Gamma-Ray Imaging Instrumentation in Oncology

Current Status, Challenges and Opportunities

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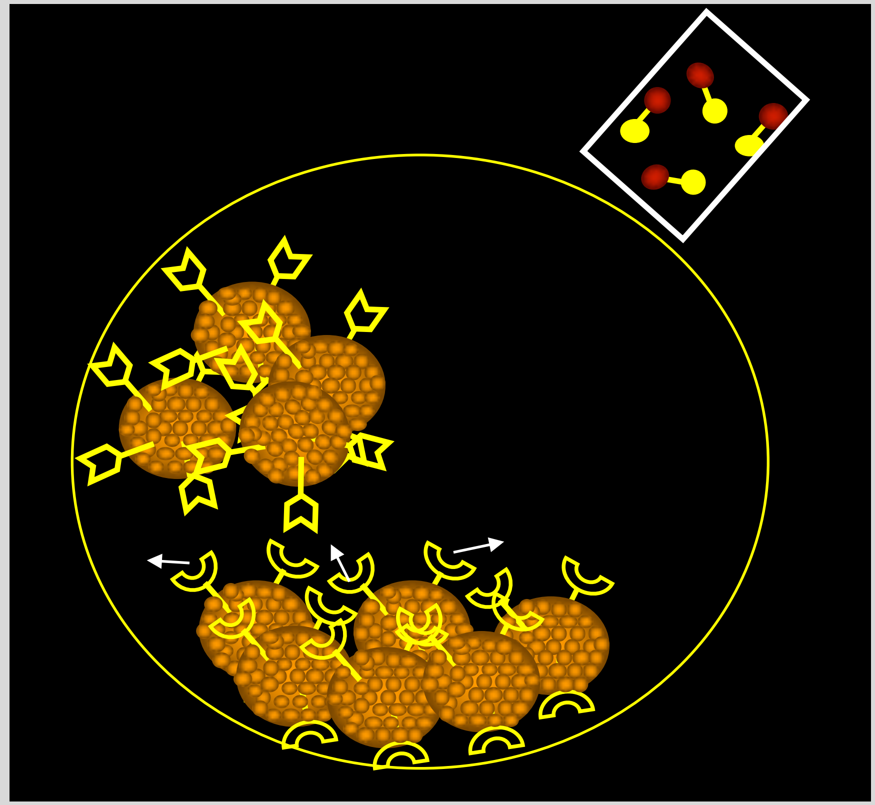
P41-EB002035

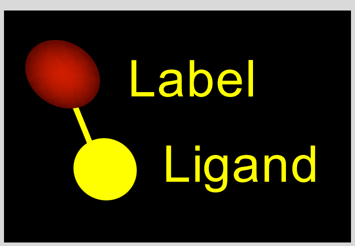
Overview

- Significance in cancer management
- The fundamentals
- Current state of the art
- Why it always comes down to better detectors
- Making use of all of the information carried by each gamma-ray photon
- Collimation strategies
- Progress and opportunity

Molecular Imaging

George Charles de Hevesy
(1885 – 1966)
1943 Nobel Prize in Chemistry





Molecular target becomes a signal source
Tracer should not affect target or organism

Current Applications of Nuclear Imaging in Oncology

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- Assess drug targeting (and off-target localization)
  - Radioimmunotherapy drugs: dose needed for therapy
  - New drug development: targeting and kinetics
- Monitor tumor metabolic response to therapy

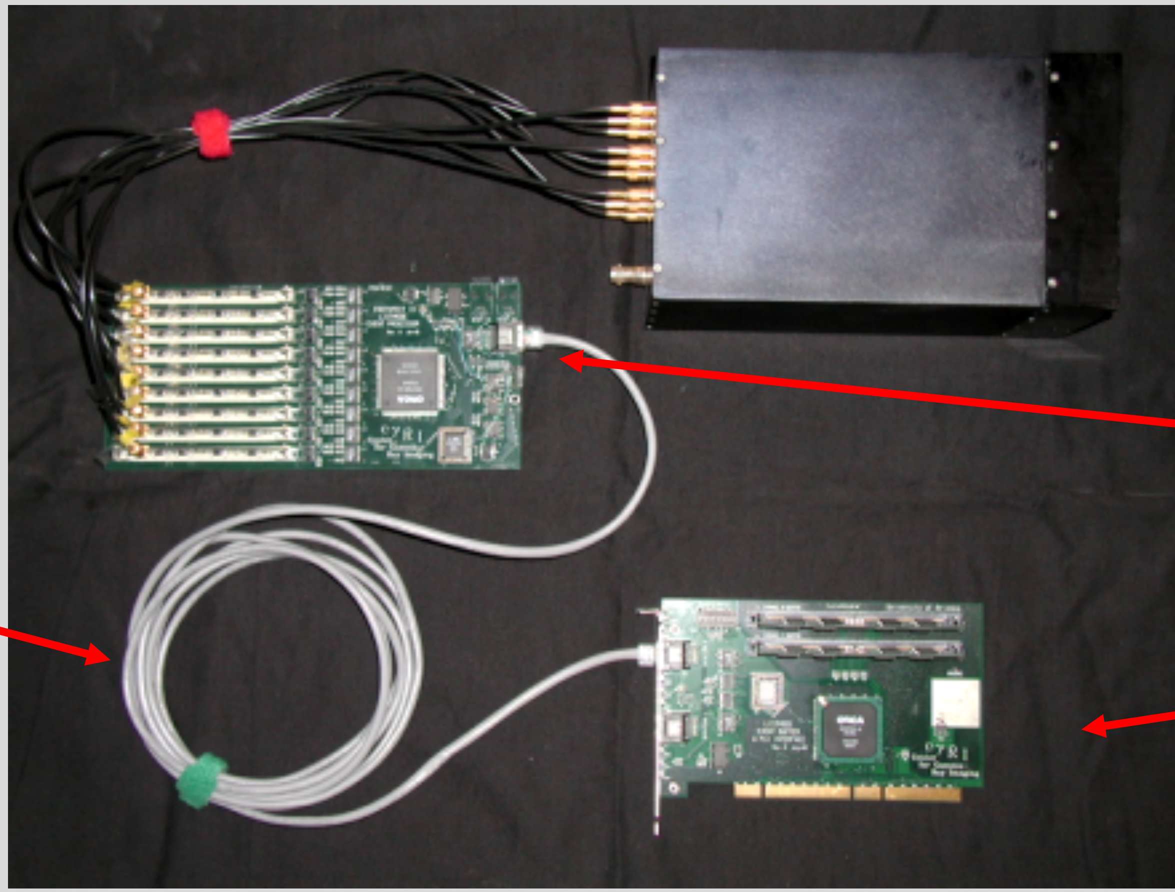
Recipe for High-Resolution Small-Animal SPECT

- Starting with: 2-3 mm intrinsic-resolution Anger camera + 1-2 mm bore parallel-hole collimator + filtered back projection reconstruction

- Move to pinhole apertures with magnification
- Develop analytical forward model and switch to statistical reconstruction (ML-EM, etc…)
- Add additional pinholes and cameras to acquire projections in parallel
- Combine with high resolution anatomical modality
- Make pinholes smaller and move closer to object, trading FOV for magnification
- Calibrate system for more accurate forward model – measured H matrix
- Gate acquisition to reduce respiratory and cardiac motion

CGRI Modular Camera

- Record all sensor values associated with an event at full precision



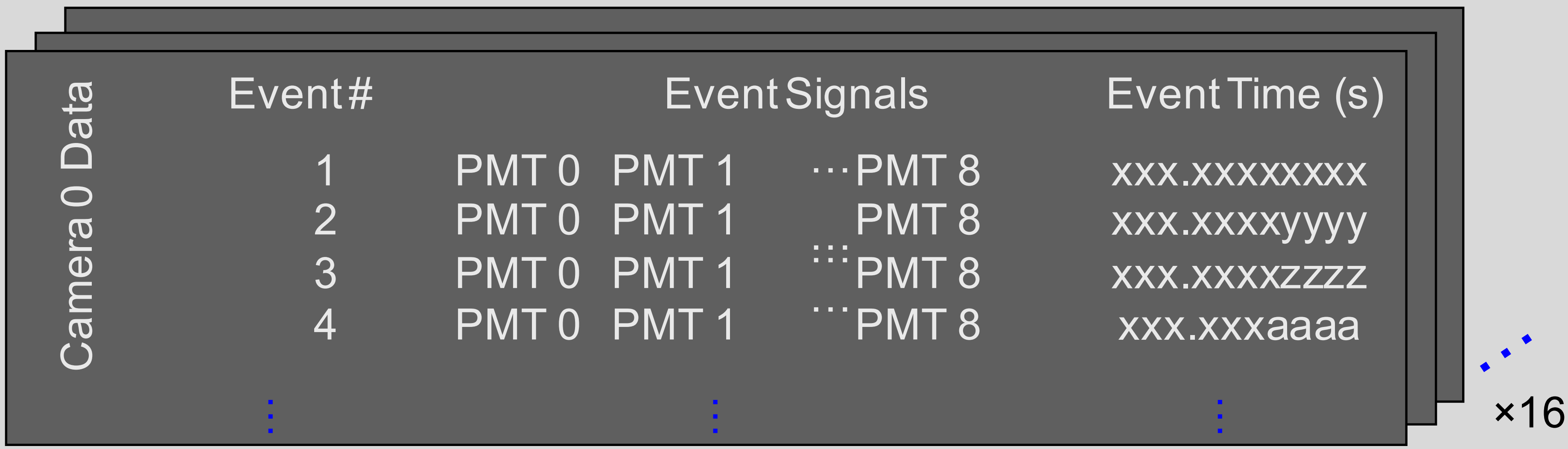
List-mode Event Processor

200 MHz LVDS Data Link

List-mode Event Buffer & PCI/PCIe Interface

Sensor Signals and Times

- Photon-by-photon list



All data acquisition in FastSPECT II is dynamic

Call it static if nothing changed in object

List-mode, double list-mode, and dynamic list-mode reconstruction are immediately important areas of research.

FastSPECT II Imager

- Second generation dynamic SPECT imager

Key Features:

16 cameras in 2 rings of 8 with adjustable radial position

5 axis robotic stage for calibration and imaging subject positioning

Exchangeable cylindrical imaging apertures for choice of magnification/field-of-view

Listmode data acquisition architecture

Full dynamic imaging capability for periodic and non-periodic processes

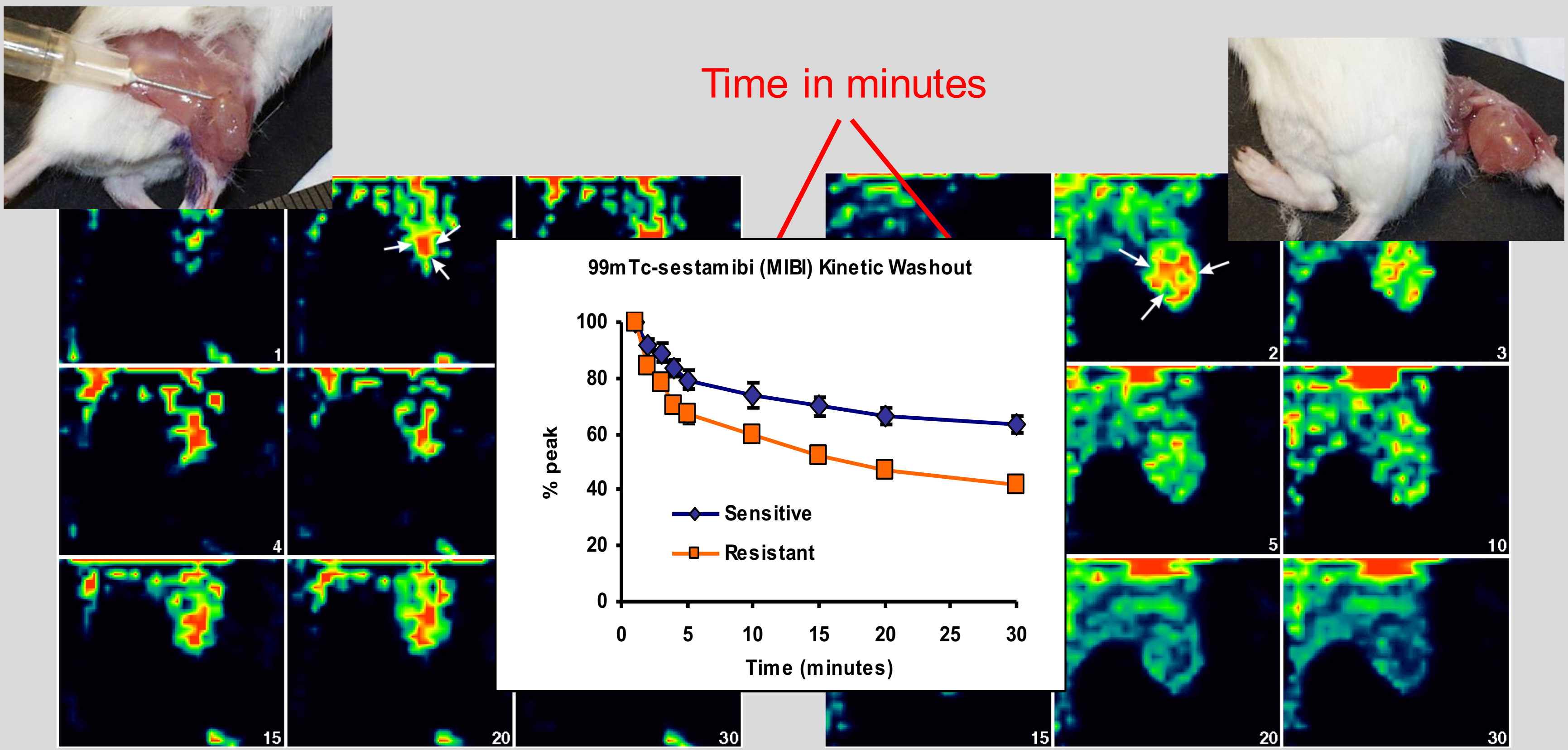
Gigabit data link

GPU-enabled real-time ML position estimation and images

Data rate: 50 Gbits/sec

Graduate Student: Jean Chen

Dynamic FastSPECT Images of Drug Resistance



Drug Sensitive Tumor

Drug Resistant Tumor

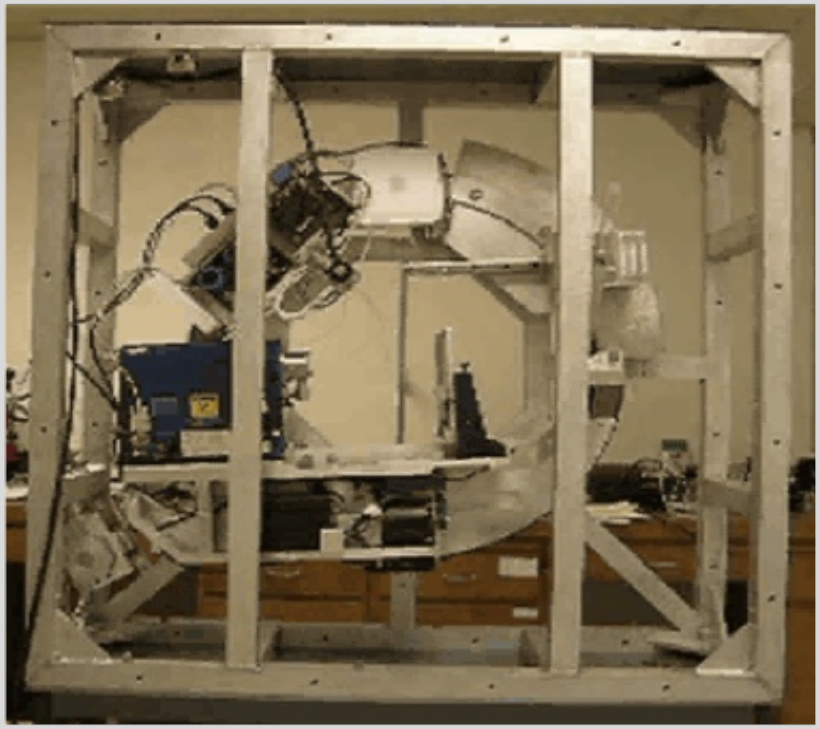
Imaging recognition of multidrug resistance in human breast tumors using ^{99m}Tc-labeled monocationic agents and a high-resolution stationary SPECT system

Zhonglin Liu*, Gail D. Stevenson, Harrison H. Barrett, George A. Kastis, Michael Bettan[1], Lars R. Furenlid, Donald W. Wilson, James M. Woolfenden

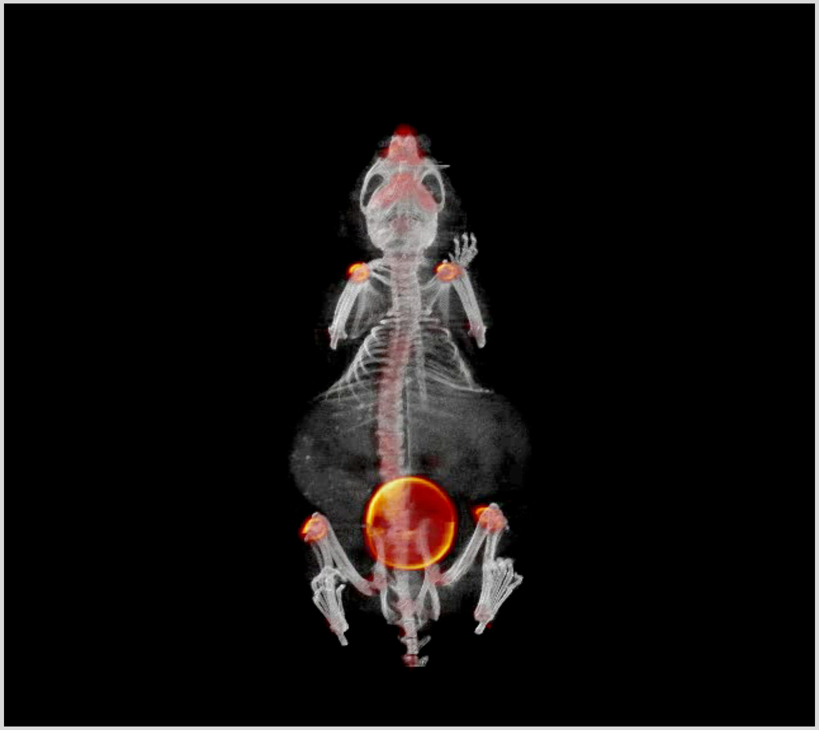
Nuclear Medicine and Biology 31(1), 53 – 65, 2004.

FaCT – An Adaptive CT

- Companion modality for FastSPECT II



FaCT: Hi-Res
Adaptive CT



Graduate Students: Jared Moore & Todd Bonham

High-Magnification Aperture

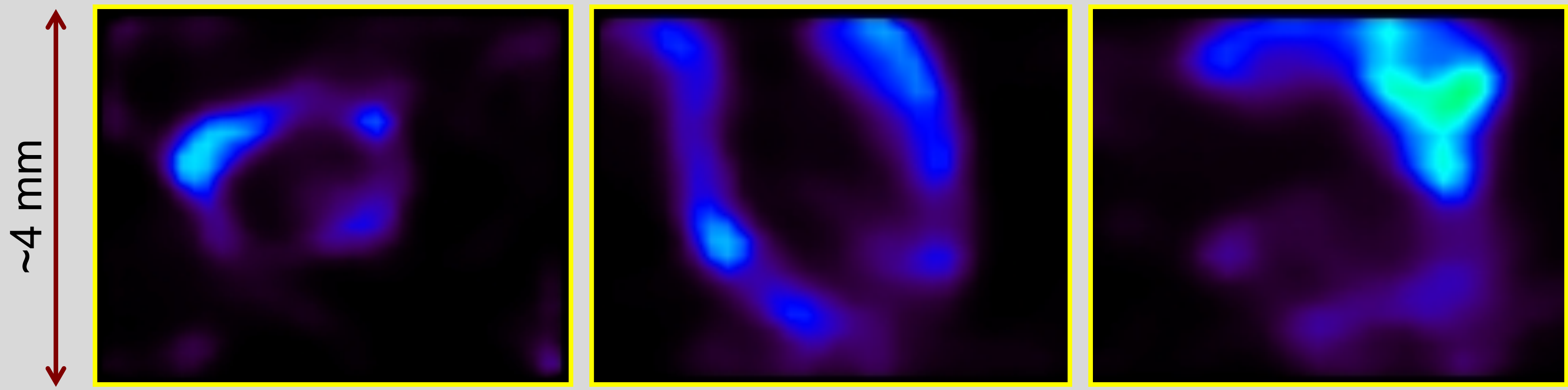
- Application: neuroblastoma invasion in mouse knee

Magnification ~ 20
Pinholes = 100 µm
Resolution ~ 100 µm
FOV ~ (5 mm)^3

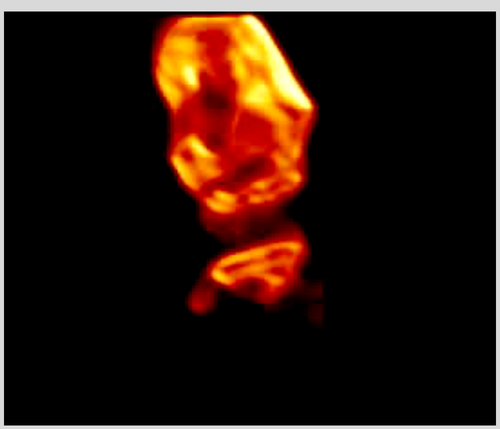
Graduate Student: Mick Crawford

High-Magnification SPECT

- Neuroblastoma invasion in the mouse knee



Axial | Coronal | Sagittal



High-magnification FSII images of mouse knee with invading neuroblastoma tumor

Above: Tomographic slices

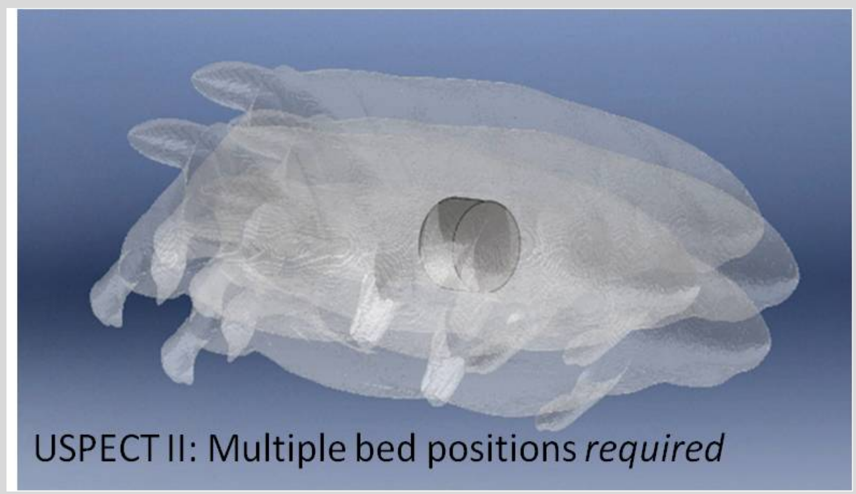
Right: CT showing field of view

Left: Movie illustrating insult and response of femur

Resident: Bret Abbott

Current State of the Art

- ~ 1 × 1 × 1 mm^3 in a mouse-sized field of view
- ~ .5 × .5 × .5 mm^3 in a small field of view
- 9% energy resolution at 140 keV

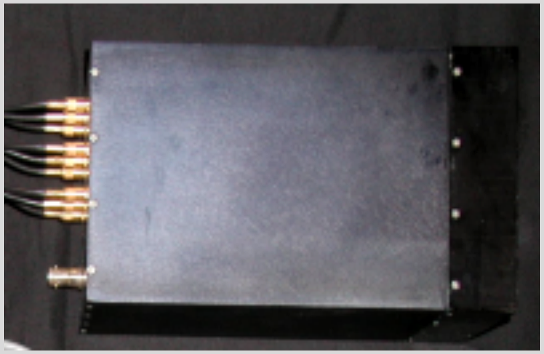


USPECT II: Multiple bed positions *required*

Recipe for Ultra-High-Resolution Small-Animal SPECT

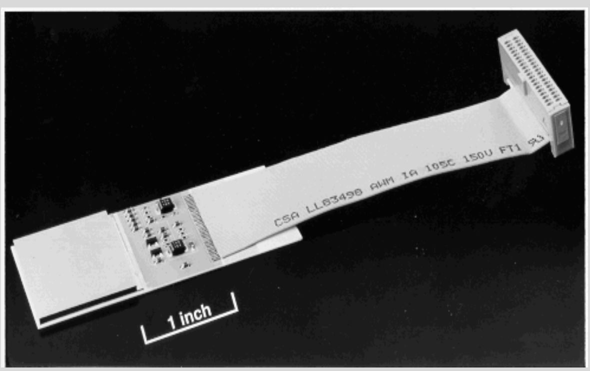
- Improve camera intrinsic resolution, add DOI to reduce parallax
- Move to direct-conversion: semiconductor detector technologies
- Eliminate events with non-local energy deposition in detector
- Incorporate scatter and attenuation in object-specific H matrix
- Reconstruct in photon-by-photon list-mode form

CGRI Detectors

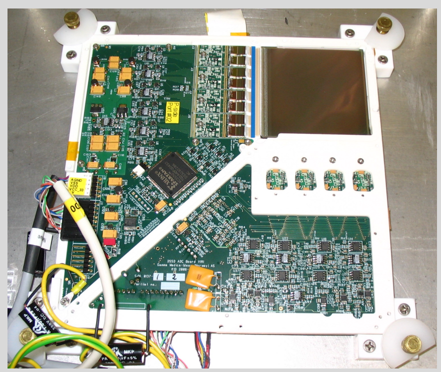


Modular Camera

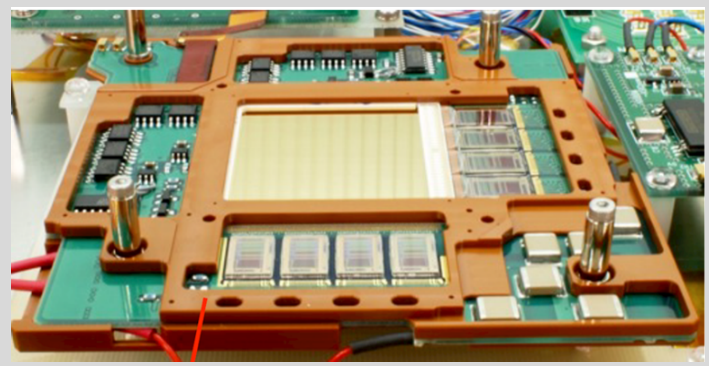
iQID Camera



Arizona CZT Pixel Detector



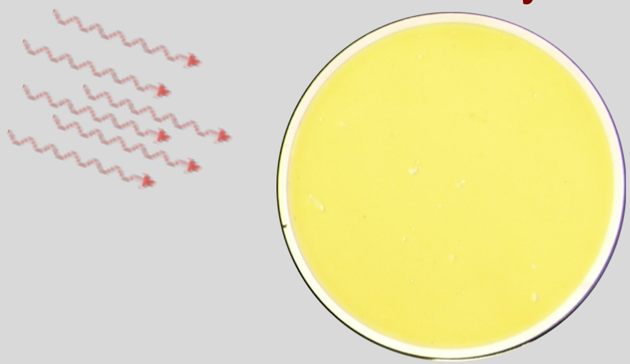
Si DSSD



Takahashi-group CdTe DSSD

The Intensified Quantum Imaging Detector (iQID)

Columnar CsI(Tl) scintillation crystal

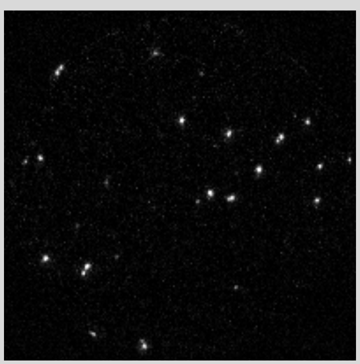


+

Gen 2 Image Intensifier

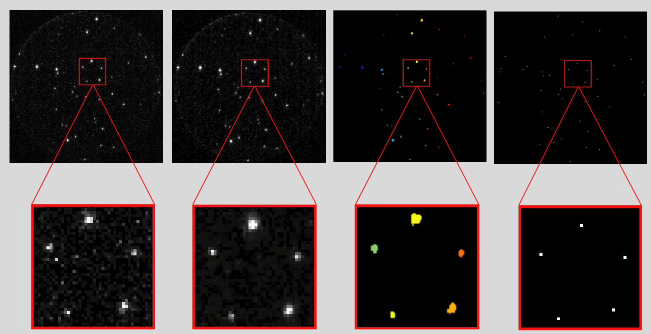
+

Lens-coupled CMOS Video Camera



Frames with images of particle/photon events

+



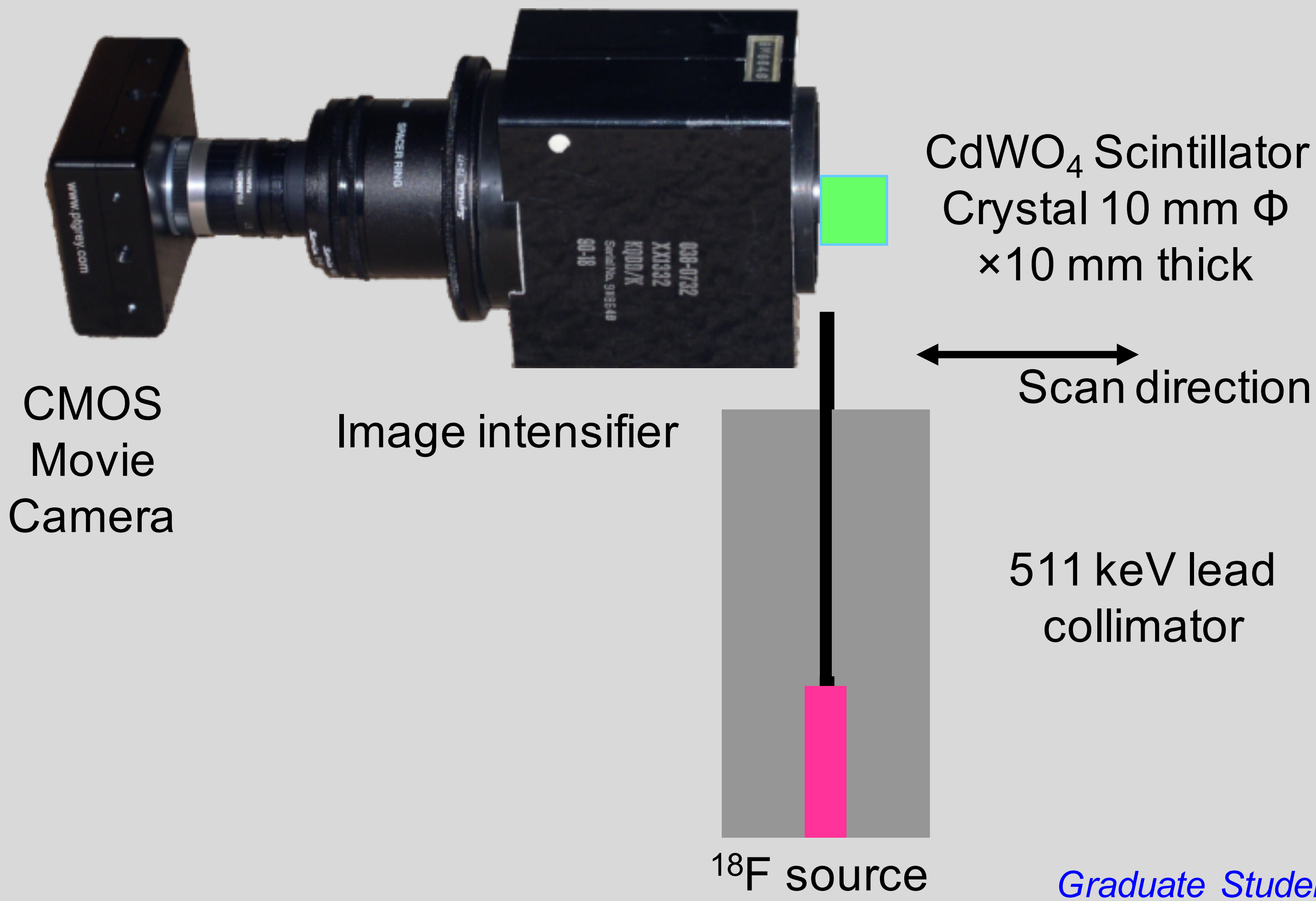
In-line processing to extract individual events

→ ~25-micron-resolution, photon/particle counting Mega-pixel imaging detector!

Graduate Students: Brian Miller & Ling Han

iQID Camera

- Add optical gain between scintillator and an imaging sensor

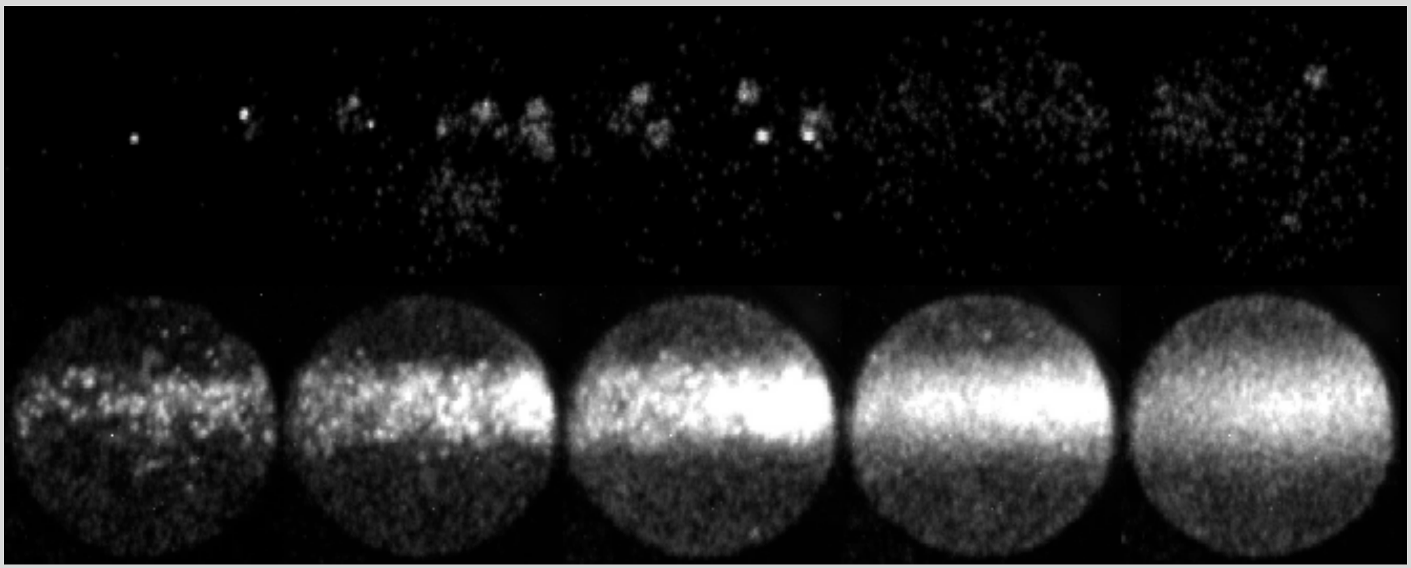


Graduate Student: Brian Miller

Imaging Single 511 keV Photons

- Direct visualization of gamma-ray photons

<u>Acquisition Mode</u>



Photon counting (fast frames with few events)

Integrating (slow frames with lots of events)

0 mm　1 mm　2 mm　3 mm　4 mm

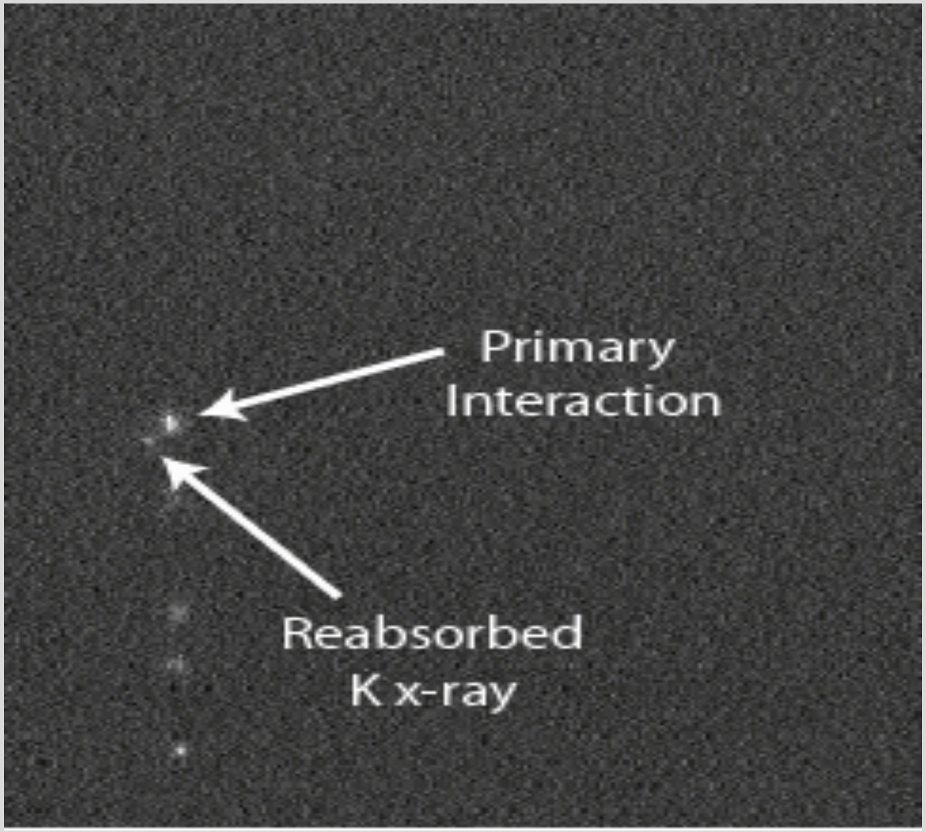
← Beam direction

<u>Distance between beam axis and scintillator exit face</u>

Graduate Students: Brian Miller & Stephen Moore

Amazing Spatial Resolution

- Identify complicated interactions in detector

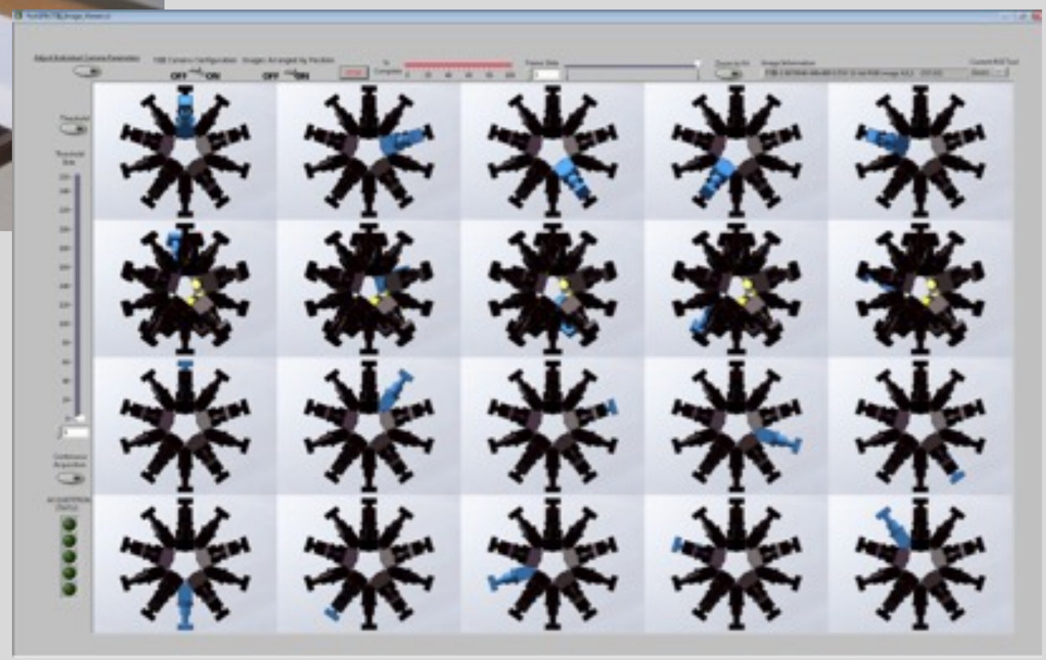


CsI(Tl) - 450µm thick film

iQID SPECT

CGRI's FastSPECT III system incorporates 20 iQID cameras viewing a common field of view

Rodent brain imaging

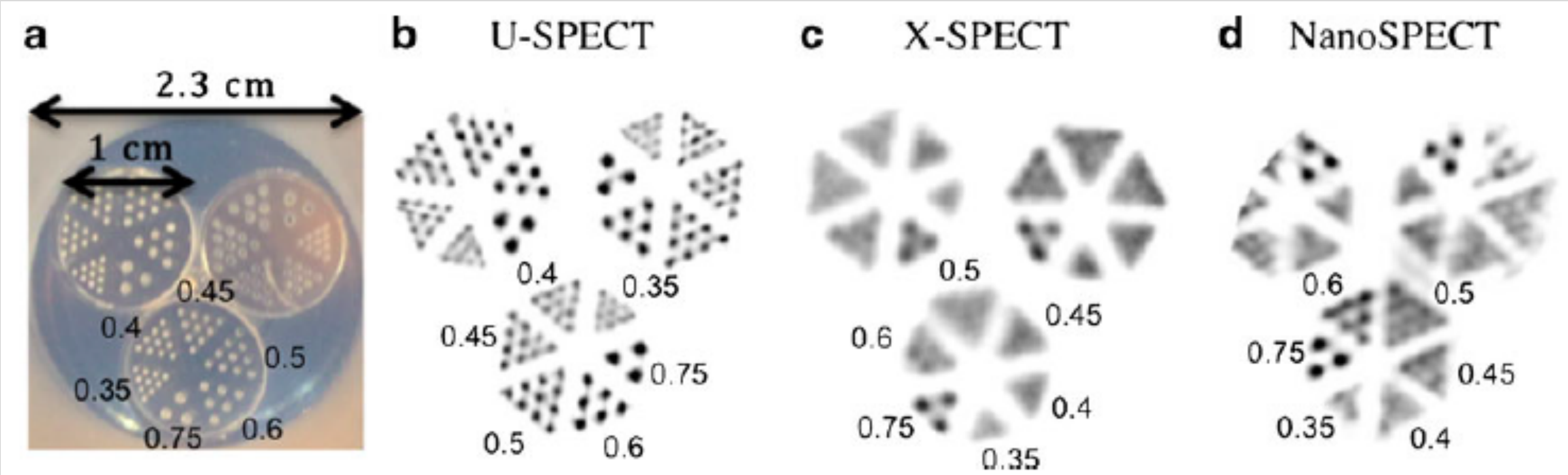


GPU-based in-line processing for all 20 cameras operating in 200-frame-per-second mode is accomplished in computing rack with 5 computers

Graduate Student: Brian Miller

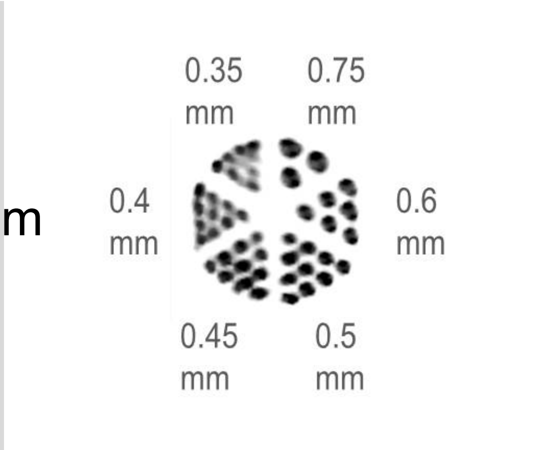
Comparison with Commercial Systems

- Each system in highest resolution mode offered



Deleye, et al
Eur J. Nucl. Med. Mol Imaging
(2013) 40: 744-758.

CGRI's FastSPECT III System

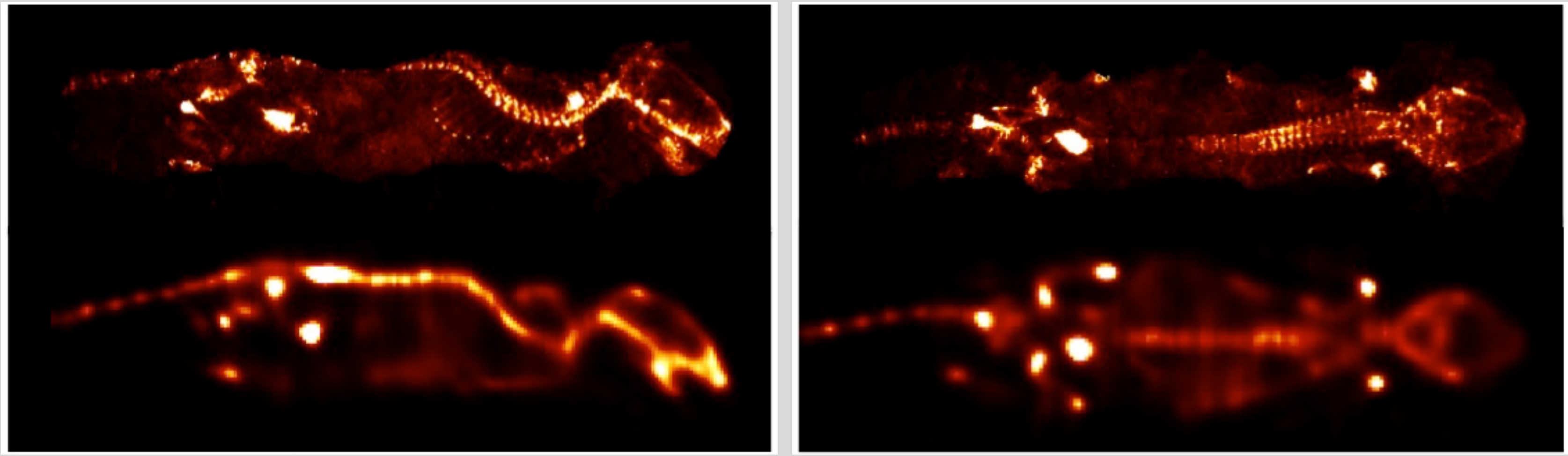


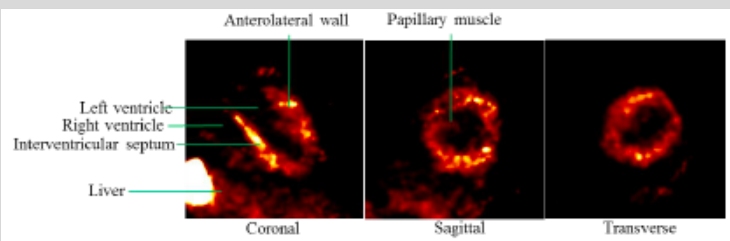
Graduate Student: Brian Miller

FastSPECT III Imaging

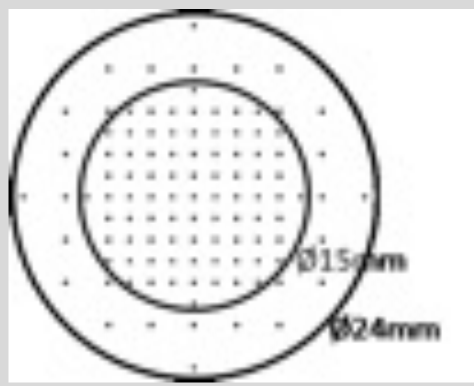
FS III

FS II



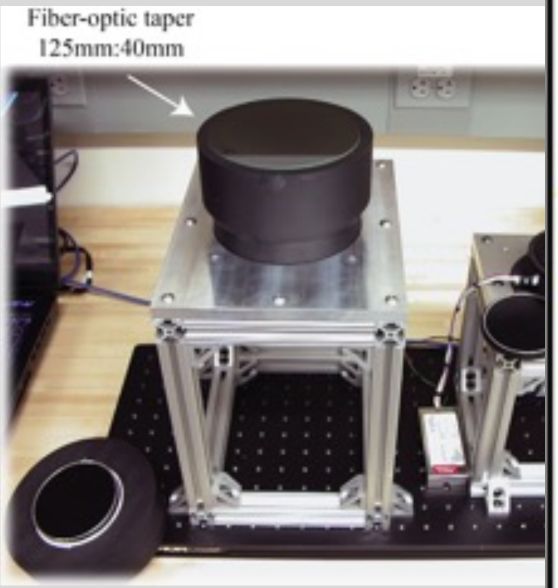


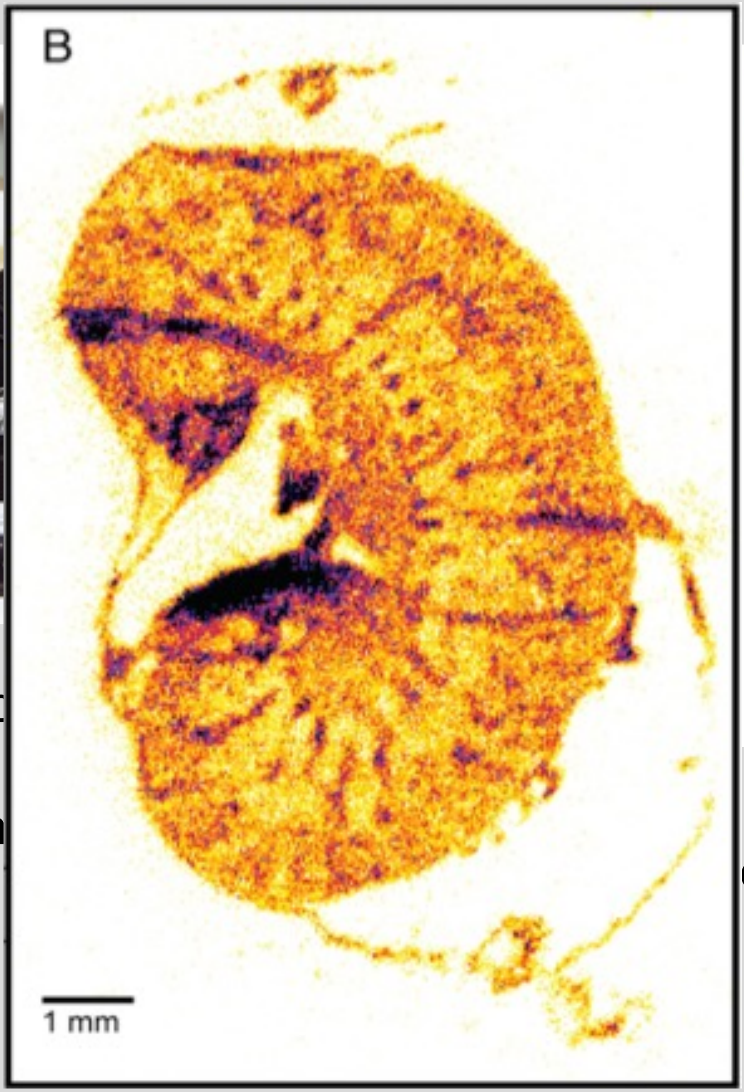
FS III mouse cardiac perfusion SPECT

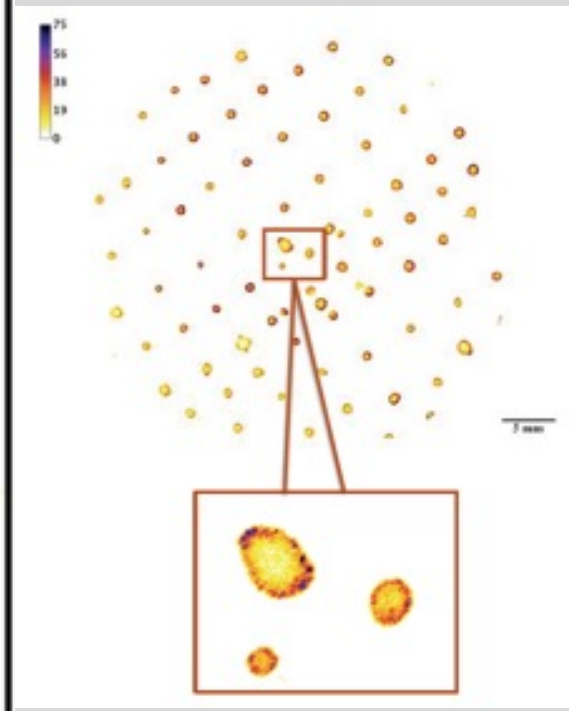


Multi-bed position acquisition and multi-scale PSF

iQID Alpha-Particle Imaging







iQID sensitive area inc
via use of optical fiber
between scintillator an
intensifier

vides a significant
e over simply integrating

Post-doc: Brian Miller

iQID Summary

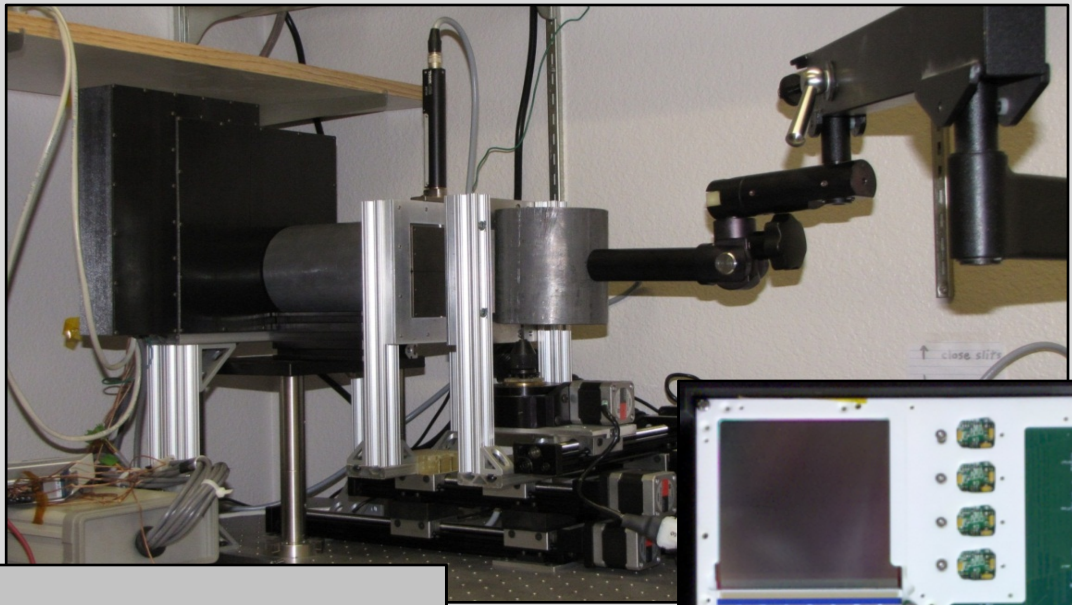
- Exquisite spatial resolution
- Limited sensitivity due to need for structured scintillator (< 3 mm so far)
- Compromised energy resolution due to gain noise in microchannel plate of intensifier
- Superb for microdosimetry in autoradiography specimens

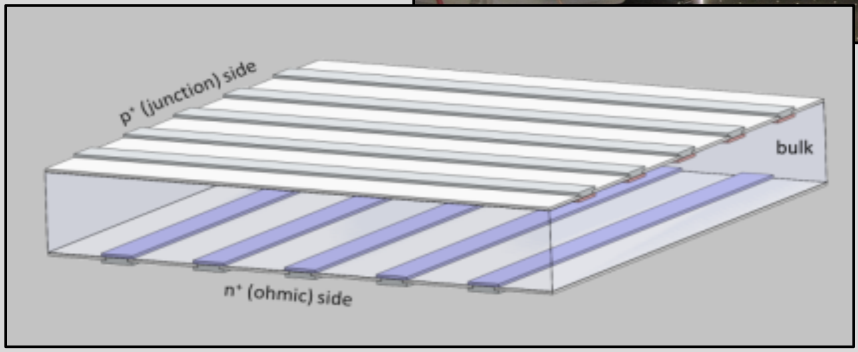
Si Double-Sided Strip Detector

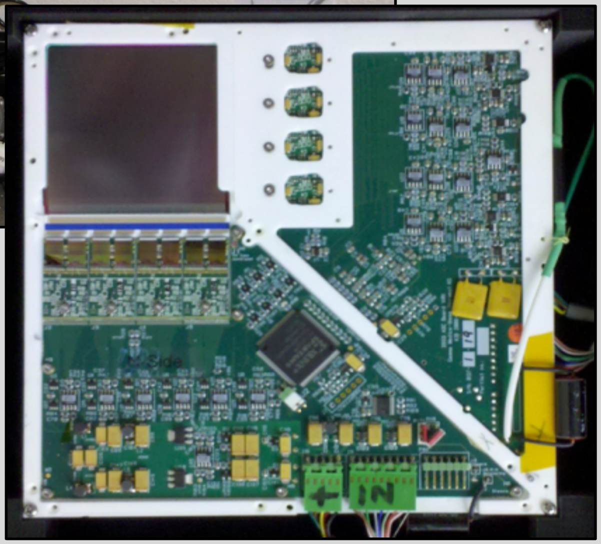
Strip pitch 58 microns

Thickness 1 mm

1024 × 1024 strips

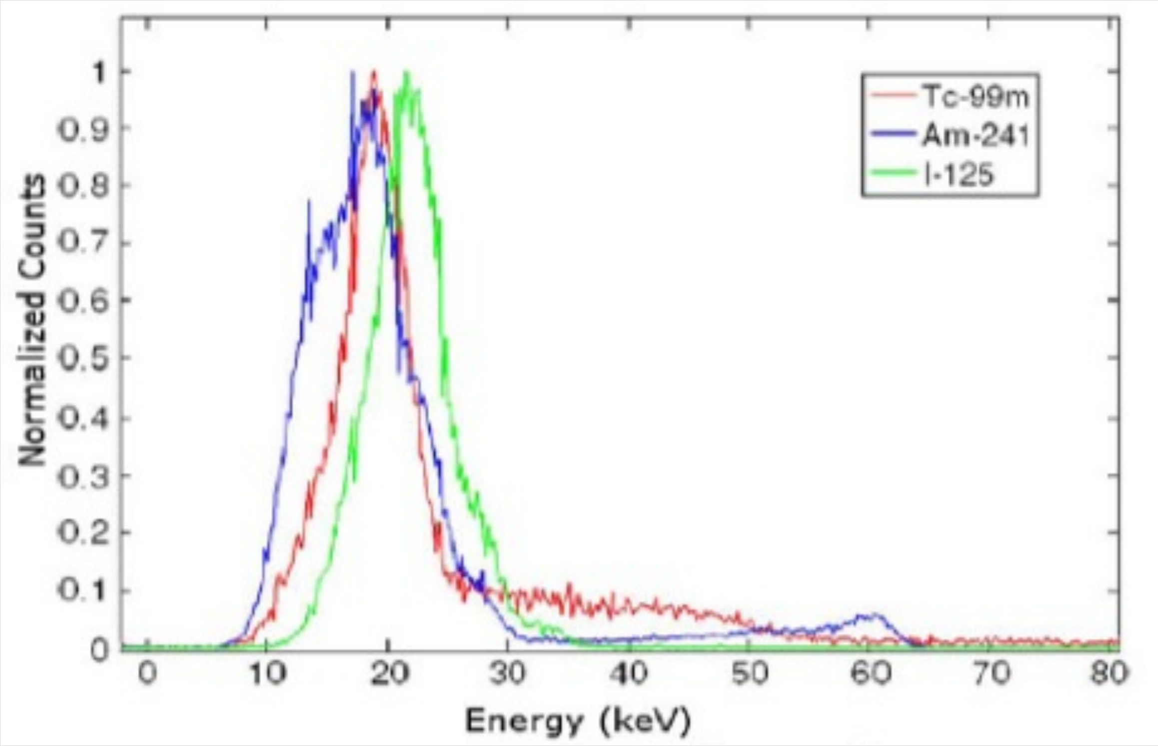






Graduate Student: Heather Durko

Raw Energy Resolution



Does not consider:

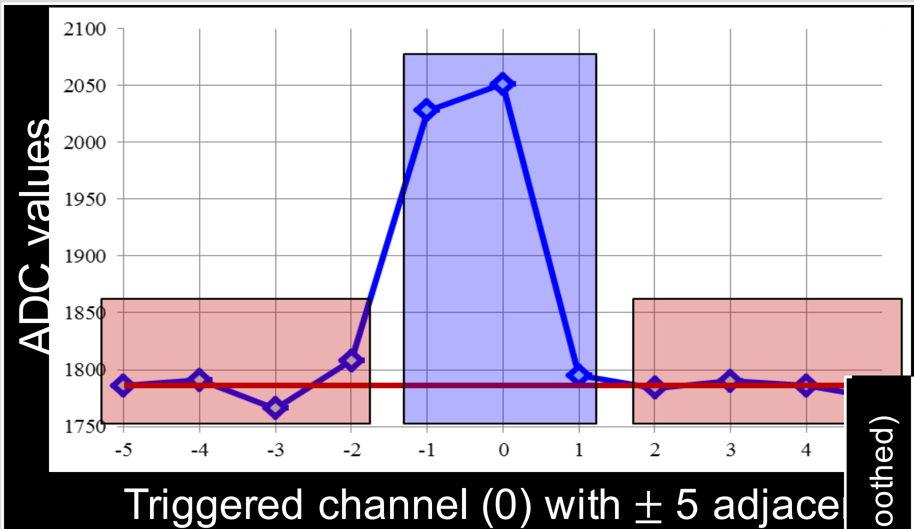
- charge-sharing between strips
- common-mode pedestal fluctuations

^{241}Am flood exposure: energy spectra, one strip

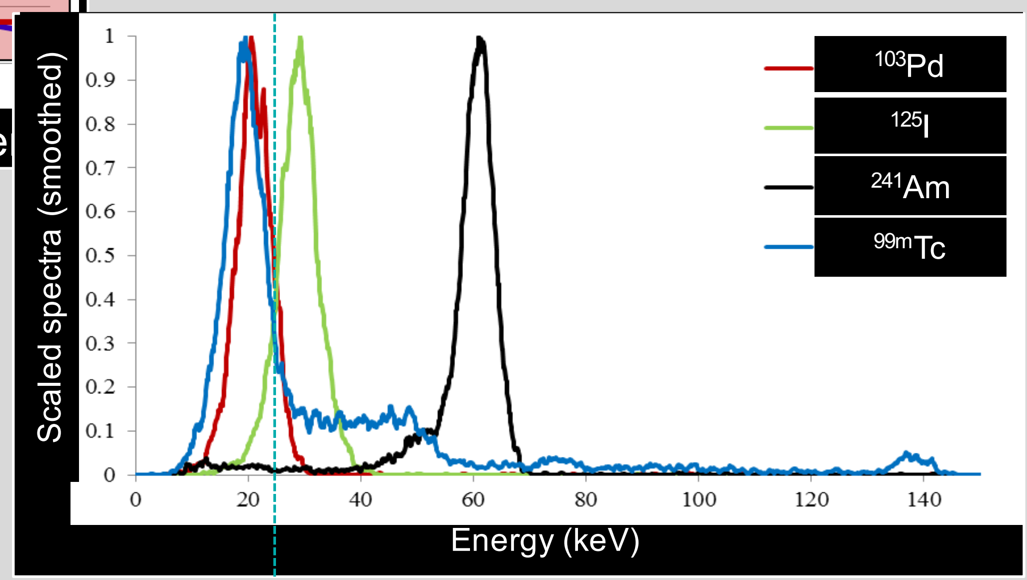
Collaboration with Vanderbilt University

Graduate Student: Heather Durko

Estimated Energy with Multiple Strips

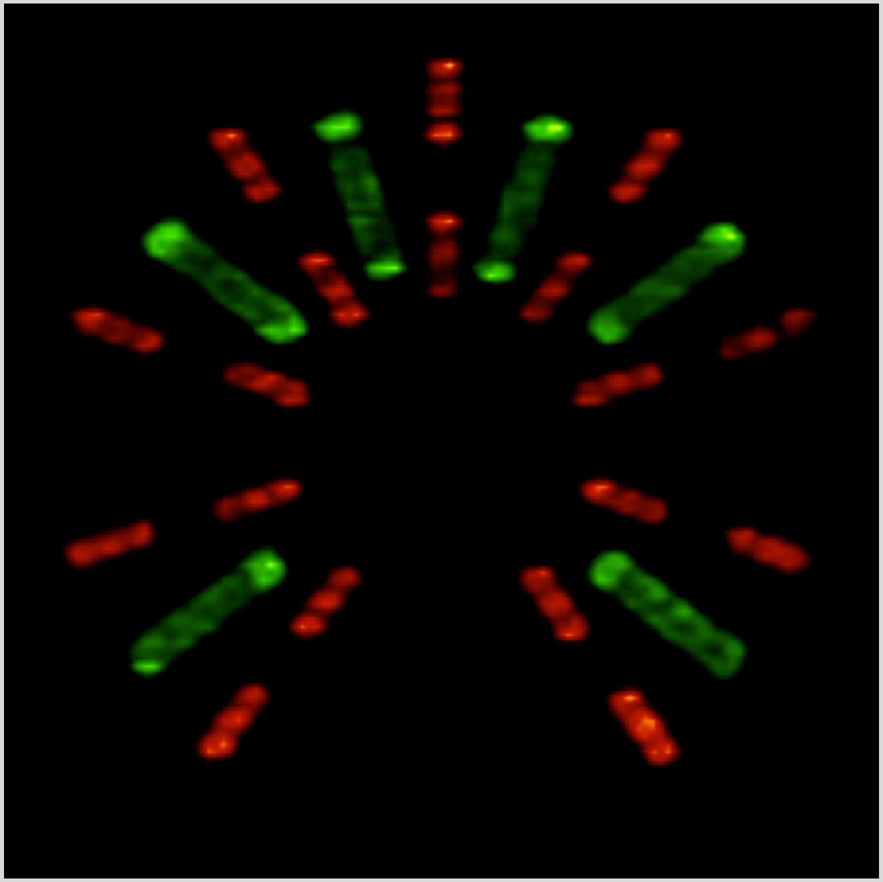


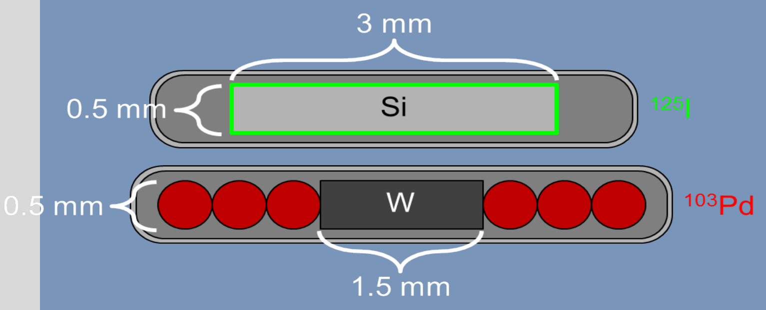
Neighbor strip readout and processing to account for common-mode fluctuations



Graduate Student: Heather Durko

Multi-isotope SPECT at low E

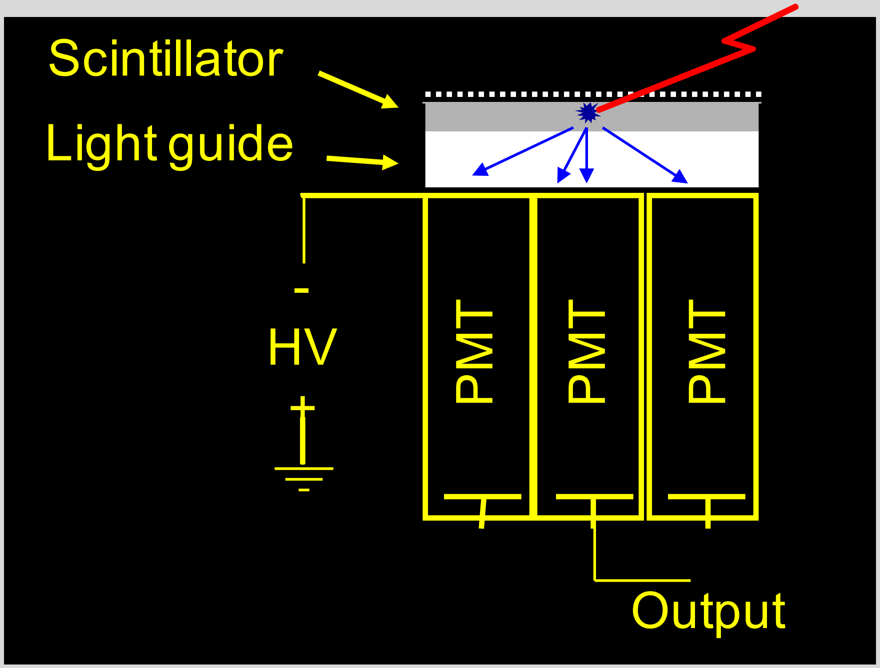


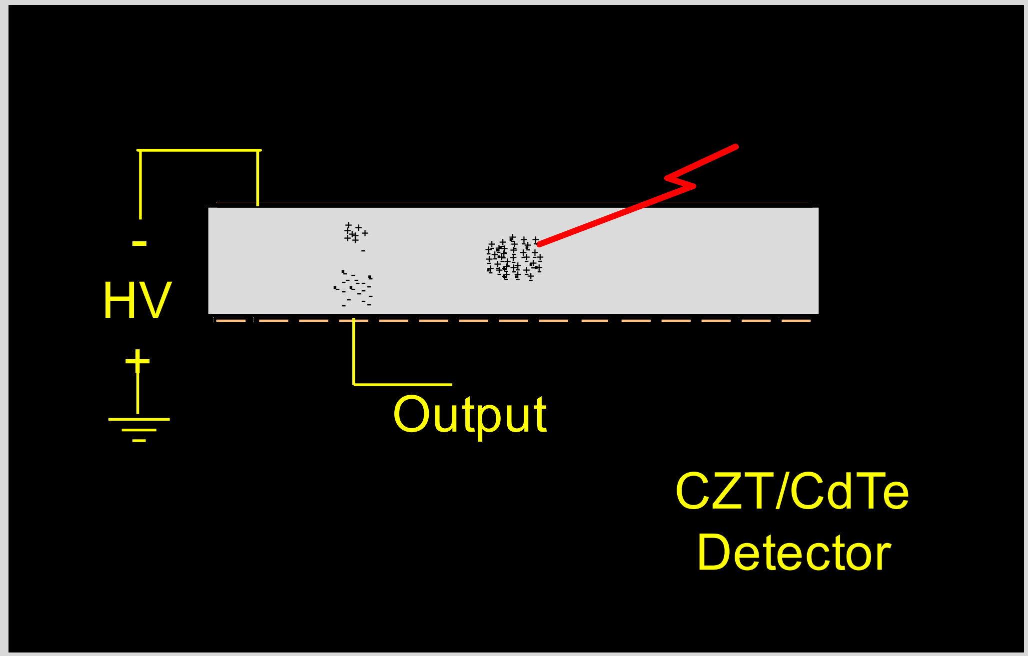


- 255 × 255 × 255 voxels
- 15 mm × 15 mm × 15 mm FOV
- 250-μm slits
- 60 10-minute projections
- 5 subsets OSEM
- 5 iterations

Graduate Student: Heather Durko

Information Carriers

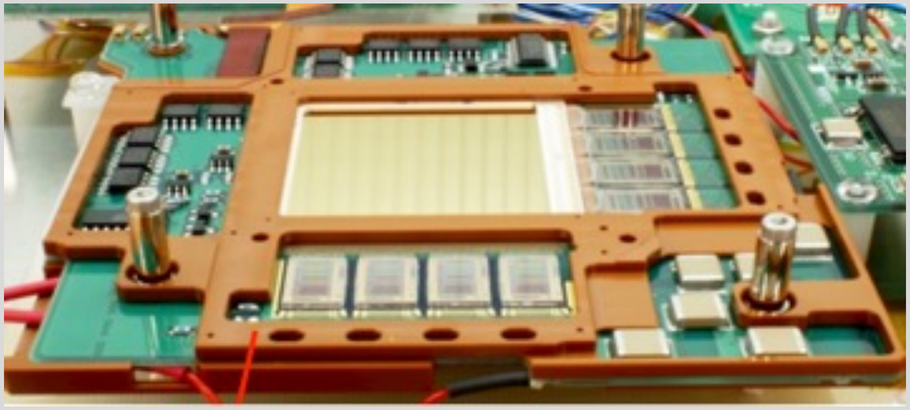




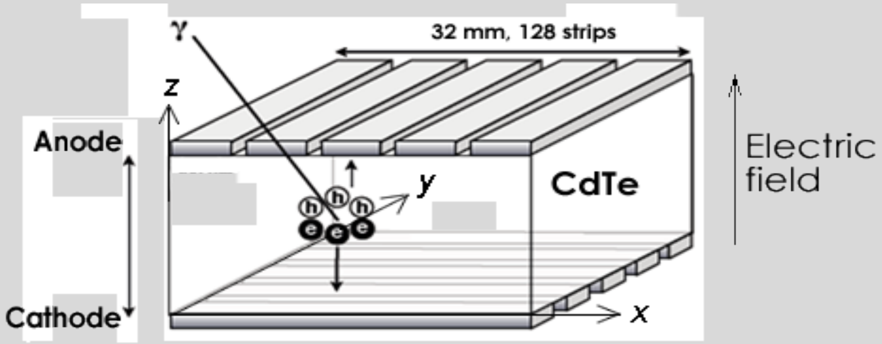
<u>Similarities</u>

- Gamma-ray initially interacts via photoelectric absorption or Compton scatter
- Interaction is local to a scale of ~100 μm
- Outputs are current pulses with comparable timing characteristics
- Multiple sensors generate output for each event (light spread for scintillator, charge spread for CZT/CdTe

Takahashi Group CdTe DSSD

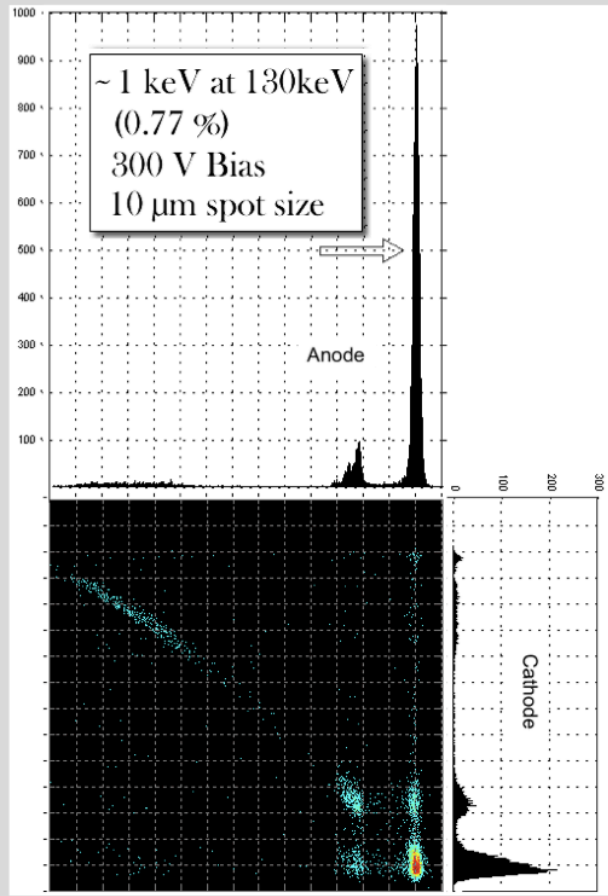


- Fano factor for CdTe is ~0.1
- Ionization energy for CdTe is 4.43 eV.
- High density, high atomic number CdTe (Z_{Cd}=48 and Z_{Te}=52). Expanded dynamic range in readout suitable for energies to 400 keV and above



CdTe DSSD Energy Resolution

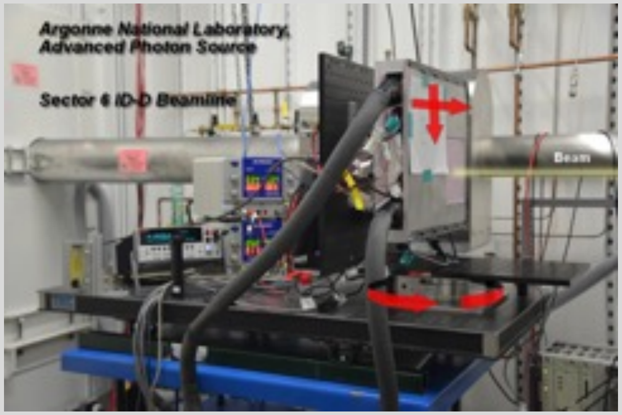
- Two independent measurements for each event: anode side and cathode side.
- Excellent electron transport, and low-noise on-ASIC A/D yields <1% energy resolution on anode side
- Depth dependence on cathode side enables DOI estimation
- APS Synchrotron measurements
  - Beamline 6-ID-D
  - 130 keV
  - $10 \times 10\ \mu m^2$ beam spot size

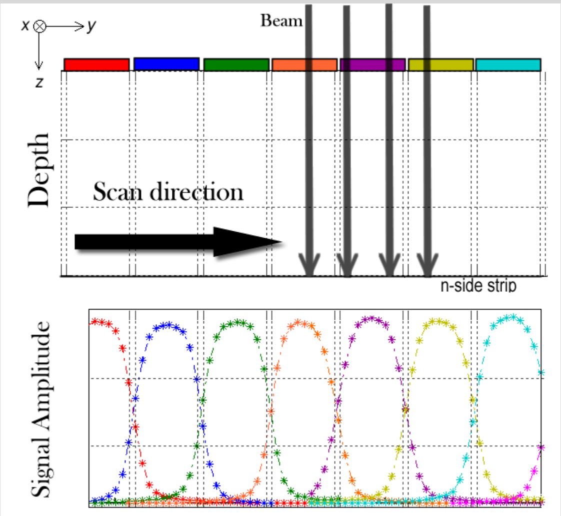


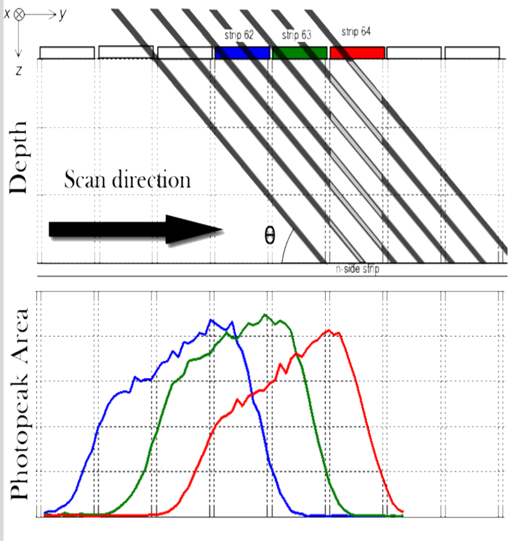
Takahashi Group DSSD

Graduate Student: Esen Salcin

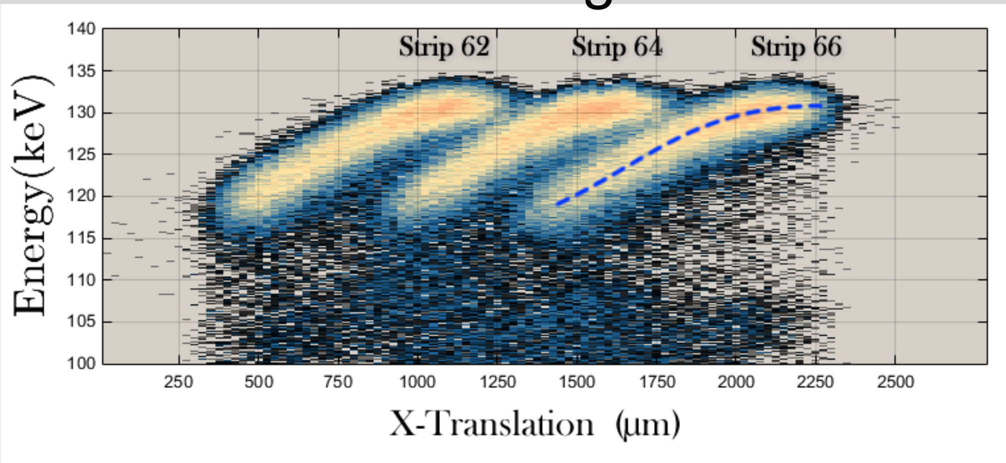
CdTe DSSD Synchrotron Beam Scanning Experiments



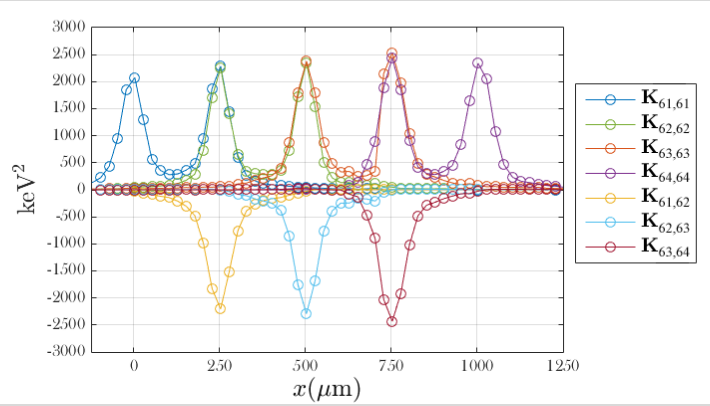




- Mean signals

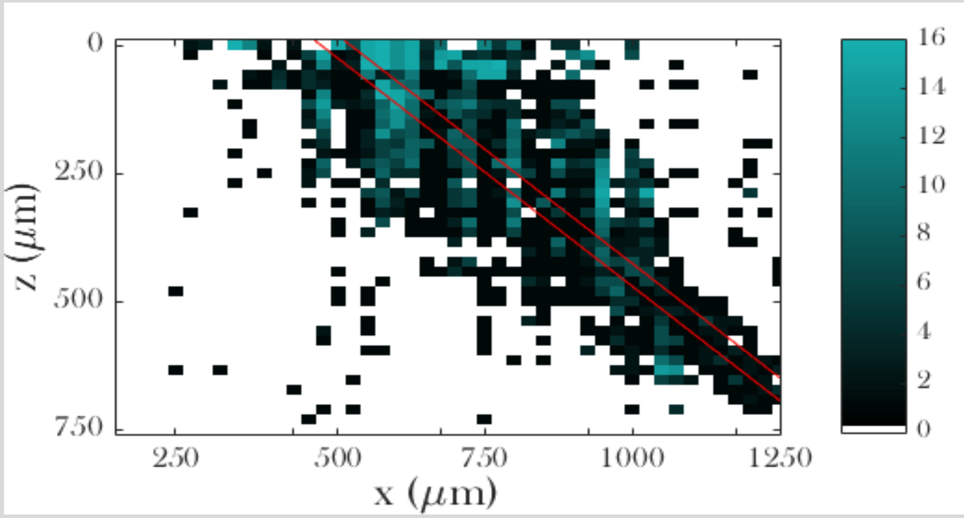


- Covariances

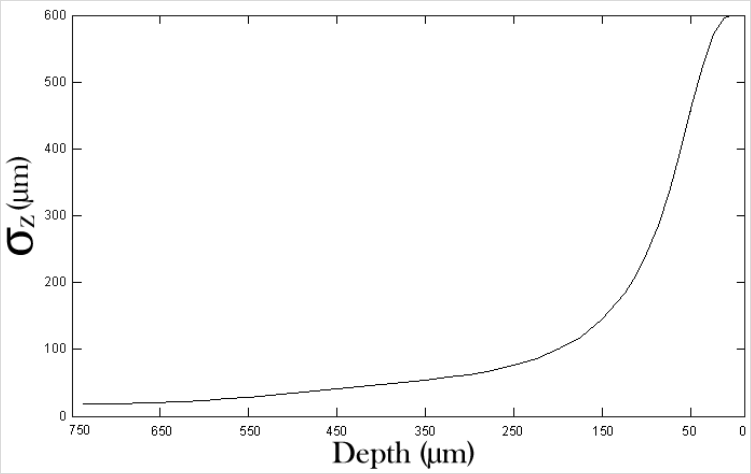


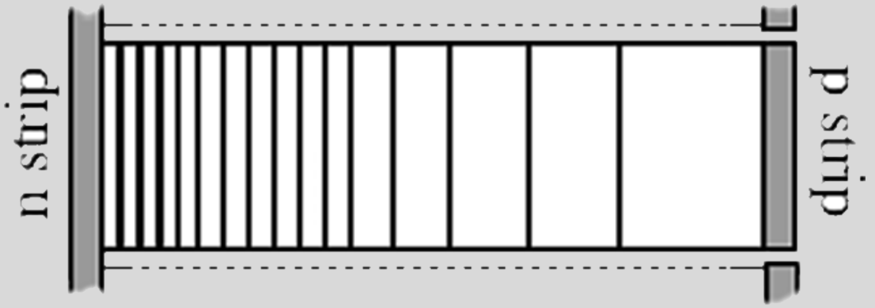
Takahashi Group DSSD
Graduate Student: Esen Salcin

Maximum Likelihood Estimation Results



- ~20 μm near anode
- ~50 μm in the middle of the detector
- Lower resolution under cathode strip.





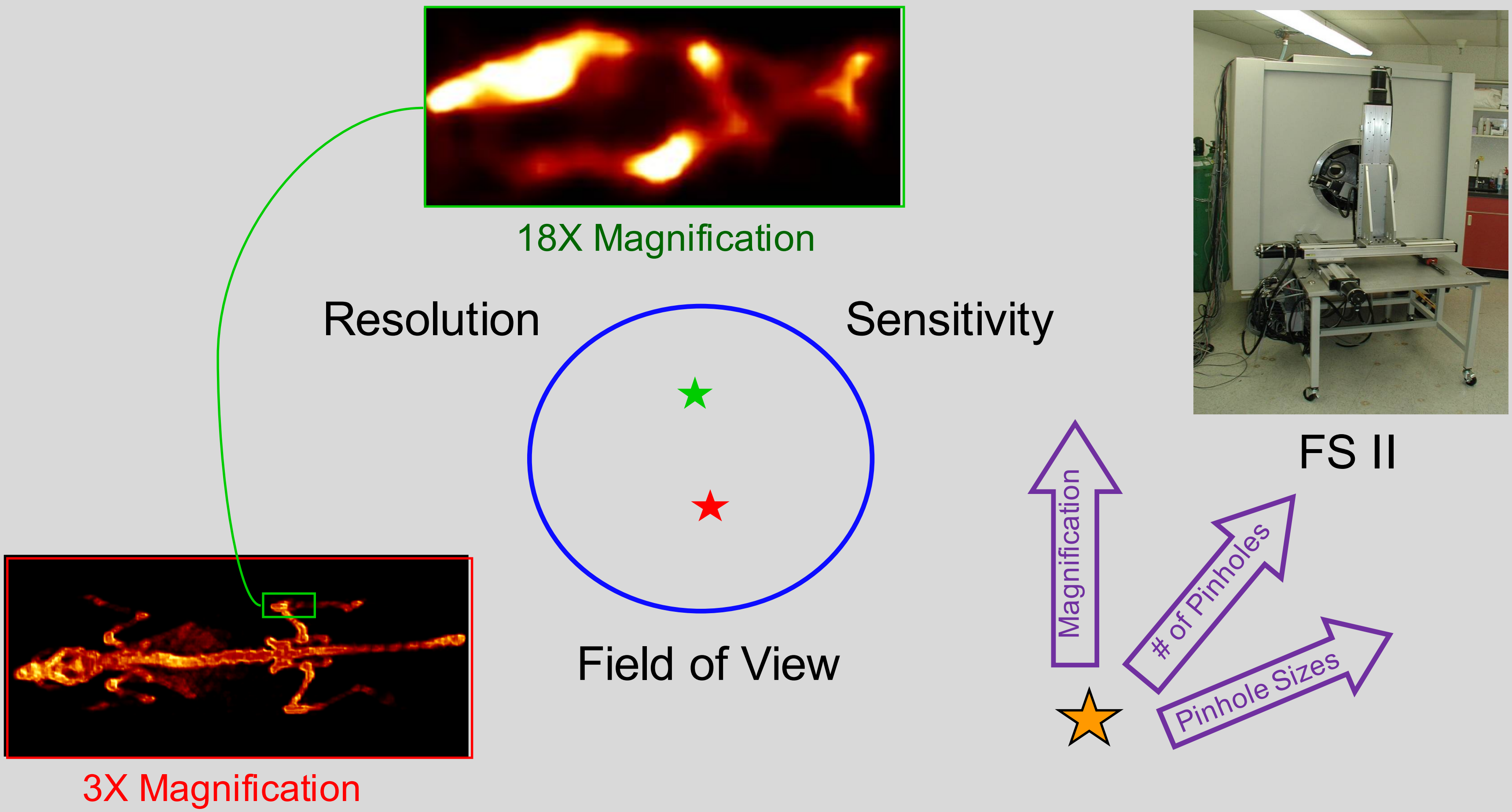
Takahashi Group DSSD
Graduate Student: Esen Salcin

Photon Processing

- Making use of all of the information carried by each gamma-ray photon
- Maintaining and using as many photon attributes as possible x, y, z, ε, t
- Using maximum-likelihood estimation when ever possible for attribute estimation
- Calibrate, calibrate, calibrate!

Multi-Scale Imaging

- Application-Specific Imager Configuration



Tomographic Imaging

Measured data

True system matrix

Known object

Random noise

Calibrate System

$$\mathbf{g} = \mathbf{H}\,\mathbf{f}_0 + \mathbf{n}$$

$$\hat{\mathbf{H}} = \arg\max_{\mathbf{H}} \left[\ln \mathrm{prob}\left(\mathbf{g} \middle| \mathbf{H}, \mathbf{f}_0 \right) \right]$$

Estimated system matrix

Measure data & reconstruct

$$\mathbf{g} = \mathbf{H}\,\mathbf{f} + \mathbf{n}$$

$$\hat{\mathbf{f}} = \hat{\mathbf{H}}^{\dagger}\mathbf{g}$$

Estimated (reconstructed) object

Reconstruction operator
(iterative algorithm)

Comparison of Iterative Algorithms

$$\hat{f}_n^{k+1} = \hat{f}_n^{k} \left\{ \frac{1}{S_n} \sum_{m=1}^{M} \frac{g_m H_{mn}}{\left[H\hat{\boldsymbol{f}}^{k} \right]_m} \right\}$$

Conventional reconstruction from images

- ML-EM – Works on projection data
- Requires binning into bitmaps

$$\hat{f}_n^{k+1} = \hat{f}_n^{k} \left\{ \frac{1}{T} \sum_{j=1}^{J} \frac{pr\left(A_j \,|\, \boldsymbol{r}_n\right)}{\sum_{n'=1}^{N} pr\left(A_j \,|\, \boldsymbol{r}_{n'}\right) S_{n'} \hat{f}_{n'}^{k}} \right\}$$

Photon-processing reconstruction

- LM-EM – Works on list-mode data (individual gamma-ray photons)
- Can include more attributes: *x, y, z,* $\mathcal{E}$*, t*
- *Doesn't require binning*
- Makes use of all measured attributes

Both versions suitable for implementation in GPU

Why It Always Comes Down to Better Detectors

Estimated event attributes (from detector signals) for j^{th} photon

Emission location in object in n^{th} voxel

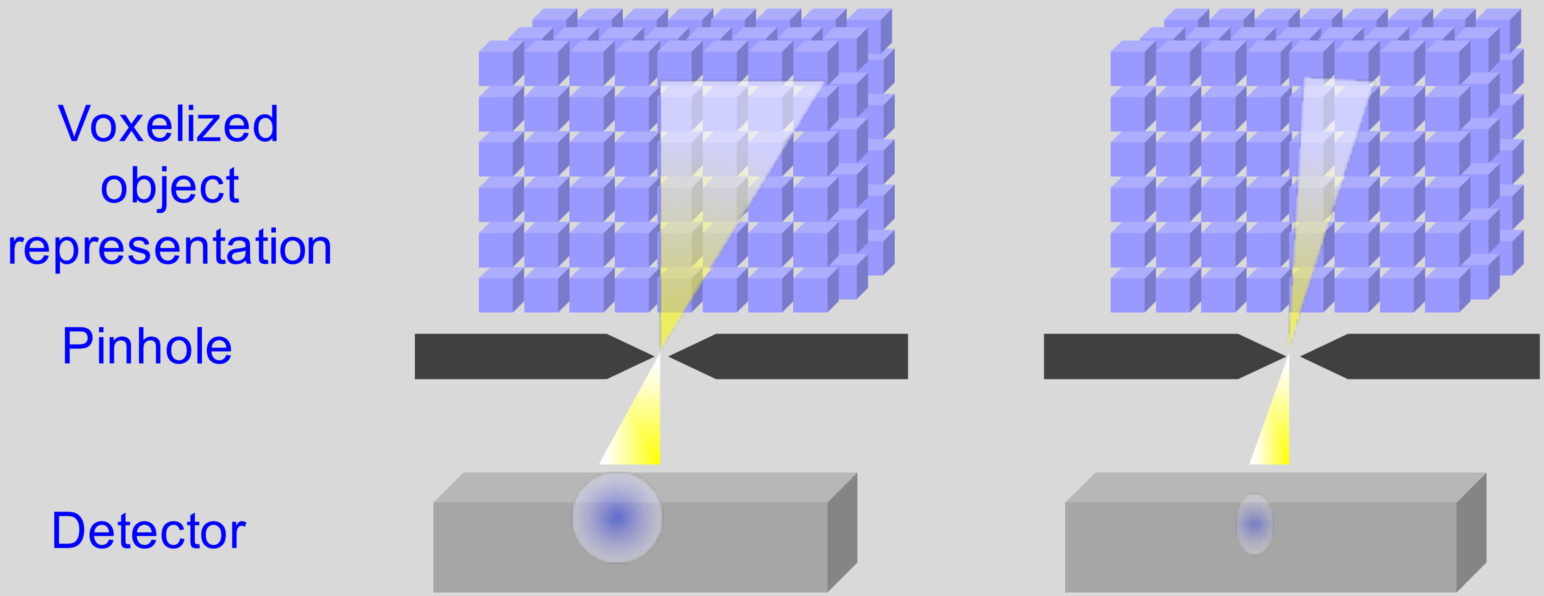
$$pr\left(\boldsymbol{A}_j \middle| \boldsymbol{r}_n\right) = pr\left(\hat{\varepsilon}_j, \hat{r}_j \middle| \boldsymbol{r}_n\right)$$

$$= \int_{Energy} \int_{Vol.\,Det} pr\left(\hat{r}_j \middle| r_j\right) pr\left(\hat{\varepsilon}_j \middle| \varepsilon_j\right) pr\left(\varepsilon_j, r_j \middle| \boldsymbol{r}_n\right) d\varepsilon_j \, d^3 r_j$$

Spatial and energy resolution in detector (detector physics)

Probability of having true attributes if originated in object in n^{th} voxel (emission and propagation physics)

Fundamental Operation is Back Projection



- Monte Carlo sampling around estimated event attributes is approximation to full integrals
- 3D-position estimation minimizes parallax error
- Possible to add all physics effects (scatter, absorption, fluorescence x-rays...)

Challenges in Clinical Application

- Scaling – need for much larger detector areas
- Much higher probabilities of attenuation and scatter
- Need for highly specific radiotracers
- Practical limitations on imaging time
- Patient motion

Future Applications of Nuclear Imaging in Oncology

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- Identify and target tumor stem cells
- Detect and characterize tumor-associated exosomes


THANK YOU! QUESTIONS?