Nuclear Physics and Medical Imaging

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In Vivo Biomedical Imaging

Anatomic
Physiologic
Metabolic
Molecular
ultrasound
x-ray CT
MRI
PET/SPECT
optical imaging

UCDAVIS
UNIVERSITY OF CALIFORNIA

CMG
Probing Tissue with Radiation

\[ E = h\nu = \frac{hc}{\lambda} \quad \text{and} \quad c = \lambda\nu \]

ELECTROMAGNETIC SPECTRUM

WHAT IS NUCLEAR IMAGING?
NUCLEAR IMAGING

• Imaging the distribution of radioactively tagged substances that are introduced into a living subject

• The radiolabeled agents that are injected are called
  – Radiotracers (or just tracers for short)
  – Radiopharmaceuticals
  – Probes

BRIEF HISTORY
1896: DISCOVERY OF RADIOACTIVITY
HENRI BECQUEREL - NOBEL PRIZE 1903

1923: FIRST USE OF RADIOACTIVE TRACER
GEORG DE HEVESY - NOBEL PRIZE 1943

1923: $^{212}$Pb to study absorption and translocation of lead nitrate in bean plants
1935: $^{32}$P - first use of artificially produced radioisotopes
1942: in vitro labeling of red blood cells
1930’s: DEVELOPMENT OF THE CYCLOTRON
ERNEST O. LAWRENCE - NOBEL PRIZE 1939

1938: DISCOVERY OF $^{99m}$Tc and $^{131}$I
GLENN SEABORG - NOBEL PRIZE 1951
EMILIO SEGRE - NOBEL PRIZE 1959

TECHNETIUM WAS FIRST ARTIFICIALLY MADE ELEMENT
1956: INVENTION OF THE GAMMA CAMERA
HAL ANGER

1975: FIRST PET SCANNER
MICHAEL PHELPS, EDWARD HOFFMAN & MICHAEL TER-POGOSSIAN
MODERN NUCLEAR IMAGING -- SPECT AND PET --

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY
Clinical SPECT and SPECT/CT Scanners

Types of Collimation used in Gamma Cameras

Pinhole Collimation

Parallel-Hole Collimation
In Vivo Imaging as a Translational Tool

Preclinical SPECT and SPECT/CT Scanners

Courtesy of MILabs and Bioscan
Molecular Imaging with SPECT

Myocardial perfusion, $^{99m}$Tc-sestamibi (Bioscan)

Dopamine transporter, $^{123}$I-Ioflupane (MILabs)

Tumor targeting, $^{125}$I-telodendrimer loaded with paclitaxel (Kit Lam, UC Davis)

POSITRON EMISSION TOMOGRAPHY
Clinical PET and PET/CT Scanners

What is PET?

Provides molecular or functional information of a biological system by imaging the distribution of a targeted radiotracer

Applications
- **Oncology**: Detection and staging in cancer
- **Cardiology**: Myocardial viability
- **Neurology**: Psychiatry, differentiating NGD (Alzheimer’s, Parkinson’s, etc.)

Figures from Cherry *et al.*, *Physics in Nuclear Medicine*.
Angular Projections in PET

Reconstruction in PET/SPECT
Scintillation Detector

- **Scintillator**
  - Emits light when radiation strikes it
  - Amount of light released is proportional to amount of energy deposited
  - Amount of light released is small (10^4-10^5 photons per MeV)
  - Optically transparent (to its own emissions)

- **Sensitive Photodetector**
  - Converts light into an electrical signal
    - Photomultiplier Tubes (PMTs)
    - Photodiodes, Avalanche Photodiodes, SiPMs

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<table>
<thead>
<tr>
<th>Property</th>
<th>NaI(Tl)</th>
<th>BGO</th>
<th>LSO(Ce)</th>
<th>GSO(Ce)</th>
<th>CsI(Tl)</th>
<th>LuAP(Ce)</th>
<th>LaBr3(Ce)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density (g/cm³)</td>
<td>3.67</td>
<td>7.13</td>
<td>7.40</td>
<td>6.71</td>
<td>4.51</td>
<td>8.34</td>
<td>5.3</td>
</tr>
<tr>
<td>Effective atomic number</td>
<td>50</td>
<td>73</td>
<td>66</td>
<td>59</td>
<td>54</td>
<td>65</td>
<td>46</td>
</tr>
<tr>
<td>Decay time (nsec)</td>
<td>230</td>
<td>300</td>
<td>40</td>
<td>60</td>
<td>1000</td>
<td>18</td>
<td>35</td>
</tr>
<tr>
<td>Photon yield (per keV)</td>
<td>38</td>
<td>8</td>
<td>20-30</td>
<td>12-15</td>
<td>52</td>
<td>12</td>
<td>61</td>
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<tr>
<td>Index of refraction</td>
<td>1.85</td>
<td>2.15</td>
<td>1.82</td>
<td>1.85</td>
<td>1.80</td>
<td>1.97</td>
<td>1.9</td>
</tr>
<tr>
<td>Hygroscopic</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Slightly</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Peak emission (nm)</td>
<td>415</td>
<td>480</td>
<td>420</td>
<td>430</td>
<td>540</td>
<td>365</td>
<td>358</td>
</tr>
</tbody>
</table>

*Typical values—there are many different plastic scintillators available.
BGO, Bi4Ge3O12; GSO(Ce), Gd2SiO5(Ce); LSO(Ce), Lu2SiO5(Ce); LuAP(Ce), LuAI2O4(Ce)
Detector Technology Used in PET

PET Applications

Images courtesy of GE Medical Systems
Radiotracers/Radiopharmaceuticals

- Usually introduced by i-v injection
- Agent must have access to target
  - Stable in plasma
  - For extravascular targets, passive diffusion or active transport into extracellular space
  - For targets in the brain, cross blood-brain barrier
  - For intracellular targets, must get across cell membrane
- Agent must be modified by interaction with target
  - Binding, trapping, ....
- Unmodified agent must be cleared away
  - Efficient clearance and excretion from body
- Many parallels with drug design, but some important differences as well

COMPACT BIOMEDICAL CYCLOTRON
11 MeV negative ion

Power Supplies and Target Support Unit
Retractable Shields
Water System

$^{18}$F (110 mins)
$^{11}$C (20 mins)
$^{13}$N (9.9 mins)
$^{15}$O (120 s)
Some Examples of Radiopharmaceuticals for PET

- $^{18}$F-FDG ([$^{18}$F]fluoro-2-deoxy-D-glucose)
  - Targets glucose transporters and hexokinase
  - Rate of glucose utilization
- $^{18}$F-FLT (3’-deoxy-3’-[$^{18}$F]fluorothymidine)
  - Targets thymidine kinase 1
  - Proliferation (thymidine uptake and phosphorylation)
- $^{18}$F-FMISO ([$^{18}$F]fluoromisonidazole)
  - Targets hypoxic tissue
- $^{18}$F-FHBG (9-(4-[$^{18}$F]fluoro-3-hydroxymethylbutyl)guanine)
  - HSV-tk transgene expression
- $^{64}$Cu or $^{124}$I-labeled biomolecules
  - Peptides, antibodies, nanoparticles and cells

99Mo–99mTc GENERATOR

- 99Mo bound to alumina column as molybdate ion (MoO$_4$)
- 99mTc activity is not bound to column (chemically different)
- Eluted from column with 5-25 mL saline
- 75-85% of available 99mTc extracted
- Typically used for one week
<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Decay Mode</th>
<th>Principal Photon Emissions</th>
<th>Half-life</th>
<th>Primary Use</th>
</tr>
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<tbody>
<tr>
<td>$^{11}$C</td>
<td>$\beta^-$</td>
<td>511 keV</td>
<td>20.3 min</td>
<td>imaging</td>
</tr>
<tr>
<td>$^{13}$N</td>
<td>$\beta^-$</td>
<td>511 keV</td>
<td>10.0 min</td>
<td>imaging</td>
</tr>
<tr>
<td>$^{15}$O</td>
<td>$\beta^-$</td>
<td>511 keV</td>
<td>2.07 min</td>
<td>imaging</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>$\beta^-$</td>
<td>511 keV</td>
<td>110 min</td>
<td>imaging</td>
</tr>
<tr>
<td>$^{32}$P</td>
<td>$\beta^-$</td>
<td>–</td>
<td>14.3 days</td>
<td>therapy</td>
</tr>
<tr>
<td>$^{67}$Ga</td>
<td>EC</td>
<td>93, 185, 300 keV</td>
<td>3.26 days</td>
<td>imaging</td>
</tr>
<tr>
<td>$^{82}$Rb</td>
<td>$\beta^+$</td>
<td>511 keV</td>
<td>1.25 min</td>
<td>imaging</td>
</tr>
<tr>
<td>$^{89}$Sr</td>
<td>$\beta^-$</td>
<td>–</td>
<td>50.5 days</td>
<td>therapy</td>
</tr>
<tr>
<td>$^{99m}$Tc</td>
<td>IT</td>
<td>140 keV</td>
<td>6.03 hours</td>
<td>imaging</td>
</tr>
<tr>
<td>$^{111}$In</td>
<td>EC</td>
<td>172, 247 keV</td>
<td>2.81 days</td>
<td>imaging</td>
</tr>
<tr>
<td>$^{123}$I</td>
<td>EC</td>
<td>27-30 keV x-rays</td>
<td>60.2 days</td>
<td>in vitro assays</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>EC</td>
<td>159 keV</td>
<td>13.0 hours</td>
<td>imaging</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>$\beta^-$</td>
<td>364 keV</td>
<td>8.06 days</td>
<td>therapy/imaging</td>
</tr>
<tr>
<td>$^{153}$Sm</td>
<td>$\beta^-$</td>
<td>41, 103 keV</td>
<td>46.7 hours</td>
<td>therapy</td>
</tr>
<tr>
<td>$^{186}$Re</td>
<td>$\beta^-$</td>
<td>137 keV</td>
<td>3.8 days</td>
<td>therapy</td>
</tr>
<tr>
<td>$^{201}$Tl</td>
<td>EC</td>
<td>68-80 keV x-rays</td>
<td>3.05 days</td>
<td>imaging</td>
</tr>
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</table>
Aside on speaker's background...
SLAC E154/E155/E155X
(Late 1990's at SLAC)
Polarized inclusive DIS to measure spin structure functions

\[
\begin{align*}
\frac{dN}{dy} &= \frac{F_1(x, Q^2)}{2 \sin^2 \theta} \left( A_1 + \tan(\theta/2) A_2 \right) \\
\frac{dN}{dy} &= \frac{F_1(x, Q^2)}{2 \sin^2 \theta} \left( E + E \cos(\theta) A_3 - \sin(\theta) A_4 \right)
\end{align*}
\]
\[ \bar{n} + p \rightarrow d + \gamma \]

The NPDGamma Experiment (LANSCE at LANL and FNPB at SNS)

Polarized cold neutron capture on LH$_2$ target

ppb up-down asymmetry $\rightarrow$
Parity violation to study the hadronic weak interaction
JLab E02-020

Measure the parity-violating asymmetry in e-p elastic scattering at $Q^2 = 0.03$ GeV$^2$ to 4% relative accuracy

Extract the proton weak charge and thus the weak mixing angle at low momentum transfer

$$Q_{\text{weak}}^p = 1 - 4 \sin^2 \theta_W \sim 0.072$$

PET AND SPECT SYSTEMS ARE NUCLEAR PHYSICS EXPERIMENTS
Photodetectors at UC Davis

Some specific research projects at UC Davis
New detector materials: Thallium Bromide (TlBr)

Gamma ray detectors for PET

- Efficiency & energy resolution

Table 1. Properties of Detector Materials Used for PET

<table>
<thead>
<tr>
<th>Detector type</th>
<th>LSO</th>
<th>LaBr$_3$</th>
<th>BGO</th>
<th>CZT</th>
<th>TlBr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z$_{\text{eff}}$</td>
<td>66</td>
<td>47</td>
<td>75</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>Density (g/cc)</td>
<td>7.4</td>
<td>5.1</td>
<td>7.1</td>
<td>6</td>
<td>7.56</td>
</tr>
<tr>
<td>Photofraction, 511 keV (%)</td>
<td>34</td>
<td>15</td>
<td>41</td>
<td>17</td>
<td>42</td>
</tr>
<tr>
<td>Attenuation Length, 511 keV (cm)</td>
<td>1.2</td>
<td>2.1</td>
<td>1.1</td>
<td>1.8</td>
<td>1.05</td>
</tr>
<tr>
<td>Number of photons (or e-h pairs) per 1 MeV γ-ray Energy</td>
<td>24,000 photons</td>
<td>63,000 photons</td>
<td>8,200 photons</td>
<td>2x10$^5$ e-h pairs</td>
<td>1.5x10$^5$ e-h pairs</td>
</tr>
</tbody>
</table>
RMD grown crystals

Figure 11. Photograph of a 1.6 cm diameter TiBr ingot with >3 cm length grown by vertical Bridgman method.

Figure 6. TiBr ingot, purified and grown with traveling molten zone method, 30-mm diameter by 270-mm long.

Figure 9. Photograph of a TiBr ingot taken out from the quartz ampoule. This ingot was zone refined (30 ±1 passes) under an atmosphere of ~250-mm Hg of HBr. The last pass was ten times slower than the 30 zone refining passes to allow growth of a good crystal.
Cutting, polishing, surface treatment, electrodes

Figure 7. Photograph of a TiBr device with Au and Pd electrodes deposited on both crystal faces for comparison.

Figure 8. Photograph of two faces on 0.5 mm thick TiBr detectors with orthogonal strip design. The area covered by both sets of strips is 10x10 mm². One set of strips provides very high spatial resolution (0.5 mm pitch), while the coarser strips placed orthogonally to the high resolution strips provide DOI.

Timing

- Due to poor charge mobility, timing performance is the biggest drawback for useful semiconductor detectors for PET.

RMD Measurement: 0.5 mm thick detector, 350 KeV LLD, 300 V bias

Figure 3. Timing resolution plot for a 0.5-mm thick TiBr detector in coincidence with a LSO-PMT detector and irradiated with 511 keV gamma-ray pairs.
Significant progress has been made on TiBr detector development, reflecting the improvement of material purification, crystal growth and detector fabrication techniques for TiBr over the years.

Figure 9. Photograph of a 10x10 mm² TiBr detector with orthogonal strip design, mounted and with electrical connections established by hand.

Figure 17. One-ring scanner design using blocks of TiBr detectors as developed in this project.

Large Field of View PET Scanner: EXPLORER
Why total-body PET?

EXPLORER: 40 fold sensitivity increase for whole-body imaging
- High sensitivity data for all organs simultaneously
- Low dose imaging
- Rapid imaging
- Late stage imaging (~5 half lives)
- Improved statistical quality

Two issues: DOI and TOF
Depth-of-interaction

DOI encoding:
• Reduces effective crystal length $\propto$ DOI resolution.
• Improves intrinsic detector resolution for large $\theta$

\[ d' = d \cos \theta + x \sin \theta \]
\[ R_{\text{in}}' = \frac{d}{2} \right\{ \cos \theta + \frac{x}{d} \sin \theta \} \]
\[ R_{\text{in}}' = R_{\text{in}} \times \left[ \cos \theta + \frac{x}{d} \sin \theta \right] \]

Time-of-flight

\[ \Delta d = \frac{(t_1 - t_2) \times c}{2} \]

\[ \text{SNR}_{\text{TOF}} = \frac{2D}{c \Delta t} \text{SNR} \]
Developing TOF-DOI PET detectors needed for EXPLORER scanner

Conventional radiotracer positioning

- Reduce blurring from axial DOI parallax error
- Increase effective sensitivity / reduce noise with TOF

Siemens Block Detector
- 12 x 12 array of chemically etched crystals (4 x 4 x 20 mm) separated by ESR (specular/mirror-like reflector)
- Hamamatsu R9800 PMTs
- Internal light guide + 6 mm glass plate for light spreading
**Phosphor-coated crystals for TOF - DOI**

- DOI encoding with phosphor-coated crystals previously investigated (Du et al 2009) for small animal PET
- Phosphor layer causes depth-dependant signal shape changes

![Figure from Du et al 2009](image)

- DOI resolution = 8 mm
- Unpolished crystals $\rightarrow$ poor timing, energy
- Small crystals with PS-PMT

**Preliminary investigations with single crystals**

Single phosphor-coated crystals directly coupled to fast PMTs

Phosphor-coated 3x3x20 mm$^3$ LYSO crystals.
Coating thickness $\sim$100 μm.
Custom block detector with coated crystals
Several complete detectors with phosphor-coated crystals constructed
• Developed methods to apply phosphor coating and assemble 225 crystals
• Crystal size is 3.34 x 3.34 x 20 mm.

Results for central 5 x 5 crystals
<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Energy Resolution</td>
<td>13-14%</td>
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<tr>
<td>Timing Resolution</td>
<td>440 ps</td>
</tr>
<tr>
<td>DOI encoding</td>
<td>2 bins (85%)</td>
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</table>

Nuclear Imaging of Plants
**SPECT: Single-Photon Emission Computed Tomography**

Gamma rays detected by gamma cameras

*Un-collimated SPECT*

- Improved sensitivity
- Improved temporal resolution
- Less time per imaging subject
- Less radiotracer (safety & cost)

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**SPECT: Single-Photon Emission Computed Tomography**

System set-up for imaging

Two un-collimated detector heads (in red)

Flexible and compact geometry

Walker KL et al., PMB, 2014
Detector Head

Scintillator array
2 MCPMTs
2 PCBs
Foam
Screws

Figure from: Walker KL, Cherry SR, and Mitchell GS. "Detector Performance Characterization for High Sensitivity Single-Photon Imaging," IEEE TNS

$^{65}$Zn dynamic scans following 1 h radioactive incubation and final nutrient water rinse. Color scale units are counts/mm$^2$/h. [upper figure] Six frames (each 15 min long) of a scan for the A. halleri genotype, beginning at 0 h, 12 h, 24 h, 36 h, 48 h, and 60 h. The images show initially a signal from the roots and then a signal from the above ground biomass. [lower figure] Five frames (each 20 min long) of a scan for the A. halleri HMA4-RNAi genotype, beginning at 0 h, 12 h, 24 h, 36 h, and 48 h. The images show initially a signal from the roots and then dilution of that signal (back into the solution) over time; the images do not show migration of the radiotracer into the above ground biomass.
Cerenkov Imaging

Cerenkov Radiation
Optical wavelength photons emitted by fast charged particles

Frank-Tamm formula
(number of photons per distance traveled):

\[
\frac{dN}{dx} = 2\pi\alpha \left( 1 - \frac{1}{\beta^2 n^2} \right) \int_\lambda_1^{\lambda_2} \frac{d\lambda}{\lambda^2}
\]

\(\beta = \frac{v}{c}\) ratio of particle velocity to speed of light

\(n\) index of refraction

\(\alpha\) fine structure constant
Threshold for Cerenkov Production

Threshold: \( \beta n > 1 \)

For relativistic electrons/positrons, \( \beta \) is related to particle kinetic energy \( E \) by:

\[
\beta = \sqrt{1 - \left( \frac{1}{\frac{E(keV)}{511} + 1} \right)^2}
\]

Threshold energy in…
water \( n = 1.332 \) \( E = 263 \) keV

tissue \( n = 1.36 - 1.40 \) \( E = 219-244 \) keV

Some CLI Physics…

[Graph showing probability per 0.01 MeV for \( {}^{18}\text{F} \) and \( {}^{90}\text{Y} \) with Cerenkov threshold (water).]

[Graph showing \( dN/dx \) (photons per mm) for different materials with Cerenkov threshold (water).]
Monte Carlo Simulation of Spatial Distribution of Emitted Photons
(colors show the portion of each track above Cerenkov threshold)

Monte Carlo Simulation Results

Light intensity

Light spatial distribution
In Vivo Imaging

nu/nu mouse with U87 (glioma) cells expressing engineered antibody 2D12.5/G54C as a reporter gene

with yttrium-(S)-2-(4-acrylamidobenzyl)-DOTA (*Y-AABD) as a reporter probe

previously published reporter approach, see:

*Engineered Antibody Fragments with Infinite Affinity as Reporter Genes for PET Imaging*


Syringe with 190 µCi ⁹⁰Y-AABD next to mouse (with side mirrors)

Ex vivo tumor : liver contrast = 1:5
Cerenkov Luminescence Imaging Example: Probe Development Screening

[ dx.doi.org/10.1021/bc2002049 ]

2 similar 90Y labeled molecules: 1/2/3 cohort tests 90Y probe #1 A/B/C cohort test 90Y probe #2

Left tumor control Right tumor engineered reporter gene

~10 μCi per animal T=48 hs post-injection

Dissected organs: tumors (arrows); heart, lungs, liver, kidneys, stomach, spleen, intestines.

Non-invasive in vivo imaging of beta minus emitter

Small Animal PET Imaging
Requirements

<table>
<thead>
<tr>
<th></th>
<th>Clinical PET</th>
<th>Animal PET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Spatial Resolution</strong></td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Energy Resolution</strong></td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td><strong>Timing Resolution</strong></td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td><strong>Count-Rate Capability</strong></td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td><strong>Depth-of-Interaction</strong></td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td><strong>Detector Area</strong></td>
<td>~3000-7000 cm²</td>
<td>~50-500 cm²</td>
</tr>
</tbody>
</table>

**High Resolution Mouse Brain Scanner**

16 dual-ended readout tapered detectors
FOV: axial 7 mm, transaxial 40 mm

**Crystal Array:**
14x14 elements, LSO

Crystal size:
Front: 0.44×0.44 mm²
Back: 0.8×0.44 mm²
Length: 13 mm

**PSAPDs:**
Front: 10×10 mm²
Back: 10×15 mm²
Small-animal PET is an important application area and lends itself well to early evaluation of novel radiation detector technologies for nuclear medical applications.

Performance improvements are still possible and needed to address critical targets such as the mouse brain.
Nuclear Imaging

• Advantages:
  – High sensitivity (nM-pM)
  – Labeling of small molecules with little or no change in biological action
  – Whole body 3D volumetric imaging (tomographic)
  – Quantitative
  – Straightforward translation from mouse to man

• Disadvantages
  – Involves ionizing radiation
  – Access to radiolabeled molecules, especially for short half life radionuclides
  – Limited spatial resolution (~0.5 mm SPECT, ~ 1 mm PET)
Health Care

...by the early 2020s the taxpayer will be footing the bill for half of America's health spending, which will have risen to a staggering $5 trillion, equivalent to one-fifth of the country's entire economic output.

[The Economist, Dec. 21, 2013]
• Nuclear medicine uses many techniques from nuclear physics
• Gamma-ray imaging systems (PET/SPECT) are essentially small nuclear physics experiments

Research includes:
detectors--new scintillators, photodetectors, solid-state materials
electronics & DAQ
multimodality systems
reconstruction & image processing

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Simon Cherry and Cherry Lab at UCD
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