Detecting Compton Scatters in Liquid Media for Low-Dose High-Resolution TOF-PET

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Dr. Bernhard Adams
Prof. Juan Collar
Fermilab test beam
UChicago Med small animal irradiator

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Cameron Poe

Special thanks:
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Electronics and detectors for high-energy physics
TOF-PET detection
Computational medical imaging + image reconstruction

Single-molecule spectroscopy + superres. Imaging
TOF-PET detection
Computational medical imaging + image reconstruction

Electronics and detectors for high-energy physics
TOF-PET detection
Computational medical imaging + image reconstruction
PROBLEM: What are detector-imposed vs. fundamental limitations of TOF-PET?

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Resolution (FWHM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial</td>
<td>1-2%</td>
<td>4-5mm</td>
</tr>
<tr>
<td>Full-body</td>
<td>10-17%</td>
<td>3-4mm</td>
</tr>
<tr>
<td><strong>Ideal</strong></td>
<td><strong>100%</strong></td>
<td><strong>&lt; 1mm</strong></td>
</tr>
</tbody>
</table>

Higher sensitivity would...
- Reduce radioactive dose to patient
- Decrease imaging time
- Enhance contrast-to-noise
- Expand geographical access

Better resolution would...
- Reveal smaller lesions
- Improve anatomical registration
- Enable new applications
PROPOSAL: Determine lines-of-response via Compton scattering in low-Z media

Requirements:
• Determine location, energy of recoil e⁻
• Deduce line of response @ first scatter

Complications:
• Less energy deposited by e⁻ at track start
• Multiple Compton scatters in a chain
• Electron trails must be erasable
SIMULATION: Full TOPAS / GEANT4 Monte Carlo simulation of TOF-PET

**Simulation:**
- GEANT4 + customized TOPAS to generate ground truth
- Apply parameterized uncertainty to ground truth
- Determine LORs via max. likelihood of scatter ordering
- Direct image reconstruction from LORs
- NEMA NU-2 2018 protocols for resolution, sensitivity

**Tunable parameters:**
- Spatial resolution (1 mm)
- Energy resolution (1 keV/switch)
- Temporal resolution for TOF (500 ps)

**Results:**
1. Validation
2. Compare to LYSO state-of-the-art
3. Understanding possible pitfalls
4. Determine influence of tunable parameters to set minimum specs for experimental implementation
SIMULATION: Validation of simulated data

Linear attenuation: 12.05 cm (first scatter)

Energy of recoil electron by scattering event order (Klein-Nishina)

Scattering angle – energy distribution for first scatter (K-N)

SIMULATION: Sensitivity and resolution of Compton scattering vs. scintillation

LYSO

Contrast 5x enhanced

Sensitivity: 15%

LAB

Sensitivity: 70%

(61.4% correct LOR, 8.8% incorrect)

FWHM

~5mm

SIMULATION: Not all misidentified Compton scattering chains degrade resolution

Misidentifications are bimodal
Small initial scatter or close scatters can result in a “near miss” LOR

SIMULATION: How do spatial and energy resolution influence detector performance?

Energy Resolution: 1, 10, 100 keV/switch
Mostly affects sensitivity

Spatial Resolution: 0.1, 0.3, 1, 3 mm
Mostly affects resolution

SIMULATION: XCAT brain phantom with lesion, down to 1/10,000 dose

EXPERIMENT: Energy deposited in solvent leaves a temporary “trail”

Compton scattering

Low-Z detection media
e.g.: linear alkylbenzene

Photoswitchable fluorophore
e.g.: diarylethene BTFO

High energy electron transfers energy to solvent along its path

Solvent transfers energy to activate detector molecule

Typically, BTFO is switched to the ‘on’ state by direct absorption of UV light.

It can be switched ‘off’ with green light

1,2-Bis(2-methyl-6-phenyl-1-benzothiophen-1,1-dioxide-3-yl) perfluorocyclopentene (BTFO)

EXPERIMENT: BTFO is switched “ON” by recoil electrons from ~500 keV irradiation

**Dose estimation:**

Monte Carlo N-Particle (MCNP) simulation

**(Rough) Efficiency Bounding:**

\[ \Delta C = +10^{-8} \text{ Molar per day} \]

→ so \( \sim 10^{12} \) or \( 10^{13} \) molecules per day in \( \sim 1 \text{ ml} \)

1 mCi = \( 3 \times 10^{12} \) gamma photons (total) per day

**MCNP Compton estimate:**

\( \sim 23 \) kHz, or \( 2 \times 10^9 \) per day interact with the sample

**Need:** >100 switching events per gamma photon

**Get:** \( 10^3 \)-\( 10^4 \) switched molecules per Compton scatter (\(< 1 \text{ keV/switch}\))

**Exposure:**

Antimony-124 source

1.04 mCi

2 weeks (every 2 days)
SUMMARY: Compton scattering in low-Z media shows promise for TOF-PET detection

Next steps and future possibilities:
- Implement experimentally
- Incorporate Compton scattering geometry and timing information in ordering likelihood
- Modify for other applications

Conclusions:
- Simulations show high sensitivity (70%) and resolution (2mm) for TOF-PET
- Reasonable baseline specs: 1 keV/switch, 0.5mm resolution
- BTFO (diarylethene) could be used as a reversible fluorescent marker
The Squires Group at the University of Chicago

Collaborators

Prof. Henry Frisch (Physics)  Dr. Asif Ali (MCGB)
Prof. Patrick La Riviere (Med)  Prof. Andy Ferguson (PME)
Prof. Juan Collar (Physics)  Prof. Aaron Esser-Kahn (PME)
Prof Allan Drummond (BMB)  Dr. Justin Jureller (MRSEC)
Prof. David Pincus (MCGB)  Prof. Cheryl Kerfeld (MSU/LBNL)

Postdoc and Ph.D. positions available!
E-mail asquires@uchicago.edu
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PROBLEM: PET Scan Resolution is Limited by Detector Size and Precision

Few ~mm resolution at best

SIMULATION: Expected energy, scattering direction, and spacing of recoil electrons

First recoil electron characteristics

- Energy
- Direction
- Separation
SIMULATION: Disambiguate multiple scatters to determine original gamma trajectory

Compton Kinematic Chain

Use electron energy AND scattering direction to reconstruct kinematic chain

**Ordering:** ~90% accuracy (brightest 3)
IMAGE RECONSTRUCTION: Use scattering sites to determine LOR for each gamma pair

3D Likelihood Gaussian “Needle” Shaped

Uncertainty along the axis: Tens of centimeters (timing)

Uncertainty transverse to axis: Tens of microns (100x improvement)

Intersections of needles produce high image resolution due to transverse uncertainty improvement

1000x reduced dose simulation

Simulation – ground truth

Back-projection: S/N > 3
EXPERIMENT: Can BTFO be switched by gamma rays ~500 keV (similar to PET)?

Light-tight vials

2mL glass vial holding 0.4mL of solution

Sb-124 source holder

3D Printed Base

3D Printed Snaps to hold vials

Exposure: Antimony-124 source
1.04 mCi
2 weeks (2 day time points)
MEASUREMENTS: Post-exposure confocal fluorescence (compared to control)

Exposure does not (measurably) inactivate or damage BTFO
RESULTS: BTFO can also be switched to the fluorescent state by X-rays

Exposure: 100 kVp, 29 mA
30 min increments
NEXT STEPS: Visualizing trails of Compton-scattered electrons

Future application: Improved PET detection by mapping Compton scatter kinematic chain

Optical recording: Scanned imaging + reset system

Imaging: single BTFO in LAB → photoswitched
Generalizability

Visualize any process that deposits energy spatially in the solvent

E.g. Double-beta decay;
X-rays;
Y-rays;

Excitation
Fluorescence

Energy transfer from solvent
Visible light

bridging bond causes extended fluorescent orbital

Short range energy transfer
Controls

Control A: Stored in foam in the light-proof box with the rest of the samples.
Control B: Wrapped in cinefoil in the light-proof box with the rest of the samples.
Control C: Wrapped in cinefoil and stored in a dark cabinet, untouched for the duration of the experiment.
## ASSUMPTIONS: Switchillator simulations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scintillator Properties</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Scintillation Yield</td>
<td>$Y_{scint}$</td>
<td>$&gt; 2 \times 10^3$</td>
<td># of scintillation photons per MeV</td>
</tr>
<tr>
<td>2 Scintillation Rise Time</td>
<td>$\tau_r$</td>
<td>TBD</td>
<td>1/e rise time of scintillation light</td>
</tr>
<tr>
<td>3 Scintillation Decay Time</td>
<td>$\tau_d$</td>
<td>TBD</td>
<td>1/e decay time of scintillation light</td>
</tr>
<tr>
<td><strong>Switchillator Properties</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Activation Yield</td>
<td>$Y_{act}$</td>
<td>$&gt; 5 \times 10^3$</td>
<td># of ON fluorophores per MeV deposited</td>
</tr>
<tr>
<td>2 Activation Wavelength</td>
<td>$\lambda_{act}$</td>
<td>$&lt; 400$ nm</td>
<td>Peak inactive to active wavelength</td>
</tr>
<tr>
<td>3 Excitation Wavelength</td>
<td>$\lambda_{ex}$</td>
<td>350-650 nm</td>
<td>At max separation</td>
</tr>
<tr>
<td>4 Dye Ratio</td>
<td>$Z_{dye}$</td>
<td>$&lt; 10^{-12}$</td>
<td>Ratio of rates of background activation to fluorescence at $\lambda_{ex}$</td>
</tr>
<tr>
<td>5 On-State Lifetime</td>
<td>$\tau_{ON}$</td>
<td>$3 \times 10^{-7}-10^{-1}$ s</td>
<td>1/e Lifetime of ON fluorophores</td>
</tr>
<tr>
<td>6 Fluorescence brightness</td>
<td>$\varepsilon \cdot \Phi_{fl}$</td>
<td>$&gt; 10^3/(M$ cm)</td>
<td>Rate of emission from active dye</td>
</tr>
<tr>
<td>7 Mean Absorption Length</td>
<td>$\chi(\lambda_{ex})$</td>
<td>$&gt; 6$ m</td>
<td>1/e absorption length at $\lambda_{ex}$</td>
</tr>
<tr>
<td>8 Emission Wavelength</td>
<td>$\lambda_{fl}$</td>
<td>400-700 nm</td>
<td>Wavelength of fluorescence light</td>
</tr>
<tr>
<td>9 # of photons per activated fluorophore</td>
<td>$N_{fl}$</td>
<td>&gt; 500</td>
<td>Mean # of fluorescent photons extracted per fluorophore before deactivation</td>
</tr>
</tbody>
</table>