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

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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

Light patient:
61 kg BMI = 22.2

Head & neck cancer
- liver, spine lesions

Heavy patient:
115 kg BMI = 38

Abdominal Cancer
Factors determining TOF PET performance

Signal detection capability
• Scintillator characteristics
• Photo-sensor performance
• Detector design
• Stable electronics and data calibrations

Image generation
• Improved data correction and image reconstruction

TOF Scintillators
• Need fast decay time and high light output $t_{\text{nr}} \propto \frac{r}{\sqrt{LO}}$
• 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.

LaBr₃(Ce:5%) 4x6x30mm³ 18 PMTs/detector: 51-mm PMT

CeBr₃ has faster rise time -> improve timing resol.

Prototype CeBr₃ array

Daube-Williams et al PAM 2008

TOF Scintillators – Ceramic Garnets

GLUGAG:Ce ([(GdₓLu₁₋ₓ)ₓ(Ga₁₋ₓAlₓ)₅O₁₂]: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)
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

- 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 0.7-3 ns, TTS < 1 ns)
  - Higher QE bialkali photocathodes
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 5x5cm² area) potentially allowing ~1-1 coupling to scintillator

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

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
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, ~4x4x20mm\(^3\) 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

<table>
<thead>
<tr>
<th>Position</th>
<th>1 PMT (Other)</th>
<th>7 PMTs (Filler + End)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time Resolution</td>
<td>Light Collected</td>
</tr>
<tr>
<td>1</td>
<td>250 ps</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>455 ps</td>
<td>37%</td>
</tr>
<tr>
<td>3</td>
<td>310 ps</td>
<td>74%</td>
</tr>
</tbody>
</table>

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
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

\[
\text{Difference in signal time} = (n-1) \frac{d}{c}
\]

Incident 511 keV photon
Scintillation photon readout

New PET detectors – Reduced light sharing

• Encoding ratio: 16:1
• 32x32 array of 1.5x1.5x15-mm³ LYSO crystals (1024 crystals)
• H11951/H8500 multi-anode PMT (64 anodes, Hamamatsu)
• 350ps timing resolution, 12.7% energy resolution

Levin et al TMI 2016

New PET detectors – Reduced light sharing

• Encoding ratio: 2:1
• MPPC array readout
• 4x5.3x25mm³ LBS crystal array
• 370ps CTR, 10.5% energy resolution

Degenhardt et al MIC 2010

Moses et al TNS 1999

Krishnamoorthy et al TNS 2014

Son et al TNS 2016
New PET detectors – DOI measurement

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

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

New PET detectors – Side readout

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

New PET Detector Concept

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

Presented by Chang et al. MIC 2016

- Energy resolution = 12.5%
- DOI accuracy = 91.4%
- CTR ~ 135 ps

New PET Detector Concept

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

Presented by Son et al. MIC 2016

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New PET Detector Concept

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Presented by Cates et al. MIC 2016

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- DOI accuracy = 91.4%
- CTR ~ 135 ps

Presented by Chang et al. MIC 2016

- Energy resolution = 12.5%
- DOI accuracy = 91.4%
- CTR ~ 135 ps
New PET detectors – Monolithic design

• 32x32x22-mm³ 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: ~1.1 mm 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

Improved lesion detection

Improved lesion quantitation

Imaging benefits of DOI and improved TOF performance

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

ALROC: 0.51
(±0.05)

ALROC: 0.43
(±0.06)

4x4x20mm³ LYSO, 3 mins. scan time, 0.5 cm diam. 6:1 uptake lesions

Surti et al. JNM 2011
Daube-Witherspoon et al. JNM 2014
Surti et al. TNS 2013
Higher sensitivity with long AFOV

<table>
<thead>
<tr>
<th>Act. (μCi/cc)</th>
<th>0.005</th>
<th>0.010</th>
<th>0.025</th>
<th>0.050</th>
<th>0.100</th>
</tr>
</thead>
<tbody>
<tr>
<td>18cm 600ps</td>
<td>0.08 ± 0.04</td>
<td>0.07 ± 0.04</td>
<td>0.19 ± 0.04</td>
<td>0.85 ± 0.04</td>
<td>0.87 ± 0.04</td>
</tr>
<tr>
<td>72cm 600ps</td>
<td>0.46 ± 0.07</td>
<td>0.79 ± 0.09</td>
<td>0.96 ± 0.05</td>
<td>0.97 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>72cm 450ps</td>
<td>0.61 ± 0.06</td>
<td>0.86 ± 0.08</td>
<td>0.97 ± 0.02</td>
<td>0.99 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>72cm 300ps</td>
<td>0.73 ± 0.06</td>
<td>0.92 ± 0.03</td>
<td>0.99 ± 0.02</td>
<td>0.99 ± 0.03</td>
<td></td>
</tr>
</tbody>
</table>

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

Parallax error in long AFOV scanners

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
**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 364,480 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.

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**PennPET XL**

- **Scalable**
- 70 cm (3 ring)
- 140 cm (6 ring)

- 70" tall male
- 45" tall child

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**PennPET XL**

- Single ring system

- Uses Philips Versus detectors – 4x4x20 mm³ LYSO+PDPC array

- Expected CTR: ≤ 900ps
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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Time-of-Flight PET

- Event localized along LOR based upon arrival time difference, \( t_1 - t_2 \)
- Localization error, \( \Delta x \), determined by coincidence timing resolution, \( \Delta t \)
  \[ \Delta x = c \Delta t / 2 \]
- In conventional imaging, \( \Delta x > D \)
- Signals from different voxels coupled, SNR ≠ \( N / (N)^{1/2} \)
- 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

<table>
<thead>
<tr>
<th>TOF</th>
<th>CsF</th>
<th>BaF₂</th>
<th>BGO</th>
<th>NaI(Tl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \tau ) (ns)</td>
<td>2.5</td>
<td>0.6620</td>
<td>300</td>
<td>230</td>
</tr>
<tr>
<td>( \mu ) (cm⁻¹)</td>
<td>0.42</td>
<td>0.44</td>
<td>0.95</td>
<td>0.35</td>
</tr>
<tr>
<td>Photons/MeV</td>
<td>2,500</td>
<td>2,100/6,700</td>
<td>7,000</td>
<td>41,000</td>
</tr>
</tbody>
</table>

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

TOF Scintillators – Decay time
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