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Instrumentation for advances in PET medical imaging

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

Traditionally excellent collaboration of the two research areas.

Novel detection techniques required in particle physics \rightarrow with modifications often applications are possible in medical physics

… and sometimes also vice versa…

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

- Electromagnetic calorimeters, RICH counters
- Positron Emission Tomography (PET) scanners

Our original expertise: Cherenkov detectors, single-photon sensors and associated electronicsphoton detector

Peter Križan, Ljubljana

Belle II Detector

KL and muon detector: Resistive Plate Counter (barrel) $-$ Scintillator $+$ WLSF $+$ MPPC (end-caps) EM Calorimeter: CsI(Tl), waveform sampling (barrel) Pure CsI + waveform sampling (end-caps) electrons (7GeV) Particle Identification **Time-of-Propagation counter (barrel)** Beryllium beam pipe, **Prox. focusing aerogel RICH (fwd)** 2cm diameterVertex Detector 2 layers DEPFET + 4 layers DSSD positrons (4GeV) Central Drift Chamber He(50%):C2H6(50%), Small cells, long lever arm, fast electronics **College**

Contents

PET – Positron Emission Tomography Current topics in PET Flexible limited angle PET scanner Cherenkov radiation-based PET scanner Conclusions and summary

PET: positron emission tomography

In the blood of the patient, a substance is administered that contains a radioactive isotope – a beta+ emitter (e.g., fluorodeoxyglucose, FDG, with ^{18}F).

Positrons from the ¹⁸F decay annihilate with electrons in the tissue, emitting a pair of collinear gammas.

PET: collection and handling 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.

The places in the body with a higher substance concentration will show a higher activity.

PET with a time-of-flight information

The emission point of the γ pair can be anywhere on the line between the two detector elements that have been hit.

Detectors can in principle also measure the time of arrival of each of the γ rays

- \rightarrow an additional constraint on the point of origin of the two γ rays along the line connecting the two detector hits
- \rightarrow time-of-flight (TOF) PET

Good resolution in time-of-flight \rightarrow limits the number of hit pixels along the line connecting the two detector hits

In the reconstruction step, each line contributes to fewer pixels

 \rightarrow less noise in the reconstructed image

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

 \rightarrow less noise in the reconstructed image Good resolution in time-of-flight \rightarrow limits the number of hit pixels along the line connecting the two detector hits In the reconstruction step, each line contributes to fewer pixels

TOF-PET: time resolution

Optimize detector CTR (∆t) to maximize the sensitivity

Motivation for Fast TOF PET

- Paradigm shift in medicine:
	- From the treatment of an obvious disease
	- To early diagnosis / prevention
- This leads to more stringent requirements on PET diagnostics
	- $-$ Sensitivity (=positive \rightarrow positive)
	- $-$ Specificity (=negative \rightarrow negative)
- Targeted Radionuclide Therapy (TRT) & Theranostics*
	- introduced an urgent need for more widespread and accurate PET

while in the treatment phase it is a strong radiation source to damage the cancer cells. R.PESTOTNIK, PANEL TOF PET IMAGER @MEDAMI 2022 *Theranostics is a two-pronged approach to diagnosing and treating cancers through the use of radiotracers. Radiotracers are compounds made of chemicals that selectively bind to a specific target in the body, and of a radiative component. In the diagnostic phase, the radioactive part is a beta emitter,

Number of PET scanners per million people

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 PET

Essential parameter: CTR – coincidence timing resolution

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

https://www.siemenshealthineers.com/molecularimaging/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***
	- $2 \times 2 \times 20$ mm LSO \rightarrow 98 ps^{*}

*measured with single crystals 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

 \rightarrow '10 ps challenge'

- − rise and decay time
- − **optical photon travel time spread in the crystal**
- − **photodetector response**
- − **readout electronics**

Limitations on timing due to optical travel time

Inherent limitation for any crystal-based annihilation gamma detector:

- optical photons, produced in the crystal, need to reach the photodetector
- inside the crystal, optical photons propagate at a lower speed (c/n) than gamma rays (c)
- refractive index, crystal dimensions \rightarrow intrinsic travel time spread due to different gamma interaction depths
- \bullet 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 \rightarrow multi-layer configuration

Can we simplify the TOF PET scanner

– and make it cheaper and flexible?

Next generation scalable time-of-flight PET

Superb time resolution enables simplifications in the scanner design

Potential benefits of a panel-based PET system

Mobility

– Portable or bedside PET imaging **Flexibility**

– Adjustable FOV and sensitivity

Modularity

 $-$ Combining multiple panels \rightarrow multiorgan/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 resolution
- Study the performance **two-panel** and **fourpanel** designs

Enabling Open Geometry systems

G. Razdevšek et al., "Multi-panel limited angle PET system with 50 ps FWHM coincidence time resolution: a simulation study," IEEE TRPMS 6 (2022) 721, doi: 10.1109/TRPMS.2021.3115704.

Simulation study of planar configurations

Simulated arrangement of 30x30 cm² flat panel detectors

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

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

G. Razdevšek et al., IEEE TRPMS 6 (2022) 721, doi: 10.1109/TRPMS.2021.3115704.

Design optimisation of a flat-panel, limited-angle TOF-PET scanner: simulation

Reconstructed NEMA phantom for various detector parameters.

A 5 mm filter is applied to all of the images.

M. Orehar et al., Design Optimisation of a Flat-Panel, Limited-Angle TOF-PET Scanner: A Simulation Study. Diagnostics 14 (2024) 1976, doi: 10.3390/diagnostics14171976.

Design optimisation of a flat-panel, limited-angle TOF-PET scanner: simulation

Image quality plots for the 13 mm sphere for different scanner parameters.

Grey circle: experimental measurement value for the reference scanner.

M. Orehar et al., Diagnostics 14 (2024) 1976

Design optimisation of a flat-panel, limited-angle TOF-PET scanner: simulation

Images of the brain phantom in the transverse plane

activity phantom

image reconstructed with the 3mm x 3mm x 10mm, CTR 75ps scanner

image reconstructed with the reference scanner.

M. Orehar et al., Diagnostics 14 (2024) 1976

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 120×60 cm² panel detectors (above and below the patient) assuming 100 ps TOF resolution and 10 mm LYSO scintillator thickness.

Next-generation scalable time-of-flight PET

Address PET system challenges of a limited angular coverage using fast CTR

Joint effort: JSI, FBK, ICCUB, I3M, Oncovision, TU Munich and Yale

- Front-end 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

Managed to get a 3 MEUR EIC EU grant for 5 years to further develop the method and construct a prototype.

https://petvision.org

Fast CTR PET module

How to achieve such a good CTR?

FastIC readout chip

FASTIC: 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

Adapted to different detectors: LYSO/LSO, BGO, Cherenkov, Monolithic, etc

First results with FastIC

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

Single photons

23.0

SPTR sigma = 64.39 ps FWHM $\tilde{G} = 151.62$ ps

SPTR sigma $=$ 59.39 ps FWHM $G+E = 151.16$ ps

22.5

 $mu G = 21.694$

 $mu G + E = 21.668$

SPTR with FBK-NUVHDLFv2b 3x3

• CTR versus crystal length for LYSO and LSO

Instrumentation advances in PET me astroparticle physics and medical applications in Spain, March 2023 D. Gascon, talk at Instrumentation for the future of particle, nuclear and

Next generation ASICs

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

D. Gascon, talk at Instrumentation for the future of particle, nuclear and astroparticle physics and medical applications in Spain, March 2023

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.

Limited angle PET scanner, conclusions

- 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 a wider spread of PET imaging by reducing different contributions to CTR :
	- Optimize scintillator thickness
	- Improve SiPM TSV
	- Fast ASIC
	- 2.5D integration
	- If new faster scintillators emerge, we should be able to make use of them

Use of Cherenkov light in TOF-PET

Use of Cherenkov radiation for TOF-PET

 $-$ lead fluoride (PbF₂) 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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https://photodetectors.ijs.si/

Imaging Cherenkov detectors

Use of Cherenkov Light in TOF-PET

γ detectors in traditional PET: scintillator crystal + photodetector

Charged particles (e- produced by γ interactions) passing through a dielectric material with $v > c_0/n \rightarrow$ **prompt** Cherenkov light Excellent Cherenkov radiator material: **lead fluoride (PbF**₂)

2.8 ns 70 ps

300 ns 40 ns

3,000 15,000 **10 (‡)**

- pure Cherenkov radiator (no scintillations)

 $511 \,\mathrm{keV}$

electron

 $(*)$ in the 250-800 nm wavelength interval

Raise time (τ_r)

Decay time $(τ_d)$

Light yield/511 keV (LY)

- excellent optical transmission (down to 250 nm), high refractive index ($n \sim 1.8$)

- low price (**1/3 BGO, 1/9 LSO**)

Mao, IEEE TNS 57:6 (2010) 3841

TOF-PET with Cherenkov light detection: proof of principle

Two detectors (back-to-back) $-$ 25 x 25 x 15 mm³ crystals (black painted or Teflon wrapped) - MCP-PMT (Hamamatsu, same as in the Belle II TOP counter)

- ²²Na source

- 15 mm long crystal: FWHM \sim 95 ps
- 5 mm long crystal: FWHM \sim 70 ps

S. Korpar et al, NIM A654 (2011) 532

Point source position

Data taken at three ²²Na point source positions spaced by 20 mm:

- average time shift 125 ps
- timing resolution \sim 40 ps rms, \sim 95 ps FWHM
- position resolution along line of response \sim 6 mm rms,

 \sim 14 mm FWHM

Black painted 15 mm $PbF₂$ crystals.

S. Korpar et al, NIM A654 (2011) 532–538

Previous results

Limitations of Cherenkov TOF-PET

Only 10-20 photons created \rightarrow only a few detected

– efficient photodetector and light collection needed

511keV gamma

Optical photon travel time spread in the crystal

– remaining limitation to TOF resolution

- Limited suppression of **scattered events**:
	- only a few Cherenkov photons detected
		- \rightarrow no energy information
	- detection efficiency drops at low gamma energies
		- \rightarrow intrinsic suppression

Essential question \rightarrow MC simulation to evaluate the effect

SiPM

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

OSEM-8it:5sub, 1.6 mm voxel, 5 mm filter

Crystal readout configurations

 \mathbf{I}

Simulation:

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

 \mathbf{I}

Reference scanner

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

 $\overline{1}$

G. Razdevšek *et al.*, "Exploring the Potential of a Cherenkov TOF PET Scanner: the mass of time resolution A Simulation Study," IEEE TRPMS 7 (2023) 52, doi: 10.1109/TRPMS.2022.3202138.

SPTR = single photon

Results: CTR distributions

G. Razdevšek et al., IEEE TRPMS 7 (2023) 52

Results: NECR - Noise Equivalent Count Rate

*The "Noise Equivalent Count" 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

G. Razdevšek et al., IEEE TRPMS 7 (2023) 52

Cherenkov based scanners, conclusion

- 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 R. Ota, Phys. Med. Biol. 64 (2019) 07LT01
	- detection efficiency (module) of 35% R. Dolenec et al, NIM A 952 (2020) 162327
- No energy information available \rightarrow 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 et al., IEEE TRPMS 7 (2023) 52

Reference-scanner-214ps

1-sided-210ps-720ps

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Cherenkov-based TOF-PET with a large area MCP-PMT

Idea: • couple short $PbF₂$ crystals as Cherenkov radiators to the •LAPPD – a large area MCP-PMT, and make use of the •flat panel concept

LAPPD with $PbF₂$ crystals

CherPET: an ERC (European Research Council) Proof-of-Principle project

LAPPD with $PbF₂$ crystals attached to the entry window: an almost ideal flat panel device

LAPPD (large area picosecond photodetector) Gen II

aser Trigger Rate (kHz).

- MCPs with 20 μ m pores at 20 μ m pitch
- two parallel spacers (active fraction \approx 97 %)
- gain $\approx 5 \cdot 10^6$ @ ROP (825 V/MCP, 100 V on photocathode)
- peak QE $\approx 25\%$
- Dark Count rate @ ROP: \sim 70 kHz/cm2 with 8x10⁵ gain

MCP-PMT: single photon pulse height and timing

Photoelectron back-scattering produces a rather long tail in timing distribution and position resolution.

Photoelectron backscattering reduces collection efficiency $\sigma \approx 27 \text{ ps}$ and gain, and contributes to cross-talk in multi-anode PMTs

S.Korpar et al, PD07

LAPPD evaluation

- Two 10 μ m devices acquired
- LAPPD installed in the dark box:
- CAEN HiVolta (DT1415ET), 8 Ch Reversible 1 kV/1 mA Desktop HV Power Supply floating channels
	- -1 kV/1 mA and 0.6 W(!) per channel
- Measure response in the lab with modular electronics, FastIC and PETSys
- Standard setup with QDC, TDC, 3D stage ...
	- TDC value corrected for time-walk
- ALPHALAS PICOPOWER™-LD Series of Picosecond Diode Lasers – 405 nm
	- FWHM ≈20ps
	- light spot diameter on the order of $100 \mu m$
- Custom segmentation to study the capacitive coupling and the charge spread

50

Characterizing MCP-PMT: time resolution and charge sharing

γ

α

↑e

 U_1 \cdots U_n \cdots U_n

 d_0 d_1

β

Time difference between downward and sideways initial direction of the photoelectron (simple model, see backup slides)

$$
\Delta t \approx t_0 \sqrt{\frac{E_0}{U e_0}}
$$

This difference is proportional to the time resolution – sigma of the main peak in the time response of the MCP-PMT

Next steps: finalize read-out, attach crystals, test the back-to-back configuration

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read-out electrodes.

M_CP₁

window with photocathode

Summary

The 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.

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Micro Channel Plate PMT (MCP-PMT)

Multiplication step: a continuous dynode – a micro-channel coated with a secondary emitter material

Micro Channel Plate PMT (MCP-PMT)

Micro Channel Plate PMT: properties

Very fast: single photon detection with sigma of \sim 30-40 ps

MCP PMTs work well in magnetic fields \rightarrow performance depends on the diameter of the microchannels

MCP-PMT: single photon pulse height and timing

Photoelectron back-scattering produces a rather long tail in timing distribution and position resolution.

Photoelectron backscattering reduces collection efficiency and gain, and contributes to cross-talk in multi-anode PMTs

S.Korpar@PD07

Modelling MCP-PMT: Photoelectrons in a uniform electric field

Photoelectrons travel from the photocathode to the electron multiplier (uniform electric field $\frac{v}{l}$, initial energy $E_0 \ll U e_0$):

• photoelectron range

$$
d_0 \approx 2l \sqrt{\frac{E_0}{Ue_0}} sin(\alpha)
$$

• and maximal travel time (sideway start)

$$
t_0 \approx l \sqrt{\frac{2m_e}{U e_0}}
$$

• time difference between downward and sideways initial direction

$$
\Delta t \approx t_0 \sqrt{\frac{E_0}{U e_0}}
$$

Backscattering delay and range (maximum for elastic scattering):

• maximum range vs. angle

 $d_1 = 2 \text{lsin}(2\beta)$

maximum range for backscattered photoelectron is twice the photocathode – first electrode distance

• maximum delay vs. angle

$$
t_1 = 2t_0 \sin(\beta)
$$

maximum delay is twice the photoelectron travel time

• time of arrival of elestically scattered photoelectrons: flat distribution up to max $t_1 = 2t_0$

Example ($U = 200$ V, $E_0 = 1$ eV, $l = 6$ mm) photoelectron:

- max range $d_0 \approx 0.8$ mm
- p.e. transit time $t_0 \approx 1.4$ ns
- $\Delta t \approx 100$ ps

backscattering:

- max range $d_1 = 2l = 12$ mm
- max delay $t_1 = 2.8$ ns

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. QDC: dual range 800pC, 200pC

LAPPD - IJS sensing electrodes

- capacitively coupled electrode produced at IJS with several different patterns:
	- pads: 5 mm, 6 mm, 12.5 mm, 25 mm
	- 50 mm long strips: 5 mm, 3 mm
	- PETSYS connector (256 6mm pads)
	- FastIC connector (12.5 mm and 25 mm pads)

LAPPD 109

LAPPD – charge sharing in Gen II capacitively coupled electrode readout

- fraction of the signal on channel 3 vs laser spot x position: $f(x) = \frac{q_3}{\sum_i q_i}$
- scan between the centres of pads 2 and 3 (top)

- central slice where signal is equally split between the pads (bottom)
- narrow peak is due to the light spot size and photoelectron spread
- longer tail from photoelectron backscattering \approx 6 mm on each side $\rightarrow \approx$ 3 mm PC – MCP1 distance

Nov. 25, 2024 **Peter Križan, Ljubljana**