Future Prospects of Time-of-Flight PET: Scintillator, Detector and Depth-of- interaction (DOI) Technologies

Suleman Surti

Physics & Instrumentation Group
Department of Radiology
University of Pennsylvania

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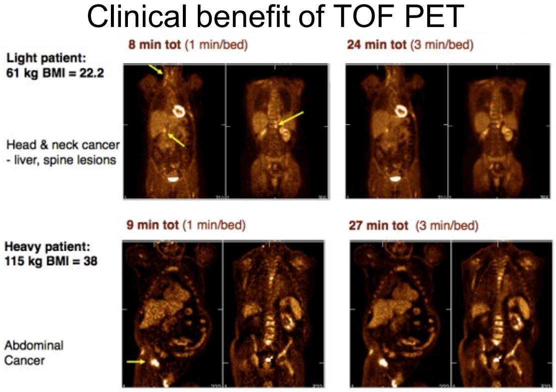
TOF scanners

- First generation developed in the 1980s
  - WashU, CEA-LETI, MD Anderson
- Primary application in brain and cardiac applications
  - High count rate capability and reduced randoms
- System TOF resolution of 450-750ps
  - Low sensitivity, limited energy and spatial resolution
- Second generation developed in mid-2000s
- System TOF resolution of 400-600ps
  - Fully-3D with high sensitivity and good energy and spatial resolution
- New (Third) generation developed in last 3-4 years
- System TOF resolution of 300-400ps

Clinical benefit of TOF PET



Factors determining TOF PET performance

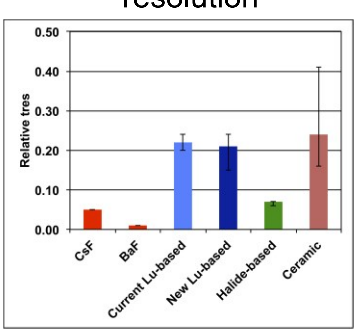
<u>Signal detection capability</u>
- Scintillator characteristics
- Photo-sensor performance
- Detector design
- Stable electronics and data calibrations

<u>Image generation</u>
- Improved data correction and image reconstruction

TOF Scintillators

- Need fast decay time and high light output $t_{res} \propto \frac{\tau}{\sqrt{LO}}$
- High stopping power is also desirable
- Group into five clusters:
  - Old TOF scintillators from 1980s: CsF, BaF_2
  - Current Lu-based, Ce doped scintillators: LSO, LYSO, LFS
  - New Lu-based scintillators: LGSO, LSO/LYSO (Ca and/or Mg co-doped)
  - Halide-based scintillators: $LaBr_3$(Ce), $CeBr_3$
  - Cerium doped, rare earth garnets: GAGG, GGAGG, GluGAG

TOF Scintillators – Relative timing resolution



TOF Scintillators – Halides

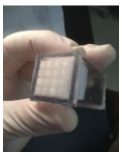
Research LaPET scanner:
~ 375ps timing resol.

$LaBr_3$(Ce:5%)
4x4x30mm³ pixels

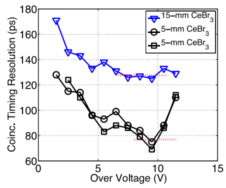
18 PMTs/detector:
51-mm PMT

Daube-Witherspoon *et al PMB 2008*

Prototype $CeBr_3$ array



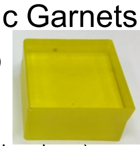
$CeBr_3$ has faster rise time
-> improve timing resol.



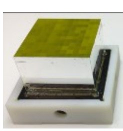
Schmall *et al MIC 2016*

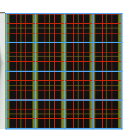
TOF Scintillators – Ceramic Garnets

GLUGAG:Ce ($(Gd_xLu_{1-x})_3(Ga_yAl_{1-y})_5O_{12}$:Ce)



- Novel rare earth garnet ceramic scintillator
- Fabricated using ceramic processing
  - Low processing cost
  - Direct molded into specific shapes (annulus, dome)
- High light yield (~54,000 ph/MeV)
- High stopping power and density 7.1 g/cm³
- Coincidence timing resolution (FWHM) of 3 x 3 x 20 mm³ GLuGAG coupled to RGB-HD SiPM: ~392 ps



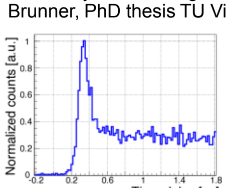


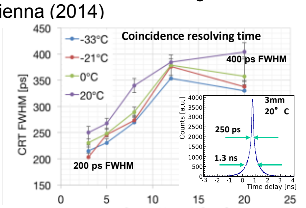
- 2.59 x 2.59 x 20mm³ pixel array coupled to PDPC SiPM
- Initial results show good crystal separation and energy resolution (10%)

Presented by Kwon *et al MIC 2016*

TOF Scintillators – BGO

- TOF not possible since the scintillation mechanism is too slow
- High refractive index (2.15) and excellent optical transparency down to 320 nm enable production and detection of Cerenkov photons due to passage of energetic electrons produced due to interaction of annihilation photons
- Possibility of achieving TOF info with BGO investigated in S. E. Brunner, PhD thesis TU Vienna (2014)

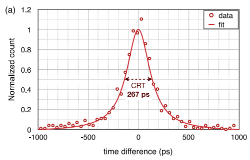




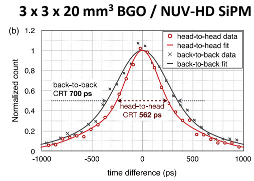
Presented by Brunner *et al MIC 2016*

TOF Scintillators – BGO

2 x 3 x 2 mm^3 BGO / NUV-HD SiPM

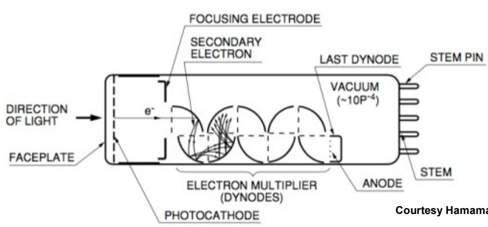


3 x 3 x 20 mm^3 BGO / NUV-HD SiPM



Presented by Kwon *et al MIC 2016*

Photo-sensor – PMT

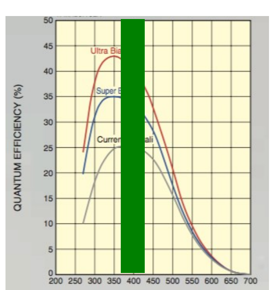


Courtesy Hamamatsu

- Timing performance determined by:
  - Quantum efficiency (QE)
  - PMT timing response

Photo-sensor – PMT

- Technological developments enabling fast timing performance
  - Plano-concave entrance window (transit time range of 0.7-3ns,TTS < 1 ns)
  - Higher QE bialkali photo-cathodes



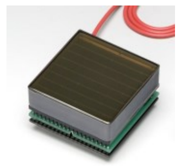
Courtesy Hamamatsu

Photo-sensor – PMT

- Other technological developments enabling improved performance
  - Fast PMTs as small as ~10 mm in diameter
  - Fast, flat-panel multi-anode PMTs (e.g. 8x8 channels per 5x5cm^2 area) potentially allowing ~ 1-1 coupling to scintillator

R1635

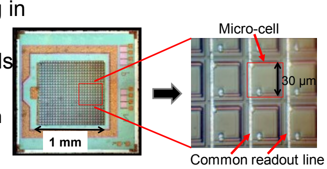
H8500



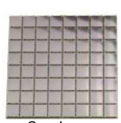
Courtesy Hamamatsu

Photo-sensor – Si-PMs

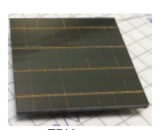
- Small APDs operating in Geiger mode with hundreds of micro cells per square mm:
  - Small, compact design
  - Available in arrays
  - Very high QE
  - Good, timing characteristics
  - High gain, thus no need for special electronics
  - Potential for favorable encoding (e.g. 1-to-1)
  - Can operate in MR



Lab. SiPM, Dept. of Experimental and Theoretical Physics, Moscow Engineering Physics Institute



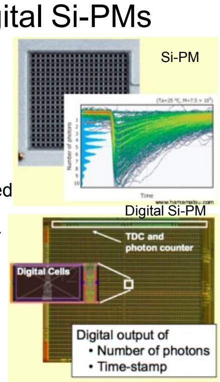
SensL



FBK

Photo-sensor – Digital Si-PMs

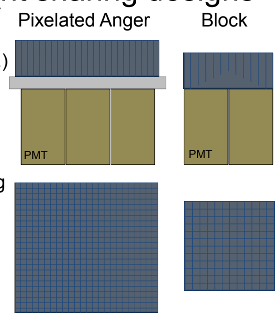
- Signals from each micro-cell firing are summed into an analog signal – proportional to number of cells firing and hence number of photons
- Electronics (TDC, ADC) are embedded on the substrate through which each micro-cell state is recorded as fired or not – output is a digital energy (# of micro-cells fired) and time value
- Does not require much electronics (ASIC) for processing
- Provides tremendous flexibility in optimizing performance



Philips Digital Photon Counting (PDPC)

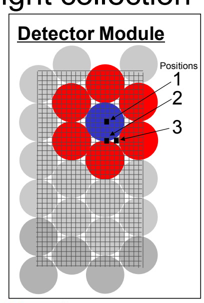
PET Detector – Light sharing designs

- In the 1980s, low light output of the scintillator led to 1-1 coupling to a PMT (~28mm dia.)
- Currently, ~ 4x4x20mm³ Lu-based scintillator pixels are coupled in a light sharing detector
- ~100:1 crystal to PMT encoding ratio
- Weighted centroid (Anger) positioning to discriminate crystals
- 25-51 mm diameter PMTs
- System timing resolution 400-600ps



PET Detector – Effect of light collection efficiency

- In the light sharing detector (~100:1 encoding ratio)
  - Loss of collected light
  - Variation in collected light as a function of crystal position
  - Variation in individual PMT performance

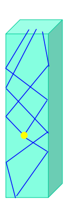


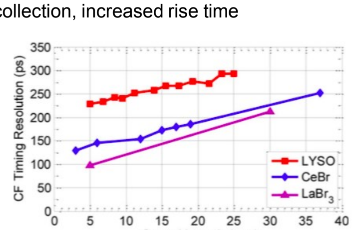
Position	1 PMT (Blue)		7 PMTs (Blue + Red)	
	Time Resolution FWHM	Light Collected	Time Resolution FWHM	Light Collected
1	350 ps	73%	295 ps	100%
2	465 ps	37%	326 ps	80%
3	-		338 ps	75%

Kuhn *et al TNS 2006*

PET Detector – Effect of light reflections in long, narrow crystals

- Multiple reflections of scintillation photons in long, narrow crystals
  - Lower light collection, increased rise time

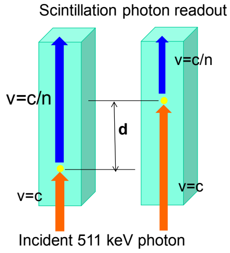


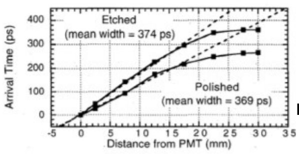


Wiener *et al TNS 2013*

PET Detector – Effect of DOI on signal arrival time

- Difference in speed of annihilation and optical photons leads to variation in signal arrival time as a function of DOI



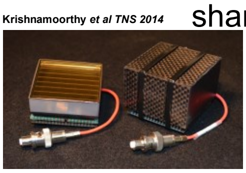


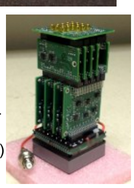
Difference in signal time=(n-1)*d/c

Moses *et al TNS 1999*

New PET detectors – Reduced light sharing

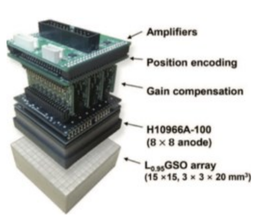
Krishnamoorthy *et al TNS 2014*





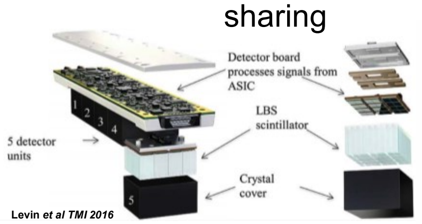
- Encoding ratio: 16:1
- 32x32 array of 1.5x1.5x15-mm^3 LYSO crystals (1024 crystals)
- H11951/H8500 multi-anode PMT (64 anodes, Hamamatsu)
- 350ps timing resolution, 12.7% energy resolution

Son *et al TNS 2016*



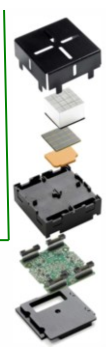
- Encoding ratio: < 4:1
- 340ps timing resolution, 11.7% energy resolution

New PET detectors – Reduced light sharing



Levin *et al TMI 2016*

- Encoding ratio: 2:1
- MPPC array readout
- 4x5.3x25mm^3 LBS crystal array
- 370ps CTR, 10.5% energy resolution

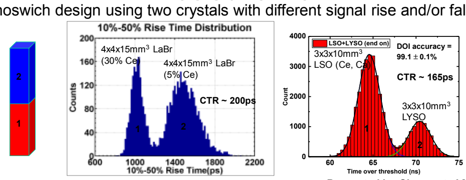


- Encoding ratio: 1:1
- 12x12 PDPC) array
- 4x4x22mm^3 LYSO crystal array
- 277ps timing resolution, 11.4% energy resolution

Degenhardt *et al MIC 2010*

New PET detectors – DOI measurement

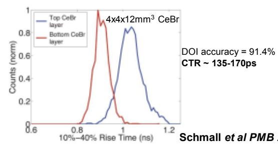
- Phoswich design using two crystals with different signal rise and/or fall times



Wiener *et al TNS 2013*

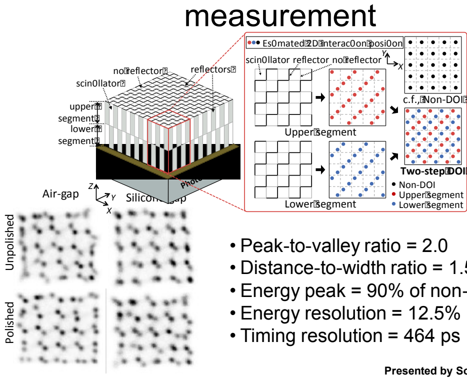
Presented by Chang *et al MIC 2016*

- Phoswich design using same crystal with change in signal rise and/or fall times due to coupling medium



Schmall *et al PMB 2015*

New PET detectors – DOI measurement

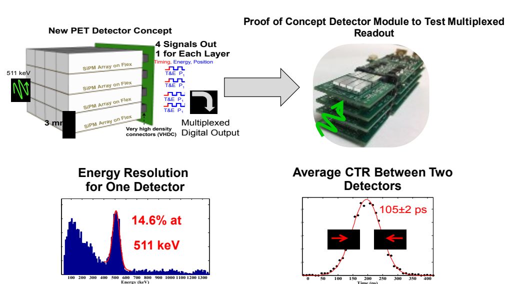


- Peak-to-valley ratio = 2.0
- Distance-to-width ratio = 1.5
- Energy peak = 90% of non-DOI det.
- Energy resolution = 12.5%
- Timing resolution = 464 ps

Presented by Son *et al MIC 2016*

New PET detectors – Side readout

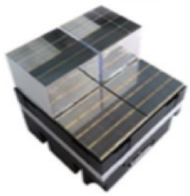
- Side readout of long scintillation crystals - complete light collection, minimal effect of reflections, DOI measurement



Presented by Cates *et al MIC 2016*

New PET detectors – Monolithic design

- 32x32x22-mm^3 monolithic LYSO crystal + PDPC SiPM array (cooled to -28° C)
- Statistical Nearest-Neighbor (NN) logic used for positioning
- Single-side readout: ~1.7 mm spatial resolution, 214ps CTR, 10.7% energy resolution, DOI resolution ~ 3.7 mm
  Borghi *et al PMB 2016*
- Dual-side readout ~1.1mm spatial resolution, 147ps CTR, 10.2% energy resolution, DOI resolution ~ 2.4mm
  Borghi *et al PMB 2016*



PMT based TOF PET/CT systems

Philips Ingenuity TF
TRes: 495 ps

Siemens mCT
TRes: 525 ps

GE Discovery 690
TRes: 545ps

Toshiba Celesteion
TRes: 450 ps

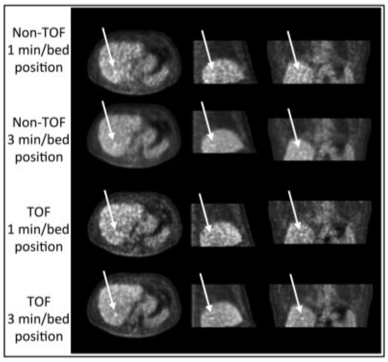
United Imaging Healthcare uMI 510
TRes: 475 ps

SiPM based TOF PET/CT systems

GE MI PET/CT
25mm thick Lu-based scintillator
~2-1 coupling with SiPM
TRes: 390-400ps

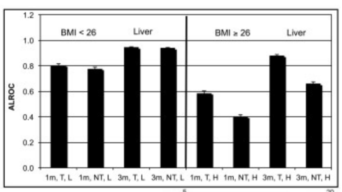
Philips Vereos PET/CT
20mm thick LYSO
1-1 coupling with digital SiPM
TRes: 310ps

Clinical benefits of TOF imaging



Surti *et al JNM 2011*

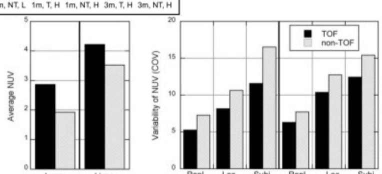
Clinical benefits of TOF imaging



Improved lesion detection

Surti *et al JNM 2011*

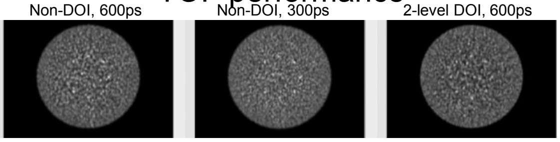
Improved lesion quantitation



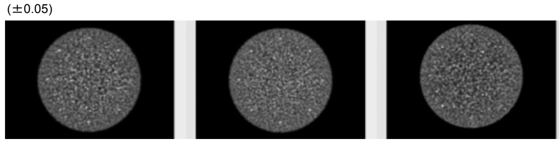
Daube-Witherspoon *et al JNM 2014*

Imaging benefits of DOI and improved TOF performance

Non-DOI, 600ps | Non-DOI, 300ps | 2-level DOI, 600ps



ALROC: 0.51 (±0.05) | 0.69 | 0.48

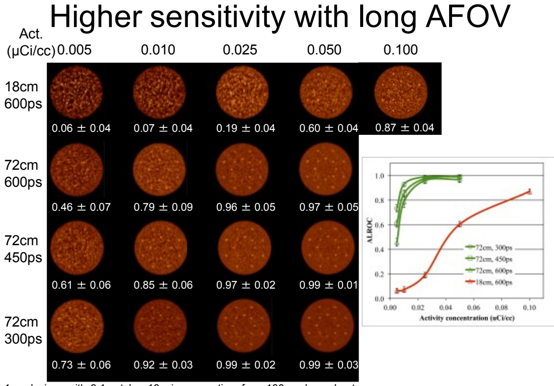


ALROC: 0.43 (±0.06) | 0.57 | 0.54

4x4x20mm^3 LYSO, 3 mins. scan time, 0.5 cm diam. 6:1 uptake lesions

Surti *et al TNS 2013*

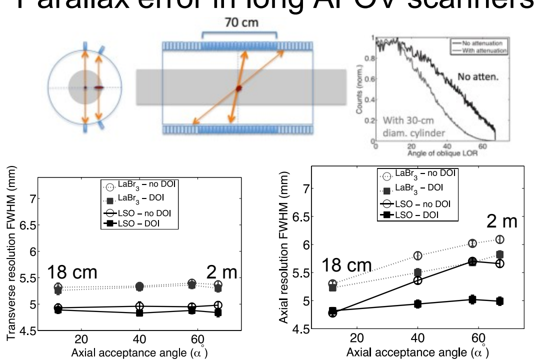
Higher sensitivity with long AFOV



1 cm lesions with 3:1 uptake, 10 mins. scan time for a 100 cm long phantom

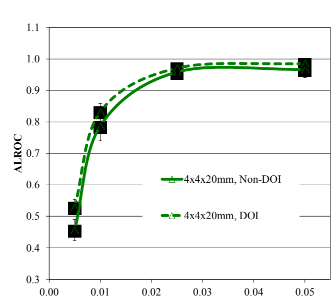
Surti *et al PMB 2015*

Parallax error in long AFOV scanners



Schmall *et al PMB 2016*

Parallax error in long AFOV scanners



1 cm lesions with 3:1 uptake, 10 mins. scan time for a 100 cm long phantom, 72 cm AFOV **Surti *et al PMB 2015***

UCDavis Explorer

The detector modules are based on 2.76 x 2.76 x 18.1 mm LYSO crystals read out by SiPMs.

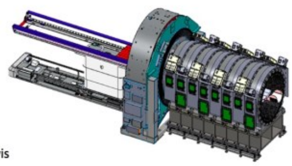
Energy resolution of ~12.5% and timing resolution of ~400 ps.

Scanner with a diameter of 78.6 cm (bore 70 cm) and an axial length of 195 cm.

Total of 564,480 crystals and 53,760 SiPMs

A 64-slice CT scanner will be mounted on the front of the system

Delivery to UC Davis expected by end of 2018

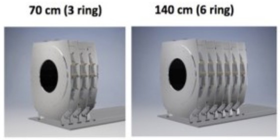


Images courtesy of S. Cherry, UC Davis

PennPET XL

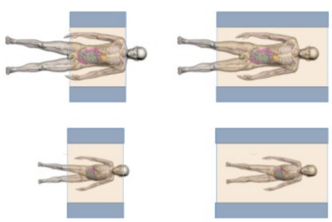
- Scalable

70 cm (3 ring) | 140 cm (6 ring)



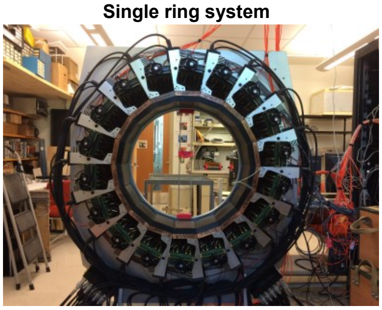
70" tall male

45" tall child



PennPET XL

Single ring system



- Uses Philips Vereos detectors – $4x4x20mm^3$ LYSO+PDPC array
- Expected CTR: ≤ 300ps

Studies enabled with long AFOV

- Clinical studies
  - Reduced dose or imaging time
  - Pediatric studies
- Whole-body dynamic imaging
  - Improved response assessment of cancer
- Bio-distribution studies
  - Dosimetry of novel radiopharmaceuticals
- Imaging long-lived isotopes with low positron yield
- Is all the high-end technology needed for benefits for long AFOV imaging?

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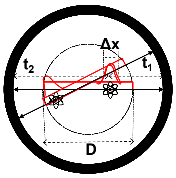
Funding - NIH, Philips Healthcare

Time-of-Flight PET



- Event localized along LOR based upon arrival time difference, $(t_1 - t_2)$
- Localization error, Δx, determined by coincidence timing resolution, Δt,

  $\Delta x = c \cdot \Delta t/2$
- In conventional imaging,

  $\Delta x > D$
- Signals from different voxels coupled, $SNR \neq N / (N)^{1/2}$
- In TOF imaging,

  $\Delta x < D$
- Reduced coupling, improved SNR

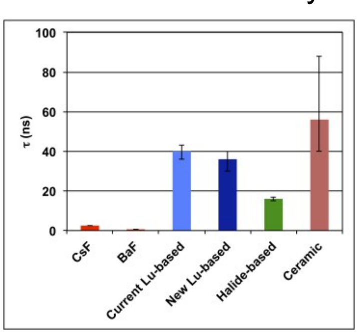
Early TOF scanners

- First generation developed in the 1980s
  - WashU, CEA-LETI, MD Anderson
- Primary application in brain and cardiac applications
  - High count rate capability and reduced randoms

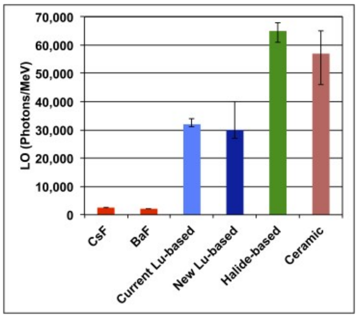
	TOF		Non-TOF	
	CsF	BaF_2	BGO	NaI(Tl)
τ (ns)	2.5	0.6/620	300	230
μ (cm^{-1})	0.42	0.44	0.95	0.35
Photons/MeV	2,500	2,100/6,700	7,000	41,000

- System TOF resolution of 450-750ps
- Low sensitivity relative to BGO system
- Low light output limited energy and spatial resolution

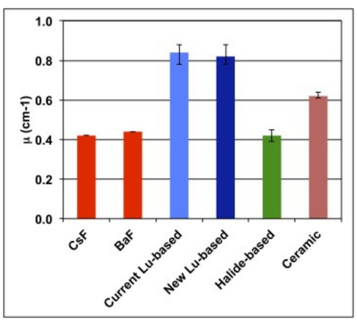
TOF Scintillators – Decay time



TOF Scintillators – Light Output



TOF Scintillators – Stopping power



Data acquisition and electronics

- Fast timing pickoff techniques typically utilize CFDs that require delay lines – implementation of several hundred of these CFDs using analog delay cables is impractical
- Implementation of non-delay CFDs together with high precision TDC in dedicated ASICs has made this task much easier
- Development of FPGAs to handle online data processing
- In the future
  - digital waveform sampling
  - Digital SiPM with integrated electronics