Design Consideration for a Prototype TOF-PET System with 100 ps Coincidence Time Resolution and 3D Event Positioning Capability

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Stanford Cancer Imaging Training (SCIT) Seminar / RSL Weekly Seminars

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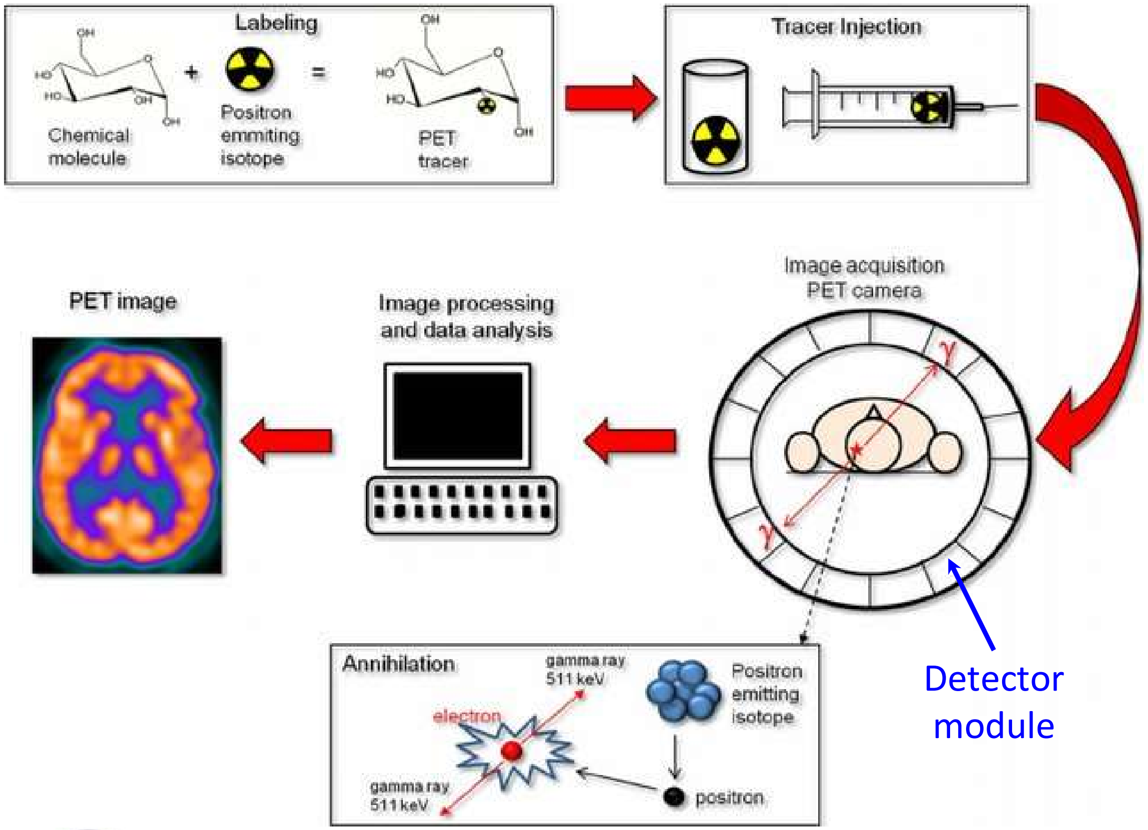
MIPS
Molecular Imaging
Program at Stanford

Stanford University
School of Medicine
Department of Radiology

Positron Emission Tomography (PET) System

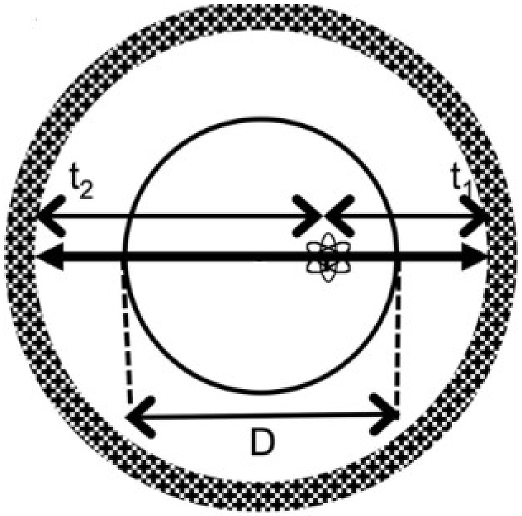
- %80 of PET usage in Cancer:
    - Detecting and staging specific types of cancer and/or assessing response to treatment
- Cardovascular and/or Neurollgical and/or Disease
    - Evaluating the function of organs, such as the heart and/or brain

Concept Behind PET



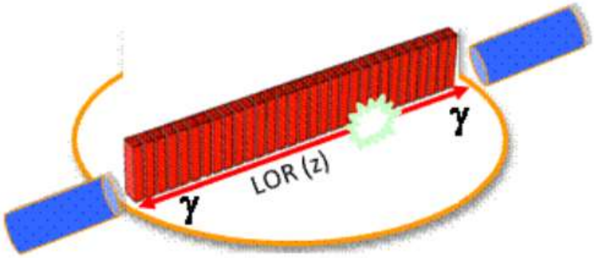
- Positron emitter radionuclides
  - e.g ^{11}C, ^{13}N, ^{15}O, & ^{18}F
- Ring of Detector modules
  - Scintillation crystals + photosensor + electronic readout
- Event localization along lines of response (LOR)
  - Arrival time difference of coincident events

Event Localization



- $\Delta t = t_2 - t_1$: Arrival time difference of coincident events
- D: Patient diameter (e.g. 40 cm)
  - c=3×10^{10} cm/s
  - Δt: coincidence timing resolution (CTR)
- Localization error Δx= c×CTR/2

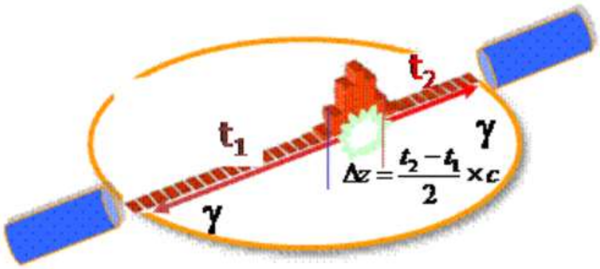
Conventional PET



Δx>D

Equal probability to all voxels along the LOR ☹

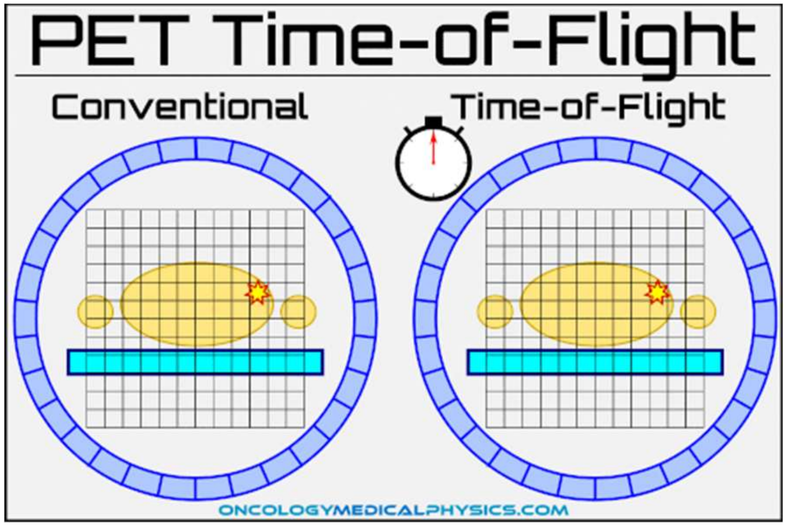
TOF-PET



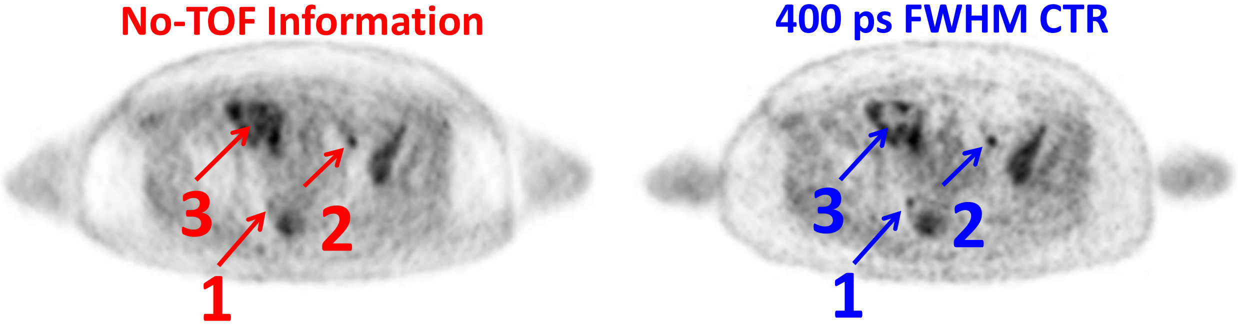
Δx<D

Confined probability to a small segment on the LOR ☺

Clinical TOF-PET Performance



Courtesy of K. Lee, Stanford



SNR improvement:

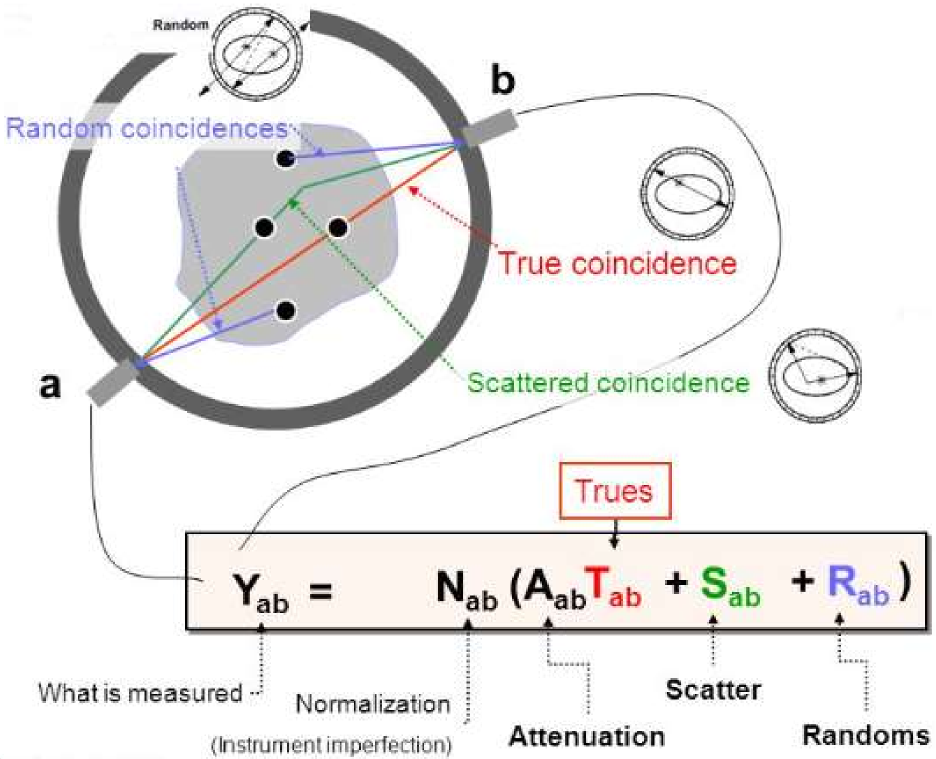
$$\mathrm{SNR}_{\mathrm{TOF}} \approx \sqrt{\frac{D}{c \times \mathrm{CTR}/2}} \cdot \mathrm{SNR}_{\mathrm{non-TOF}}$$

CTR= 1 ns: Δx=15 cm >>> G=1.6
CTR= 500 ps: Δx=7.5 cm >>> G=3.1
CTR= 400 ps: Δx=6 cm >>> G=2.6
CTR= 250 ps: Δx=4 cm >>> G=3.3
CTR= 100 ps: Δx=1.5 cm >>> G=5.2

1. Improves lesion detectability
    - e.g. signal-to-background ratio
2. Enables better lesion quantification
    - e.g. SUV precision and accuracy
3. Provides a more faithful representation of cancer biomarker distribution
    - e.g. better visualization of tumor heterogeneity

Other Advantages of TOF-PET Imaging

PET imaging limitations and data corrections:



$$Y_{ab} = N_{ab}(A_{ab}T_{ab} + S_{ab} + R_{ab})$$

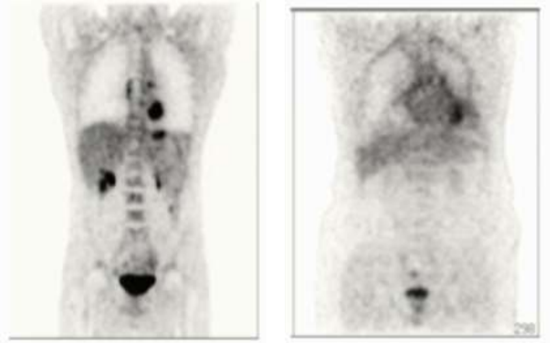
TOF-PET images are more robust:

- Being less sensitive to errors in data correction techniques
  - Leading to good image quality
- Faster reconstruction convergence with less noise
- Reducing artifacts e.g. in PET/MR
- Not really changing the spatial resolution but increasing the SNR with TOF to improve visibility
- Or alternatively substantially lower injected dose or lower scan time or combination of both

Clinical ^{18}F-FDG PET Imaging

Philips Allegro (2001)

non-TOF



80 kg **132 kg**

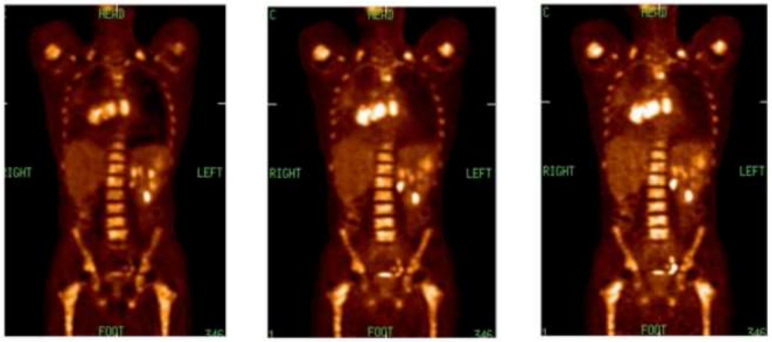
Larger volume (132 kg):

- Significant attenuation
- Lower counts overall
- Poor SNR (less quality image)

Philips Gemini TF (2005):

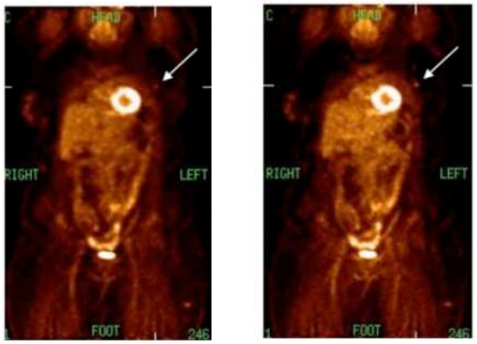
83 kg patient (small cell lung cancer)

Non-TOF-PET **TOF-PET** **TOF, 1/3 scan time**



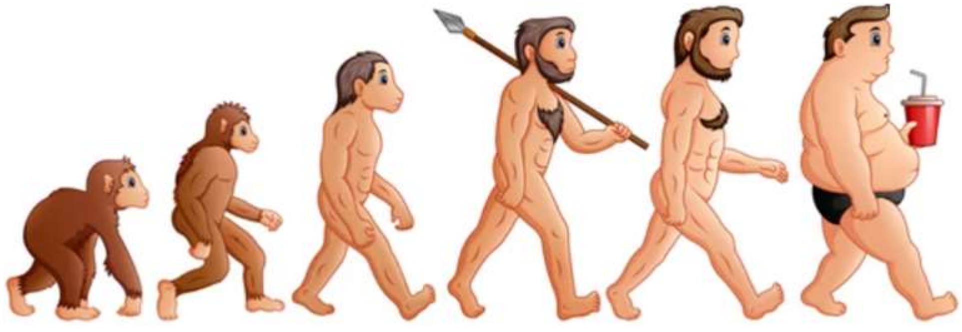
140 kg patient (non-Hodgkins lymphoma)

Non-TOF-PET **TOF-PET**



- with TOF-PET, signal amplification factor ($\sqrt{\frac{D}{\Delta x}}$) increases for favors heavy patients!

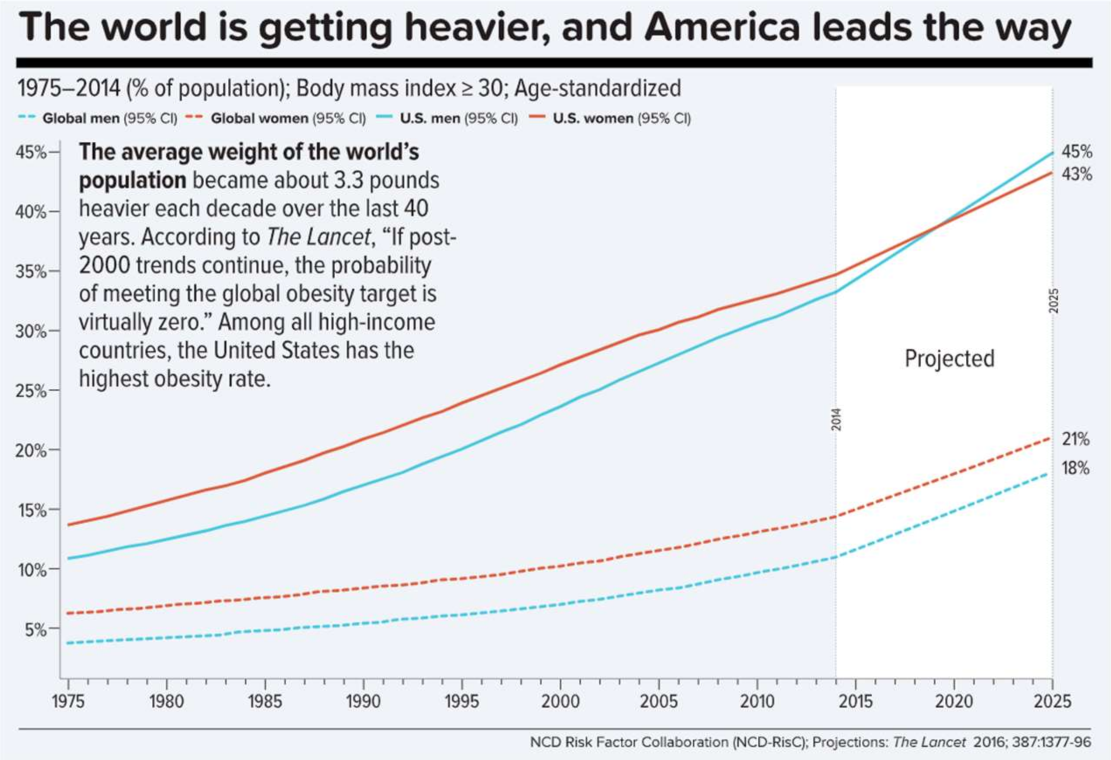
TOF-PET for Heavier Patients



- In average patients are getting larger (worldwide trend…)

TOF-PET is getting necessary, due to:

- Poor SNR of heavy patients' images
- Difficulty in scanning heavy patients



The world is getting heavier, and America leads the way

1975–2014 (% of population); Body mass index ≥ 30; Age-standardized

The average weight of the world's population became about 3.3 pounds heavier each decade over the last 40 years. According to *The Lancet*, "If post-2000 trends continue, the probability of meeting the global obesity target is virtually zero." Among all high-income countries, the United States has the highest obesity rate.

NCD Risk Factor Collaboration (NCD-RisC); Projections: *The Lancet* 2016; 387:1377-96

https://www.hsph.harvard.edu/magazine/magazine_article/obesity/

Motivation behind this Project

Motivation

- **Design and develop a practical TOF-PET scintillation detector array + readout electronics configuration with 100 ps CTR, and 3D event positioning capabilities**
- **Create a proof-of-concept partial-ring prototype TOF-PET/CT system**

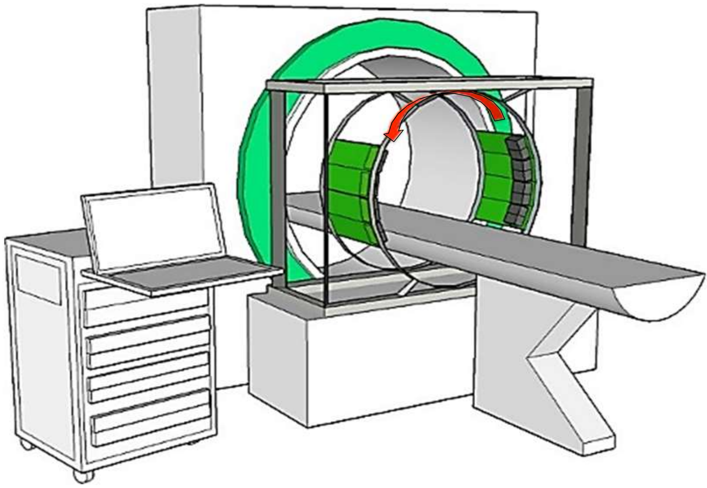
100 ps FWHM CTR means:

- Constraining events to a **Δx=1.5 cm** segment along each LOR
- >**3-fold**, **2-fold**, and **1.6-fold** SNR improvement compared to non-TOF systems, 400 ps CTR TOF-PET/MR (GE SIGNA), and 250 ps TOF-PET (Siemens Biograph), respectively

3D event positioning means:

- Determine the 3D coordinates of one or more interaction locations in the detector crystals
- Mitigates “parallax” error (3 mm DOI)

Partial-ring prototype 100 ps CTR TOF-PET system butted against a stand-alone CT scanner



Keys to Design our 100 ps CTR TOF-PET with 3D event Positioning Capability

Scintillation Crystal & Photo-Sensor

- **Scintillation crystals convert each 511 keV photon to a flash of visible light**
- **Photodetectors convert the scintillation light to electrical pulses**

Crystals: we are using fast LGSO:Ce ($Lu_{2x}Gd_{2-2x}SiO_5$:Ce) scintillation crystals owing to:

- High intrinsic detection efficiency
- High light yield
- Short scintillation decay time

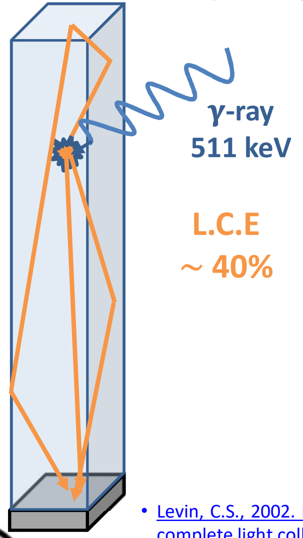
Photosensors: we are using arrays of SiPMs (On Semiconductor MicroFJ- 30035) owing to:

- High photo-detection efficiency (PDE) (>50%)
- Compactness
- High-speed response
- Excellent time resolution
- High intrinsic gain
- low operating voltage
- Robustness

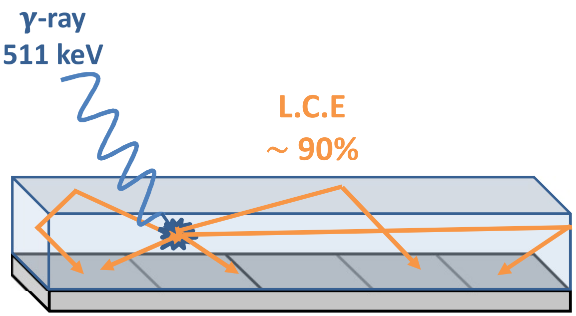
Scintillation Crystal to Photo-Sensor Coupling

- Crystal coupling to photo-sensor strongly
  - ✓ Affects the light collection efficiency (L.C.E)
  - ✓ Affects scintillation photon transit time variation to the photodetector (large impact on CTR)

End readout (one-to-one coupling)

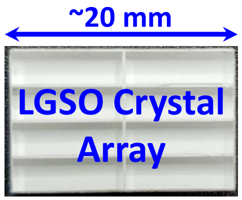


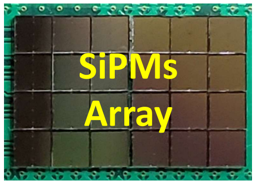
Side readout



Advantages of Side readout

- High scintillation light collection efficiency
- Low jitter in L.C.E
- Low scintillation photon transit time spread to the photodetector
- Boost in CTR performance
- **This project uses 2×4 arrays of 3×3×10 mm³ fast-LGSO crystals side-coupled to 2×4 arrays of 3×3 mm² SiPMs**





- Levin, C.S., 2002. Design of a high-resolution and high-sensitivity scintillation crystal array for PET with nearly complete light collection. *IEEE Transactions on Nuclear Science*, *49*(5), pp.2236-2243.
- Cates, J.W. and Levin, C.S., 2018. Evaluation of a clinical TOF-PET detector design that achieves ≤ 100 ps coincidence time resolution. *Physics in Medicine & Biology*, *63*(11), p.115011.

Front-end Electronic Readout

- Lowest limit in time resolution for a single photon event
  - σ_{time} : transient time jitter or estimated time variance: $\sigma^2_{time} \approx \left(\frac{\sigma^2_{noise}}{dV/dt}\right)^2 + \sigma^2_{TTS}$
  - σ_{TTS} : inherent time jitter of the photo-detector's charge carriers
  - dV/dt : signal slope at the point of time estimation (time pick-off). It is a combination of detector signal gain and detector signal time response
  - σ_{noise} : electronic and detector noise

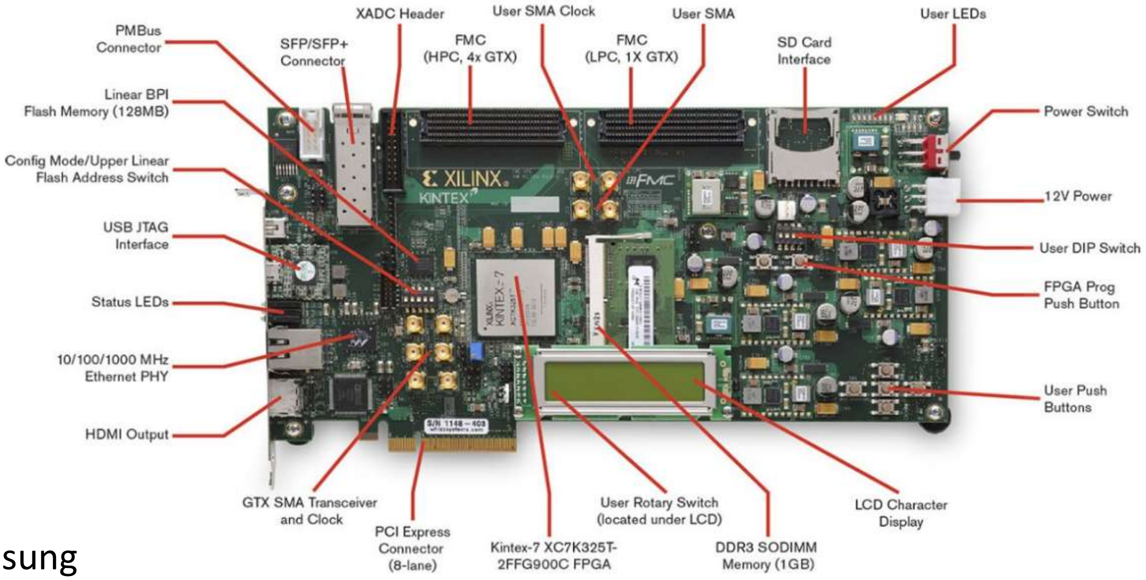
(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3230997/)

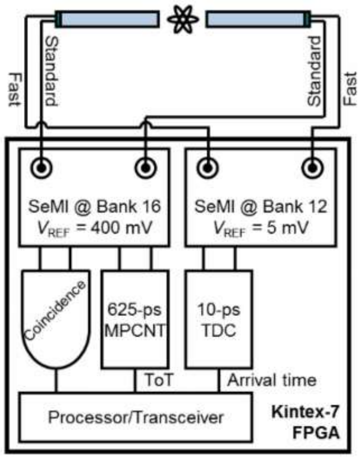
- **Needs very fast and low noise front-end electronics, including:**
  - High-performance integrated circuits (ICs)
  - Time to Digital Converters (TDCs) with very precise timing information (low jitter)

Scalable FPGA-Based TDC Solution to Achieve 100 ps FWHM CTR

Dr. Jun Yeon Won

- Seoul National University
- Currently working at Samsung

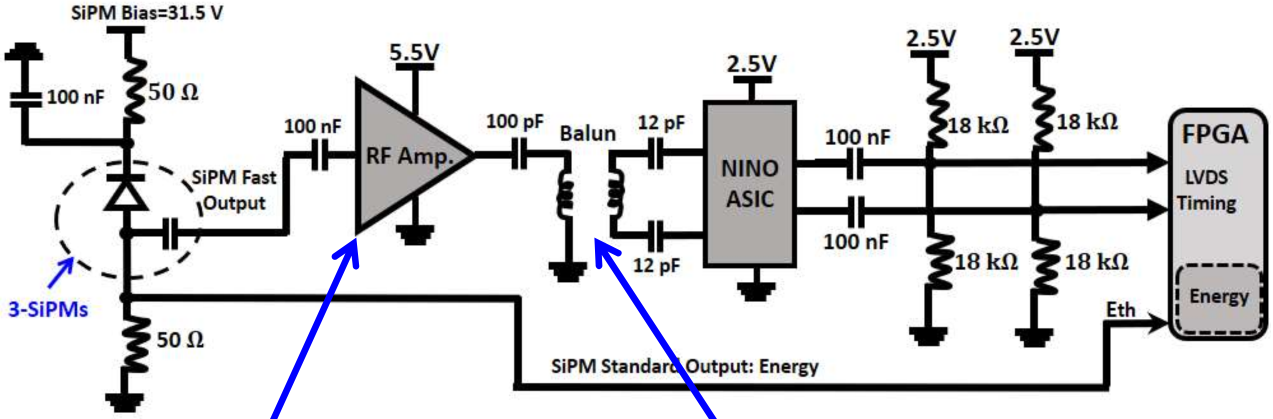




- **FPGA-based TDC implemented on** Kintex-7 FPGA (KC705, Xilinx) with very low intrinsic jitter σ=6.7 ps (15.8 ps FWHM)

J. Y. Won and J. S. Lee, "Highly Integrated FPGA-Only Signal Digitization Method Using Single-Ended Memory Interface Input Receivers for Time-of-Flight PET Detectors," in IEEE Transactions on Biomedical Circuits and Systems, vol.12, no. 6, pp.1401-1409, Dec. 2018.

Custom Electronic Chain for a Single Timing Channel

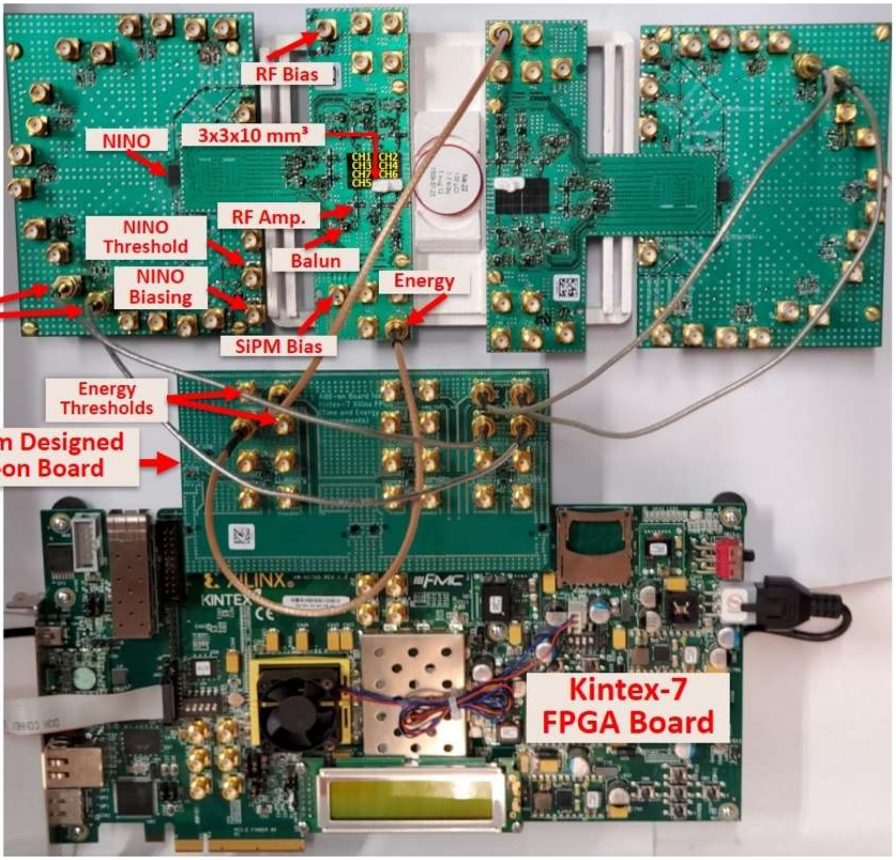


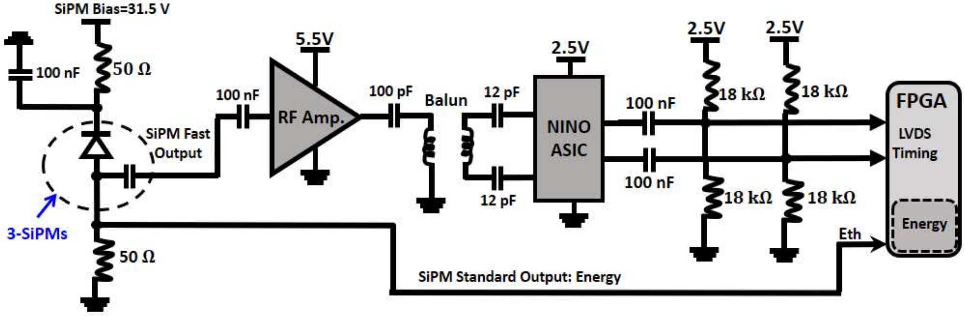
- Differential digital outputs with sharp rise time (< 0.5 ns)
- Stable against pick-up noise, common mode noise, and power supply noise

Very fast (2 GHz) radio frequency amplifier to magnify SiPMs’ timing signal way above the baseline noise level

Balun transformer generates differential amplified timing pair to feed digitizer

Single Timing Channel Readout of 100 ps TOF-PET Scanner [1]-[2]





❑ Side-coupled ~20 mm effective length crystals to 4x6 array of 3×3 mm^2 SiPMs

[1] **S. Pourashraf**, A. Gonzalez-Montoro, J. Y. Won, M. S. Lee, J. W. Cates, Z, Zhao, J. S. Lee, C. S. Levin, "Scalable Electronic Readout Design for a 100 ps Coincidence Time Resolution TOF-PET System." *Physics in Medicine and Biology (PMB)*, vol. 66, no. 8, p. 085005, April. 2021.

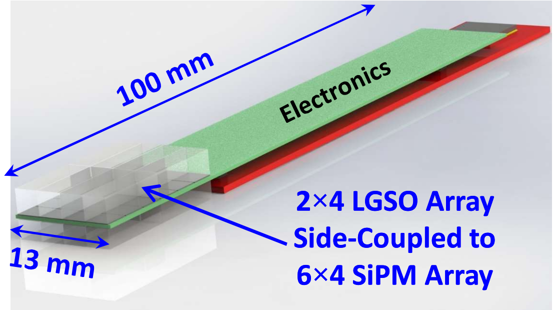
[2] **S. Pourashraf**, A. Gonzalez-Montoro, M. S. Lee, J. W. Cates, J. Y. Won, J. S. Lee, C. S. Levin, "Investigation of Electronic Signal Processing Chains for a Prototype TOF-PET System with 100 ps Coincidence Time Resolution", *IEEE Transaction on Radiation and Plasma Medical Sciences (IEEE TRPMS)*, Nov. 2021. DOI: 10.1109/TRPMS.2021.3124756.

Evolved Front-end Readout:

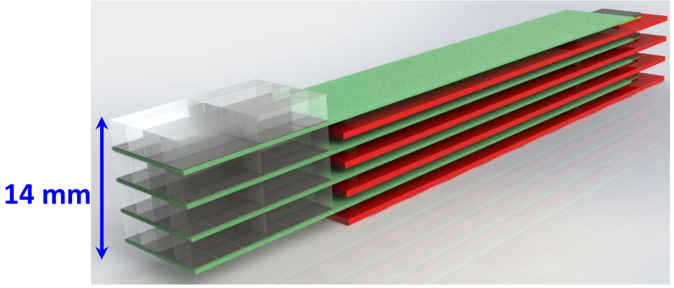
3DPS Scalable 100 ps CTR TOF-PET Detector Unit

Scalable 100 ps TOF-PET Detector Modules

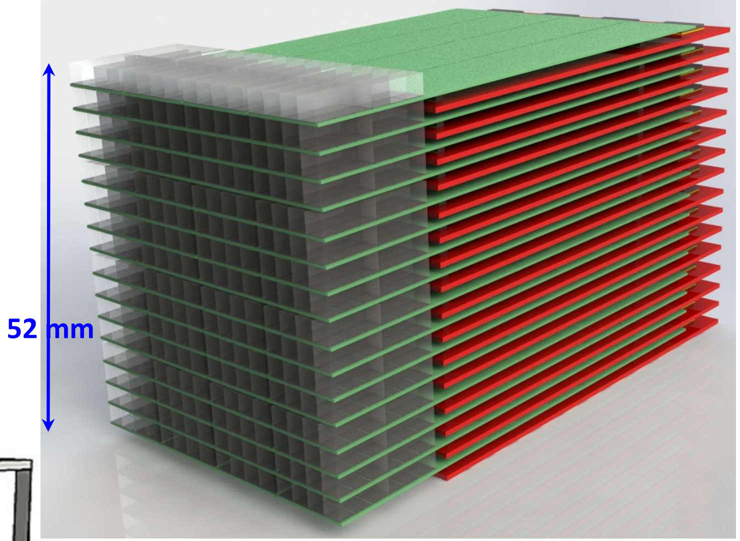
Detector Unit



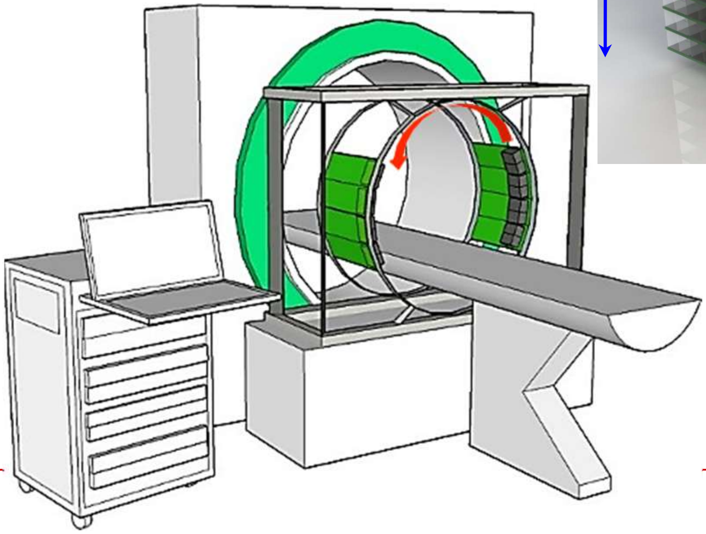
Sub-Module Unit
(4 detector units)



Detector Module
(16 sub-module units, 64 detector units)



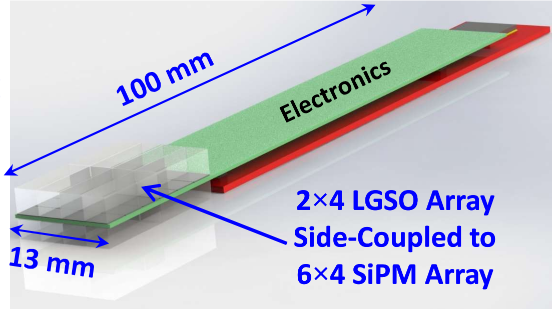
- ❑ **Full ~5x5 cm² TOF-PET module comprising crystal elements employing side readout technique!**
- ❑ **One Kintex-7 FPGA (KC705, Xilinx) per detector module**
  - ➢ **64** timing signals & **32** energy signals

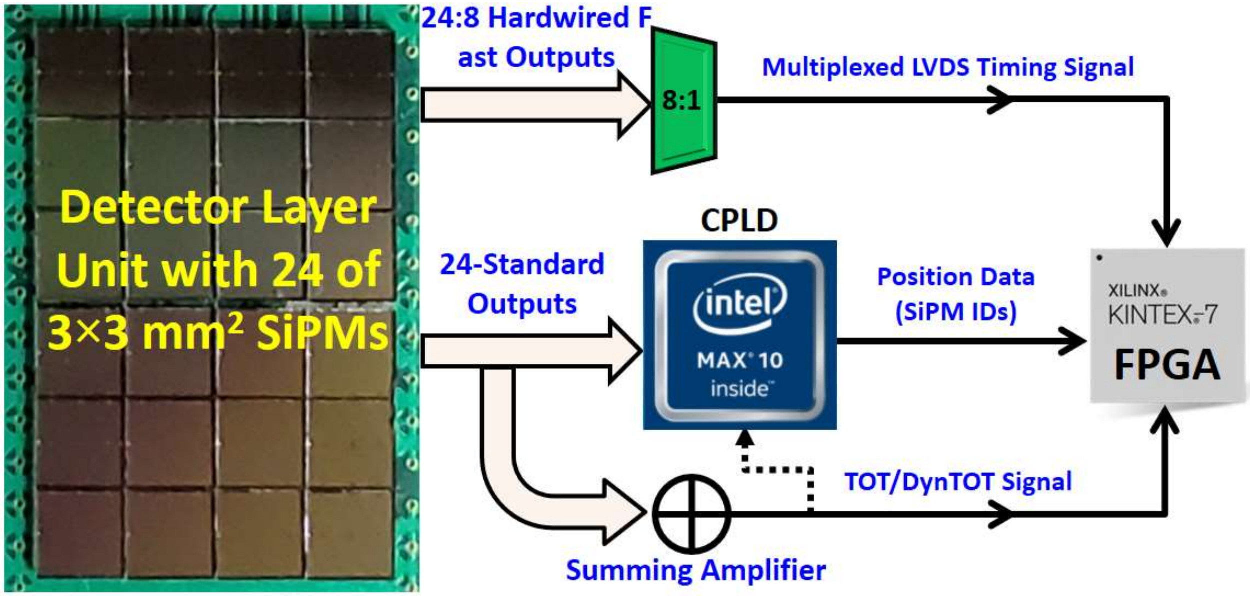


- ❑ **16-module partial-ring TOF-PET/CT System**

Accurate Energy Information & Event Positioning (3DPS)

Detector Unit:

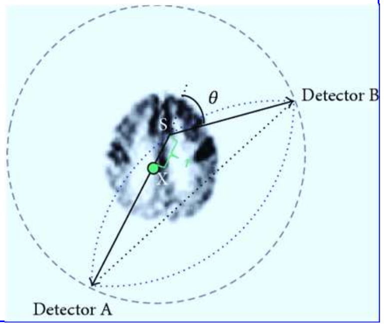




Accurate energy information of each 511 keV photon interaction in the crystal:

- Important for rejecting Compton scatter in the patient tissues
- For accuracy, the energy measurement should be linear across the energy dynamic range.

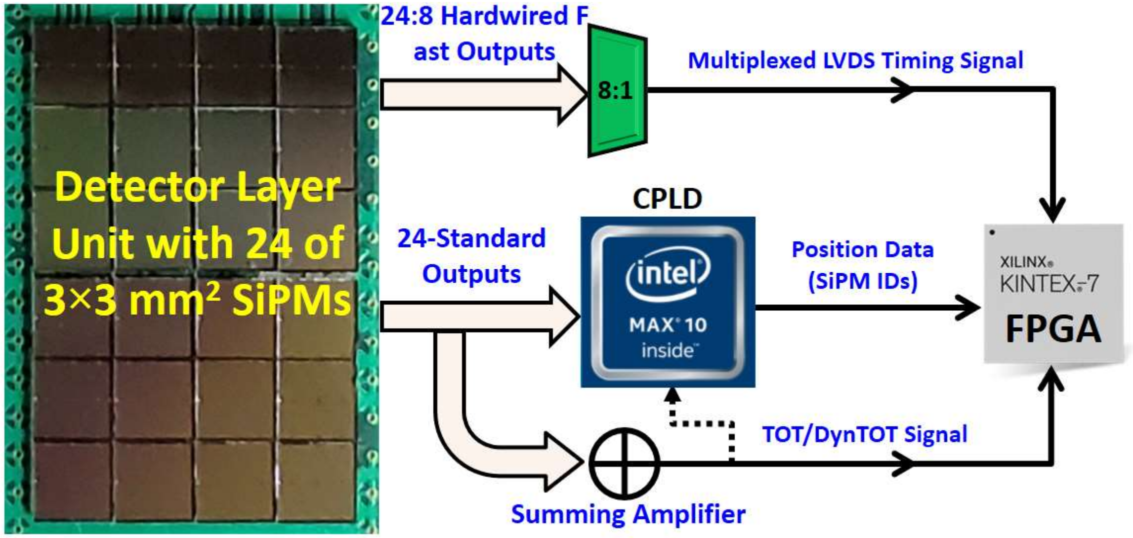
$$E_S = \frac{E}{1 + \frac{E}{m_0 c^2}(1 - \cos\ )}$$



Stanford University

School of Medicine
Department of Radiology

Accurate Energy Information & Event Positioning (3DPS)



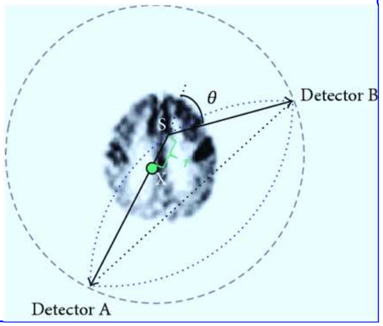
3DPS (3D position sensitivity):

- Allows to determine the 3D coordinates of one or more interaction locations in the detector crystals
- Mitigates "parallax" error (3 mm DOI)

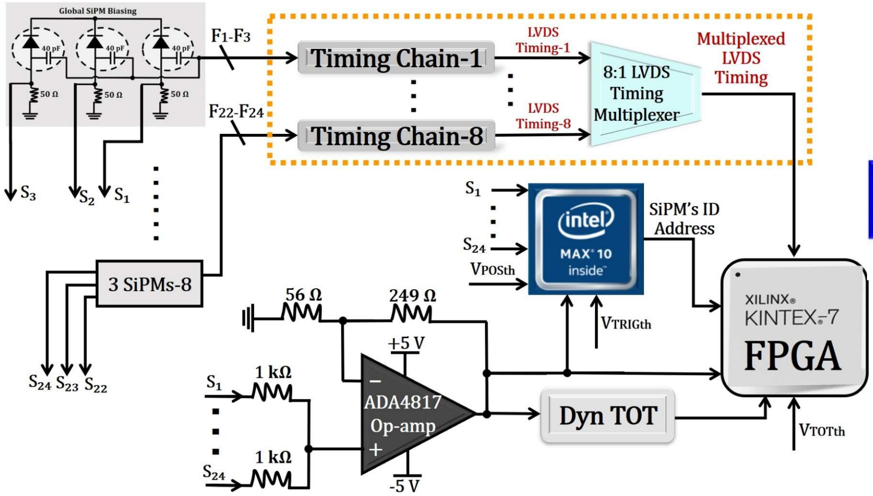
Accurate energy information of each 511 keV photon interaction in the crystal:

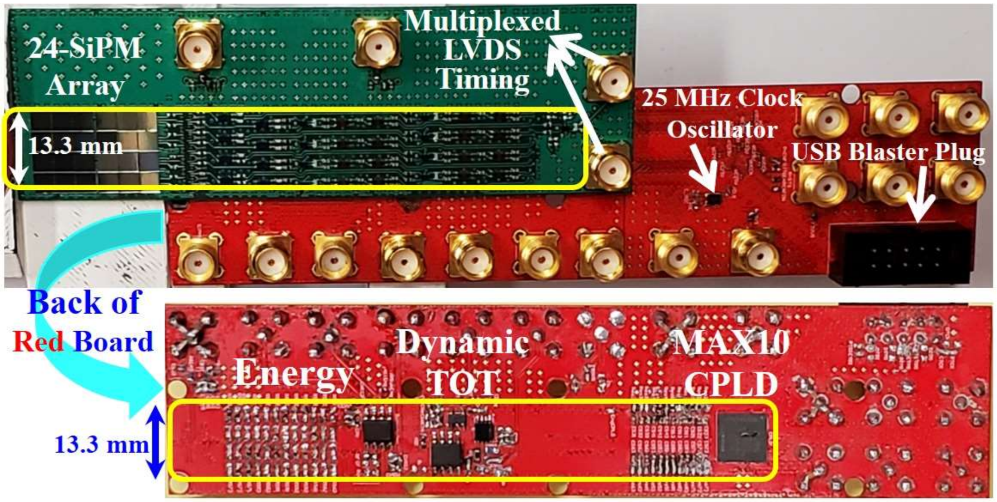
- Important for rejecting Compton scatter in the patient tissues
- For accuracy, the energy measurement should be linear across the energy dynamic range.

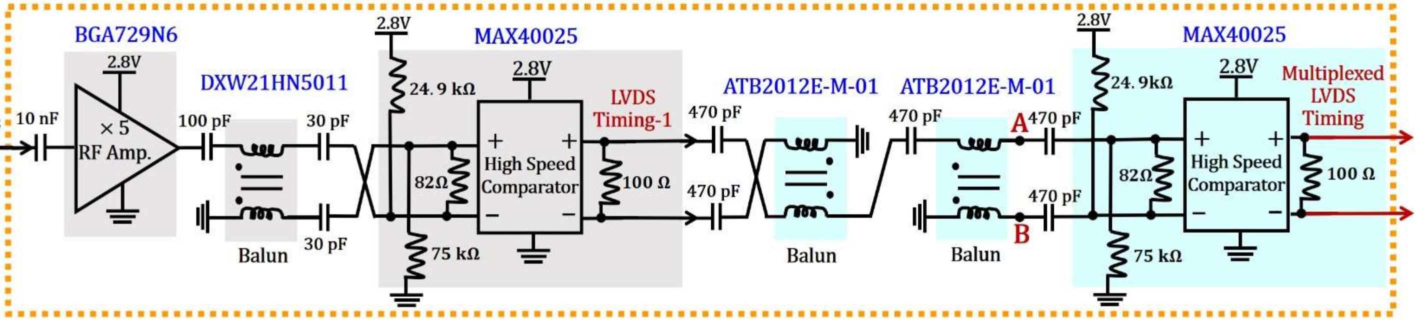
$$E_S = \frac{E}{1+\frac{E}{m_0 c^2}(1-\cos\theta)}$$



Compact (13.3 mm) Electronic Read-out of 100 ps CTR Detector Unit

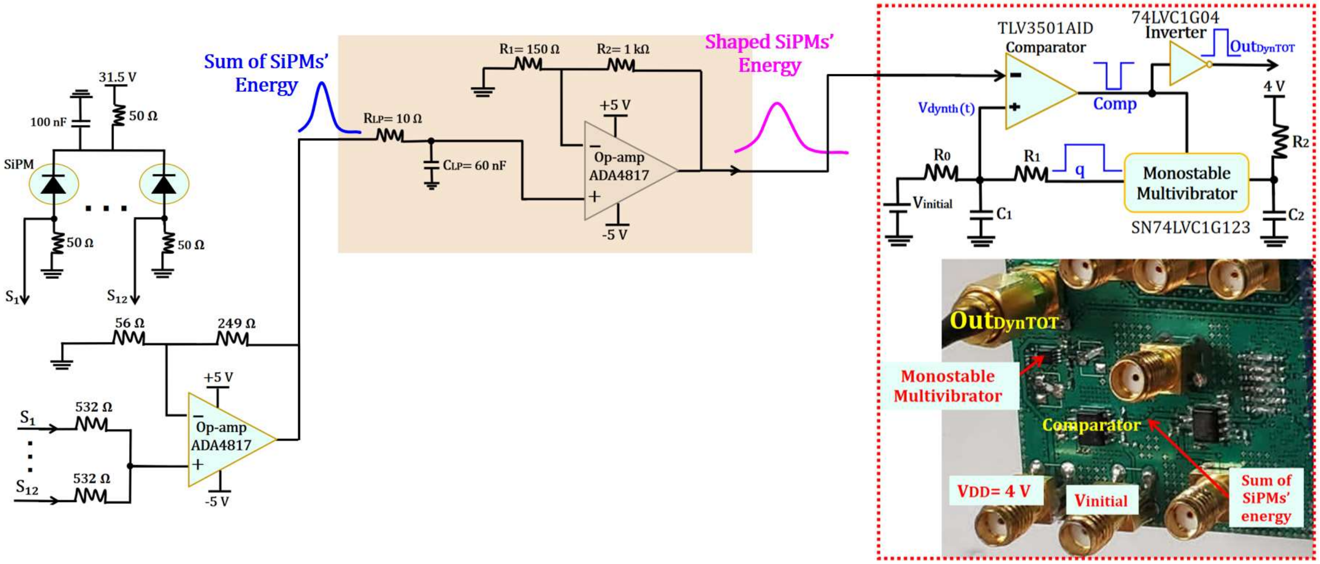


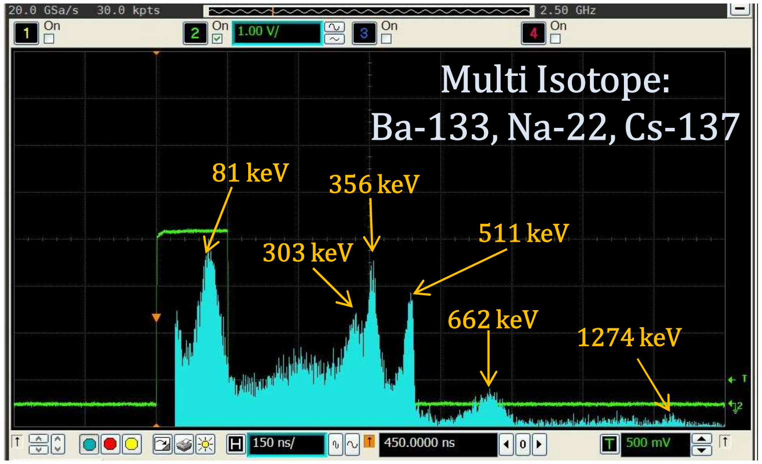


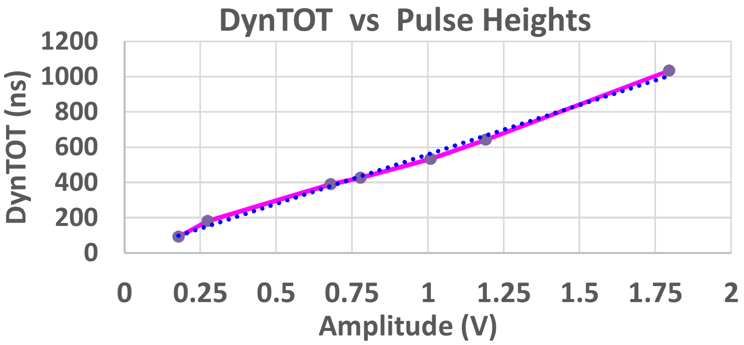


Novel power efficient electronic readout with 24:1 multiplexing timing channels (24 SiPMs' fast signals or 8:1 LVDS) per detector unit

Custom Dynamic TOT (DynTOT) Circuit of 100 ps CTRTOF-PET

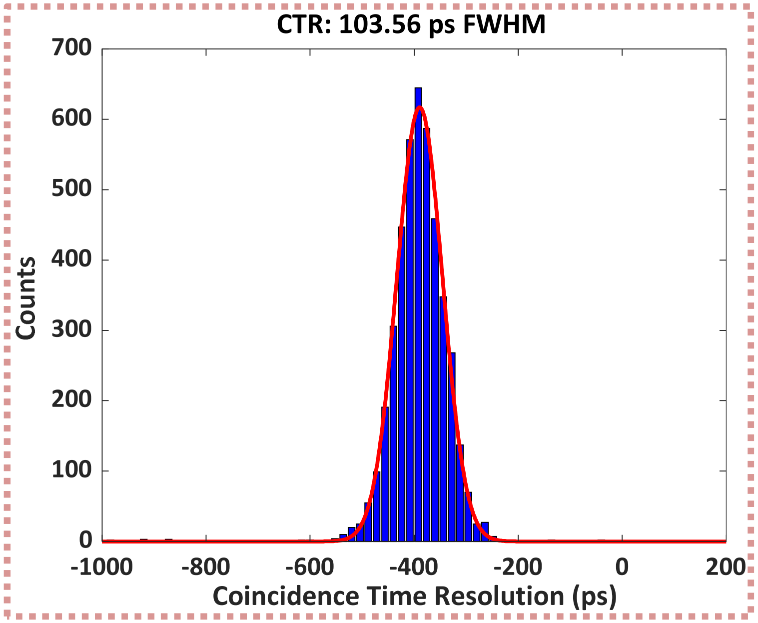






- Detectable gamma ray peaks from < 81 keV to >1274 keV
- Can recover 511 keV photons undergoing Compton scatter at angles as small as ~44° ☺
    - Boosting sensitivity and increasing the quality of reconstructed image

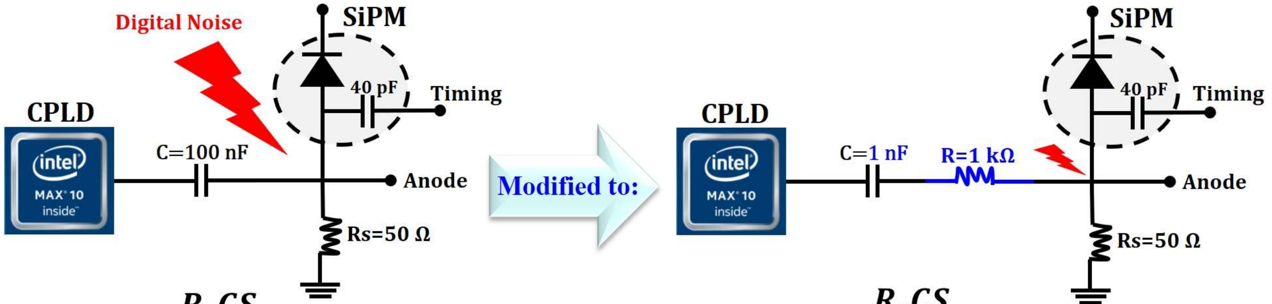
Detector Unit CTR Results using LGSO Crystal Array



❑ **This is the first demonstration of 100 ps FWHM coincidence resolving time between TOF-PET detectors having 24:1 timing multiplexing ratio and fully implemented digital architecture, including channel-dense FPGA-based TDCs.**

- Combined 8-timing channel (24 SiPMs' fast output)
- Despite challenges of multiplexing, average FWHM CTR of 107±3.6 ps achieved over multiple measurements ☺

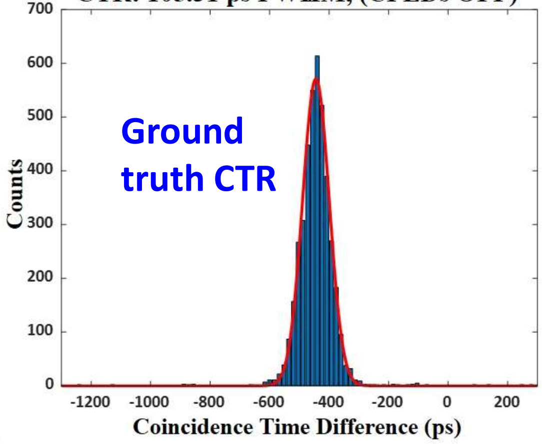
Filtering Strategy for Preventing Digital Noise of CPLDs



$$V_{Anode} = \frac{R_s C S}{1 + R_s C S} V_{CPLD}$$

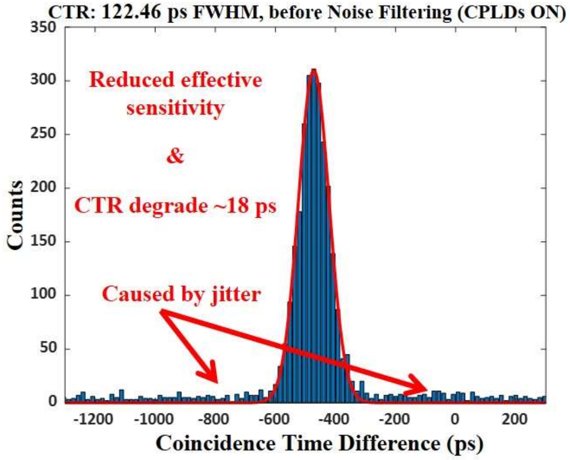
$$V_{Anode} = \frac{R_s C S}{1 + (R + R_s) C S} V_{CPLD}$$

CTR: 105.31 ps FWHM, (CPLDs OFF)



Ground truth CTR

CTR: 122.46 ps FWHM, before Noise Filtering (CPLDs ON)



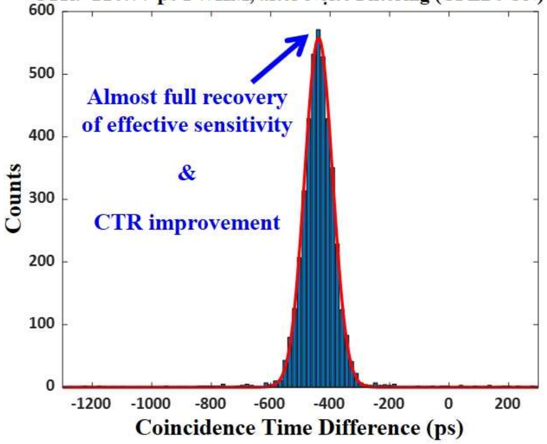
Reduced effective sensitivity

&

CTR degrade ~18 ps

Caused by jitter

CTR: 110.77 ps FWHM, after Noise Filtering (CPLDs ON)



Almost full recovery of effective sensitivity

&

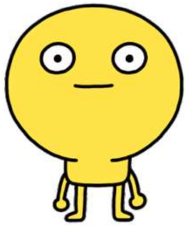
CTR improvement

Required Elements & Power Dissipation of Final Design (16-Module)

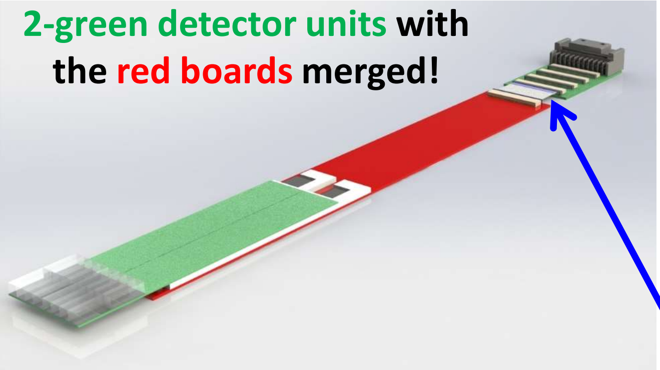
Elements	Detector Unit	Detector Module	Prototype Partial-Ring: 16 Module	Power Dissipation per Detector Unit (mW)
2x4 array of 3x3x10 mm^3 Crystals	1	64	1024	-
SiPMs	24	1536	24576	negligible
Comparator ICs	8	512	8192	360
RF Amps.	8	512	8192	140
Op-amps	2	128	2048	2x190
DynTOT (digital ICs)	1	64	1024	11
CPLD	1	64	1024	450

Total≈ 1215 mW

- Power consumption for final prototype partial-ring (16 modules) ~ 1.215 x 64 x 16≈ 1.6 kW
- Demanding a high efficiency cooling system

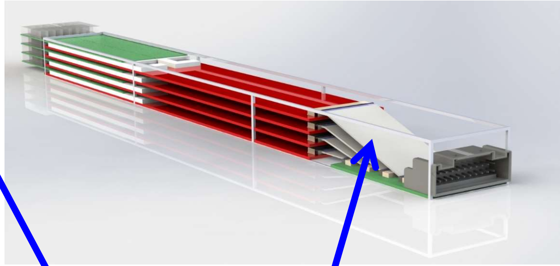


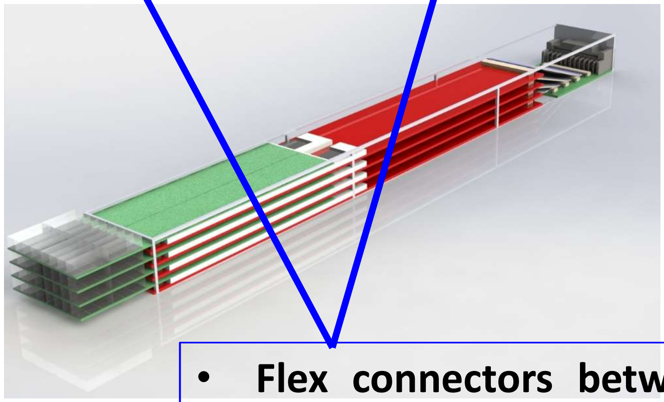
Next Steps


2-green detector units with the red boards merged!

- Merging every two red boards (More mechanical strength, saving pins needed)
- Embedding Ceramic/AlN (Aluminium Nitride) for cooling system

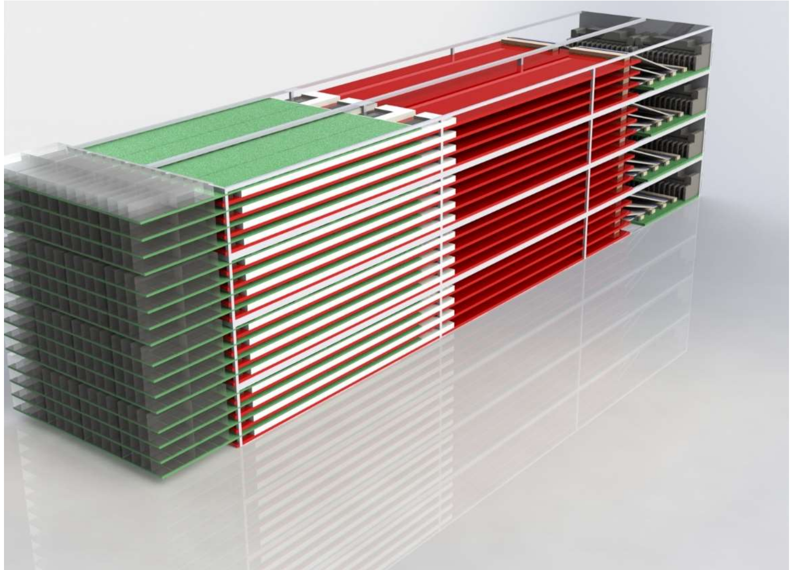
Sub-Module Unit:
8-green detector unit &
4 merged red boards





- Flex connectors between detector units and back-end electronics

Detector Module:
(8 sub-module units, 64-green detector units)



Thank You!

and

Mentors:
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