KMI seminar, Nagoya, Nov 25, 2022

Instrumentation for advances in PET medical imaging

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PET – positron emission tomography

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Flexible limited angle PET scanner

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Conclusions and summary

Interplay of detector R&D for particle physics and medical imaging

Traditionally excellent collaboration of the two research areas.

Novel detection techniques required in particle physics →with modifications a potential application in medical physics

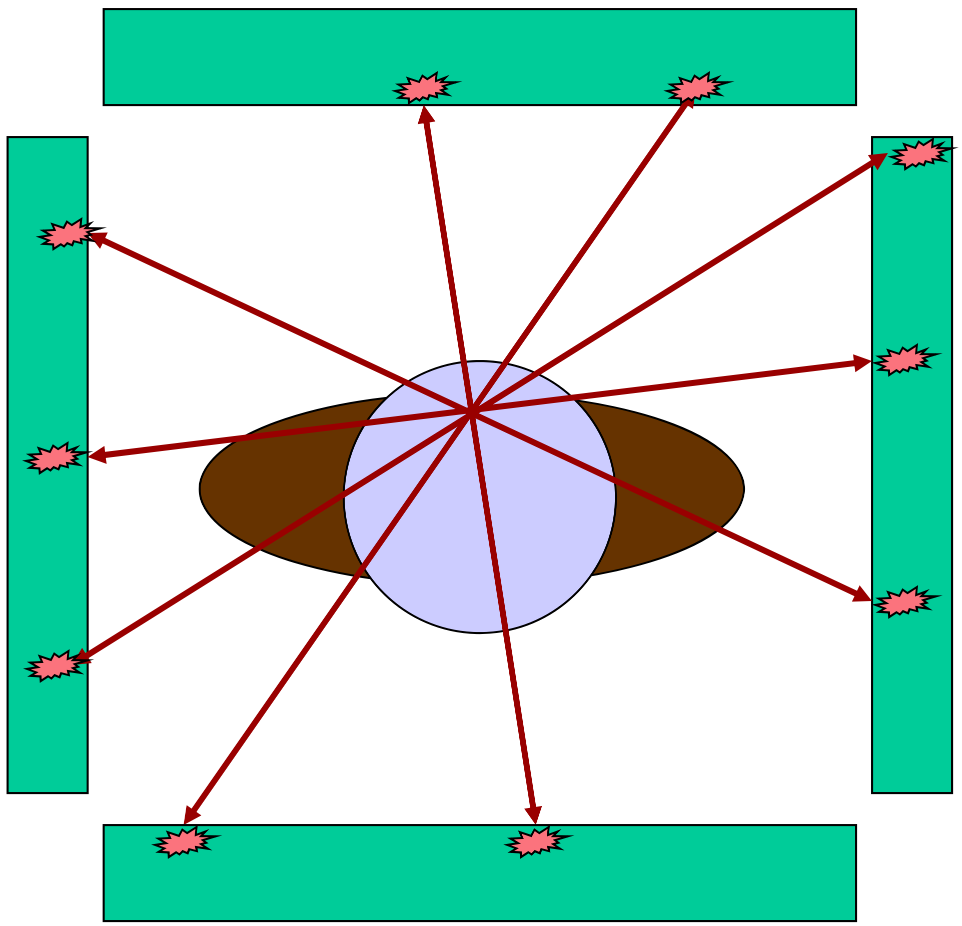
… and vice versa…

One of the recent examples: SiPMs as scintillation light sensors for

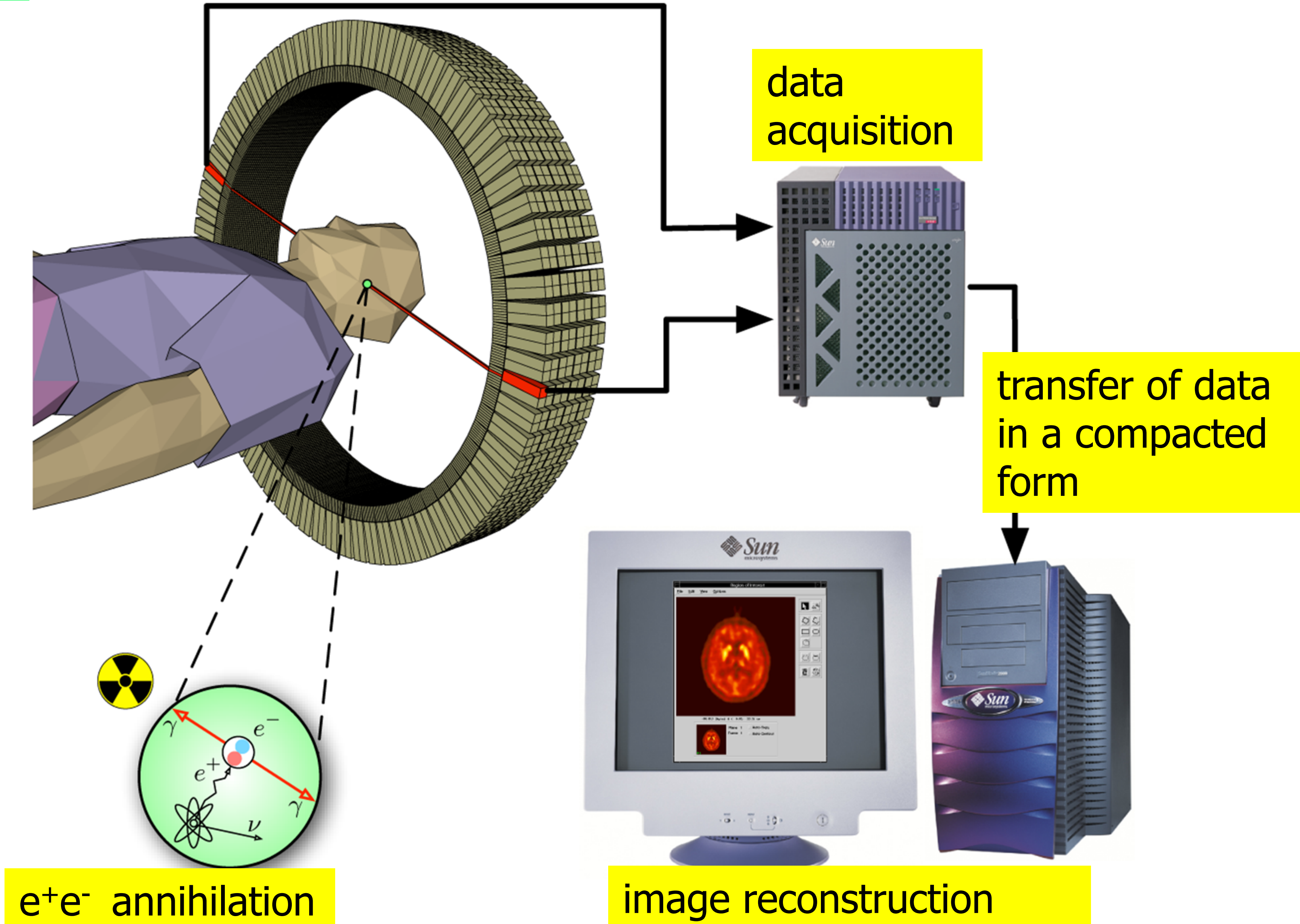
- Electromagnetic calorimeters
- PET scanners

PET: positron emission tomography 2

In the blood of the patient a substance is administered that contains radioactive fluorine (e.g. fluorodeoxyglucosis). The places in the body with a higher substance concentration will show a higher activity.

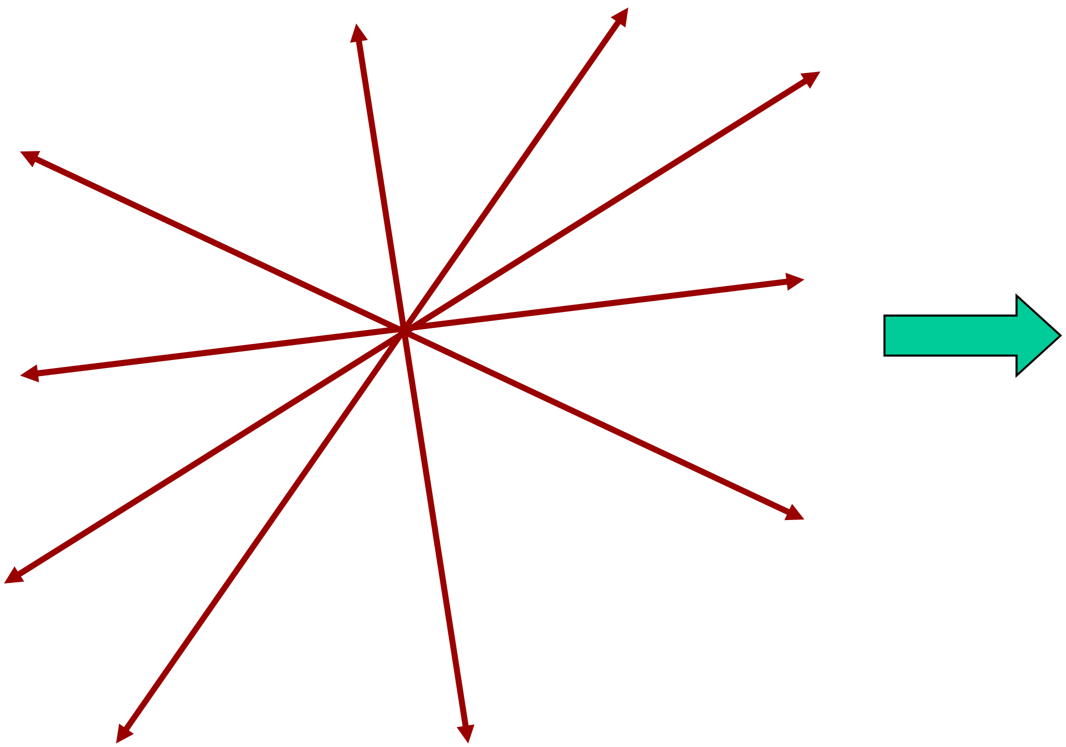


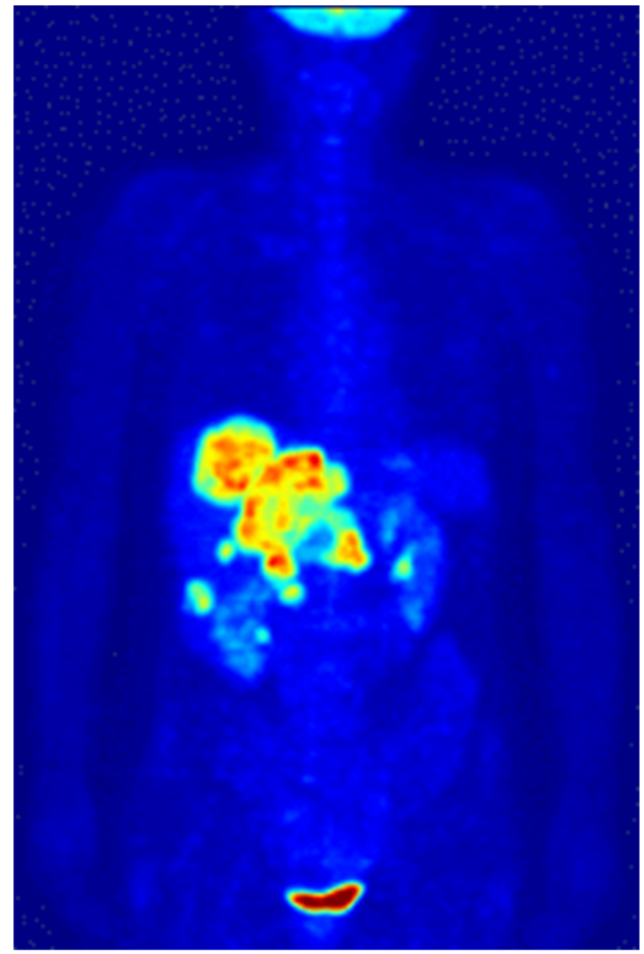
PET: collection of data



PET: image reconstruction

Image reconstruction: from the position and direction of the lines determine the distribution of the radioactive fluorine in the body – similar to the reconstruction of reactions in particle physics





PET with a time-of-flight information

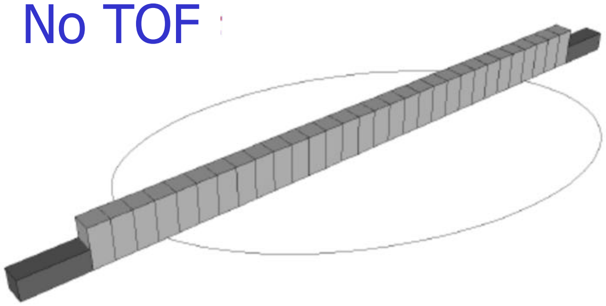
Detectors for γ rays measure also the time of arrival

– coincidence of two hits is only acceted if the two times are <10 ns appart

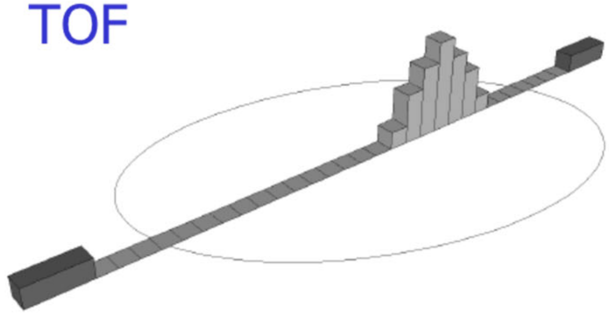
In case time is measured with a much better precision (<1ns) → an additional constraint on the point of origin of the two γ rays along the line →time-of-flight (TOF) PET

- in the reconstruction, each line contributes to fewer pixels → less noise
- good resolution in time-of-flight → limits the number of hit pixels along the line

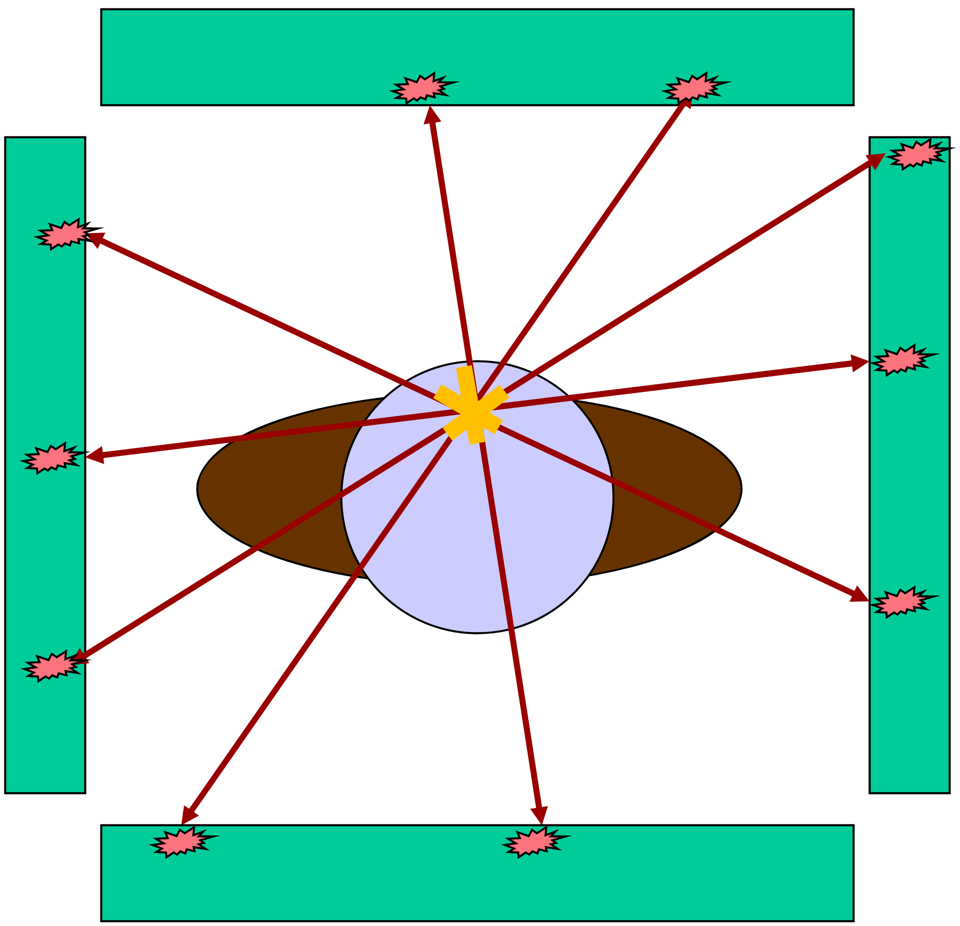
No TOF



TOF

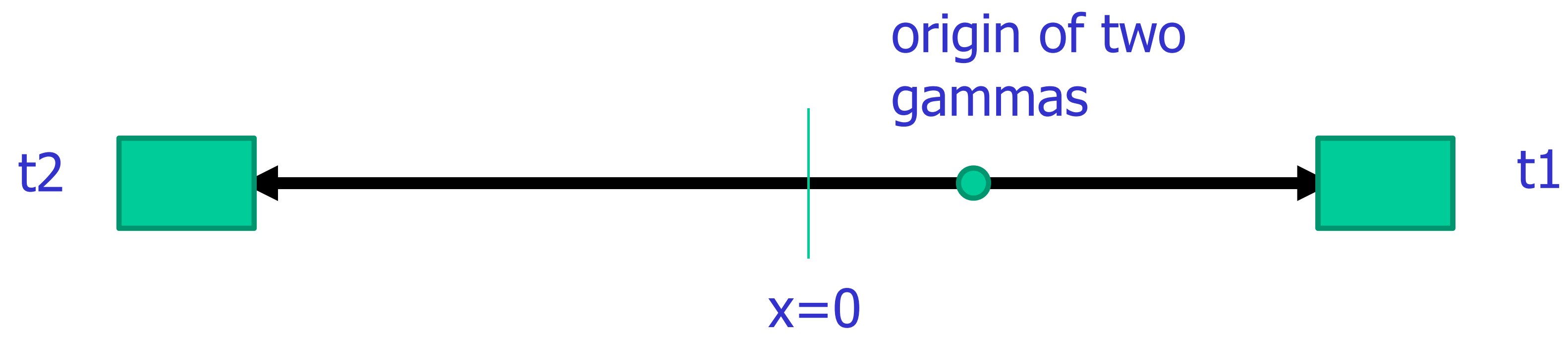


TOF-PET: positron tomography with a time of arrival measurement



TOF-PET: time resolution

What kind of time resolution is needed?



$t1 = (L/2 - x)/c$ source at x, distance between detectors = L

$t2 = (L/2 + x)/c$

$t1 - t2 = 2x/c$

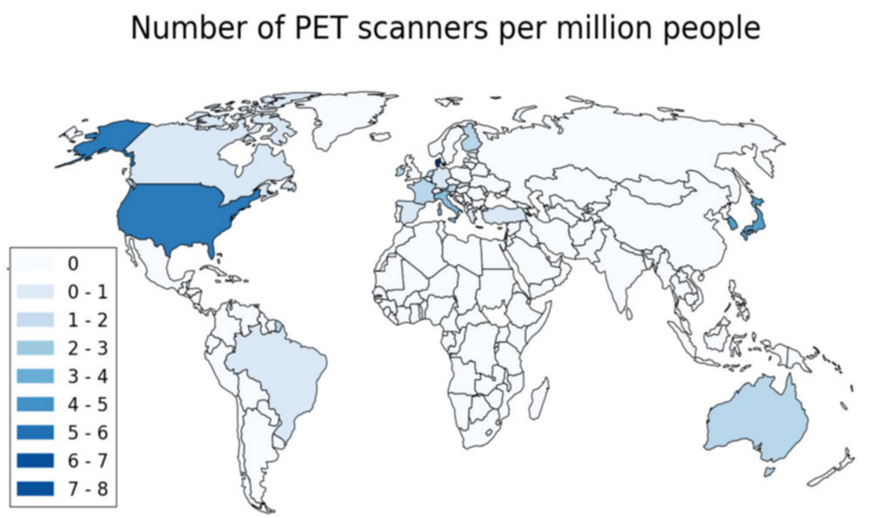
$x = (t1 - t2)\, c/2 \rightarrow \Delta x = \Delta(t1\text{-}t2)\, c\,/2$

resolution in TOF $\Delta(t1\text{-}t2) = 300$ ps $\rightarrow \Delta x = 4.5$ cm

$\Delta(t1\text{-}t2) = 66$ ps $\rightarrow \Delta x = 1$ cm

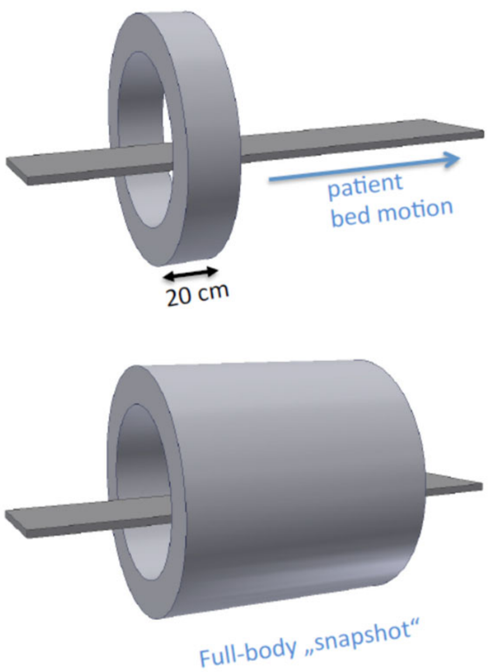
Motivation for Fast TOF PET

- Paradigm shift in medicine from:
  - From Treatment of obvious disease
  - to early diagnosis / prevention
- This leads to more stringent requirements on PET
  - Sensitivity
  - Specificity
- Targeted Radionuclide Therapy (TRT) & Theranostics
  - introduced an urgent need for more widespread and accurate PET



Current situation

- Standard clinical scanners are sub-optimal:
  - Cost of equipment, limited access, performance.
- Novel long axial PET scanners offer a very attractive solution in terms of
  - increased sensitivity and
  - enabling fast pharmacokinetics/pharmacodynamics.
- They pose significant challenges both
  - Financially
  - Logistically



State-of-the-art in TOF (CTR)

- Clinical scanner:
  - Siemens Biograph Vision PET/CT → **214 ps**

https://www.siemens-healthineers.com/molecular-imaging/pet-ct/biograph-vision

- Laboratory measurement:
  - Gundacker *et al, Phys. Med. Biol.* 65 (2020) 025001 (20pp)

2 x 2 x 3 mm LSO → **58 ps***

2 x 2 x 20 mm LSO → 98 ps*

*measured with high power readout electronics that cannot be scaled to large devices

Gamma detectors for PET

Scintillating crystal:

- converts gamma energy into optical photons

Photodetector

- converts optical photons into electrical pulses

Time resolution in TOF PET limited by

- scintillation light emission → 10 ps challenge
  - rise and decay time
- **optical photon travel time spread in the crystal**
- **photodetector response**
- **readout electronics**

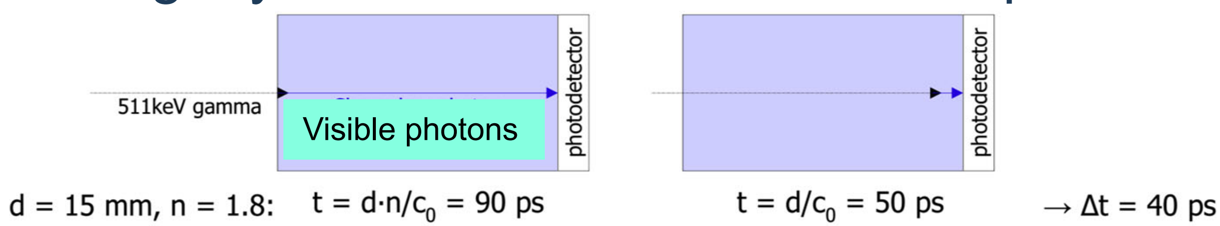
Effective sensitivity $S_{\mathrm{eff},D} \propto \eta_{\mathrm{det}}^2 \, \eta_{\mathrm{geom}} \, \frac{D}{\Delta t}$

- detection efficiency η_{det} of the detector
- η_{geom} the geometrical efficiency (angular coverage)
- D the diameter of the object imaged

Important: Optimize detector CTR to maximize sensitivity

Limitations on timing due to optical travel time

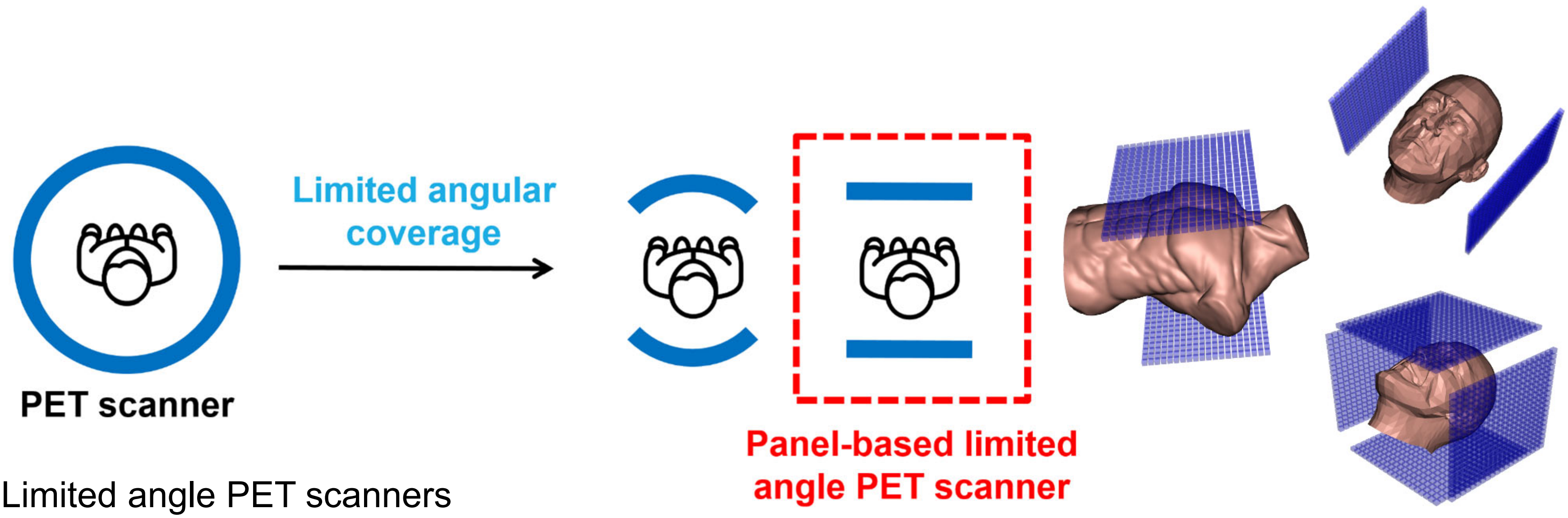
- optical photons, produced in the crystal, need to reach the photodetector
- inside the crystal, optical photons propagate with at a lower speed (c/n) than gamma rays (c)
- refractive index, crystal dimensions → **intrinsic travel time spread** due to different gamma interaction depths
- for a 15 mm long crystal this contribution is > 40 ps FWHM:



- Can in principle be corrected for by:
  - measuring the depth of interaction (DOI)
  - building the detector with shorter crystals → multi-layer configuration
  - use Cherenkov radiation doi: 10.1109/TRPMS.2022.3202138 / Potential of a Cherenkov TOF PET scanner

Next generation scalable time-of-flight PET

Superb time resolution enables simplifications in the scanner design



Limited angle PET scanners will generally produce distorted images with artefacts unless they have good **time-of-flight** information

The angular sampling requirement to obtain distortion-free images decreases
S. Surti, J. S. Karp, Physica Medica 32 (2016) 12–22

G. Razdevšek *et al.*, "Multi-panel limited angle PET system with 50 ps FWHM coincidence time resolution: a simulation study," in *IEEE TRPMS*, doi: 10.1109/TRPMS.2021.3115704.

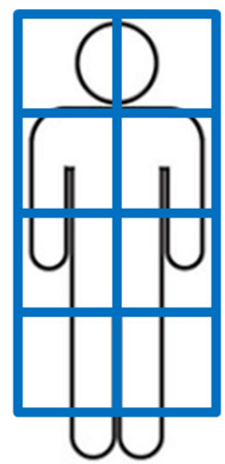
Potential benefits

Mobility
- Portable or bedside PET imaging

Flexibility
- Adjustable FOV and sensitivity

Modularity
- Combining multiple panels → multi-organ/total-body PET scanner

Accessibility
- Reduced manufacturing cost and complexity



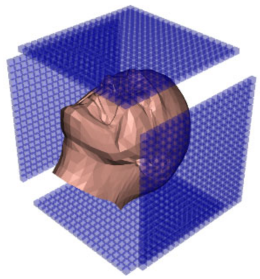
Simulation of a limited angle system

Geant4/GATE → Monte Carlo simulations of digital phantoms and different scanner designs

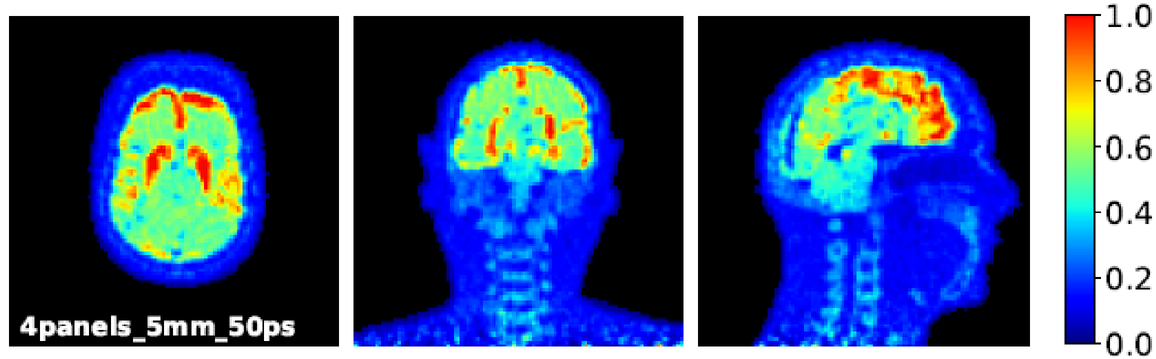
CASToR → image reconstruction with Maximum Likelihood Expectation Maximization (**MLEM**) algorithm

- Investigate the benefits of coincidence time resolutions
- Study the performance **two-panel** and **four-panel** designs

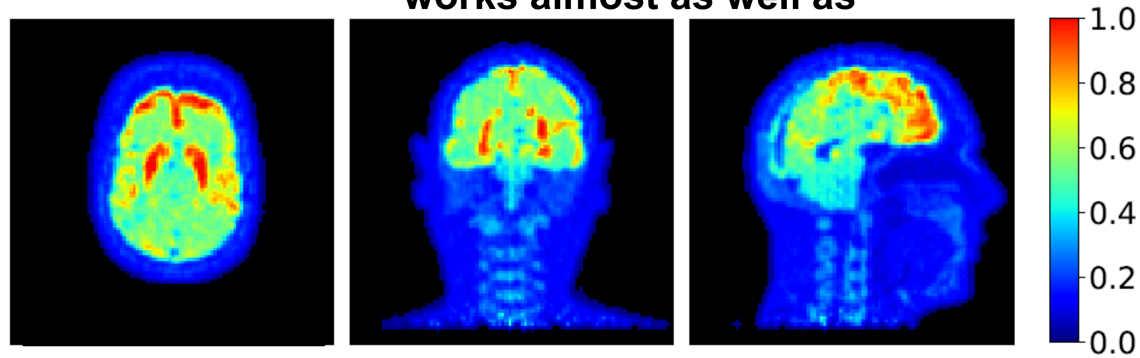
Enabling Open Geometry systems



Two pairs of 30x30 cm2 LYSO panels with 50ps CRT

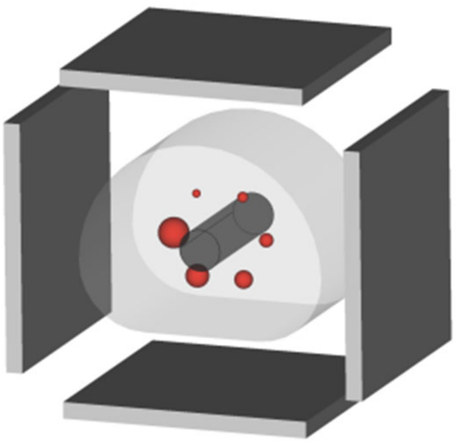


works almost as well as

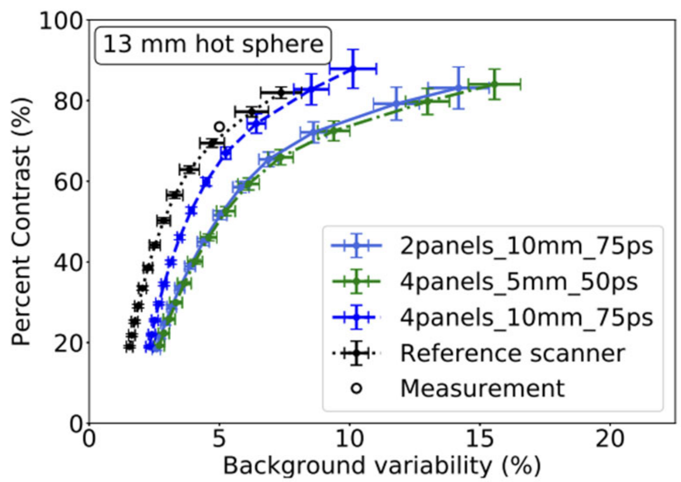


Siemens Biograph Vision

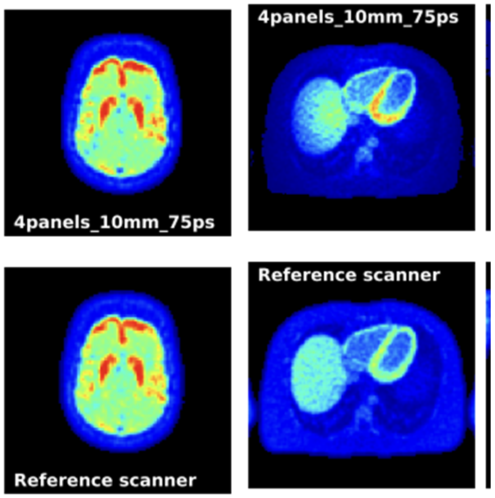
Simulation study of planar configurations



Simulated arrangement of 30x30 cm2 flat panel detectors



Percent contrast versus background variability (~noise level in the image)



Reconstructed images of a torso and head for the flat panel detectors and the reference scanner Siemens BV

Next generation scalable time-of-flight PET

Address PET challenges by decreasing different contributions using fast CTR

Joint effort: JSI, FBK, ICCUB, I3M, Oncovision and MGH-Harvard

- Front electronics: develop a low-noise, high-dynamic-range ASIC with a time resolution of 20 ps & on-chip TDC
- Improve SiPM sensor
- Explore 2.5 D integration with the photo-sensor to achieve sub-100 ps CTR

Aim: Improve (SNR) without increasing cost associated with axial coverage by resorting to very sparse angular coverage of the patient and long axial field coverage

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FONDAZIONE BRUNO KESSLER FUTURE BUILT ON KNOWLEDGE
ICCUB Institut de Ciències del Cosmos UNIVERSITAT DE BARCELONA
ONCO VISION
MGH 1811
Gordon Center for Medical Imaging

Joint project

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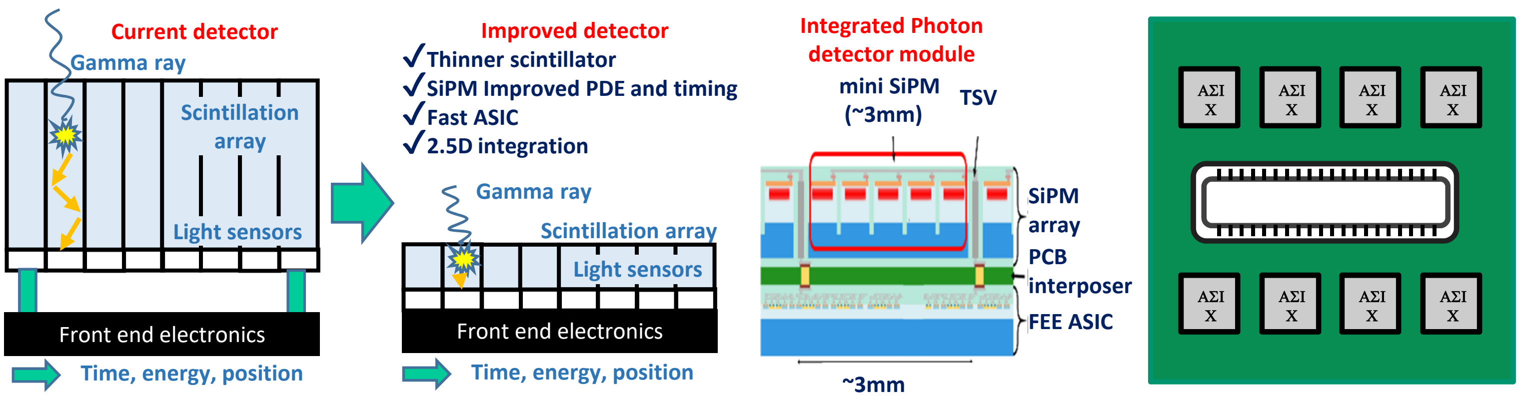
Managed to get a 3 MEUR EU grant for 5y to further develop the method and construct a prototype ☺

Fast CTR PET module

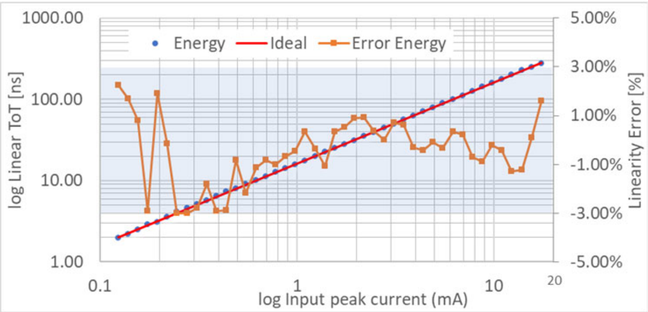
How do we plan to achieve such a good CTR?

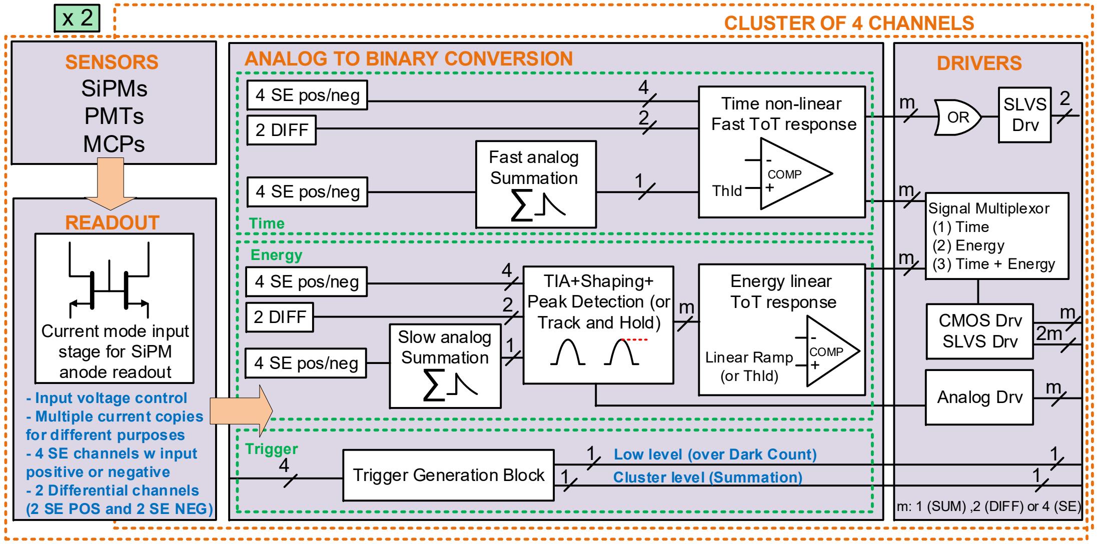


FastIC readout chip

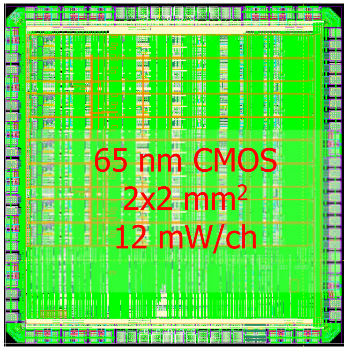
FASTIC current mode ASIC for fast single photon sensors

- **Collaboration of ICCUB (Univ. Barcelona) and CERN**
- **8 Inputs:** 8 Single Ended (POS/NEG), 4 differential and summation (POS/NEG) in 2 clusters of 4 channels.
- **3 Output modes:** (1) SLVS; (2) CMOS; and (3) Analog.
- Active analog summation of up to 4 SE channels to improve time resolution





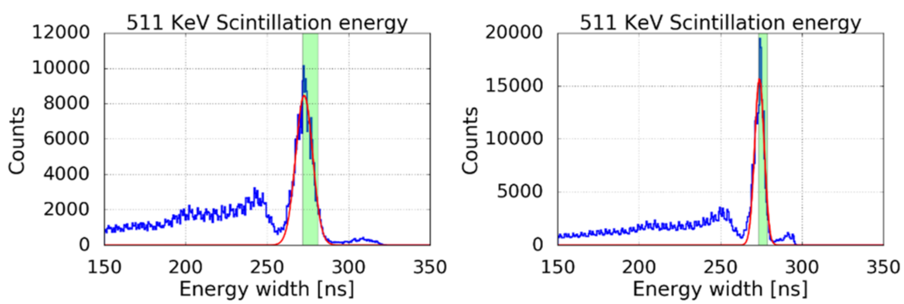
- High dynamic range with linear energy response
- Adapted to different detectors: LYSO/LSO, BGO, Cherenkov, Monolithic, etc

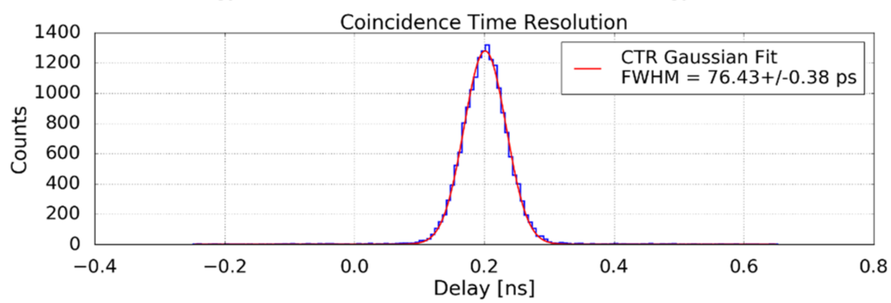


talk by David Guberman (ICCUB) at MEDAMI2022

First results with FastIC

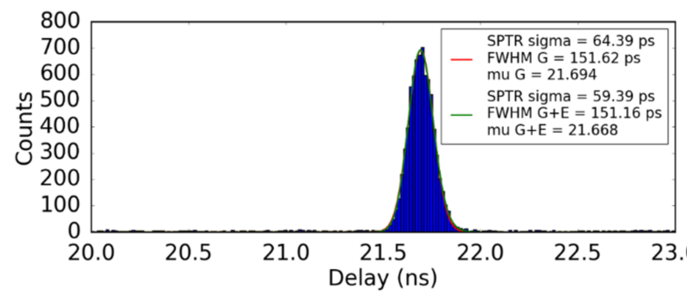
- **Sensor:** FBK-NUVHDLFv2b 3x3 mm², 40 pixel pitch.
- **Crystal:** LSO:Ce Ca 0.2% of 2x2x3 mm³.



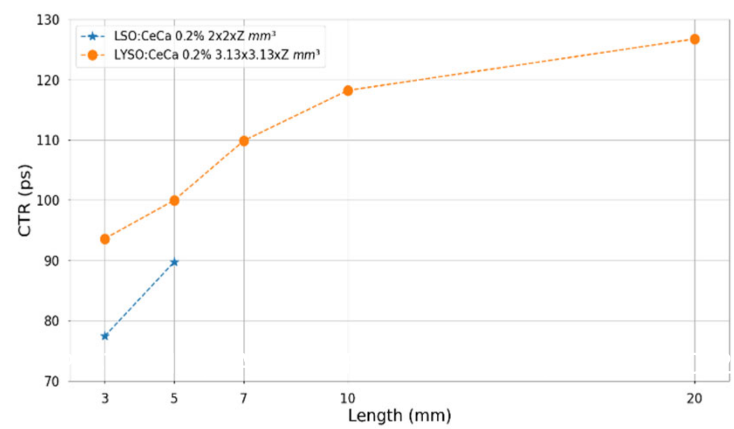


FWHM = 76.43 ps

- **SPTR with** FBK-NUVHDLFv2b 3x3



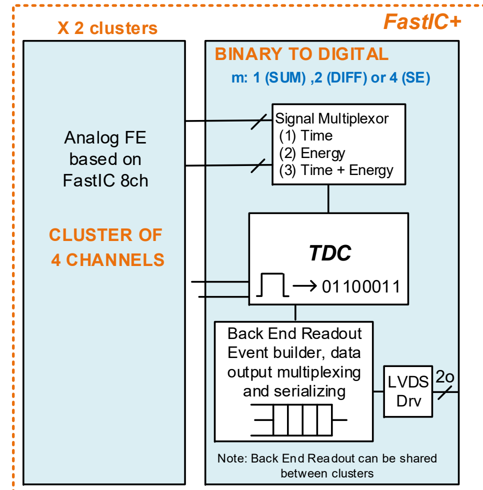
- **CTR versus crystal length for LYSO and LSO**



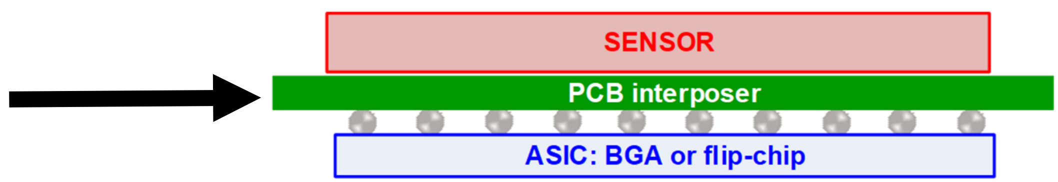
talk by David Guberman (ICCUB) at MEDAMI2022

Next generation ASICs

- ICCUB and CERN are working on FastIC+: integration of 25 ps bin TDC integration on FastIC
  - Planned for Q1 2023
- On the longer term we plan for a 32 ch. ASIC (FastIC32)
  - Pixelated structure: 2.5D (BGA, flip-chip, etc) or 3D integrated



FastIC 32



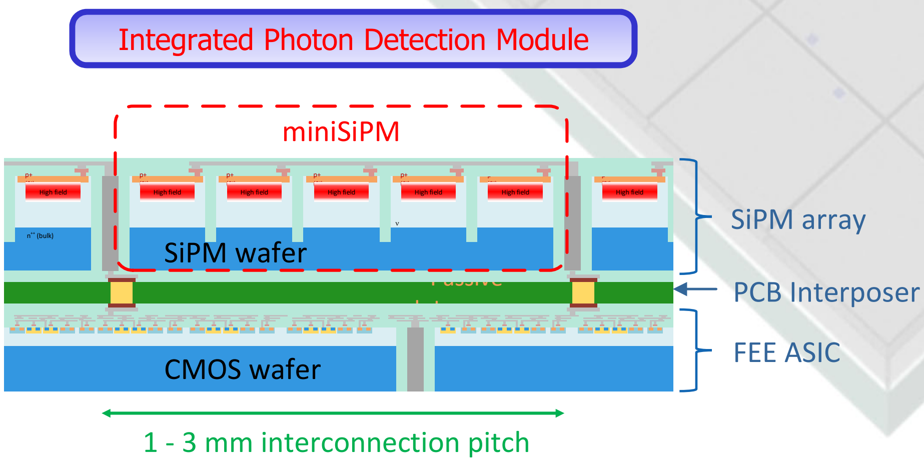
talk by Alberto Gola (FBK) at MEDAMI2022

FBK SiPM sensor

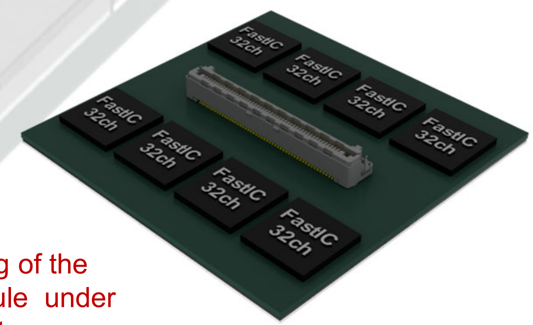
2.5D integrated SiPM tile for improved timing

In the short and medium term - medium density interconnection

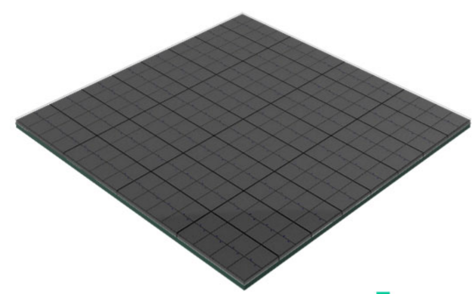
- *excellent timing on large photosensitive areas w/o increasing complexity + cost too much*.
- *SiPMs with TSVs down to 1 mm pitch* are connected to the *readout ASIC on the opposite side of a passive interposer*, in a *2.5D integration scheme*.



Hybrid SiPM module being developed for ultimate timing performance in ToF-PET

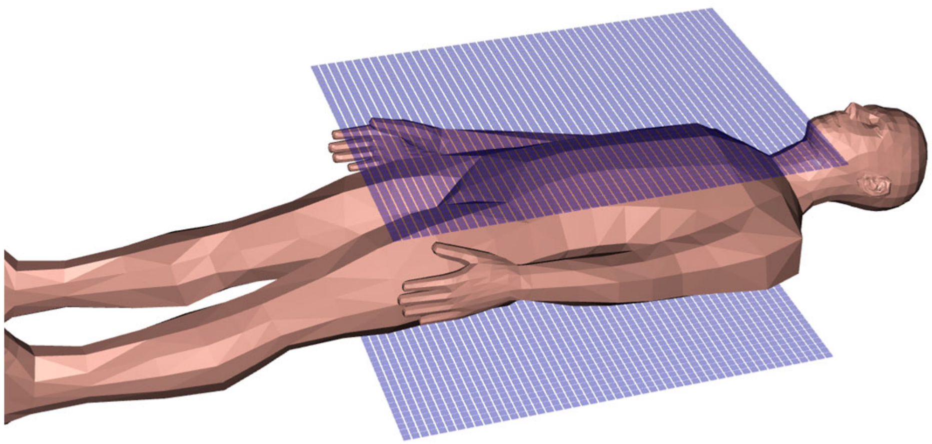


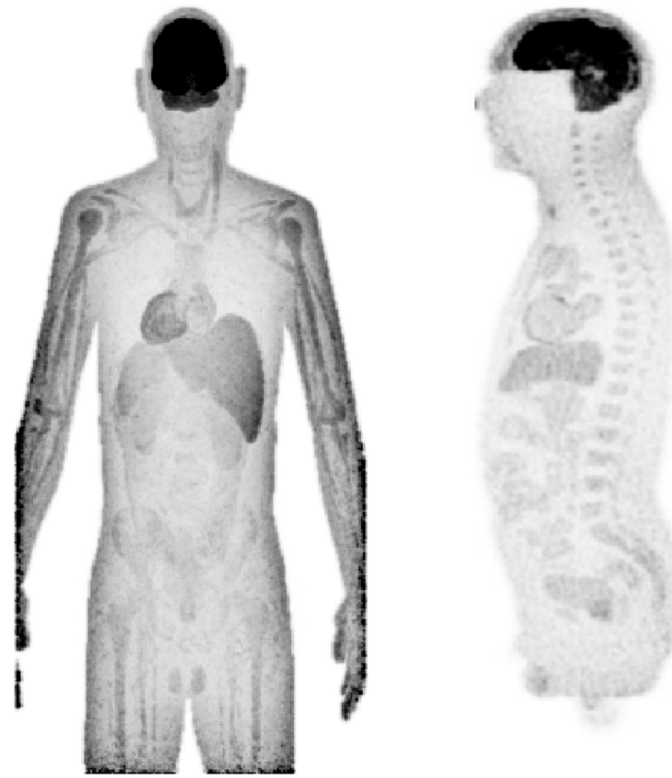
Conceptual drawing of the photon detector module under development



From Limited angle to Total-body

Increased sensitivity by larger panels





Capability of the planar TOF PET imager:
Image of a reconstructed 3 mm slice of an digital phantom acquired by two 120x60cm2 panel detectors (above and below the patient) assuming 100 ps TOF resolution and 10 mm LYSO scintillator thickness.

Conclusions: limited angle PET scanner

- **Good coincidence time resolution** can:
  - compensate for lower detection efficiency or smaller angular coverage
  - enable us to obtain **good image quality with a simple limited angle PET system** without distortions or artifacts
- We plan to enable open geometry designs and enable wider spread of PET imaging modality by reducing different contributions to CTR :
  - Optimize scintillator thickness
  - Improve SiPM – TSV
  - Fast ASIC
  - 2.5D integration
  - If new – faster scintillators emerge, all the detector components will be available to deploy them immediately

Use of Cherenkov light in TOF-PET

- **Use of Cherenkov radiation for TOF-PET**
  - lead fluoride (PbF_2) as Cherenkov radiator material
- **Previous work**
- **Limitations** of Cherenkov TOF-PET
  - single photon detection - **limited scatter suppression**
- **Image quality with Cherenkov TOF-PET**

  -whole-body scanner simulations

  -crystal readout configurations

  -results

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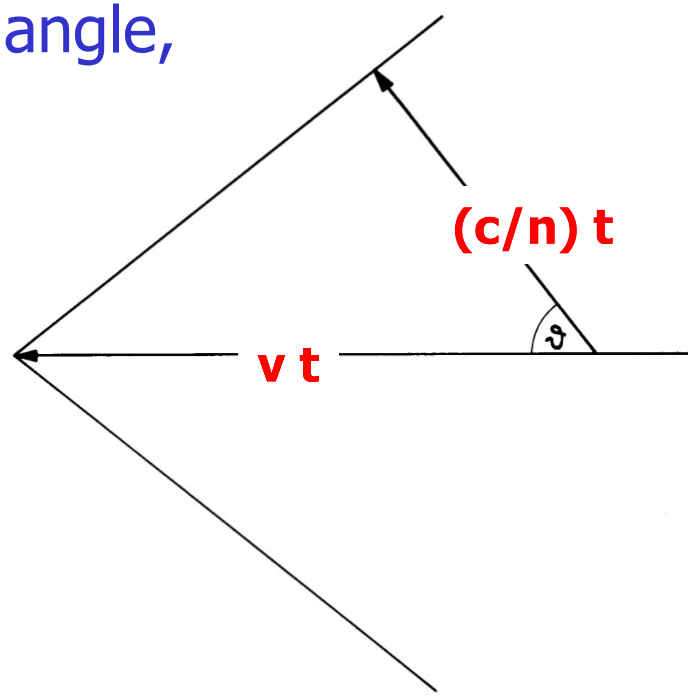
[c] Faculty of Chemistry and Chemical Engineering, **University of Maribor**, Slovenia

https://photodetectors.ijs.si/

One of the important particle identification methods in HEP: use Cherenkov radiation

A charged track with velocity $v=\beta c$ exceeding the speed of light c/n in a medium with refractive index n emits polarized light at a characteristic (Cherenkov) angle,

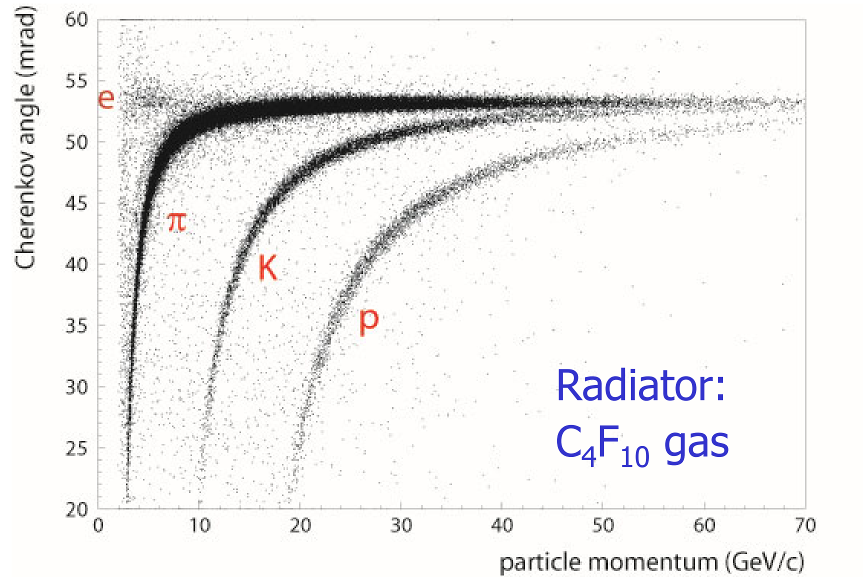
$$\cos\theta = c/nv = 1/\beta n$$



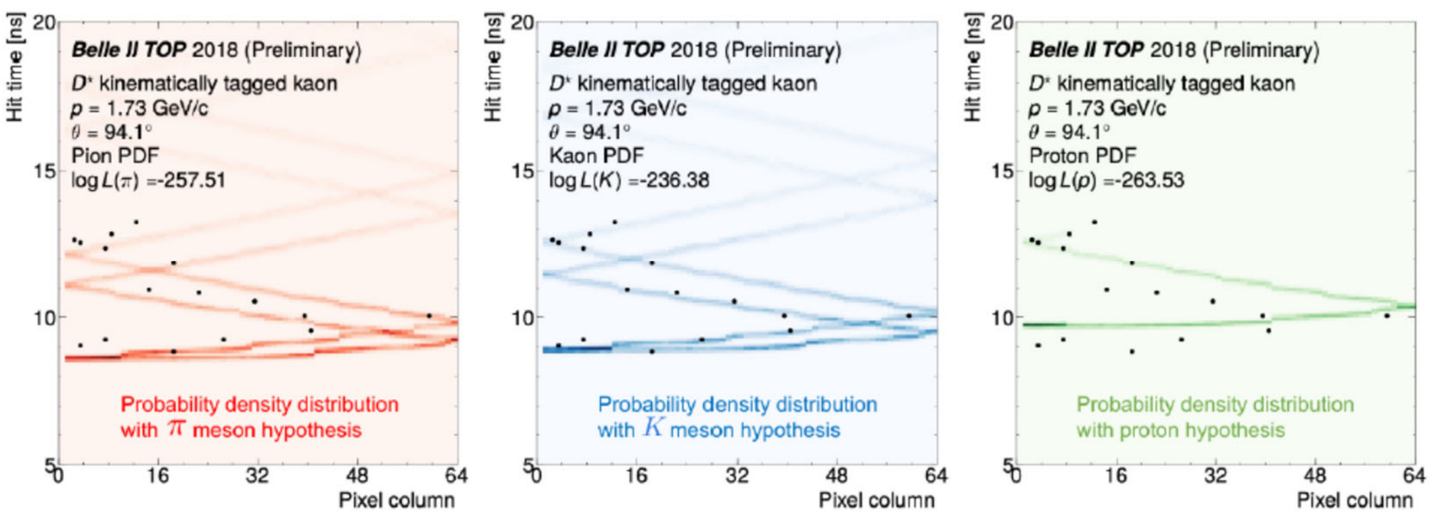
Excellent identification method, but very low light level = few detected photons

Measuring Cherenkov angle

Measure the Cherenkov angle (RICH counter)



or a pattern in the coordinate vs time space (TOP in Belle II)



Use of Cherenkov Light in TOF-PET

γ detectors in traditional PET: scintillator crystal + photodetector

Charged particles (e^- produced by γ interactions) passing trough dielectric material with $v > c_0/n$ → **prompt** Cherenkov light

Excellent Cherenkov radiator material: **lead fluoride (PbF_2)**

	BGO	LSO	PbF_2
Density (g/cm^3)	7.1	7.4	**7.77**
μ_{511keV} (cm^{-1})	0.96	0.87	**1.06**
Photofraction for 511 keV	0.41	0.32	**0.46**
Raise time (τ_r)	2.8 ns	70 ps	**-**
Decay time (τ_d)	300 ns	40 ns	**-**
Light yield/511 keV (LY)	3,000	15,000	**10** (‡)

(‡) in the 250-800 nm wavelength interval

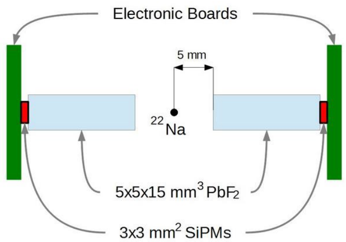
PbF_2 properties:

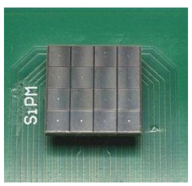
- excellent γ stopping properties
- pure Cherenkov radiator (no scintillation)
- excellent optical transmission (down to 250 nm), high refractive index (n ~ 1.8)
- low price (**1/3 BGO → 1/9 LSO**)

[Mao, IEEE TNS 57:6 (2010) p.3841]

Previous results

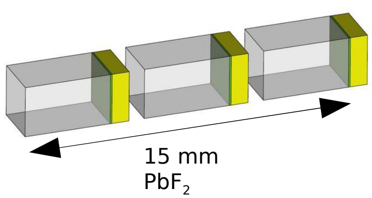
(25 * 25 * **15**) mm³ **PbF_2** (black)
+ (22.5 * 22.5) mm² **MCP-PMT**





4x4 array:
(3 * 3 * **15**) mm³ **PbF_2** (reflector)
+ (3 * 3) mm² **SiPM**

Multi-layer: 3 x
[(3 * 3 * **5**) mm³ **PbF_2** (black)
+ (3 * 3) mm² **SiPM**]



Result	Reference
Cherenkov TOF PET TOF: **95 ps** FWHM	Korpar, NIM A 654 (2011) 532
With SiPMs TOF: **306 ps** FWHM	Dolenec, IEEE TNS 63:5 (2016) 2478
Cherenkov PET module Single side efficiency: **35 %**	Dolenec, NIM A 952 (2020) 162327
Multi-layer detector (simulation) TOF: **22 ps** FWHM before photodetector timing	Consuegra, Phys.Med.Biol. 65(5) (2020) 055013

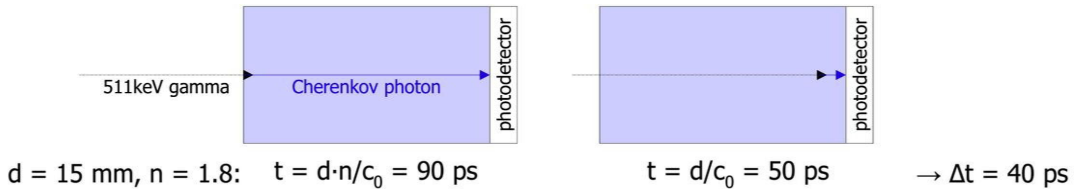
Part of it in collaboration with T. Iijima et al; some results already reported at a KMI Wine and cheese seminar in 2016

Limitations of Cherenkov TOF-PET

- Only 10-20 photons created → **only a few detected**
  - efficient photodetector and light collection needed

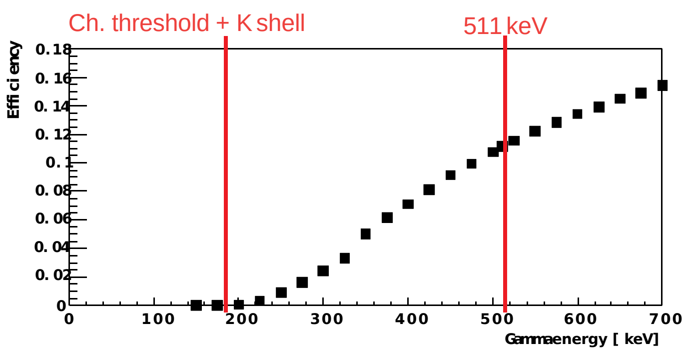
SiPM

- **Optical photon travel time spread** in the crystal
  - remaining limitation to TOF resolution



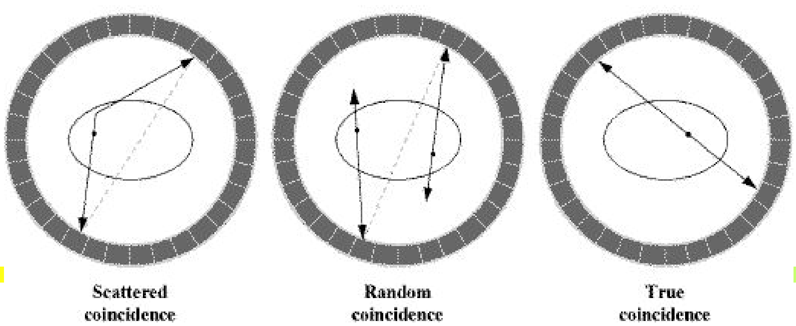
multi-layer

- Limited suppression of **scattered events**:
  - only a few Cherenkov photons detected → no energy information
  - detection efficiency drops with lower gamma energy → intrinsic suppression



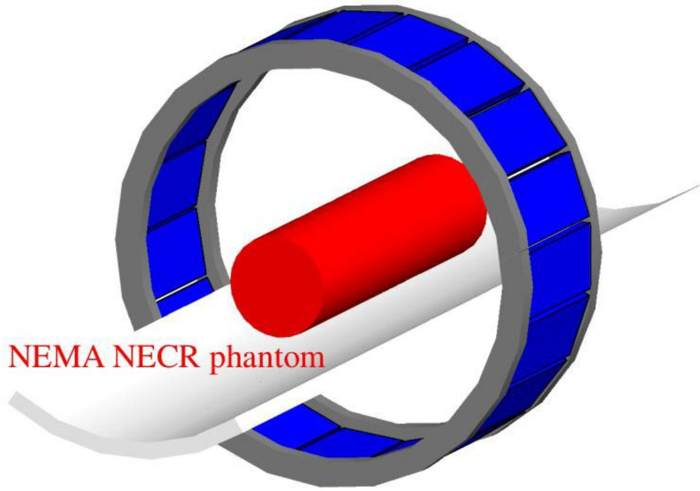
Simulation, PbF_2 with MCP-PMT photodetector

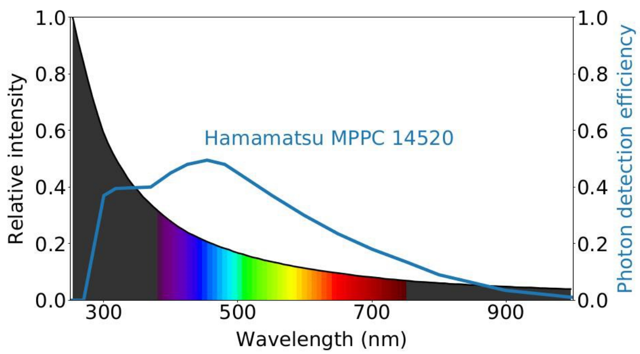
Effect of remaining scatter on image quality?



Whole-body scanner simulations

- Simulation: GATE v8.1
- Geometry:
  - Based on **Siemens Biograph Vision PET/CT**
    - ring: 19 modules (Axial FOV: 26.3 cm)
    - module: 2 x 8 block detectors
    - block detector: 4 x 2 mini-blocks
    - mini-block: 5 x 5 crystal array
    - **crystal: 3.2 x 3.2 x 20 mm³**
- Optical simulations (Cherenkov):
  - Surfaces: Geant4 UNIFIED model
    - **reflector** (diffuse, R=95%, n=1.0)
    - **black** (R=0%, n=1.5)
  - Photodetector: **Hamamatsu S14520 SiPM**
    - Single Photon Time Resolution (SPTR): **70 ps** FWHM
    - **SiPM dark counts not modeled**
- Reconstruction: CASToR v3.1.1
  - Custom double Gaussian TOF kernel [CASToR workshop]
  - OSEM-8it:5sub, 1.6 mm voxel, 5 mm filter

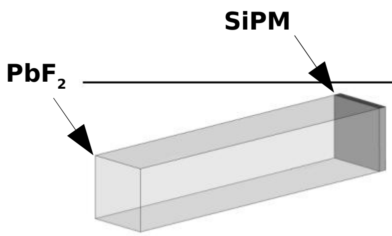
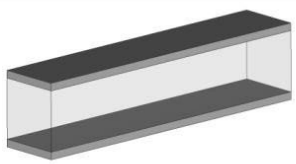
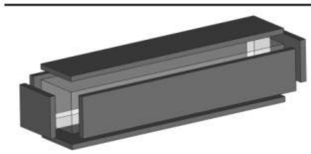




Crystal readout configurations

Reference scanner
- LSO scintillator
- Energy window: 435-585 kev
- Energy resolution: 10%
- CTR: 214 ps

- Cherenkov photon generation, propagation simulated
- Timing defined by first optical photon detected

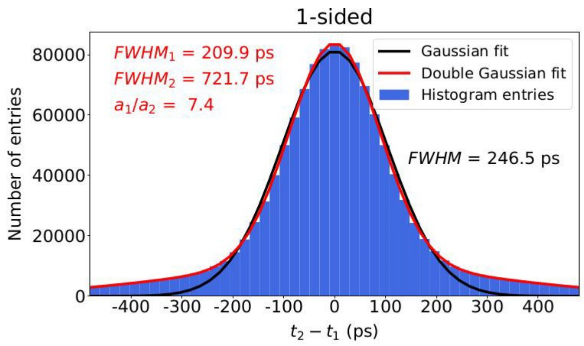
	Cherenkov detector	Surface treatment	ε^2 (%)	CTR-FWHM (ps)		FOM	
				0 ps SPTR	70 ps SPTR	0 ps SPTR	70 ps SPTR
	1-sided-back	Black	8.6	100.7	145.5	0.85	0.59
		Reflector	35.3	135.7	184.8	2.60	1.91
	2-sided-top-bottom	Black	26.2	47.0	111.1	5.57	2.36
		Reflector	40.5	48.9	117.8	8.28	3.44
	6-sided	/	44.4	54.1	115.4	8.21	3.85

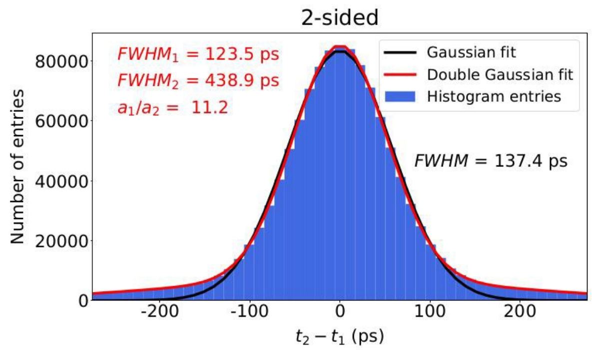
Coincidence detection efficiency: ϵ^2

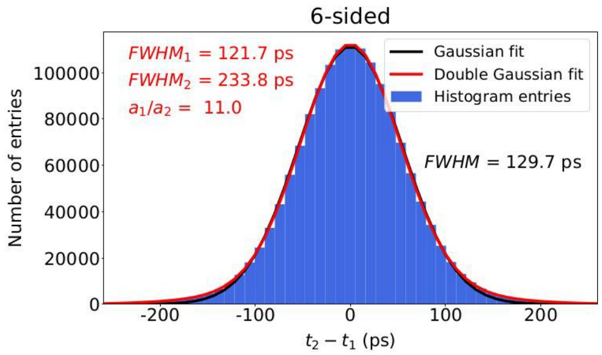
Figure-of-merit: $FOM = \frac{\epsilon^2}{CTR}$

SPTR = single photon time resolution

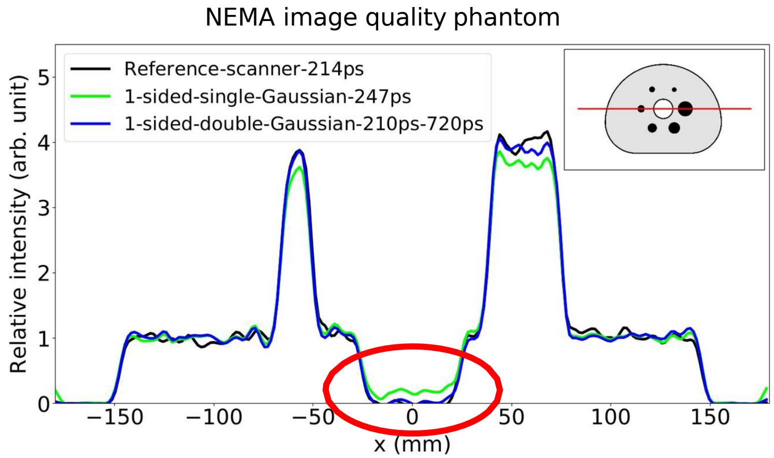
Results: CTR distributions







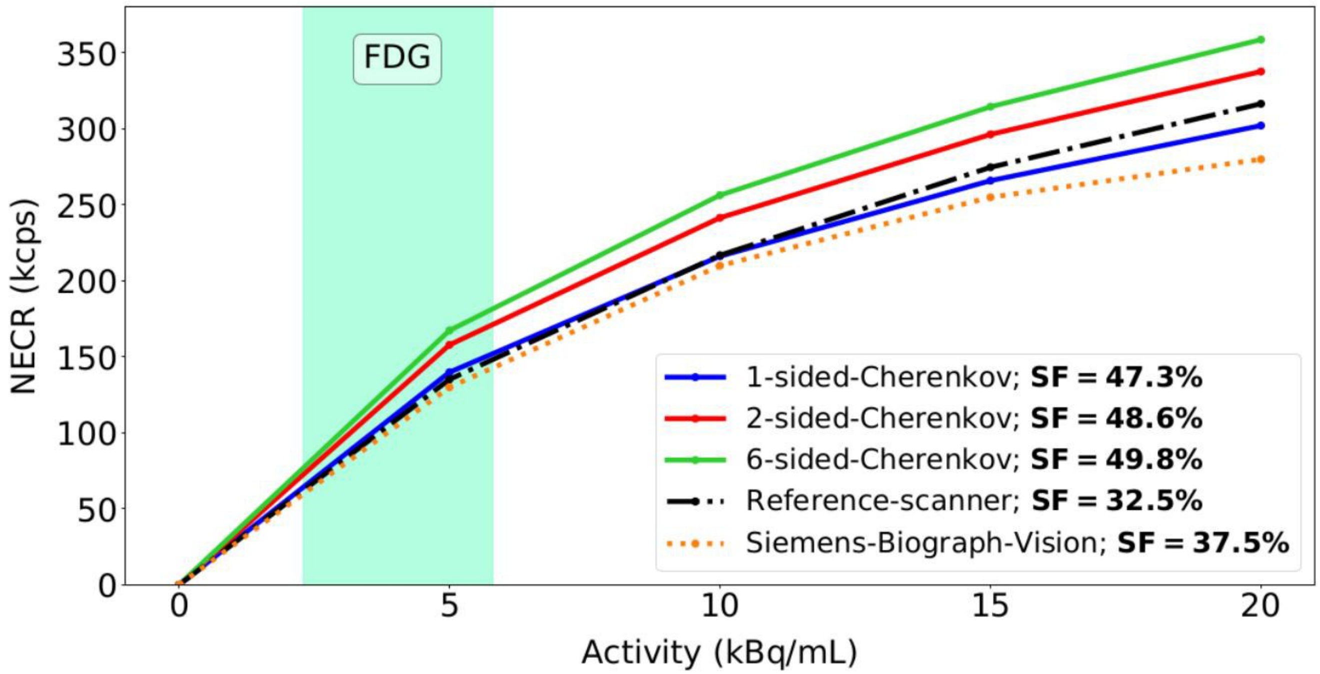
TOF kernel:
single Gaussian
double Gaussian



Results: NECR

- Noise Equivalent Count Rate: $NECR = \frac{true^2}{true + random + scatter}$
  - not influenced by TOF
- Scatter Fraction: $SF = \frac{scatter}{true + scatter}$

NEMA NU 2-2018

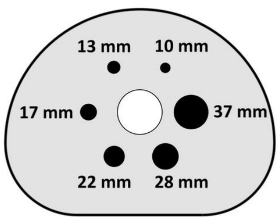


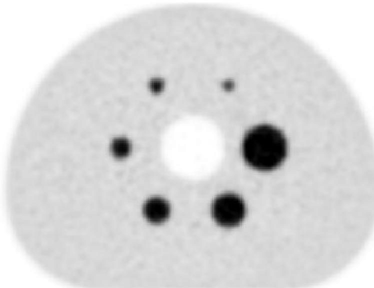
[Sluis, J. Nucl. Med. 60:7 (2019) 1031]

•The “Noise Equivalent Count” is the number is the number of counts from a Poisson distribution (standard deviation estimated by SQRT{N}) that will yield the same noise level as in the data at hand.

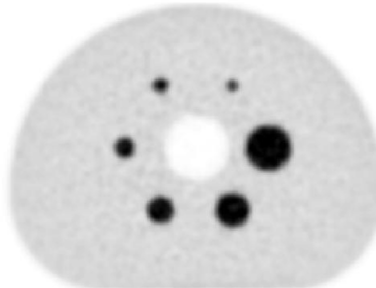
Results: Image Quality

- NEMA image quality phantom



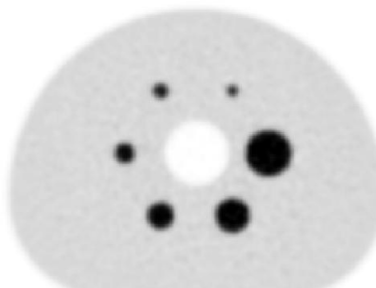


Reference-scanner-214ps

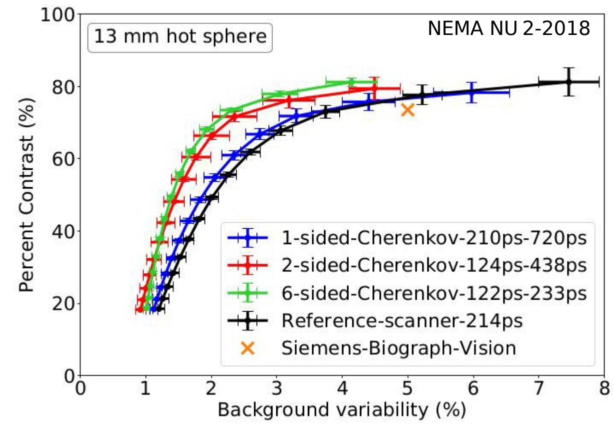


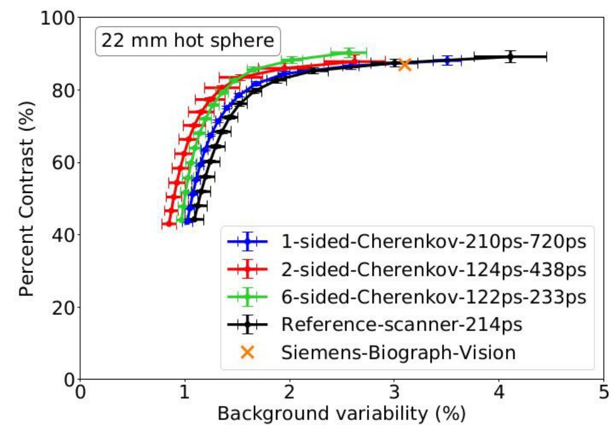
1-sided-210ps-720ps

2-sided-124ps-438ps



6-sided-122ps-233ps





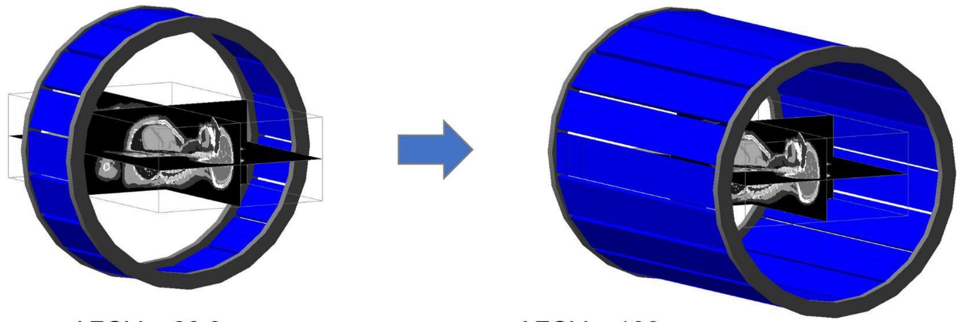
Results: Total-body

Long axial field of view (LAFOV)

~1 m Image quality metrics:

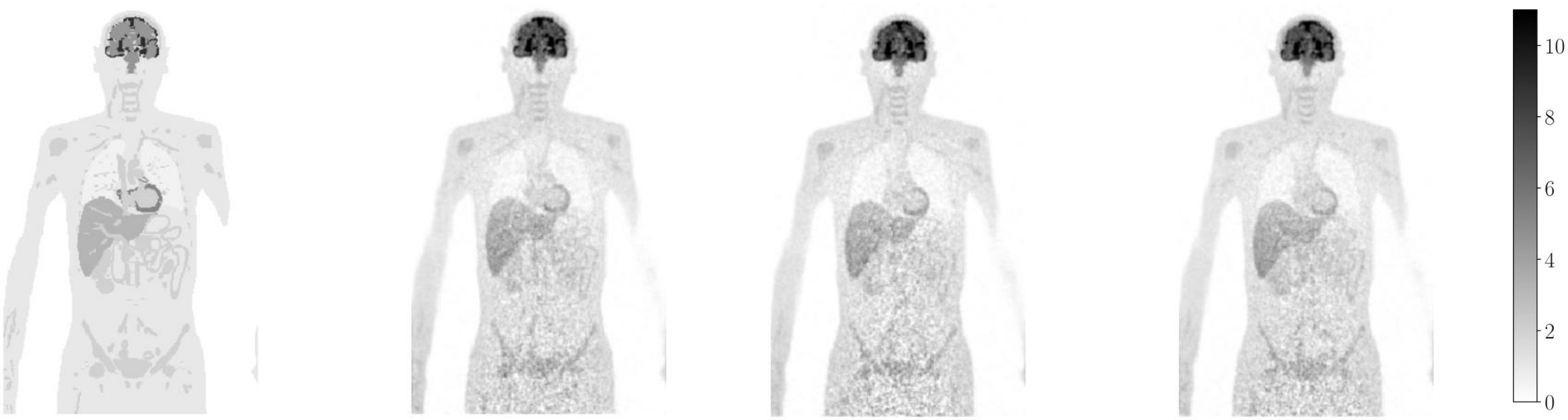
-Mean Structural Similarity Index

-Measure (MSSIM) Normalized Root Mean Square Error (NRMSE)



AFOV = 26.3 cm

AFOV = 106 cm



Ref-distribution
$(MSSIM = 1)$
$(NRMSE = 0)$

Ref-scan-ext-214ps
$MSSIM = 0.34$
$NRMSE = 0.58$

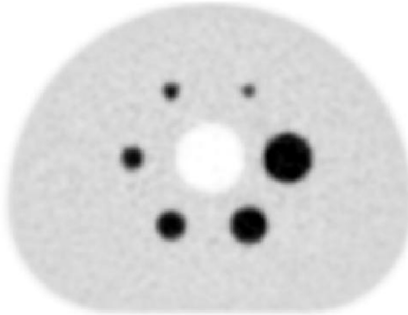
1-sided-ext-210ps-720ps
$MSSIM = 0.31$
$NRMSE = 0.64$

2-sided-ext-124ps-438ps
$MSSIM = 0.34$
$NRMSE = 0.60$

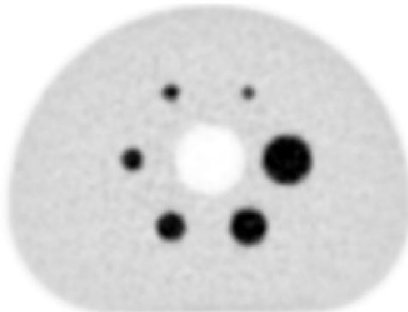
Conclusion: Cherenkov based scanners

- Using (exclusively) Cherenkov light in TOF-PET has potential to
  - improve TOF resolution
  - reduce scanner cost (total-body)
- Experiments have demonstrated
  - CTR as low as 30 ps [Ota, Phys. Med. Biol. 64 (2019) 07LT01]
  - detection efficiency (module) of 35% [Dolenec, NIM A 952 (2020) 162327]
- No energy information available → effect on image quality?
- Cherenkov TOF-PET scanner simulations
  - better sensitivity and CTR compensate higher scatter
  - **image quality comparable to state-of-the-art**
- Advanced detector geometries (2-sided top-bottom, multi-layer)
  - even better image quality

[G. Razdevšek, IEEE TRPMS (2022) DOI: 10.1109/TRPMS.2022.3202138]



Reference-scanner-214ps



1-sided-210ps-720ps

41/14

Summary

Interplay of detector R&D for particle physics and medical imaging has a long history, and this will remain one of the sources of innovation in medical imaging

Limited angle devices with very fast gamma detection look very promising – lower cost, flexibility in use, affordable total-body scanner

Cherenkov radiation based annihilation gamma detectors offer a promising method for very fast detection and potentially cheaper devices