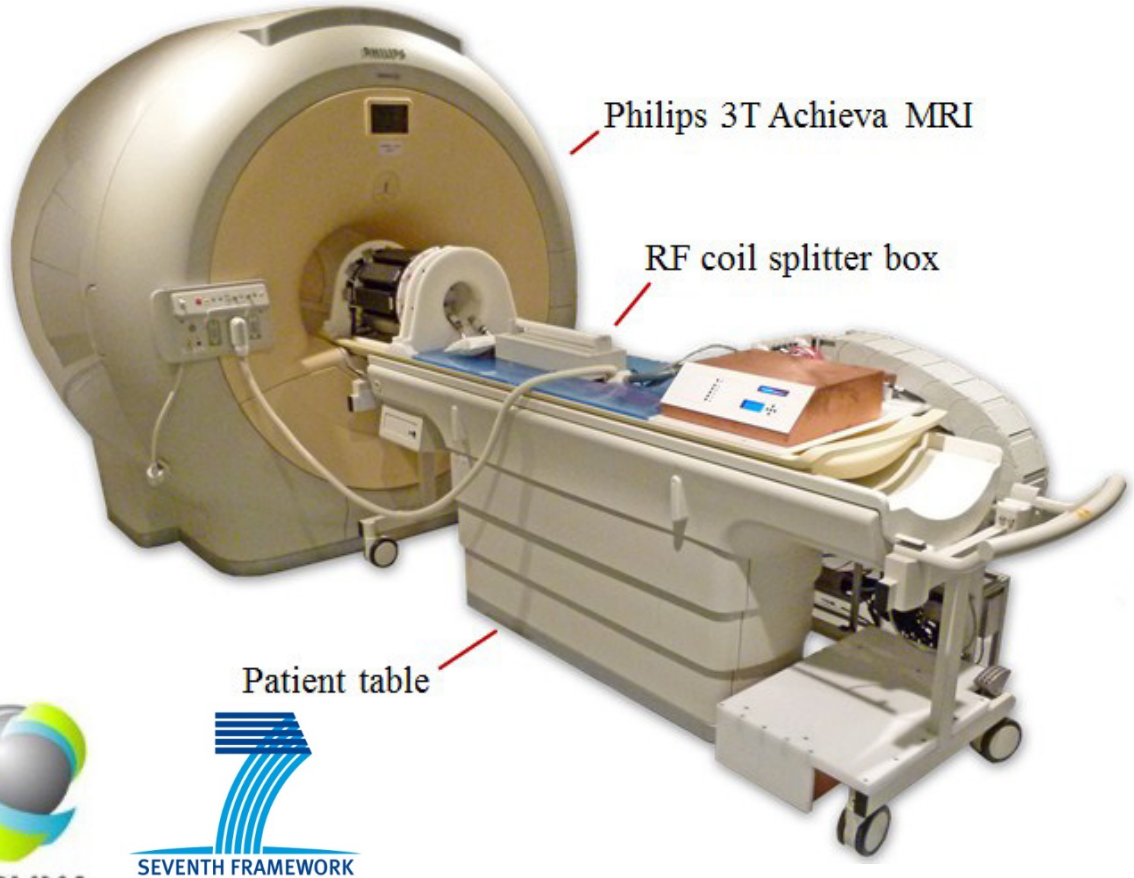


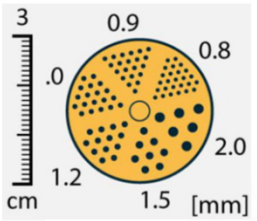
System Performance	
CRT	< 400 ps FWHM
Sensitivity	21 kcps/MBq
FOV	60 x 25 cm
Spatial res	4.1 mm
Energy res	< 12%

System Performance	
CRT	325 ps FWHM
Eff. sens.	22 kcps/MBq
FOV	67.6 x 16.4 cm
Spatial res	4.1 mm
Energy res	< 12%

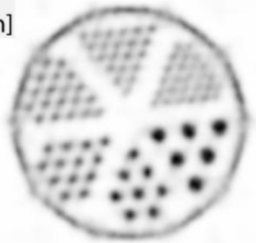
Fully digital MR-compatible PET insert

For small-animal imaging





Spatial resolution ~0.8 mm



SUBLIMA (FP7, 2010-2015)

- Philips
- RWTH
- TU Delft
- KCL
- U Gent
- UHEI
- FBK
- and others…

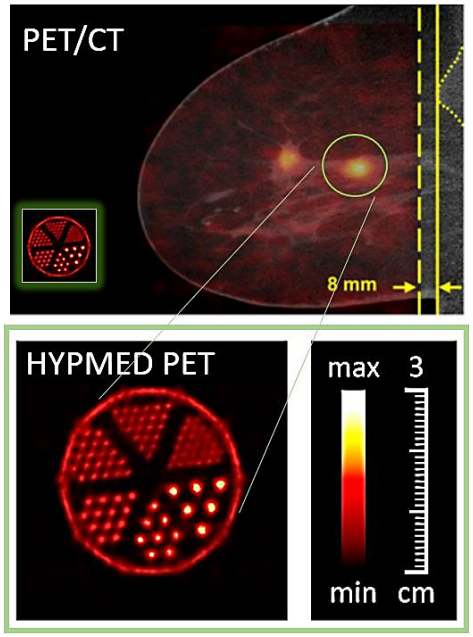
SUBLIMA

SEVENTH FRAMEWORK PROGRAMME

HYPMED: PET/MRI insert for breast

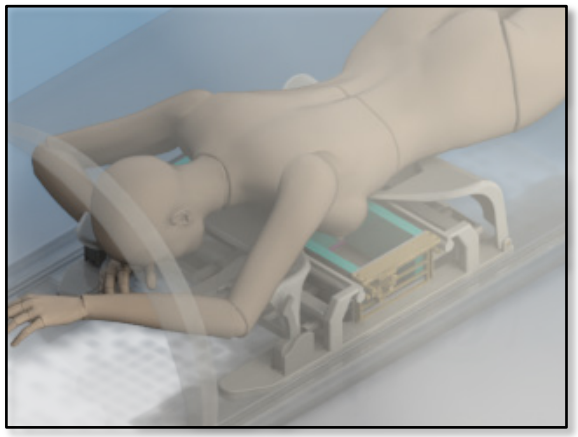
HYPMED: a new device for breast PET/MRI hybrid imaging
H2020-PHC11-2015 (2016-2020, ~6 M€)

- MRI-transparent PET-detector integrated with PET-transparent breast MRI coil
- ~ 1 mm spatial resolution, ~200 ps CRT, 4x sensitivity w.r.t. whole-body PET/MR
- prospective clinical study with 200 patients to evaluate clinical utility



Objectives:

- improve early diagnosis of breast cancer
- reduce need for invasive biopsies
- improve treatment planning
- identify novel biomarkers
- reduce dose (~8x)

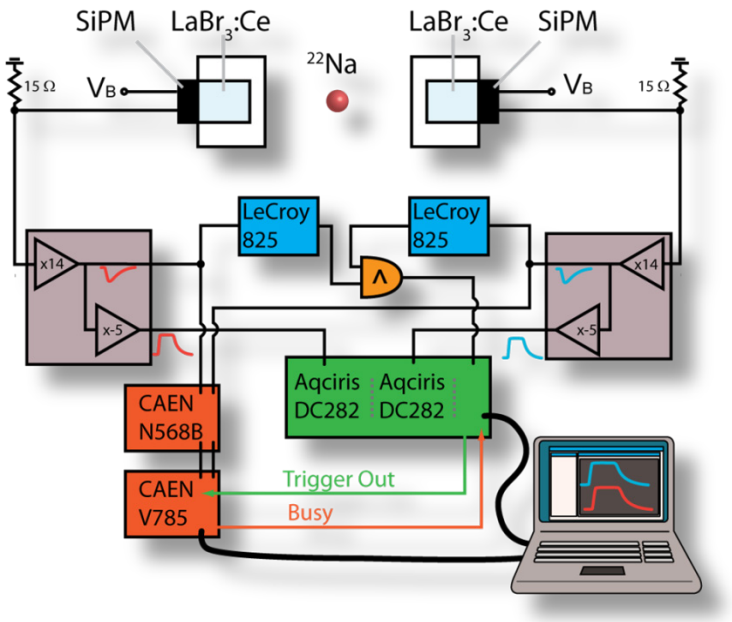


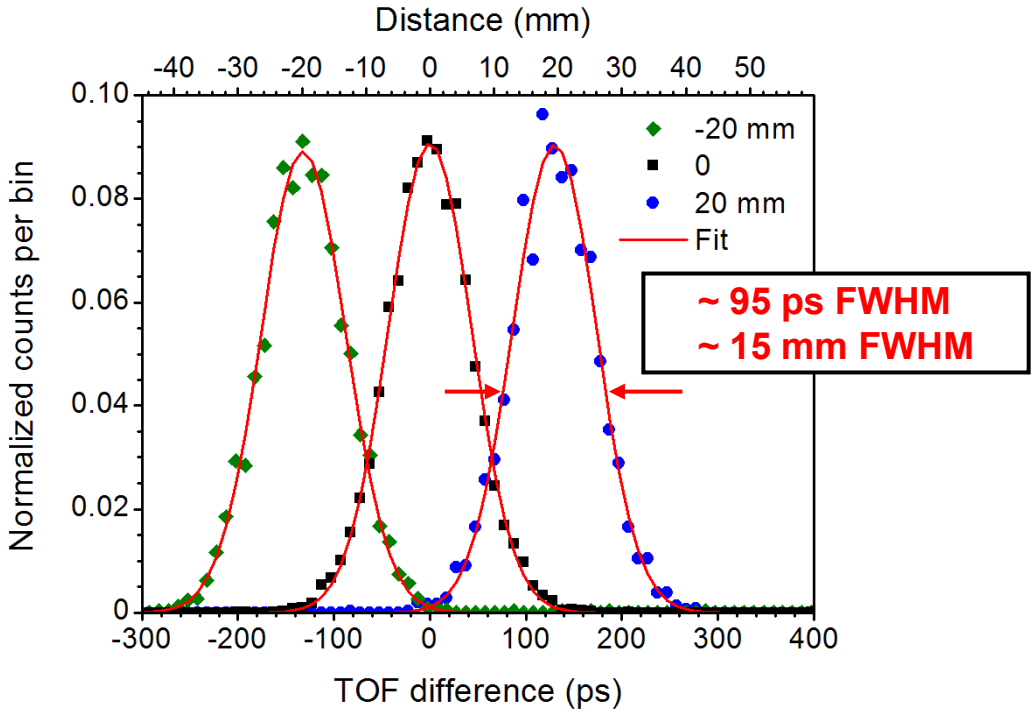
A few words on breaking speed limits…

100 ps barrier already broken in lab (2009)

Made possible by the combination of:

- Small $LaBr_3$:Ce(5%) crystals (3 mm x 3 mm x 5 mm)
- Silicon Photomultipliers (Hamamatsu MPPC-S10362-33-050C)
- Digital Signal Processing (DSP)





D.R. Schaart et al, Phys Med Biol 55, N179-N189, 2010

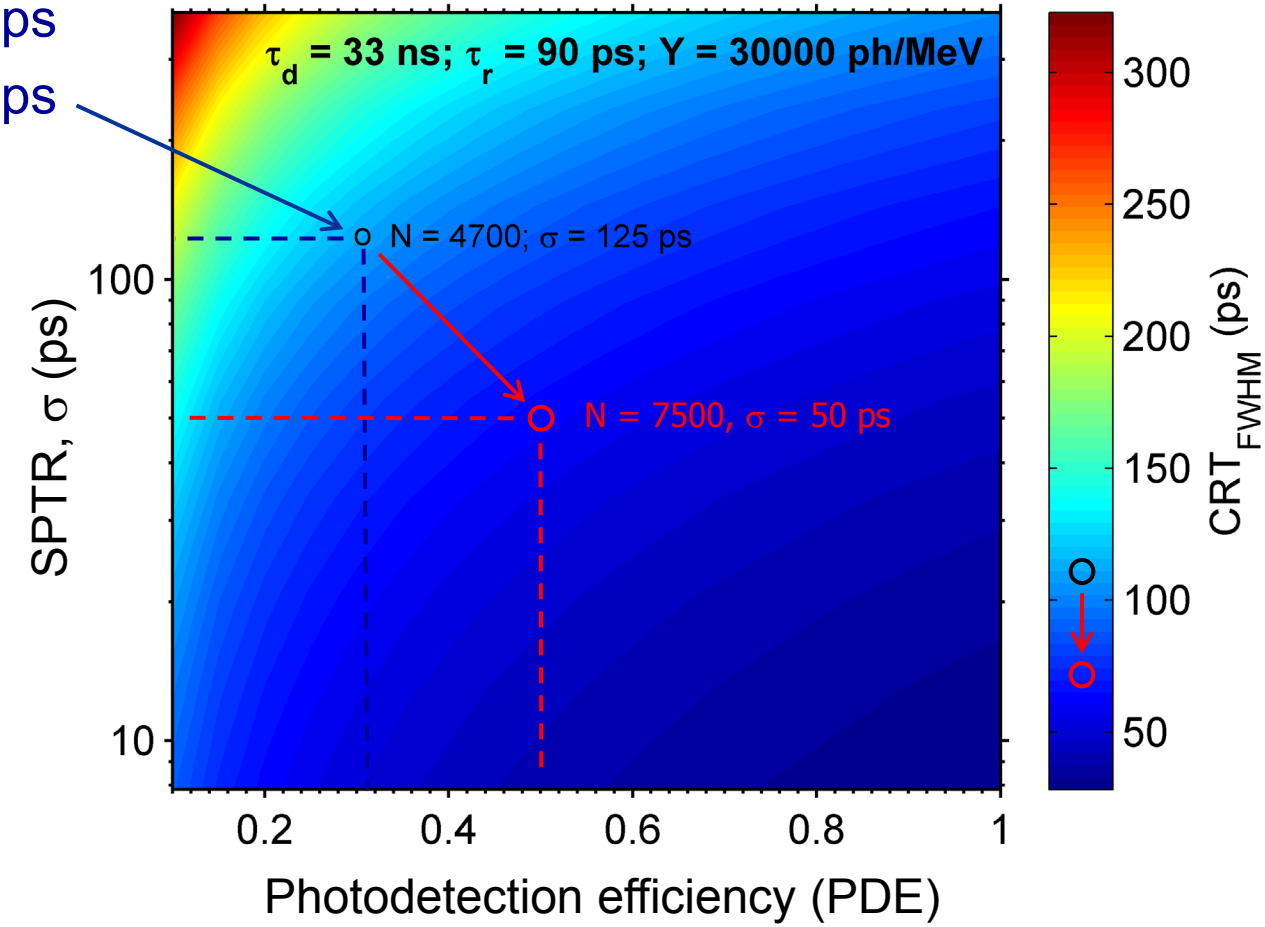
Example: CRT of LSO:Ce,Ca

Measured: ~125 ps

CRT_{LB}: ~110 ps

$$\mathrm{var}(\Xi) \geq \frac{1}{I_{T_d}(\Theta)}$$

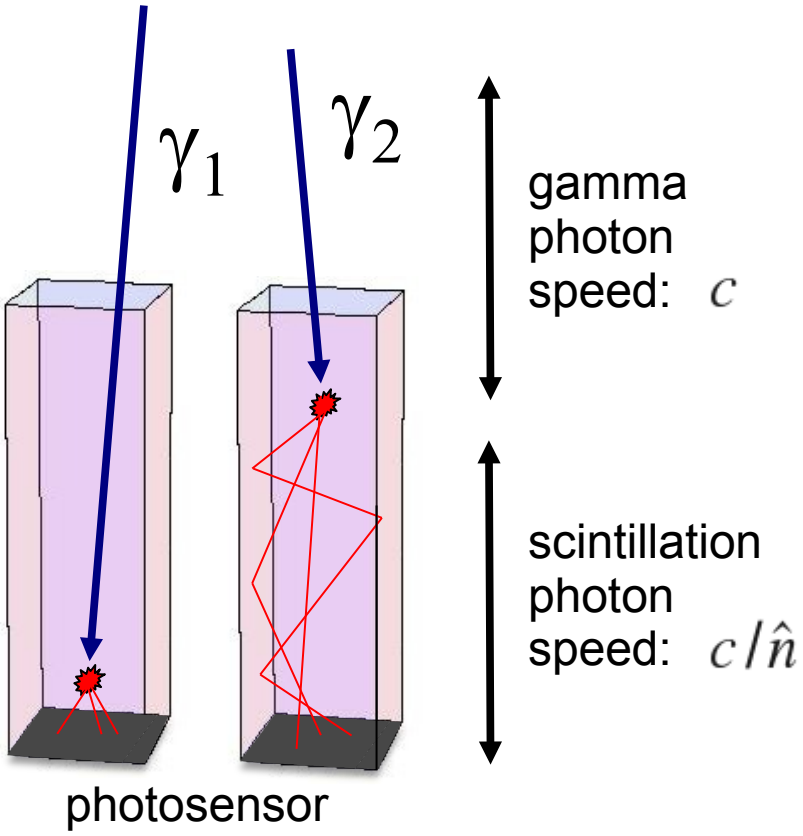
CRT < 100 ps is feasible with further (d)SiPM improvements (PDE and TTS)

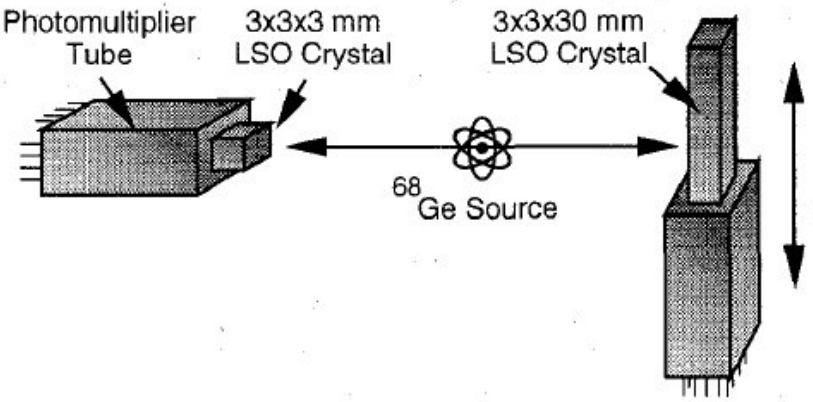


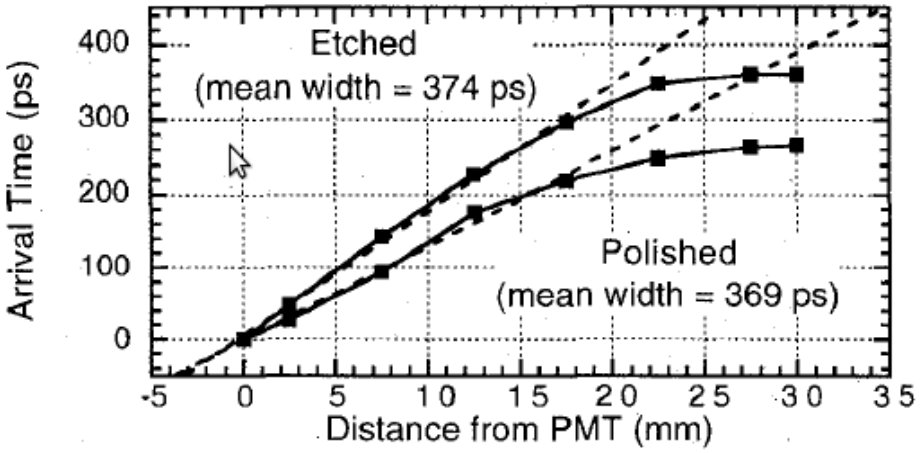
Lower bound on the CRT of LSO:Ce,Ca + MPPC as a function of PDE and TTS

DOI-dependent signal delay in crystal

Depth-of-interaction (DOI) variations deteriorate timing resolution

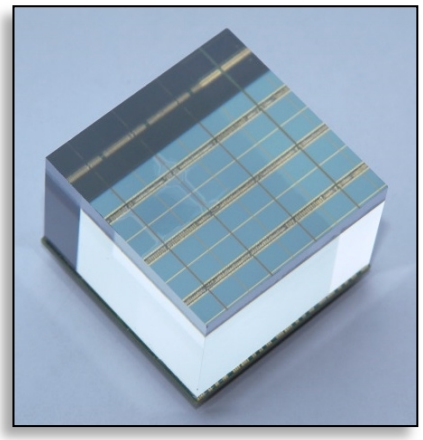




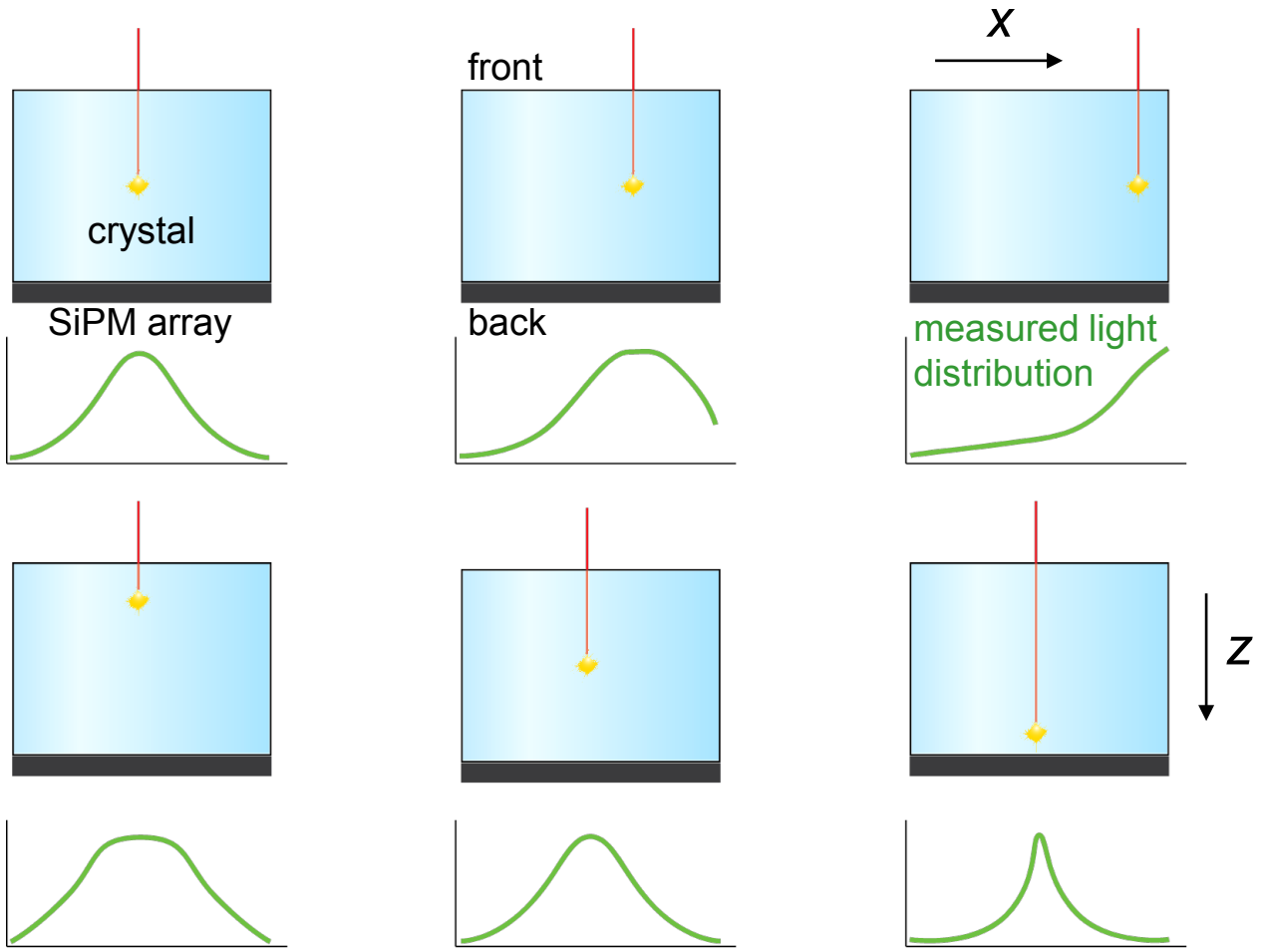


WW Moses and SE Derenzo
IEEE Trans. Nucl. Sci. 46, 474-478 (1999)

Monolithic scintillator detectors

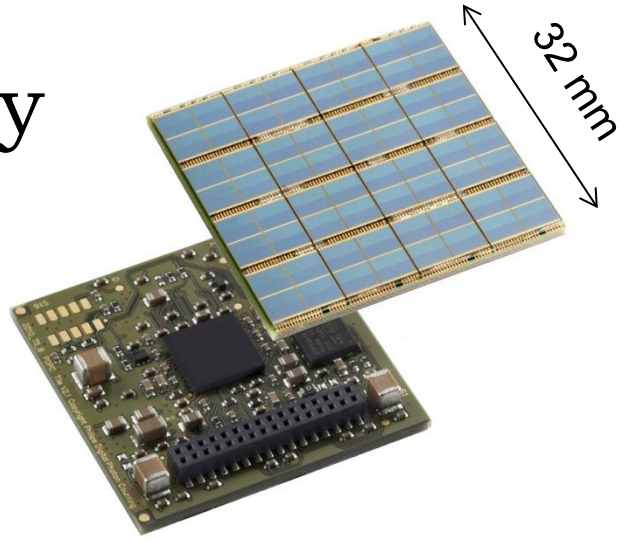


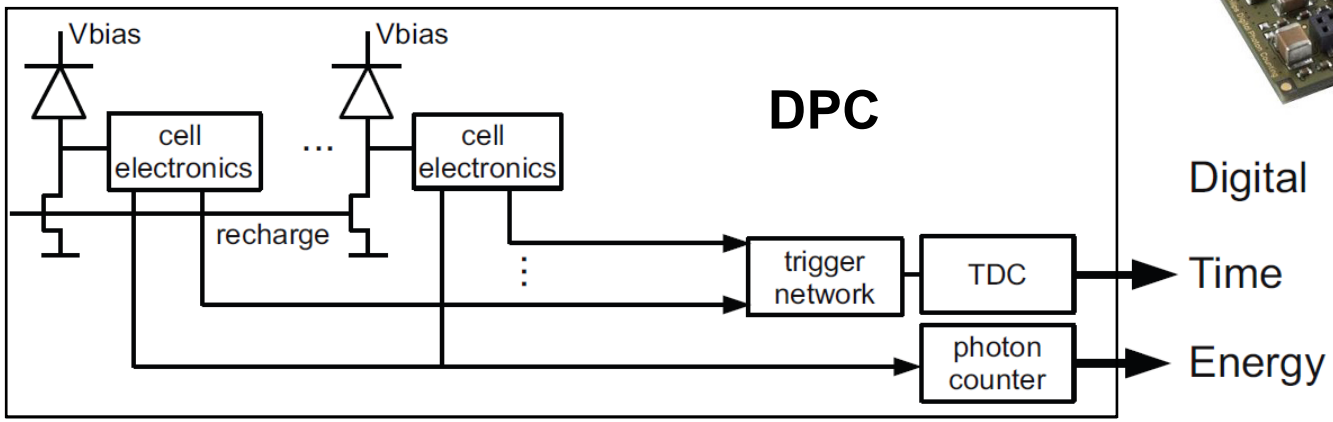
32 mm x 32 mm x 22 mm monolithic LYSO:Ce crystal on digital silicon photomultiplier (dSiPM) array



Monolithic scintillator operating principle

Readout: digital SiPM array



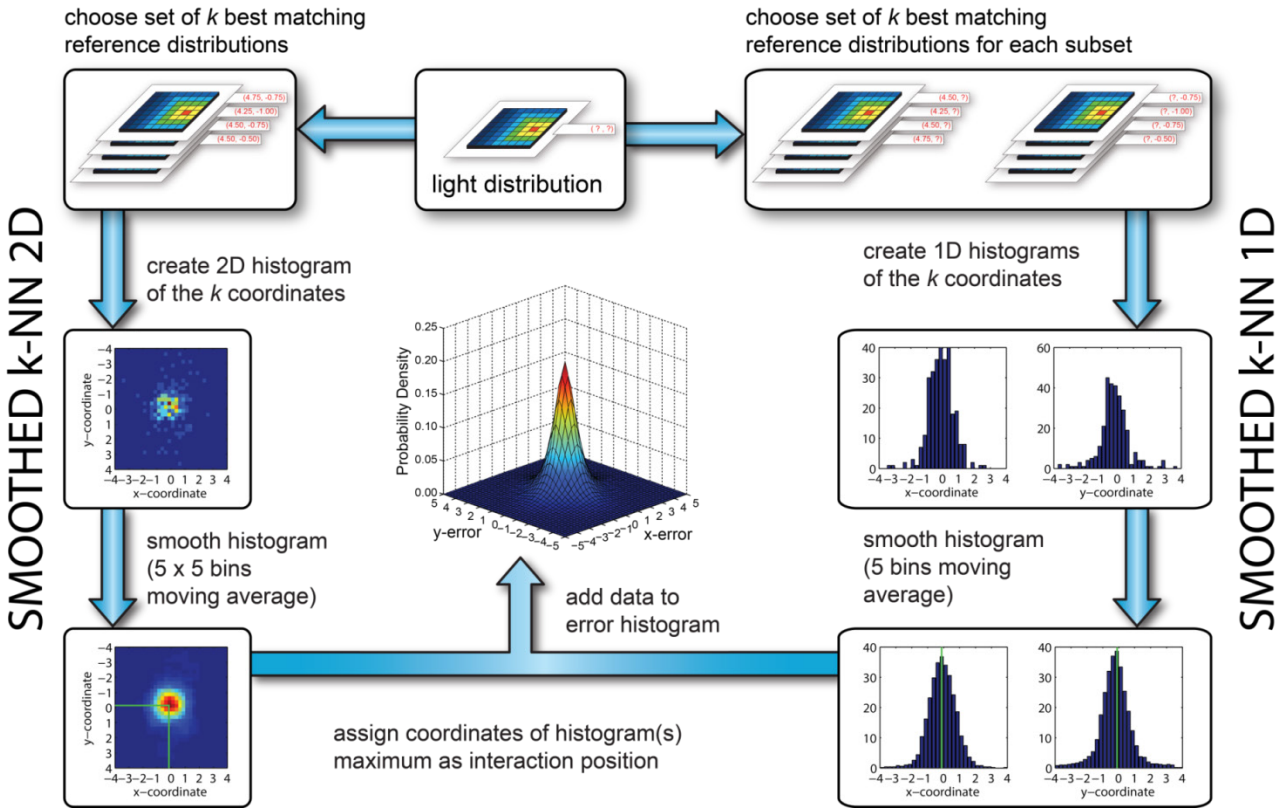


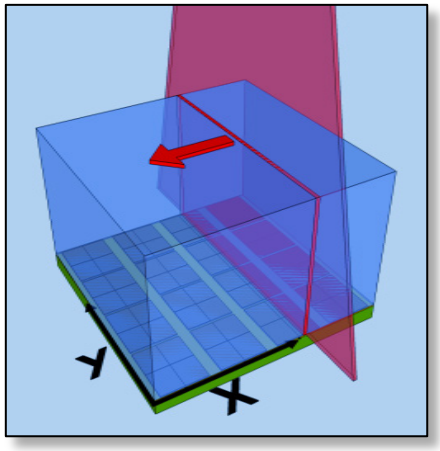
++ small single-photon time jitter
++ negligible noise at the single photon level
++ ~ 30% photon detection efficiency
+ MR-compatible

16 Si chips (4 x 4)
→ 16 time stamps
→ 64 pixel values (no. of counts)

See also: D. R. Schaart et al "Advances in Digital SiPMs …," NIM A 809, 31-52, 2016

k-NN position estimation





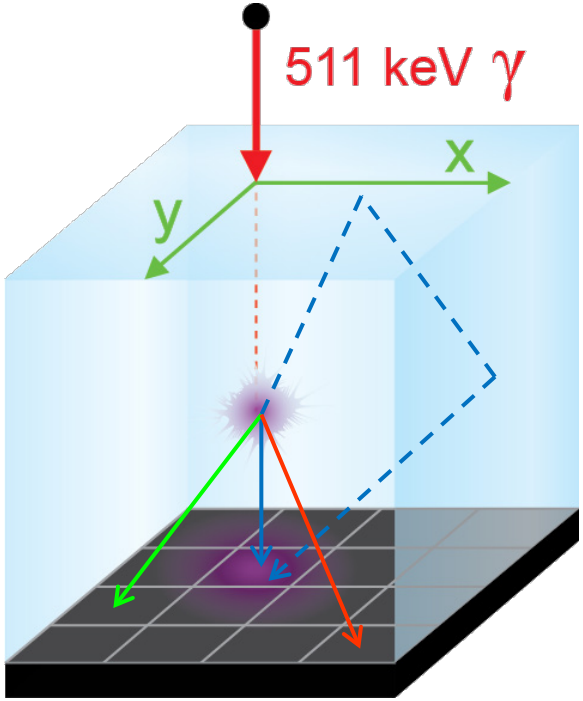
Fast calibration: separate collection of reference events for each coordinate using a fan-beam

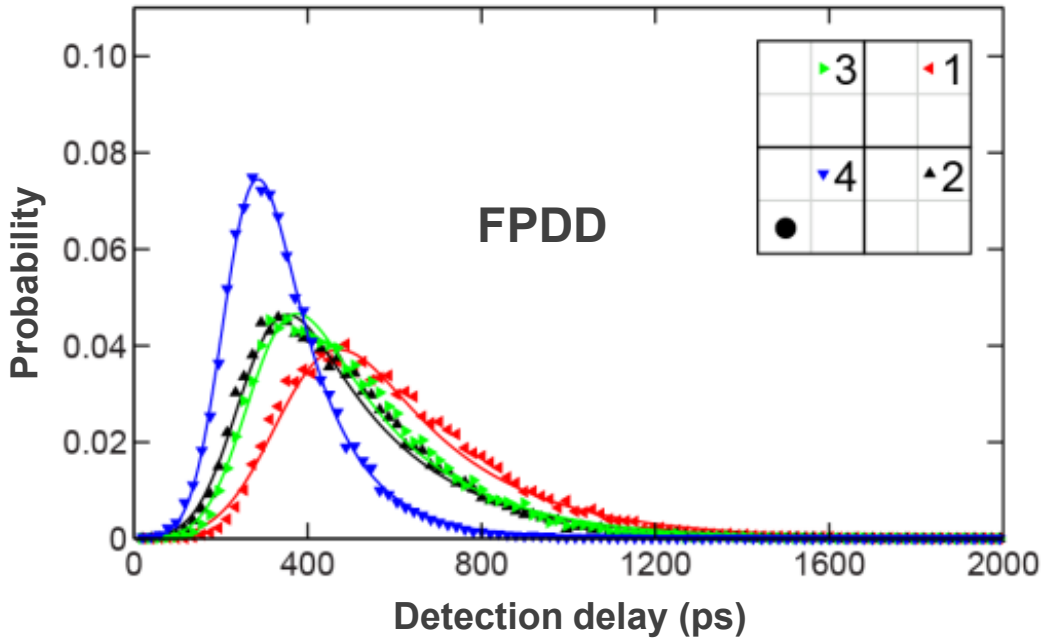
Smoothed *k*-NN 2D: Van Dam et al, Phys Med Biol 56, 4135-45, 2011

Smoothed *k*-NN 1D: Borghi et al, IEEE Trans Nucl Sc 62, 57-67, 2015

ML interaction time estimation (MLITE)

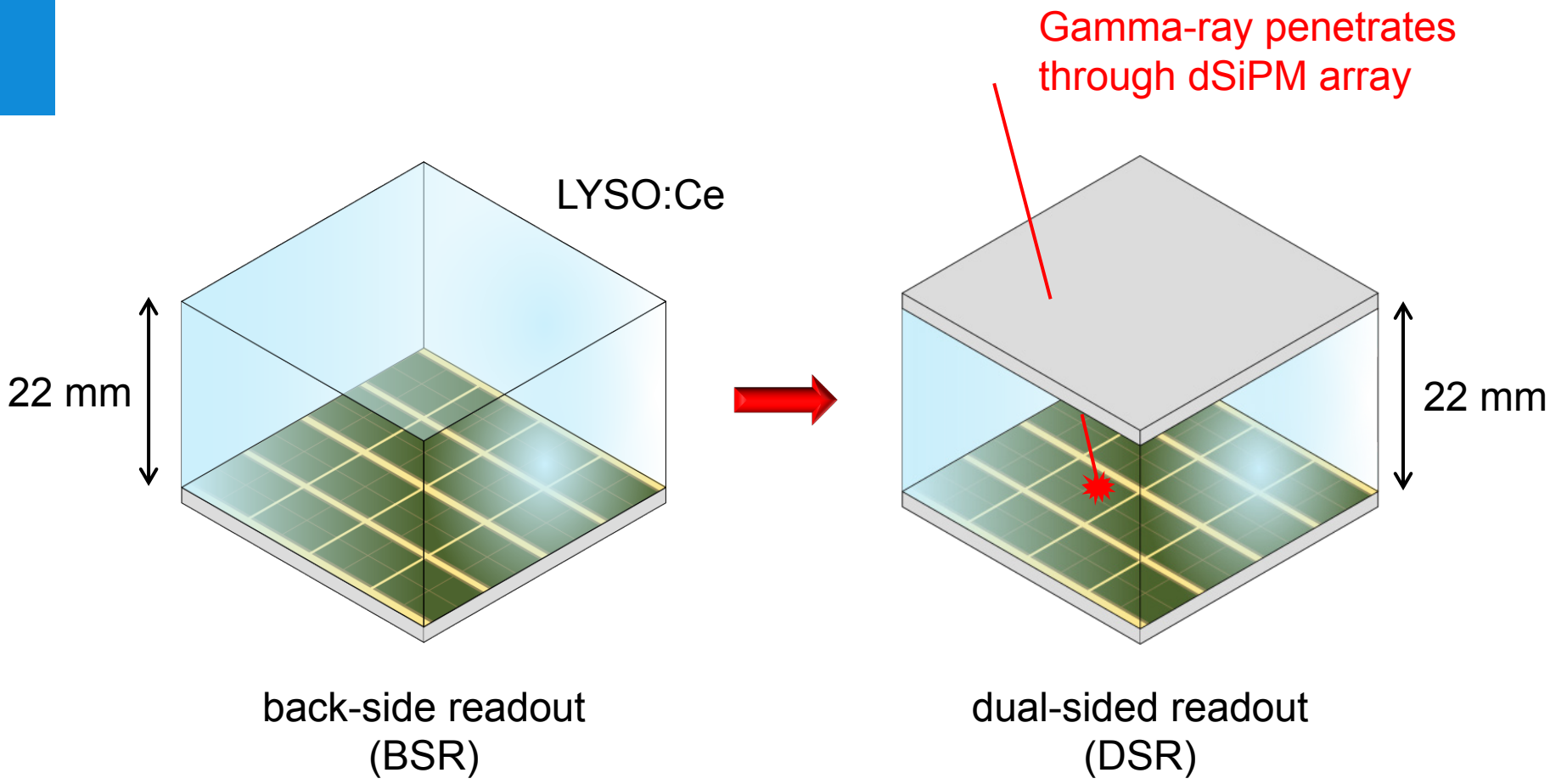
MLITE enables sub-200 picosecond timing in monolithic crystals using measured first photon detection delay (FPDD) probability distribution for each (x,y,z) position





H.T. van Dam et al, Sub-200 ps CRT in monolithic scintillator PET detectors using digital SiPM arrays and maximum likelihood interaction time estimation, PMB 58, 3243-3257, 2013

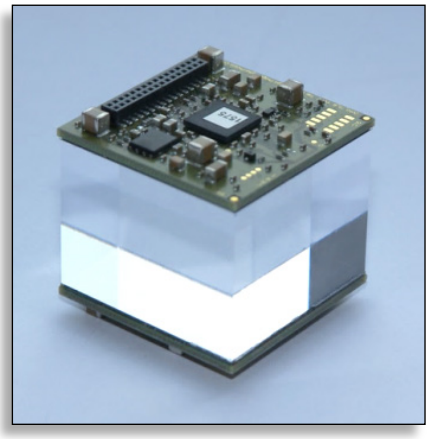
Back-side vs. dual-sided readout



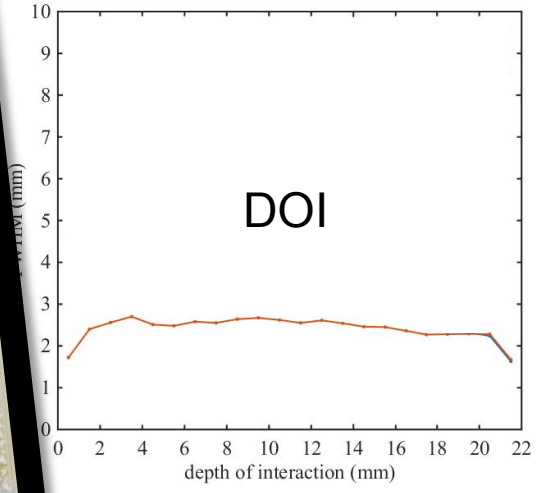
Performance summary

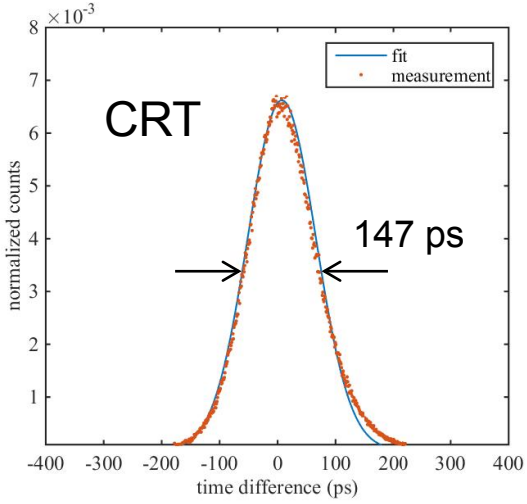
A practical and cost effective detector for PET/CT and PET/MRI with ultrahigh spatial resolution, CRT, and detection efficiency

Performance parameter	State of the art	BSR monolithic	DSR monolithic
Energy resolution	< 12%	**~10%**	**~10%**
Spatial resolution	~4 mm	**1.7 mm**	**1.1 mm**
DOI resolution	None	**3.7 mm**	**2.4 mm**
Coincidence resolving time	325 - 400 ps	**214 ps**	**147 ps**



32 mm x 32 mm x 22 mm commercial-grade LYSO:Ce with double-sided dSiPM readout





B.J. Peet et al, SNMMI 2015

SUBLIMA

Table-top gantry

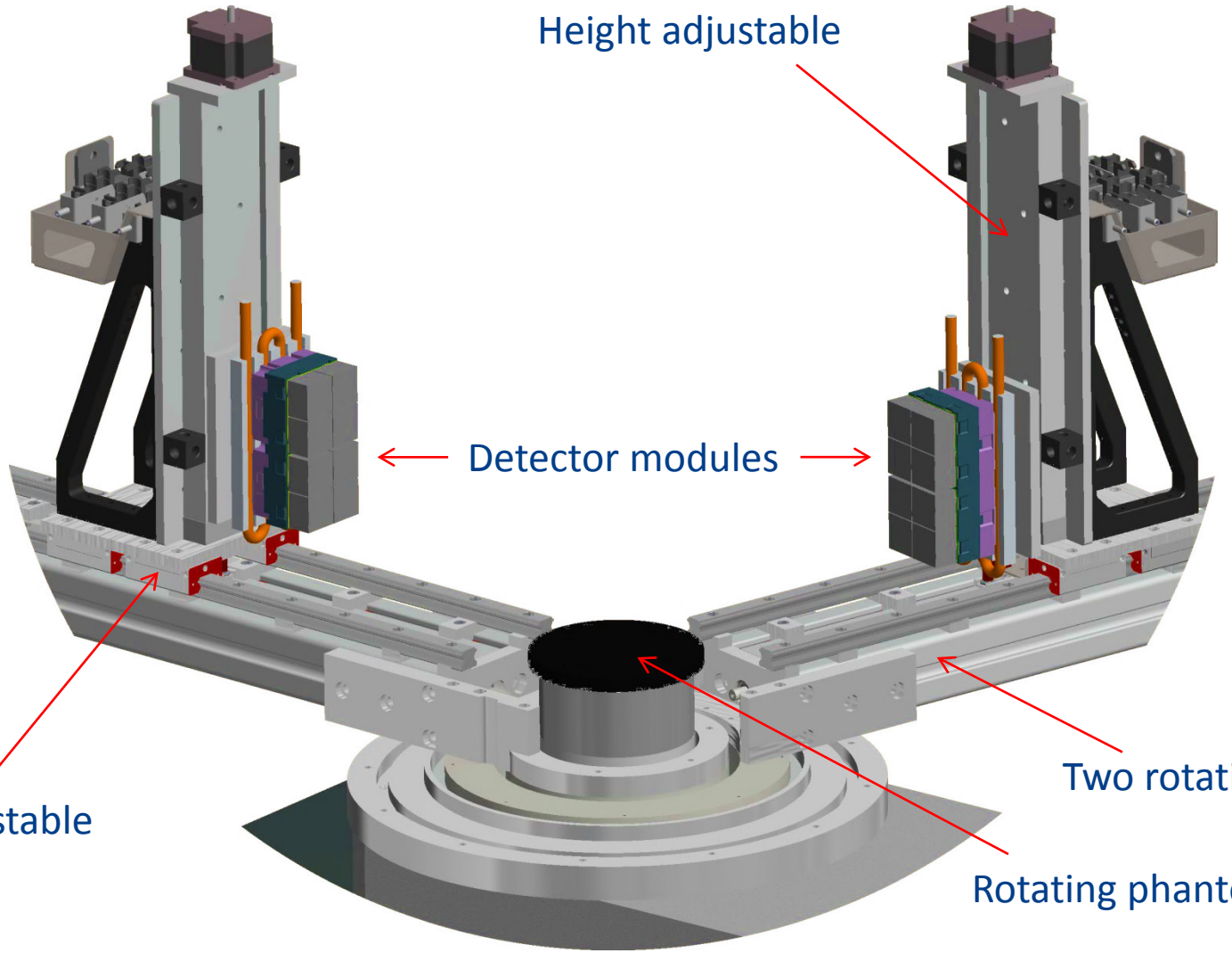
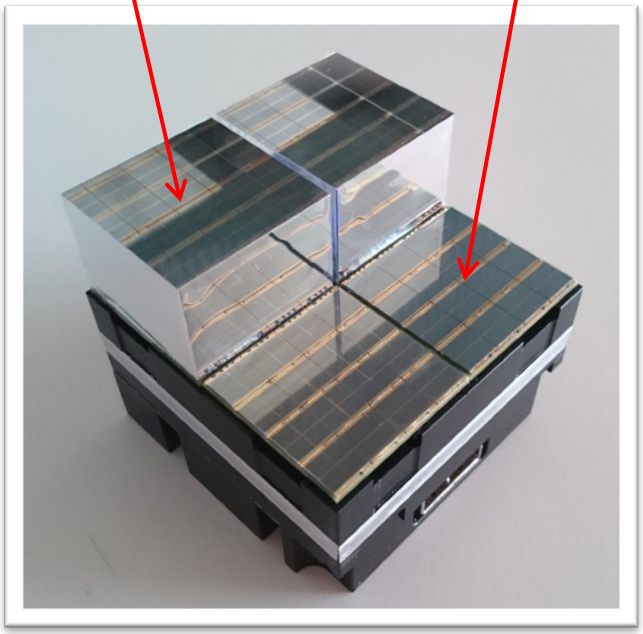


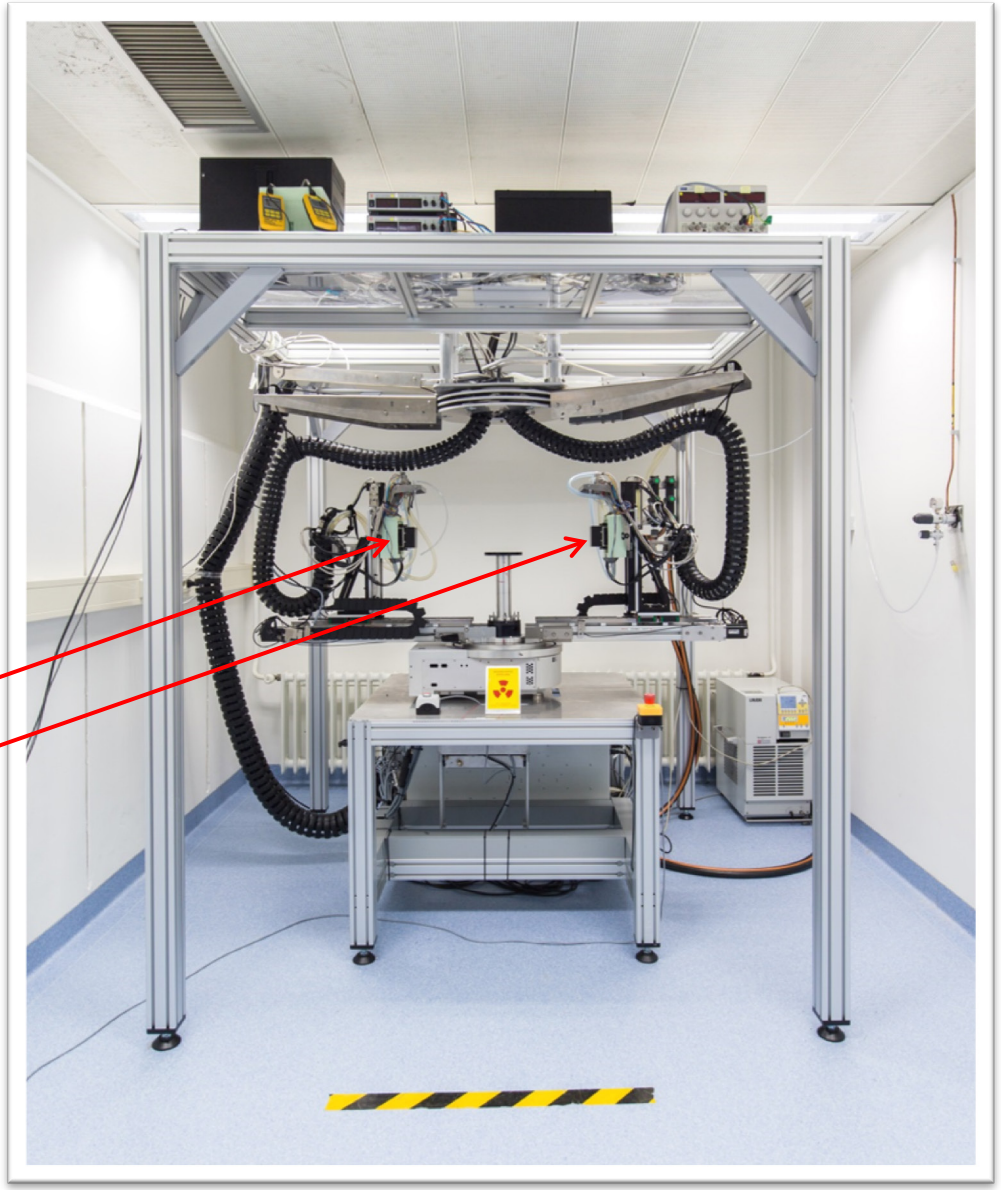
Table-top gantry

32 mm x 32 mm x 22 mm LYSO:Ce

DPC 3200-22-44



Detector module with 4 monolithic scintillators (2 mounted)

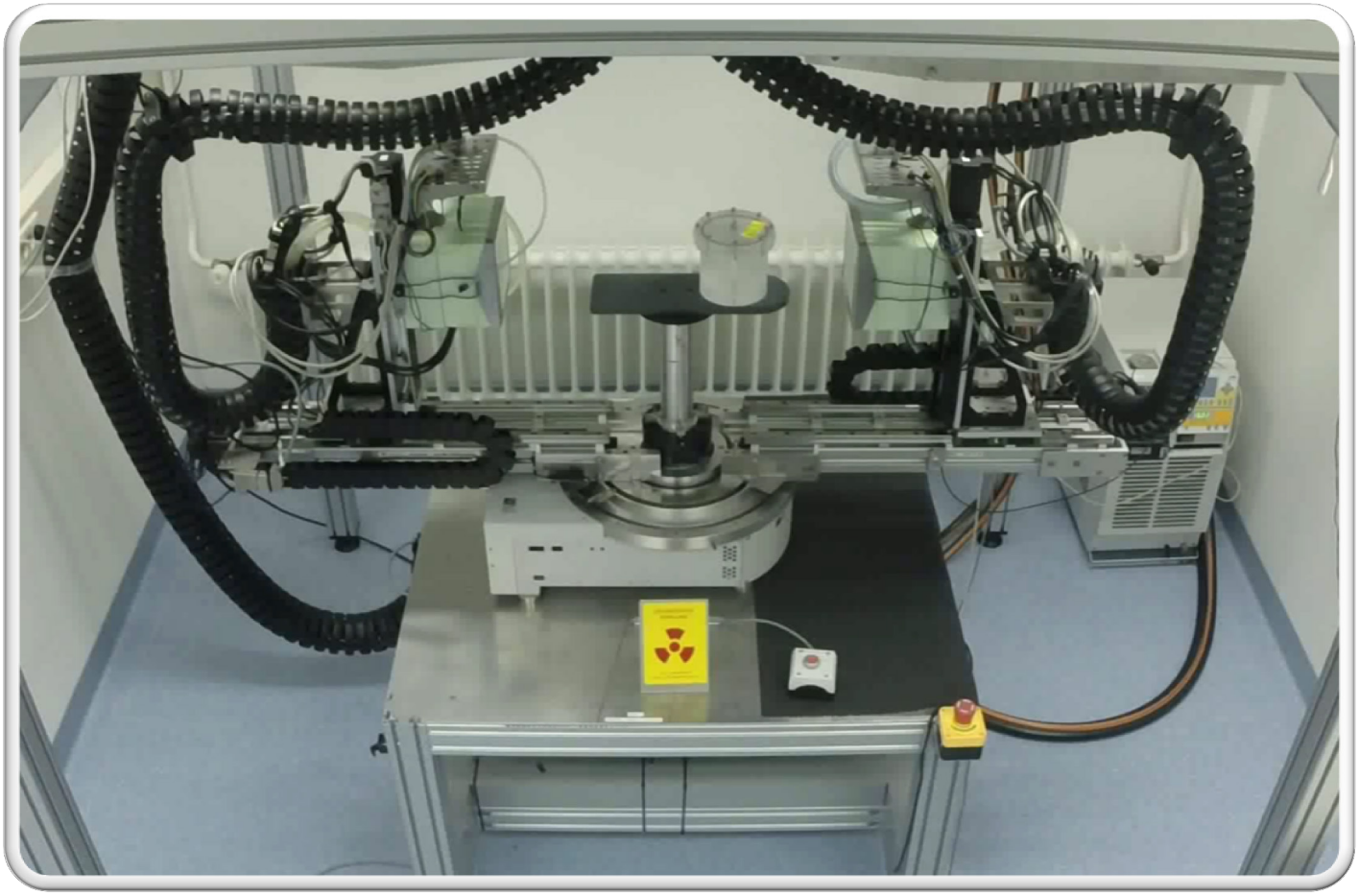


Na-22 filled Derenzo phantom

In-house made Derenzo phantom. Rod diameters 2.5 mm, 3.0 mm, 3.5 mm, 4.0 mm, 5.0 mm and 7.0 mm. Filled with ~20 MBq of Na-22 in H_2O.

Table-top gantry

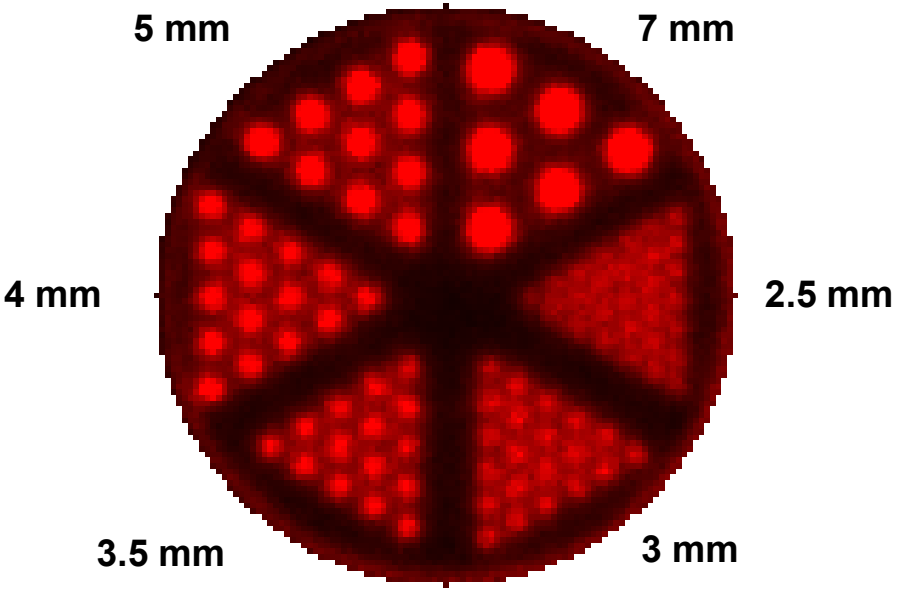
Time-lapse: full-ring image acquisition of Na-22 filled Derenzo phantom

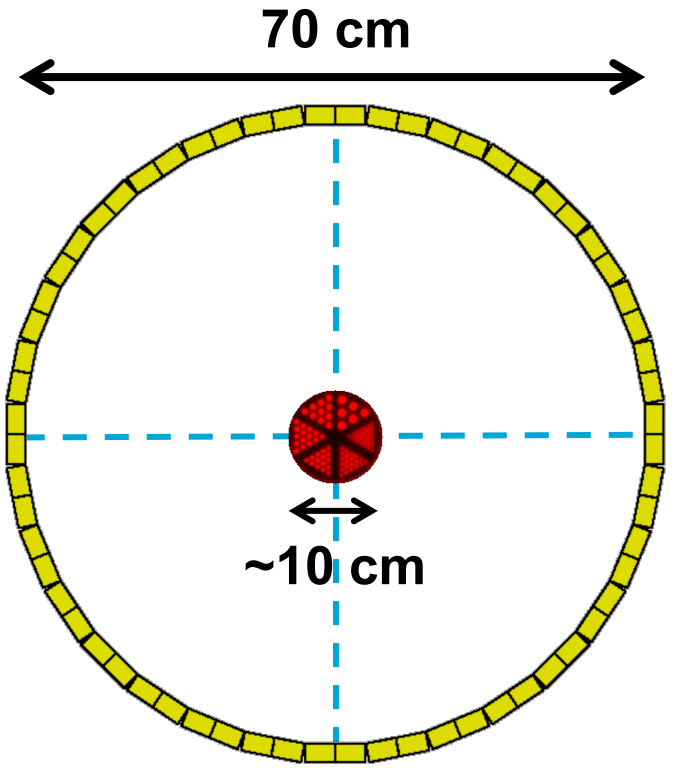


Na-22 filled Derenzo phantom (ML-EM)

PRELIMINARY

ML-EM reconstructed image of
Na-22 filled Derenzo phantom



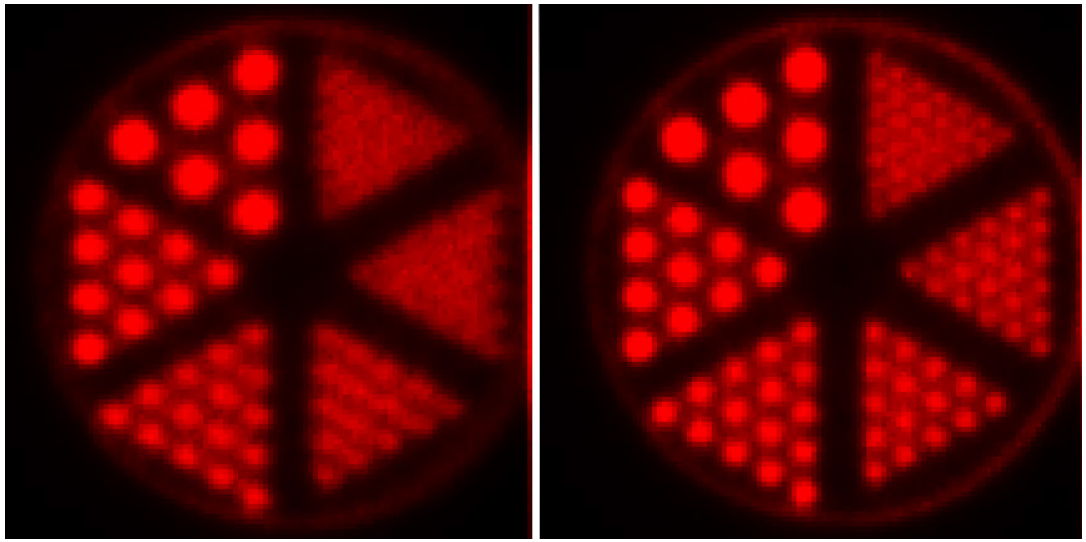


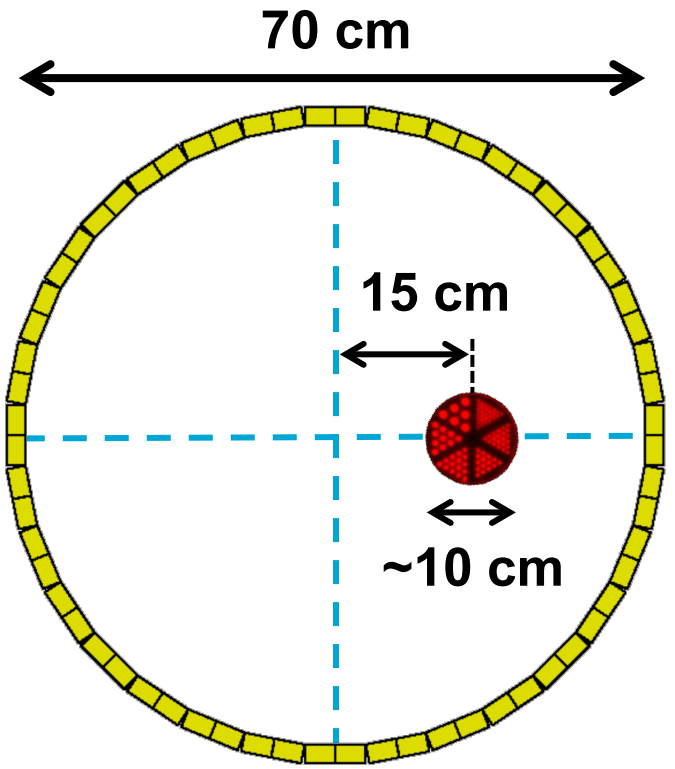
Sub-3 mm spatial resolution & 212 ps timing in a whole-body clinical TOF-PET geometry using monolithic LYSO:Ce scintillators and digital SiPM arrays

Na-22 filled Derenzo phantom (ML-EM)

PRELIMINARY

No DOI **DOI**





ML-EM reconstructed images of the Na-22 filled Derenzo phantom at 15 cm off-center, with (right) and without (left) depth-of-interaction (DOI) correction.

Paediatric PET

Princess Máxima Centre for paediatric oncology (PMC)

- National treatment and research centre
- Opening of new building planned 2017
- Treatment of almost all children with cancer within The Netherlands
- Increase cure rate to > 90%
- Reduce side effects of treatment

Princess (now queen) Máxima at the opening of the Centrum Princess Máxima Centre

PMC Partner Institutes:

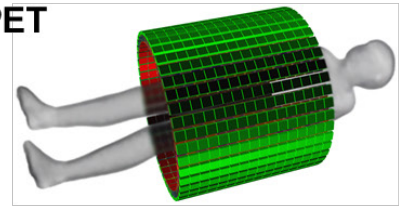
UMC Utrecht

Wilhelmina Kinderziekenhuis

Hubrecht Institute

Netherlands Cancer Institute – Antoni van Leeuwenhoek

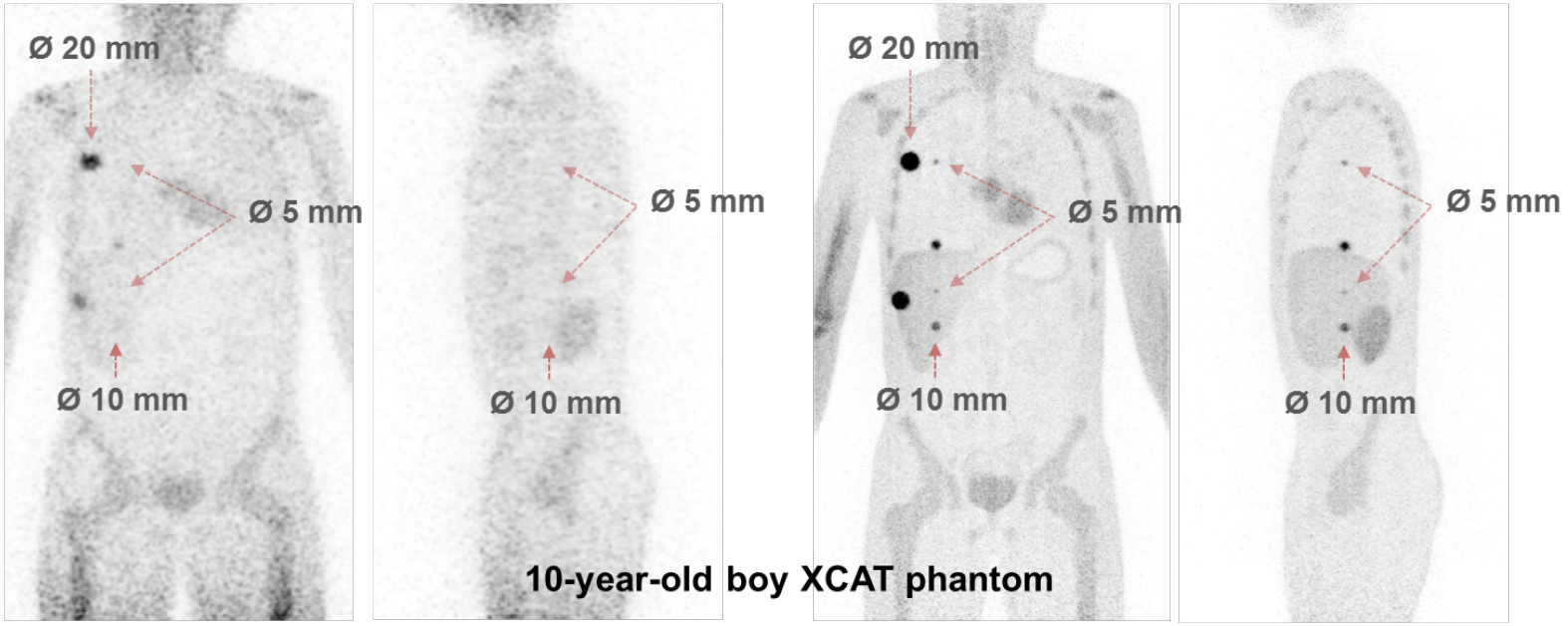
Example application: paediatric



GEMINI-TF		Paediatric PET
9	no. bed positions	2
20	T_{acq} per bed position (s):	90
3 min.	total T_{acq} :	3 min.
9 M	total counts:	142.5 M
200 × 200 × 340	image matrix size (pix.):	400 × 400 × 681
2 × 2 × 2	image voxel size (mm^3):	1 × 1 × 1
10	LM-OSEM iterations:	8 sub-iterations

- 4 mm pixels
- 600 ps TOF
- 18 cm axial length
- 90 cm bore

- 1.5 mm FWHM
- 150 ps TOF
- 54 cm axial length
- 53 cm bore



Equal low activity of 40 MBq & equal total acquisition time of only 3 min

E. Mikhaylova et al, in preparation


Thank You
VOORZICHTIG
STRALING
LAUDA