Nuclear Medical Imaging — Techniques and Challenges

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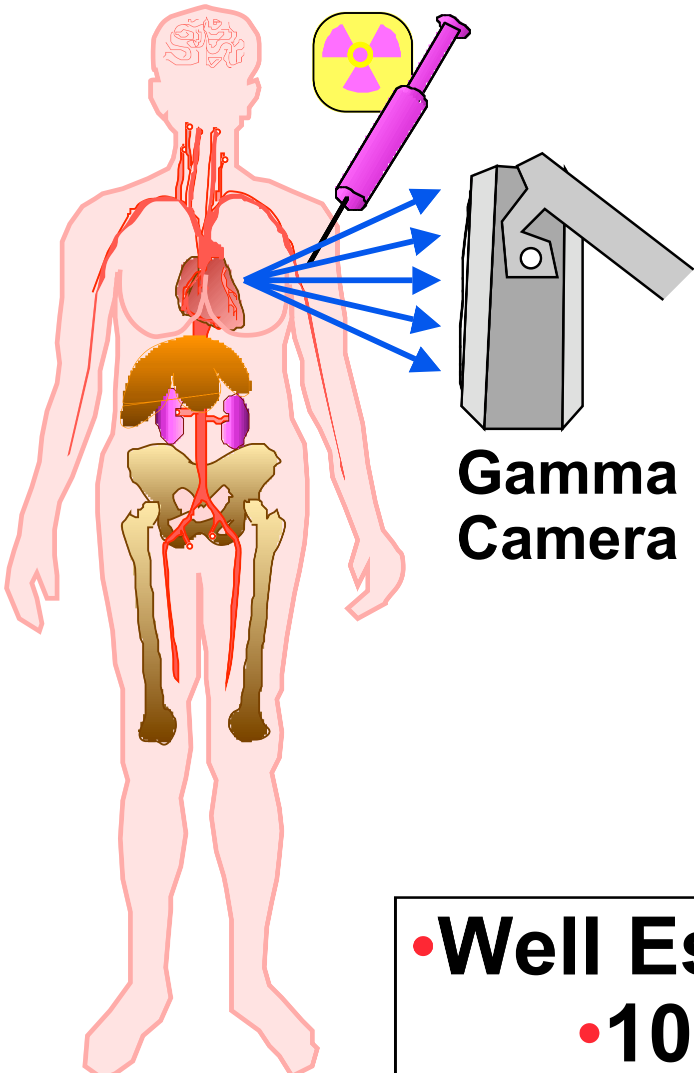
Outline:

- Introduction
- Requirements
- Opportunities
- Our Research…

Nuclear Medicine



- Patient injected with *small* amount of radioactive drug.
- Drug localizes in patient according to metabolic properties of that drug.
- Radioactivity decays, emitting gamma rays.
- Gamma rays that exit the patient are imaged.

•Well Established Clinical Technique
•10 Million Studies Annually

Ideal Tracer Isotope

- Interesting Chemistry
  - Easily incorporated into biologically active compounds.
- Appropriate Energy
  - Too low ⇒ absorbed in patient.
  - Too high ⇒ passes through detector.
- 1 Hour Half-Life
  - Maximum study duration is 2 hours.
  - Gives enough time to do the chemistry.
- Easily Produced
  - Short half life ⇒ local production.

Common Gamma-Emitting Tracer Isotopes

^{99m}Tc

+ 140 keV Gamma Ray.
– Chemically Awkward.
+ Generator Produced.

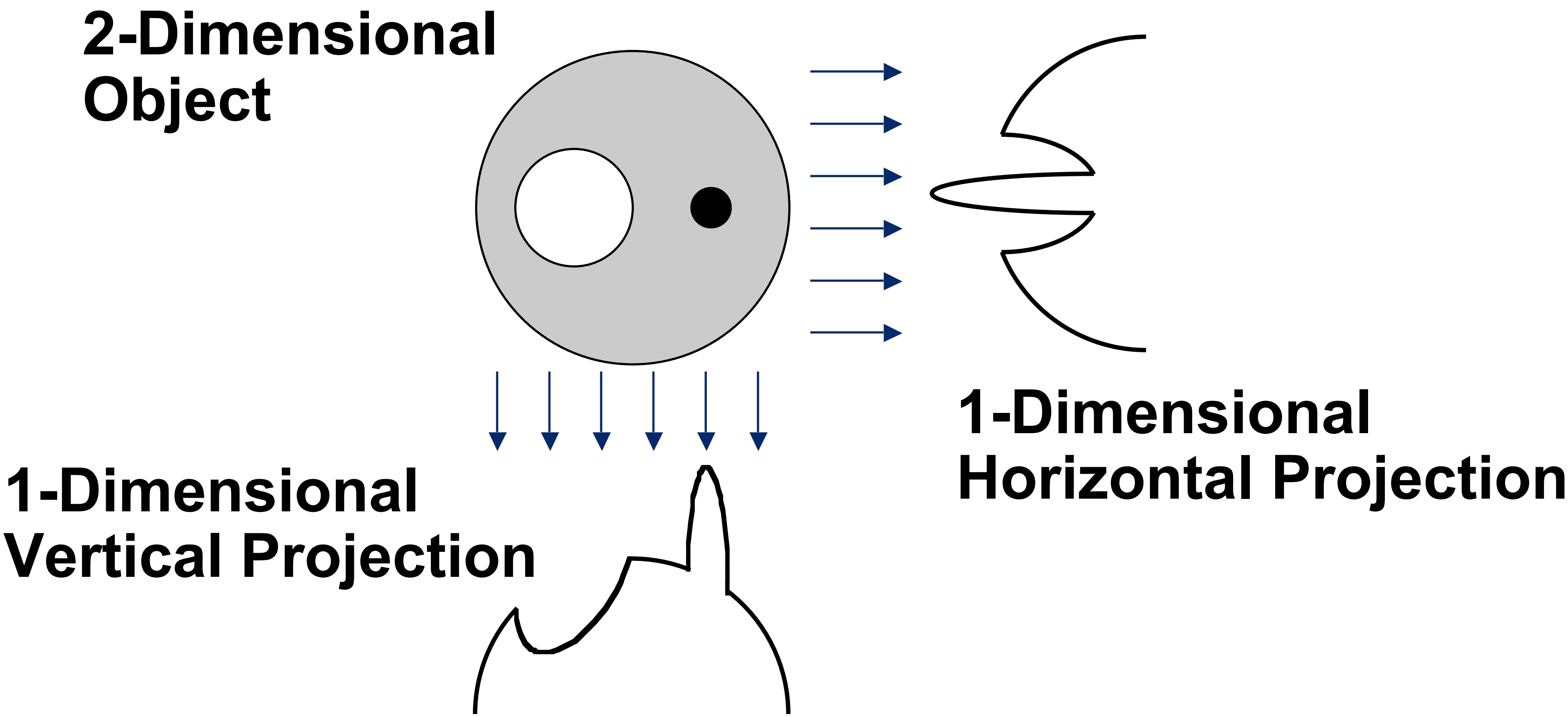
^{201}Tl

+ 80 keV Gamma Ray.
– Chemically Awkward.
+ Generator Produced.

^{123}I

+ 160 keV Gamma Ray.
± Chemically So-So.
+ Generator Produced.

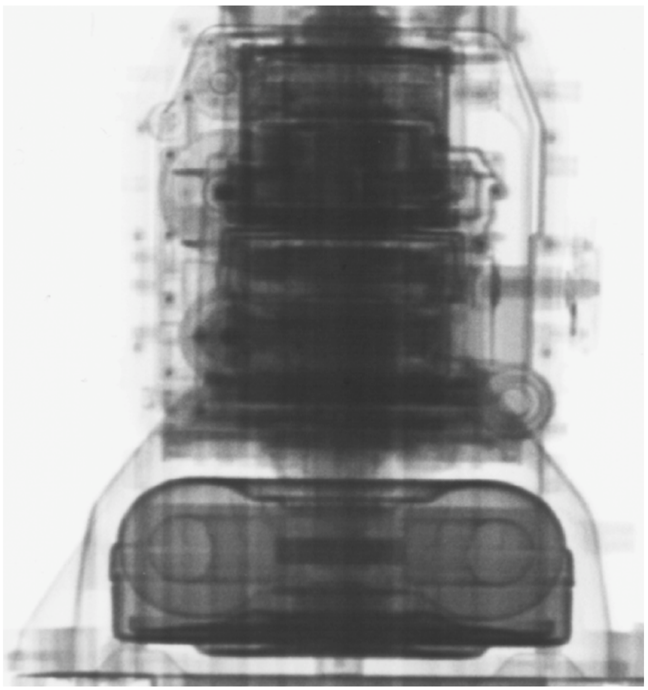
Principle of Computed Tomography



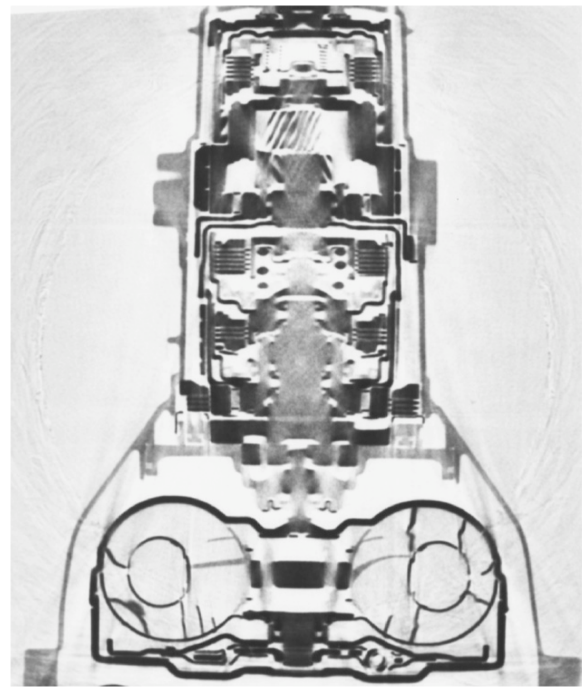
By measuring all 1-dimensional projections of a 2-dimensional object, you can reconstruct the object

Computed Tomography

Planar X-Ray



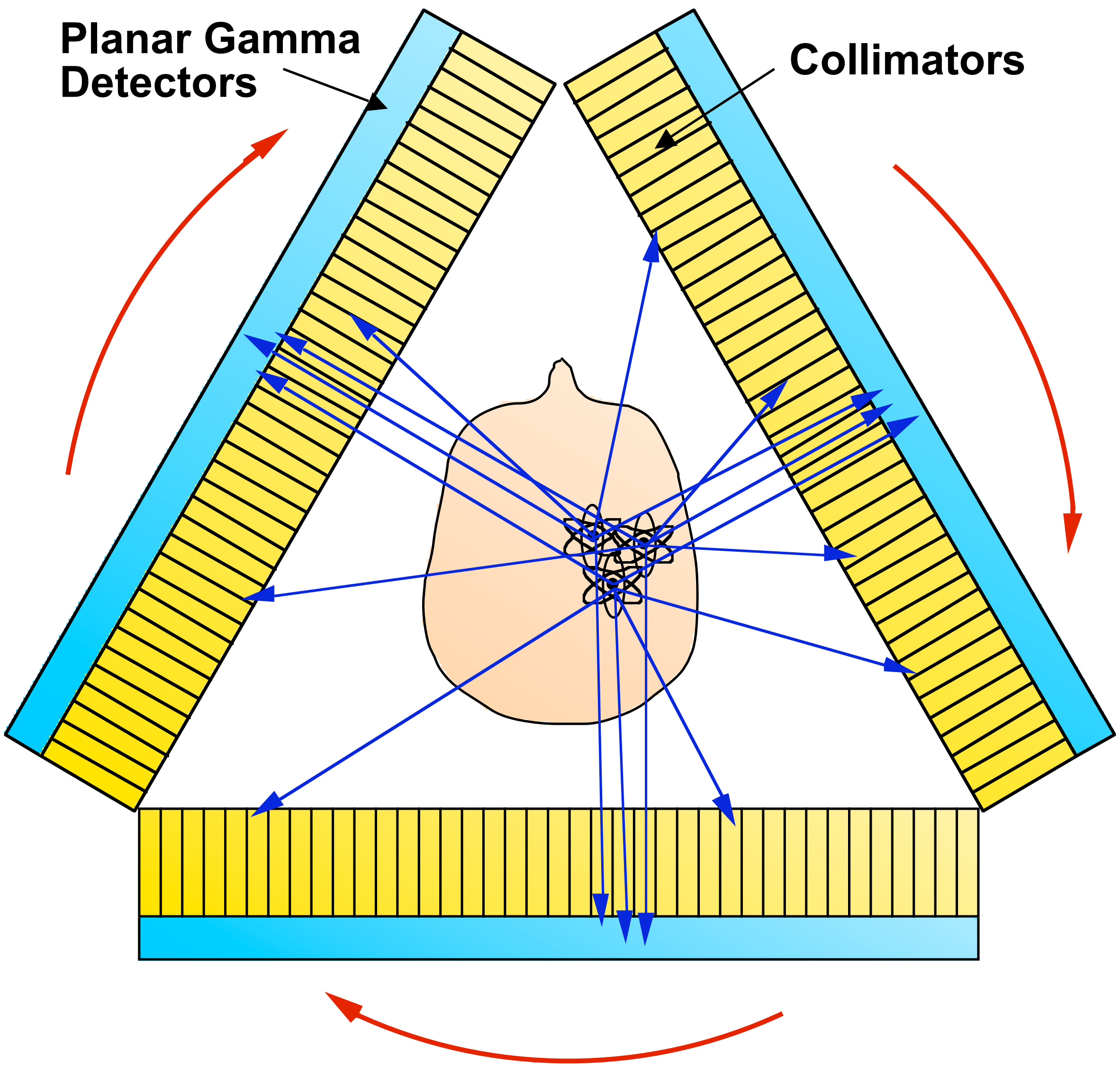
Computed Tomography



Separates Objects on Different Planes

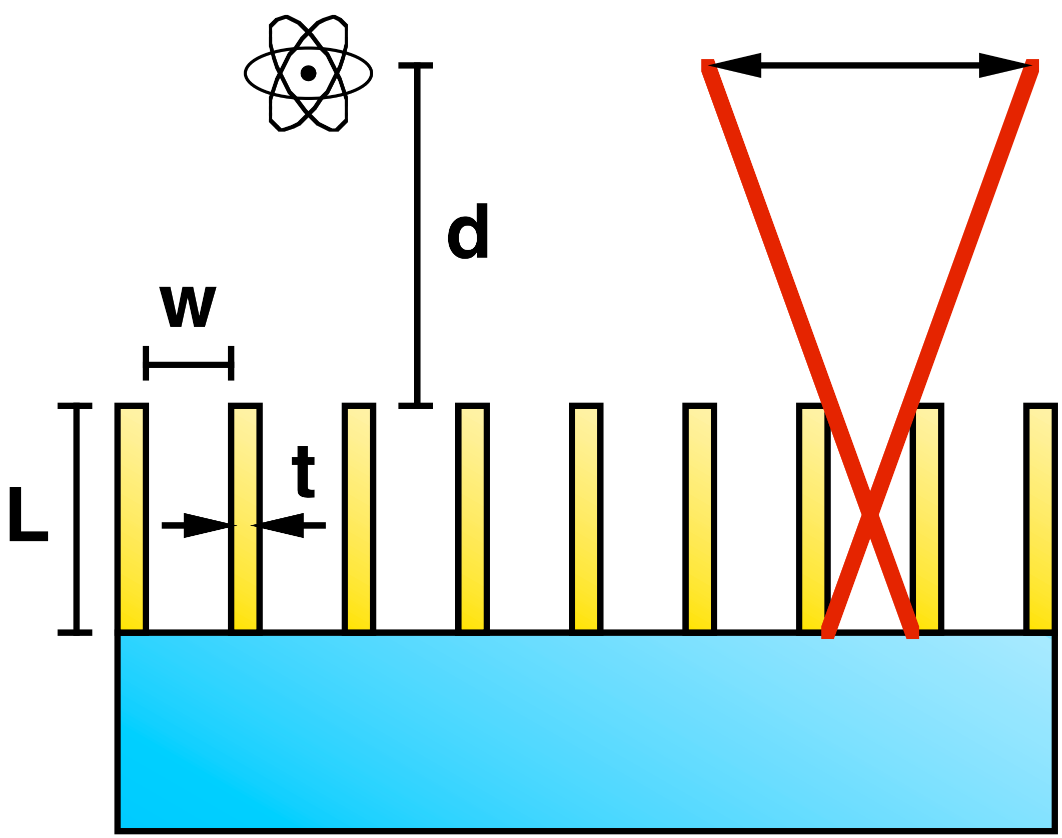
Images courtesy of Robert McGee, Ford Motor Company

Single Photon Emission Computed Tomography (SPECT)



- One, two, or three imaging heads (cost / performance tradeoff)
- Parallel hole collimators.
- Multiple views obtained by rotating the imaging heads around the patient.

Collimator Tradeoffs



$$\text{Resolution} = 2\frac{w}{L}\left(d + \frac{L}{2}\right)$$

$$\text{Efficiency} \propto \left(\frac{w}{L}\right)^2$$

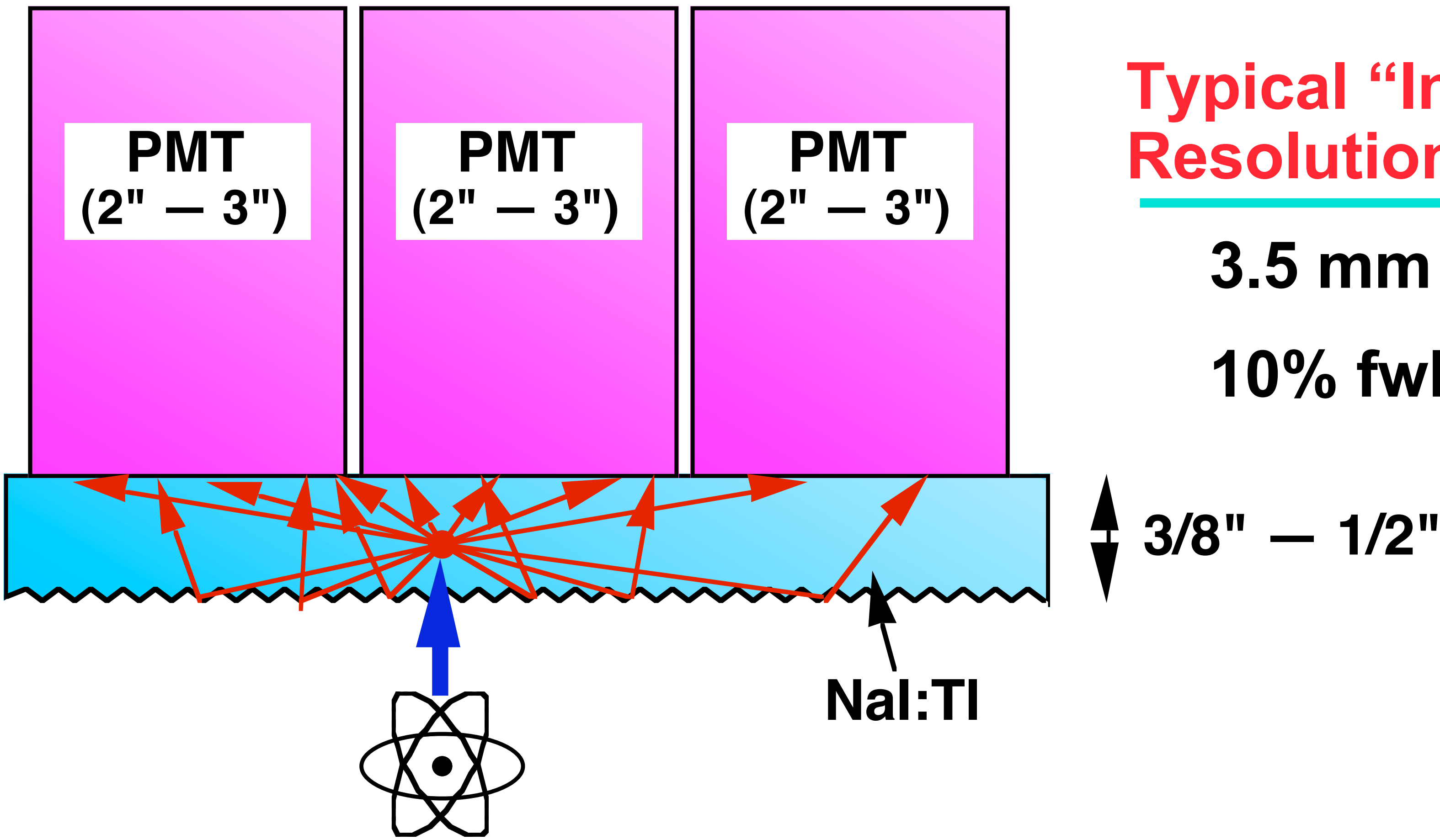
Typical Values:

w= 2 mm
L= 30 mm
t= 0.25 mm

Resol. (@5 cm) = 6 mm
Efficiency = 0.02%

Collimator Dominates Imaging Performance

SPECT "Anger Camera" Detector



Typical "Intrinsic" Resolution:

3.5 mm fwhm

10% fwhm

Position Measured by PMT Analog Signal Ratio

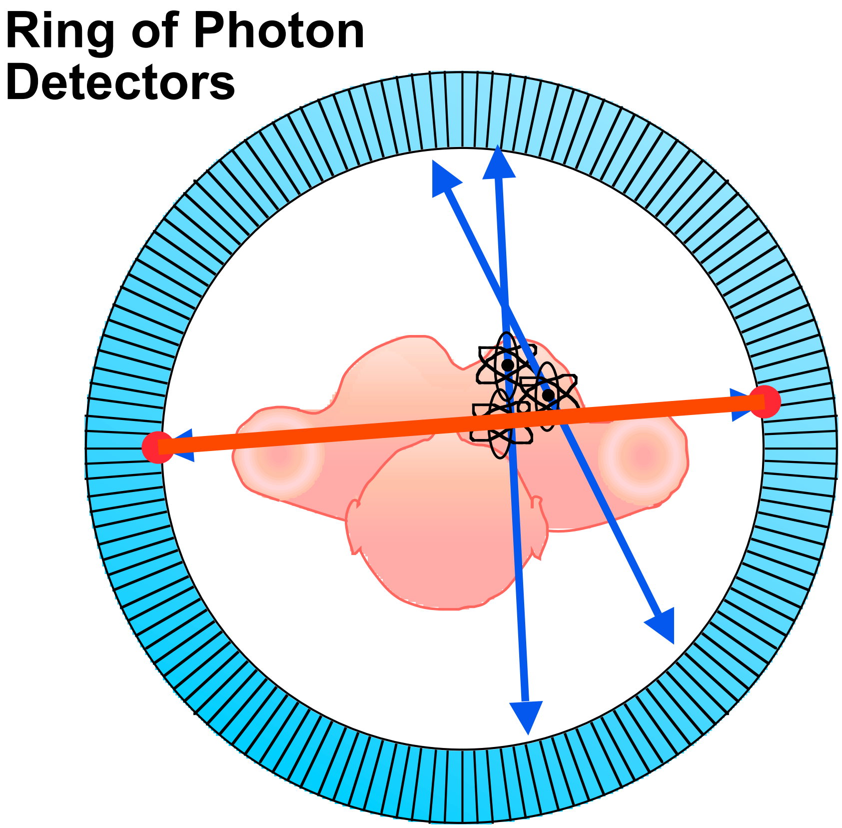
SPECT Camera

- Cost ~$0.5 – $1 million.
- Spatial resolution ~1 cm.

Common Positron-Emitting Tracer Isotopes

	+ 2 hour half-life.
^{18}F	± Chemically very good (replaces H).
	– Cyclotron produced.
	+ Chemically excellent.
^{15}O, ^{11}C, ^{13}N	– 2 to 20 minute half-life.
	– Cyclotron produced.
	+ Generator produced.
^{82}Rb	– 2 minute half-life.
	– Chemically OK (acts like Na and K).

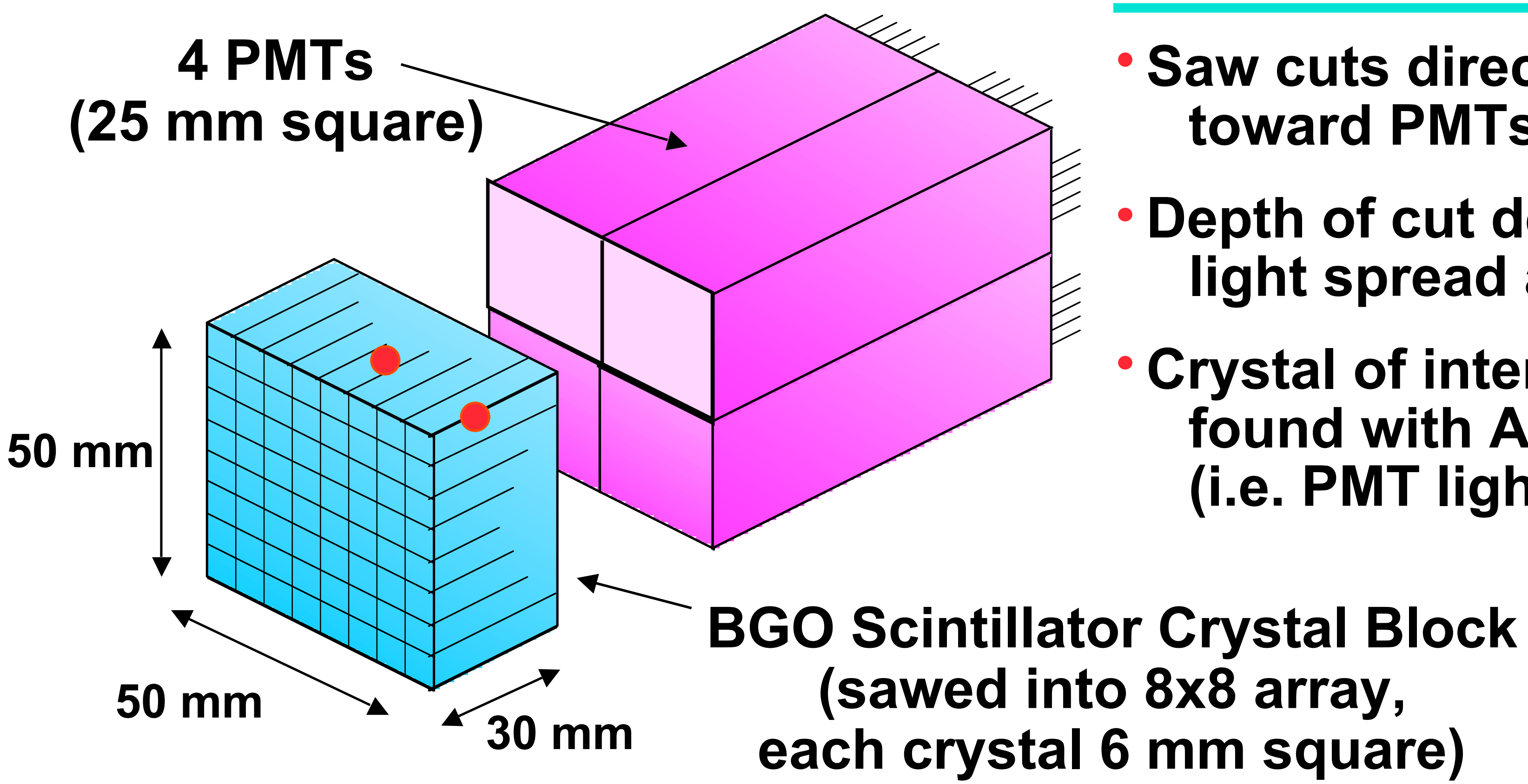
Positron Emission Tomography (PET)



- Radionuclide decays by emitting a positron (β^+).
- β^+ annihilates with e^- from tissue, forming back-to-back 511 keV photon pair.
- 511 keV photon pairs detected via time coincidence.
- Positron lies on line defined by detector pair.

- **Detects Pairs of Back-to-Back 511 keV Photons**
- **No Collimator Needed $\Rightarrow$ High Efficiency**

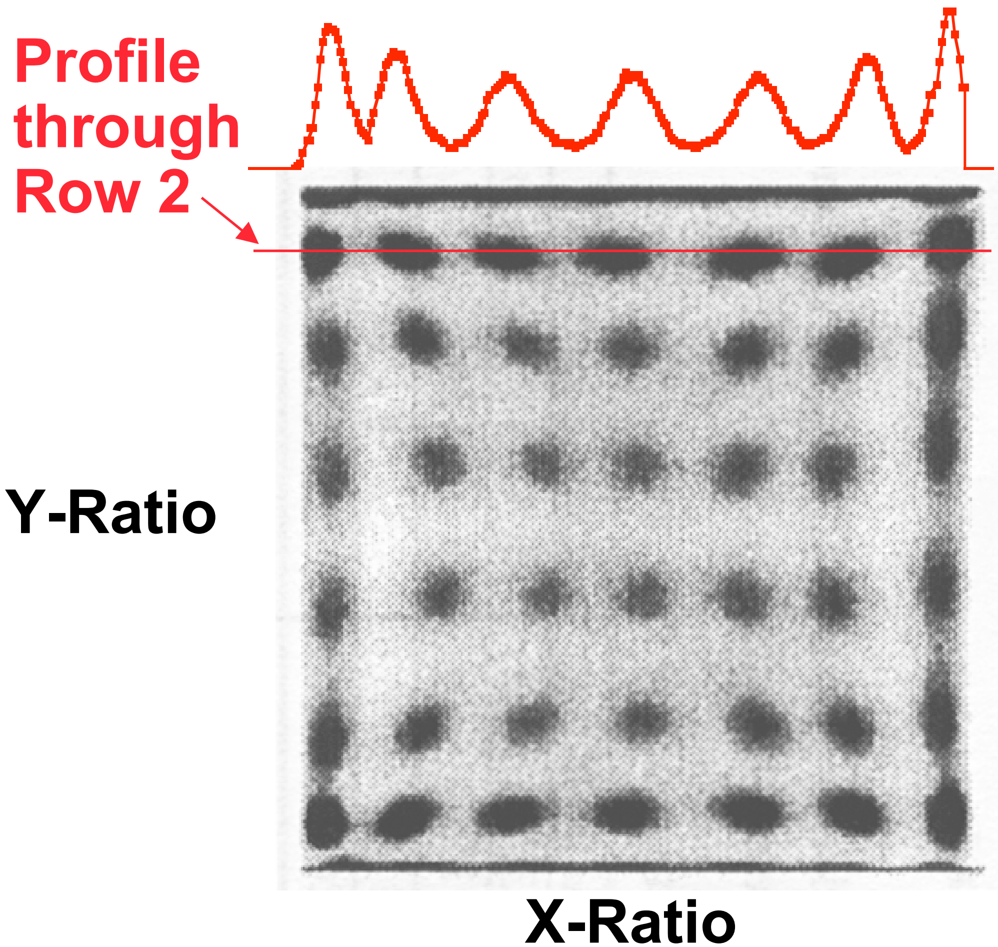
PET "Block Detector" Design



- Saw cuts direct light toward PMTs.
- Depth of cut determines light spread at PMTs.
- Crystal of interaction found with Anger logic (i.e. PMT light ratio).

Good Performance, Inexpensive, Easy to Pack

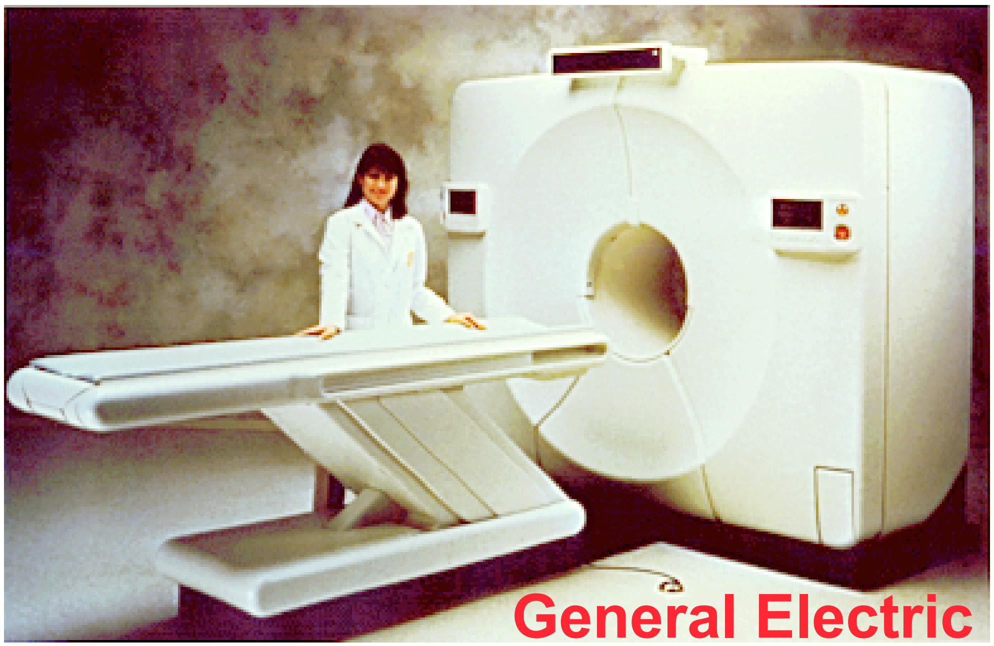
Crystal Identification with Anger Logic



- Uniformly illuminate block.
- For each event, compute X-Ratio and Y-Ratio, then plot 2-D position.
- Individual crystals show up as dark regions.
- Profile shows overlap (i.e. identification not perfect).

Can Decode Up To 64 Crystals with BGO

PET Cameras



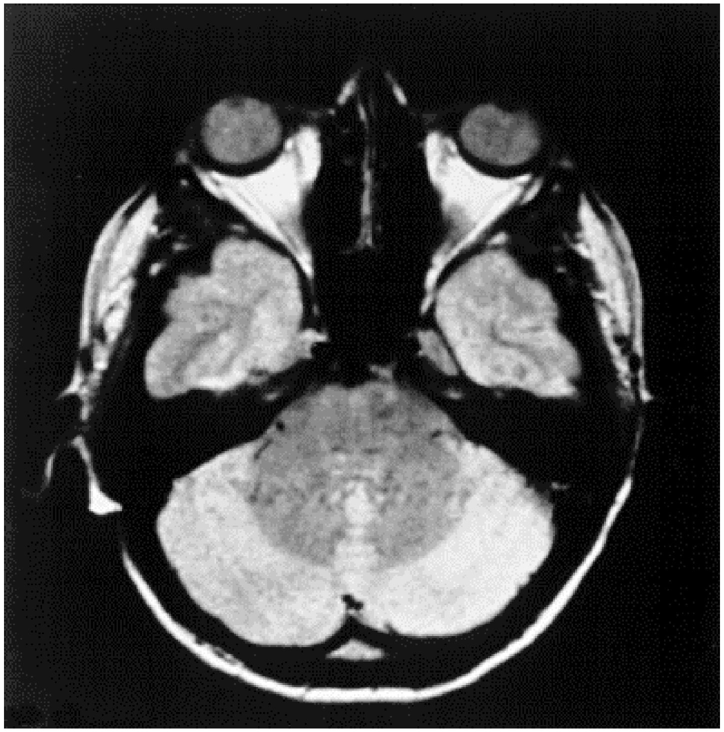
- Cost ~$1 – $2 million.
- ~5 mm spatial resolution.
- Often sold with x-ray CT attached.

Common Clinical Uses of Nuclear Medicine

- Cancer / Oncology
- Heart Tissue Viability
- Brain Dysfunction
  - Stroke
  - Epilepsy
  - Alzheimer's Disease

Images Function, Not Structure!

MRI & Nuclear Medicine Images of Epilepsy



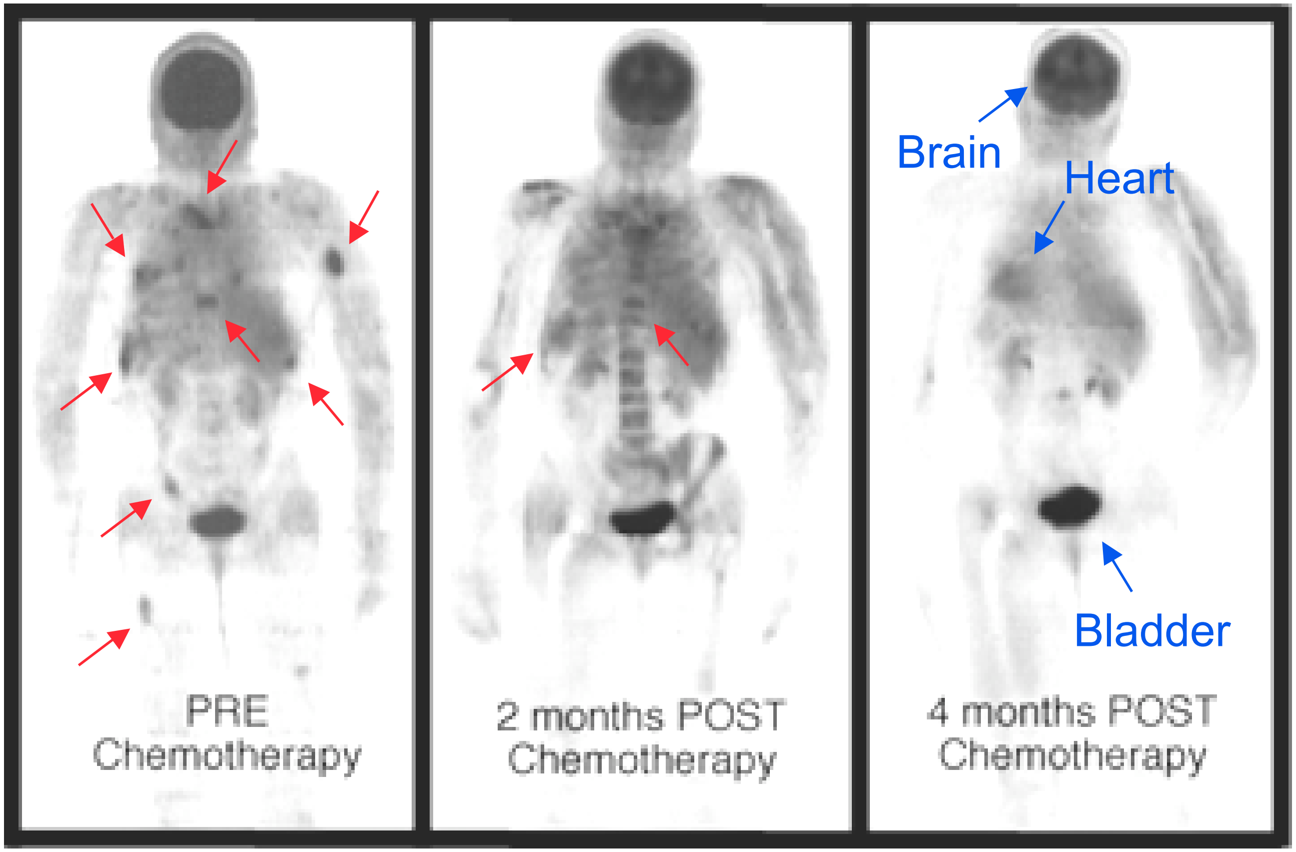
MRI

Nuclear Medicine

- MRI "Sees" Structure with 0.5 mm Resolution
- Nuclear Medicine "Sees" Metabolism with 5.0 mm Resolution

Breast Cancer

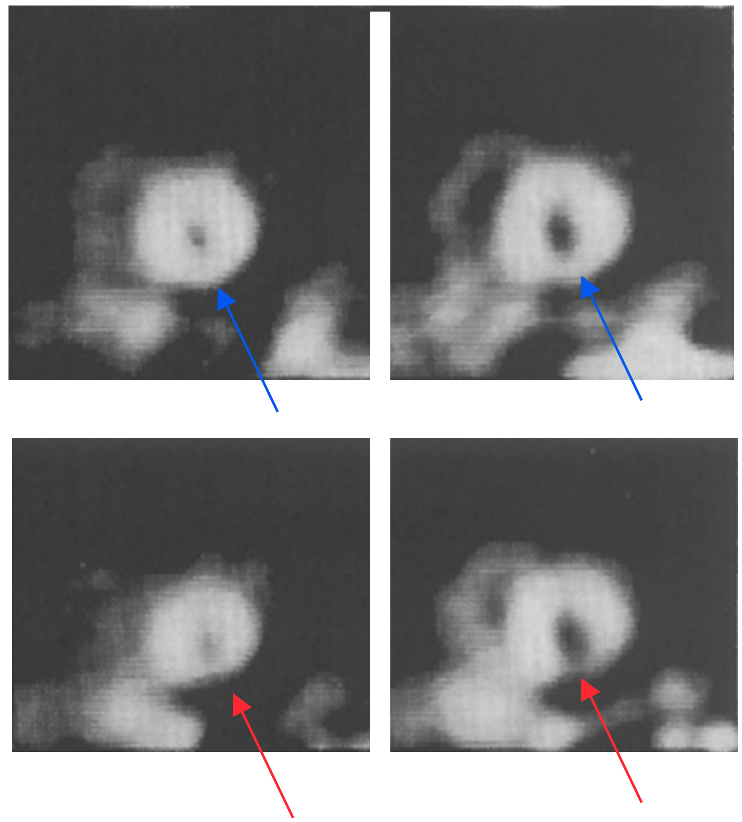
Metastases Shown with Red Arrows



Normal Uptake in Other Organs Shown in Blue

- Determine Disease Extent / Plan Treatment
- Measure Effectiveness of Therapy

Cardiac Disease

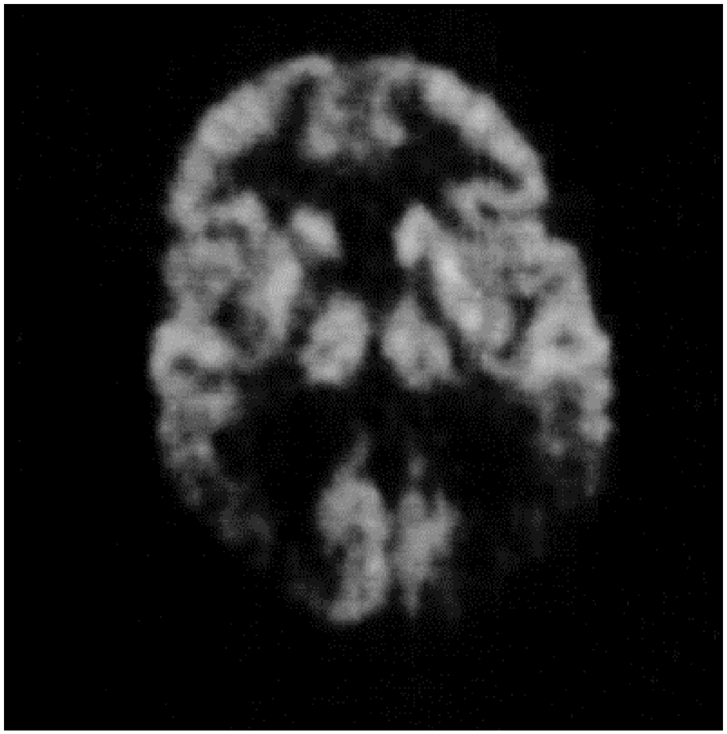


Rest

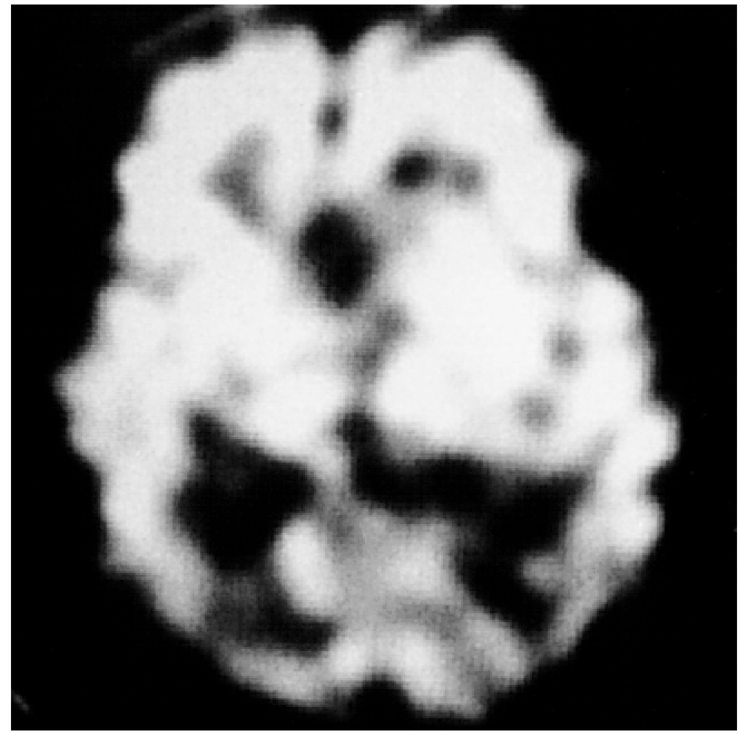
Stress

Cardiac Stress
Can Reduce Blood Flow
to Regions in the Heart

Comparison of PET & SPECT Images (Alzheimer's Disease Patient)



PET



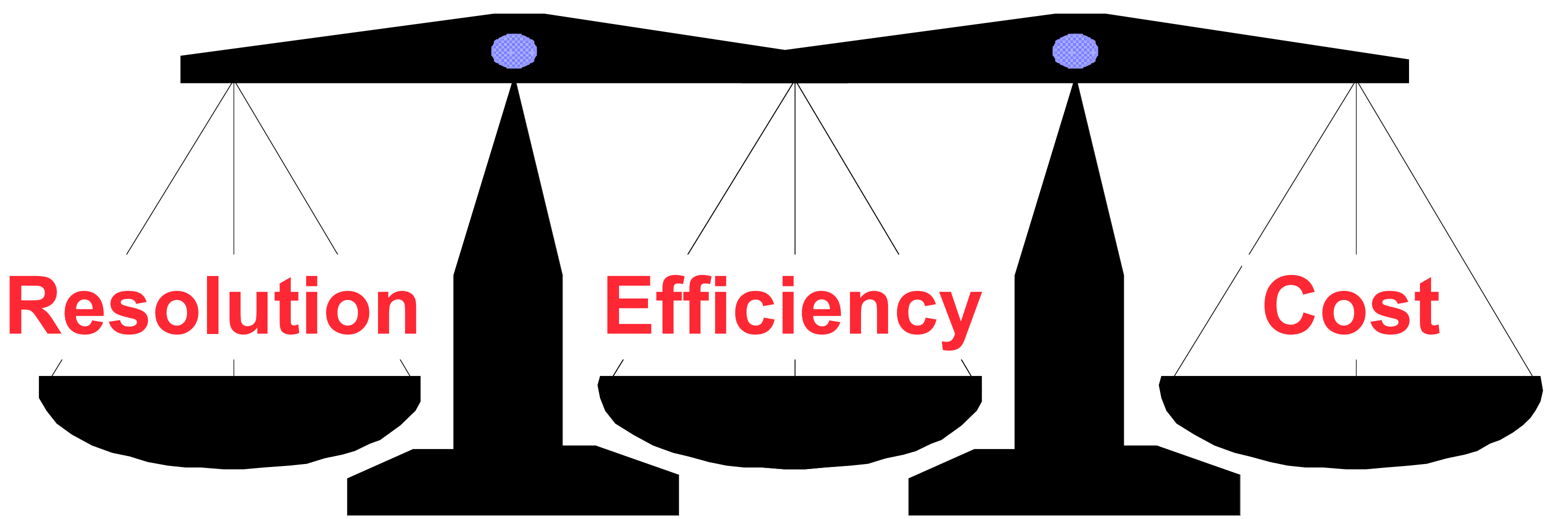
SPECT

- PET has Higher Resolution, Higher Efficiency
- SPECT is Cheaper and Better Established Clinically

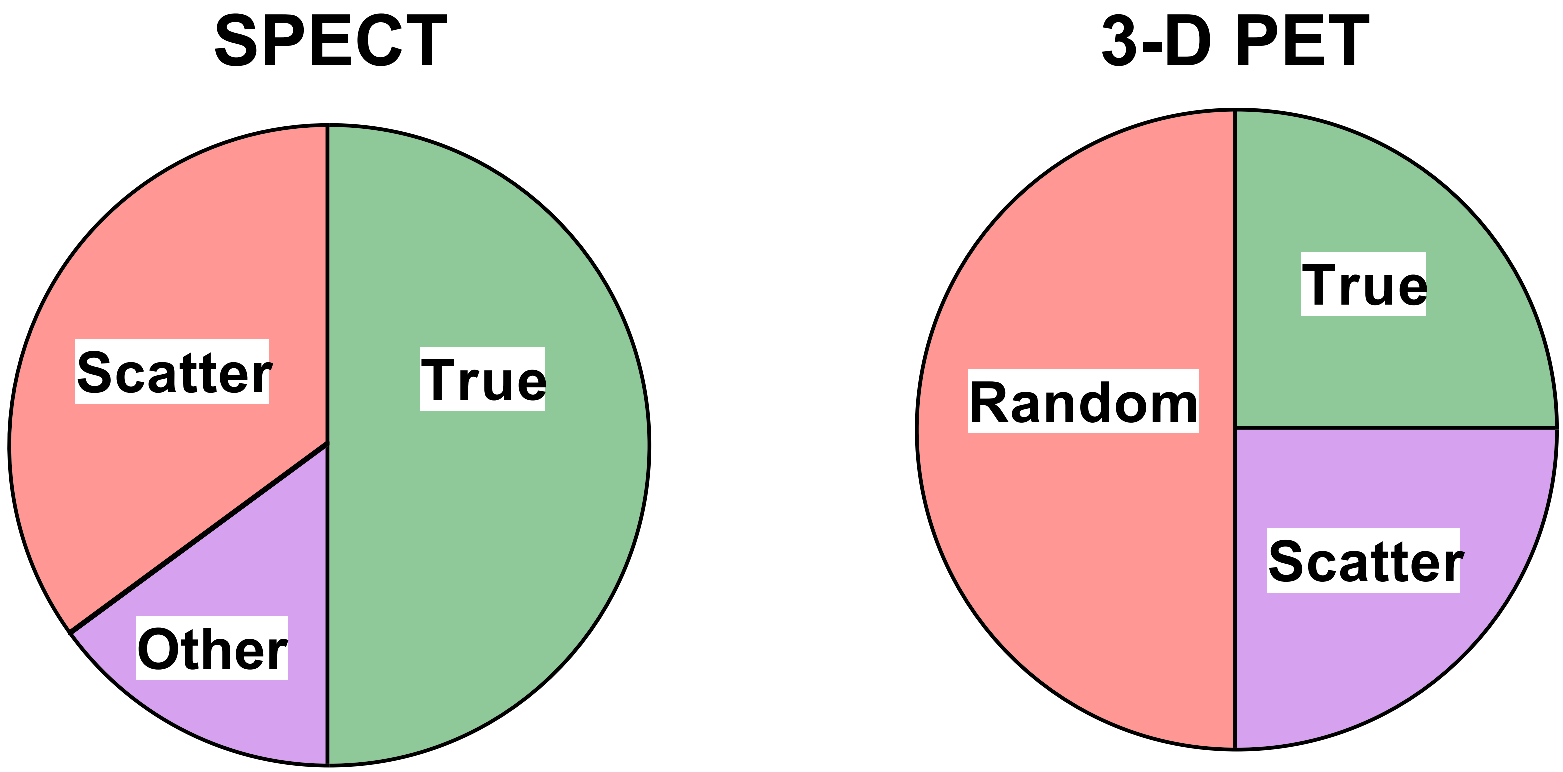
What Does Nuclear Medicine Need?

Improved Signal-to-Noise Ratio

(without sacrificing other properties)



Is This Reasonable?



- Spatial Resolution is Near Theoretical Limit
- Can Increase SNR by Reducing Backgrounds

SPECT Detector Requirements

Photomultiplier Tubes (~50 / head)

Scintillator Crystal (NaI:Tl, 50 cm square x 1 cm thick)

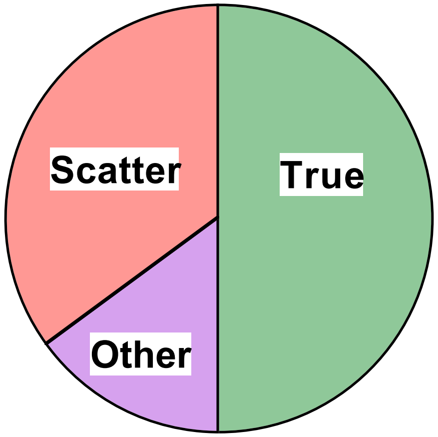
At 140 keV:

- High Efficiency (>85%)
- Good Energy Resol. (<15 keV fwhm)
- High Spatial Resol. (<4 mm)
- Low Cost (<$15/cm^2)
- "Short" Dead Time (<2000 μs cm^2)

Based on the "Anger Camera"

*Image courtesy of L. Shao, Philips Medical Systems

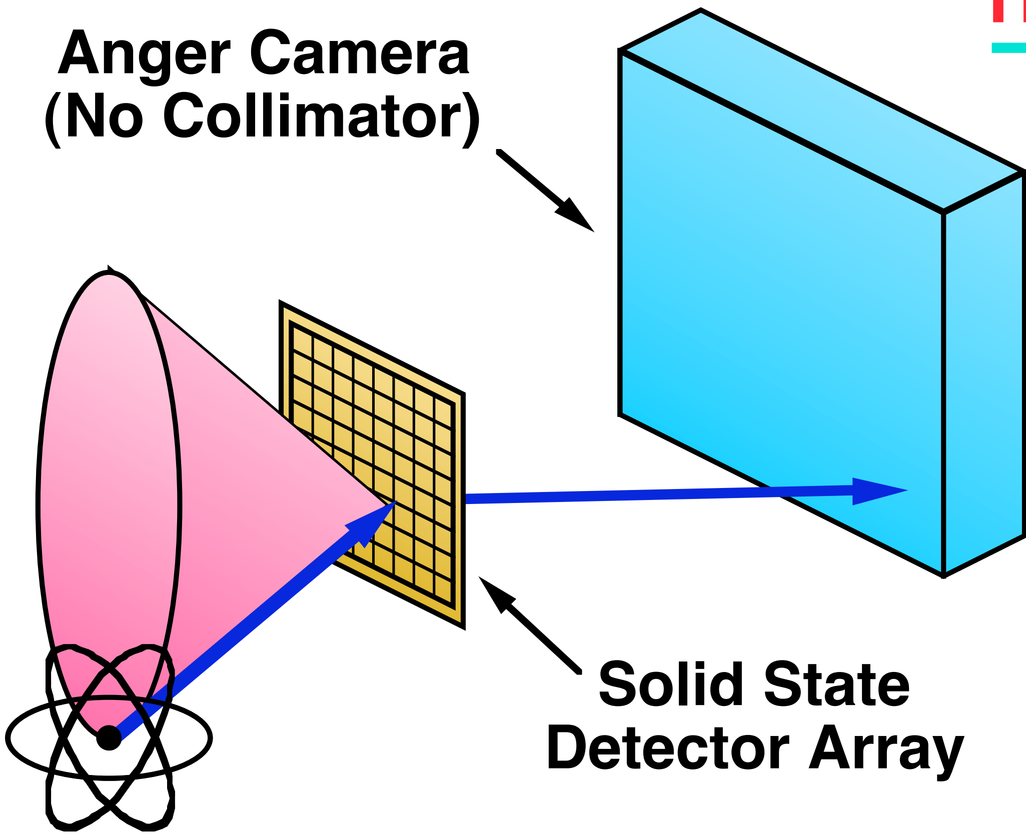
Opportunities for SPECT



- Better Energy Resolution
  - Presently 9% fwhm for 140 keV
  - Over 35% of SPECT events are scatter
  - Scatter fraction linearly proportional to resolution
  - Other effects dominate if resolution <4% fwhm
- Lower Cost
  - Less expensive scintillator & photodetector
  - Fewer PMTs
- Better Resolution / Sensitivity Tradeoff
  - Compton Cameras?

Collimators, NaI:Tl, & PMTs Used for >40 Years...

Compton Cameras



How They Work:

- Measure first interaction with good *Energy* resolution.
- Measure first and second interaction with moderate *Position* resolution.
- Compton kinematics determines scatter angle.
- Source constrained to lie on the surface of a cone.

- **No Collimator, but Reconstruction Difficult**
- **Progress, but the Jury is Still Out...**

PET Detector Requirements

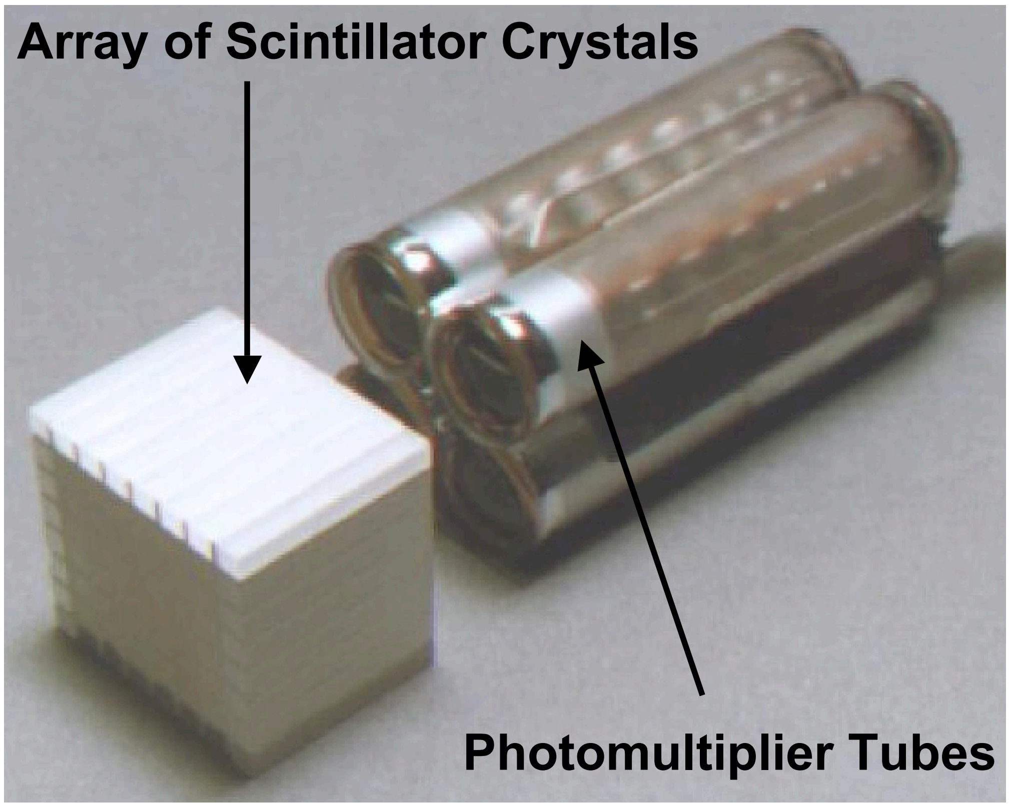


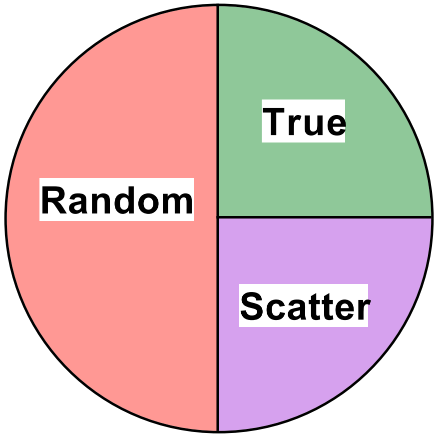
*Image courtesy of M. Casey, CPS Innovations

At 511 keV:

- **High Efficiency** (>85%)
- **High Spatial Resolution** (<5 mm)
- **Low Cost** (<\$100/cm^2)
- **Short Dead Time** (<1 μs cm^2)
- **Good Timing Resolution** (<5 ns fwhm)
- **Good Energy Resolution** (<100 keV fwhm)

Based on BGO or LSO "Block Detector"

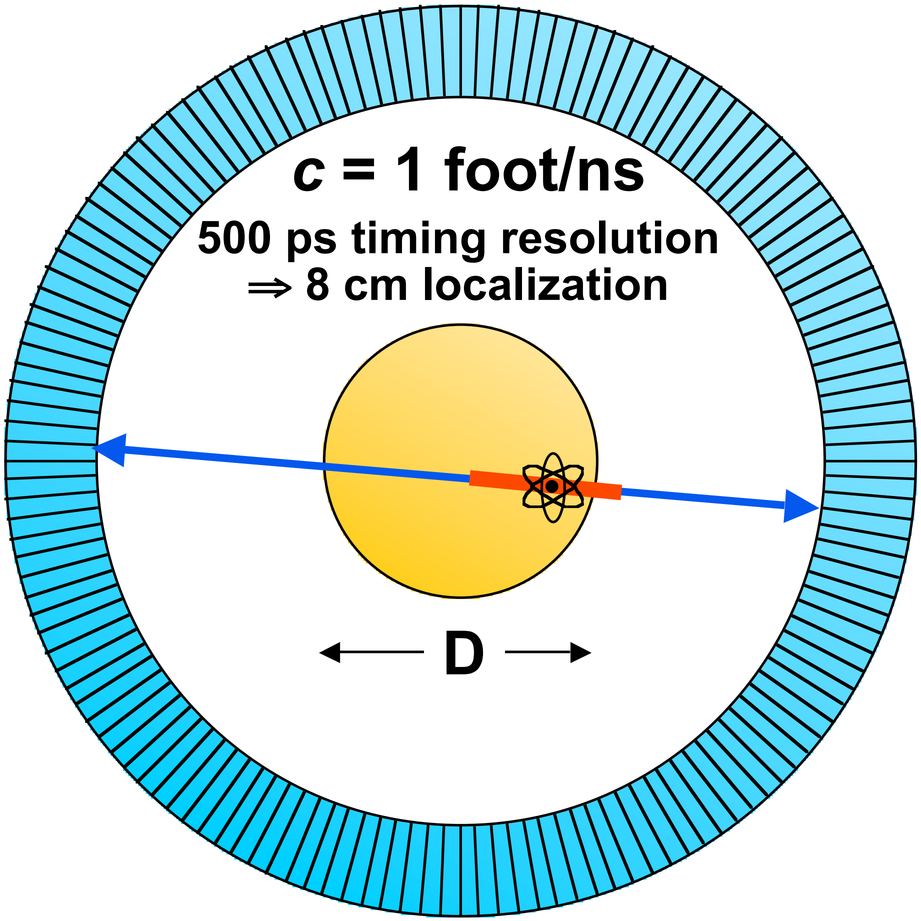
Opportunities for PET



- **Uniform Spatial Resolution**
  - Measure depth of interaction
- **Better Energy Resolution**
  - Scattered events often outnumber true events
- **Lower Cost**
  - Less expensive scintillator & photodetector
  - Fewer PMTs
- **Better Timing Resolution**
  - Reduce random events (up to 50% of total events)
  - Time-of-flight PET to reduce noise variance (by ~5x)

Significant Room for Improvement

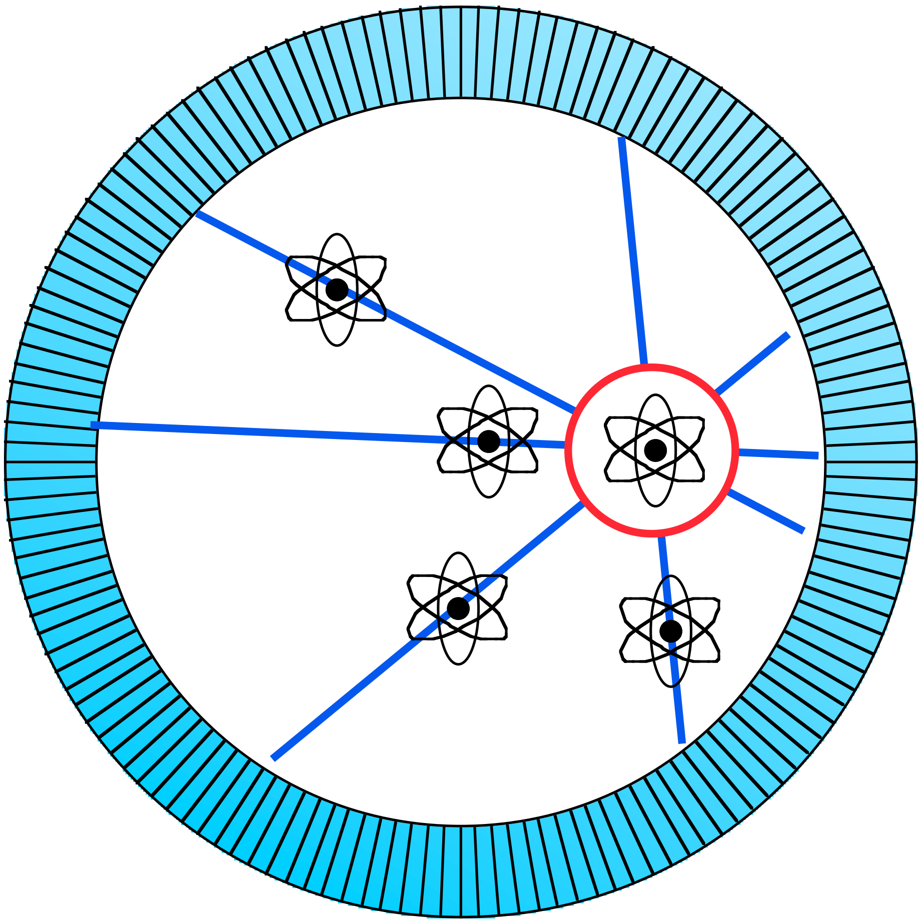
Time-of-Flight in PET



- Can localize source along line of flight.
- Time of flight information reduces noise in images.
- Time of flight cameras built in the 80's with BaF_2 and CsF.
- These scintillators forced compromises that prevented TOF from flourishing.
- TOF not dead, just dormant?

- Variance Reduction Given by $2D/c\Delta t$
- 500 ps Timing Resolution ⇒ 5x Reduction in Variance!

Statistical Noise in PET



~~If there are *N* counts in the image,~~

~~$$SNR = \frac{N}{\sqrt{N}}$$~~

Signals from Different Voxels are Coupled
⇒ Statistical Noise Does Not Obey Counting Statistics

New Scintillator Materials

- Ancient History
  - LSO, LuAP, LuYAP
- Last Few Years
  - $RbGd_2Br_7$, $LaCl_3$, $LaBr_3$
- Very Recently
  - LPS , LuI_3
- The Future
  - Semiconductor Scintillators
  - Ceramic Scintillators

Lots of New Scintillators Developed...

$LaBr_3$ and $LaCl_3$ are Promising for SPECT...

1″ $LaCl_3$:Ce

Compared to NaI:Tl:

- **Excellent Energy Resolution**
  (reduce scatter fraction from 35% to 25%)
- **High Light Output**
  (use larger diameter PMTs
  ⇒ cuts PMT cost by factor of 2)
- **Short Decay Time**
  (little value for SPECT)
- **$LaBr_3$ also has Shorter Attenuation Length**
  (reduce scintillator volume by 25%)

Economical Growth is *Absolutely* Necessary

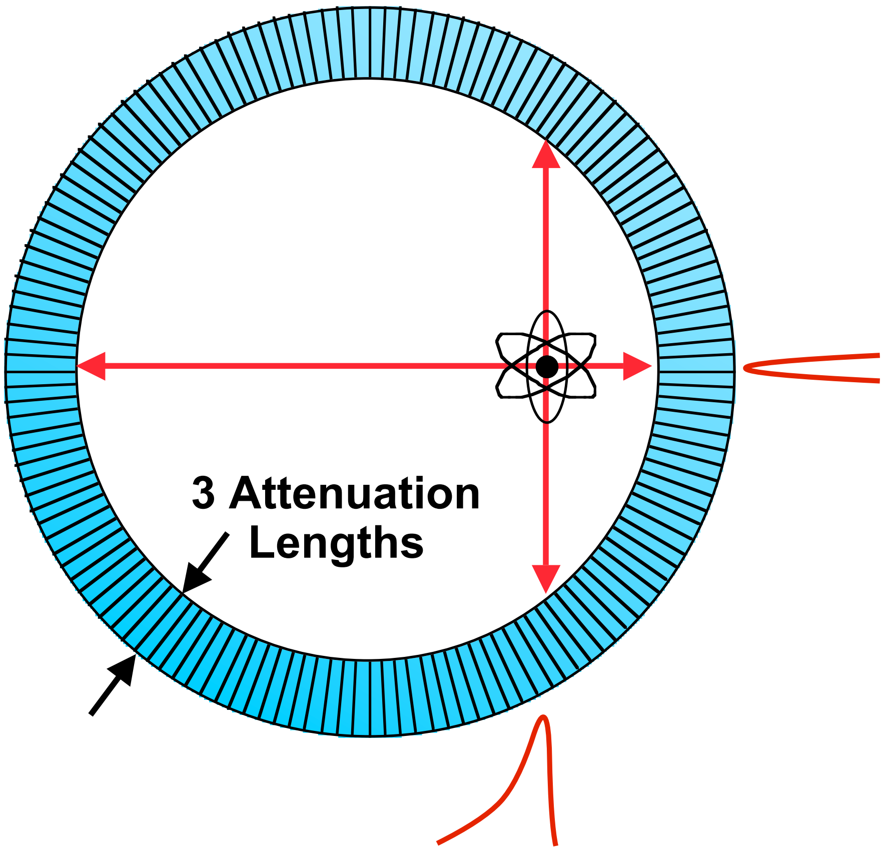
*Image courtesy of M. Balcerzyk, Soltan Institute

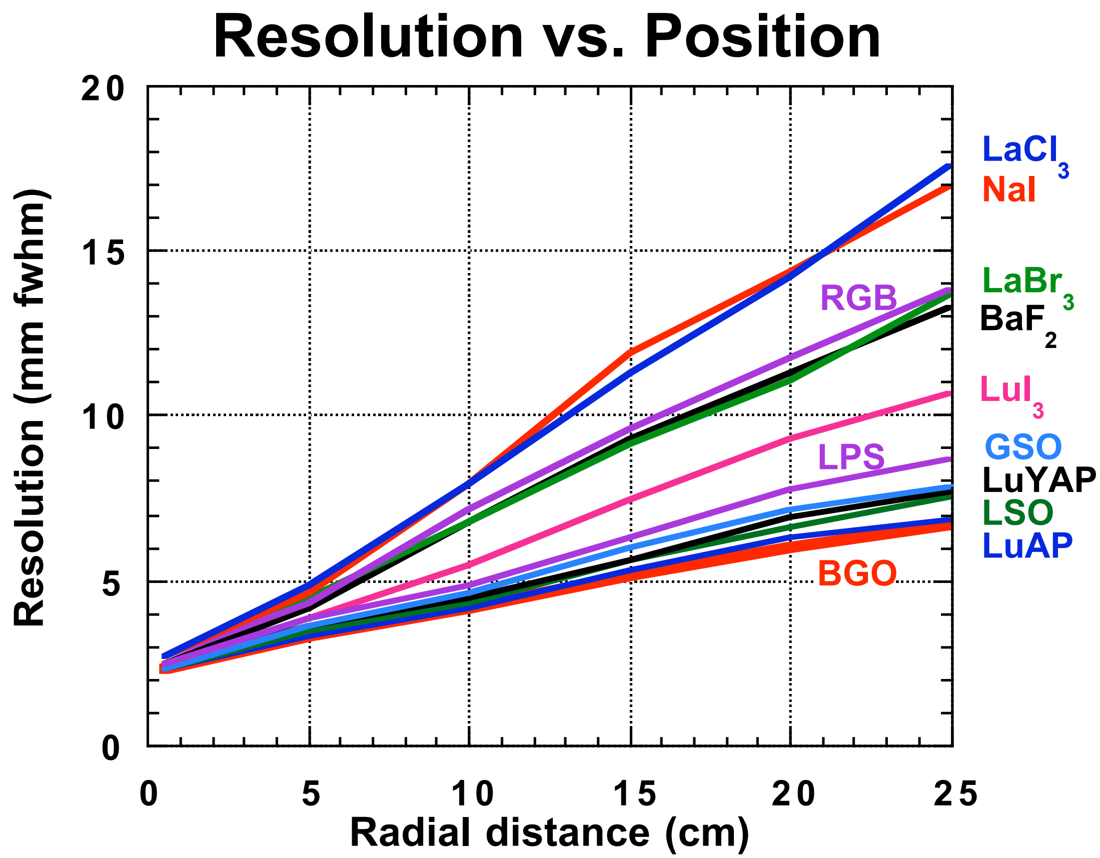
Promising PET Scintillators

	BGO	LSO	LPS	LuYAP	$LaBr_3$	LuI_3
Luminosity (ph/MeV)	8,200	25,000	26,000	12,500	60,000	47,000
Energy Resol.	12%	10%	10%	8%	3%	8%
Decay Time (ns)	300	40	38	25, 200	25	30
Density (g/cc)	7.1	7.4	6.2	7.4	5.3	5.6
Atten. Length (mm)	11	12	15	13	22	18
Photofraction	43%	34%	31%	27%	14%	29%
Wavelength (nm)	480	420	385	390	370	470
Natural Radioactivity?	No	Yes	Yes	Yes	No	Yes
Hygroscopic?	No	No	No	No	Yes	Yes

No Scintillator with Superior Properties in *All* Aspects

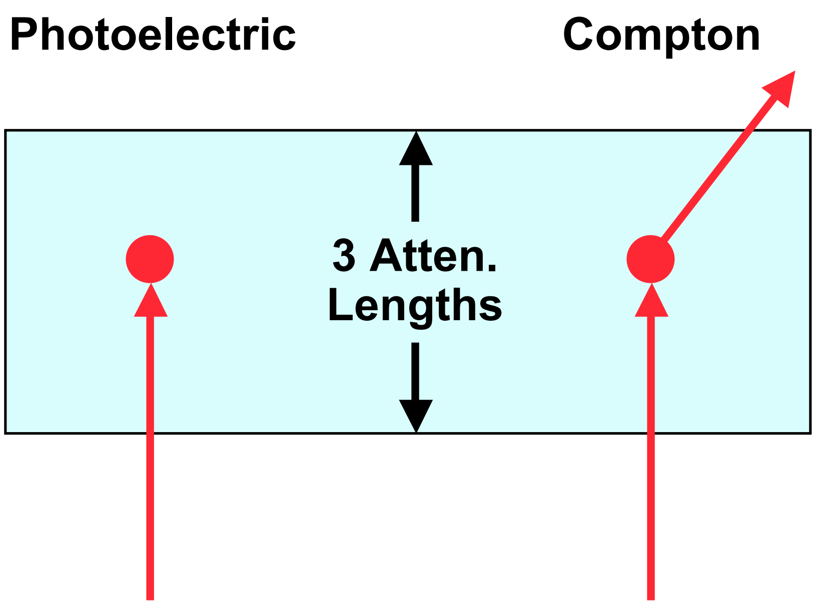
Low Density ⇒ Radial Elongation

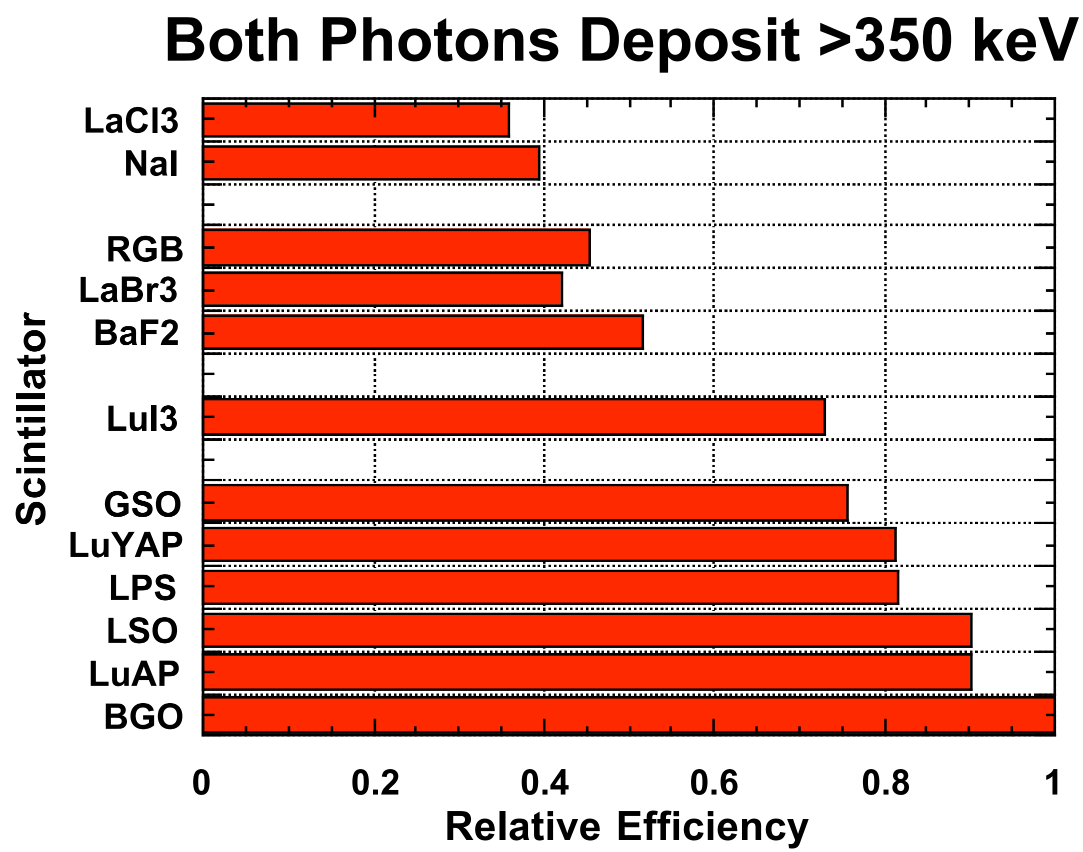




- Little Degradation with LPS, LuAP, or LuYAP
- Some Degradation with LuI_3, More with $LaBr_3$

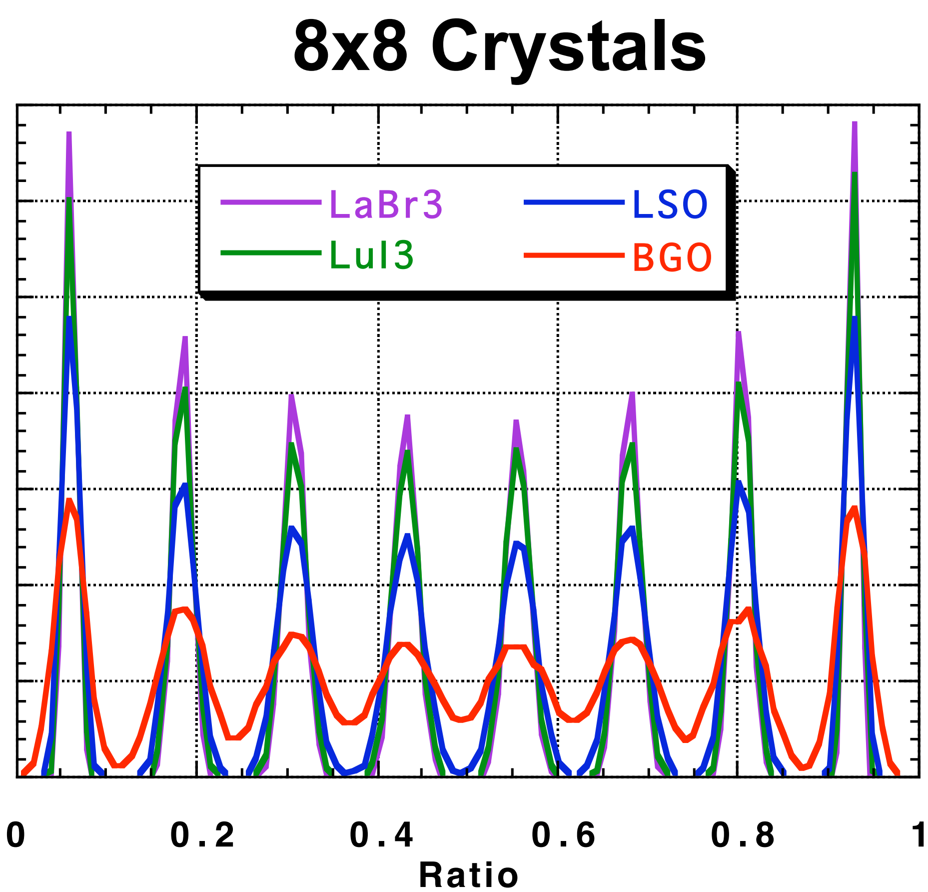
Low Photoelectric Fraction
⇒ Low Coincidence Efficiency

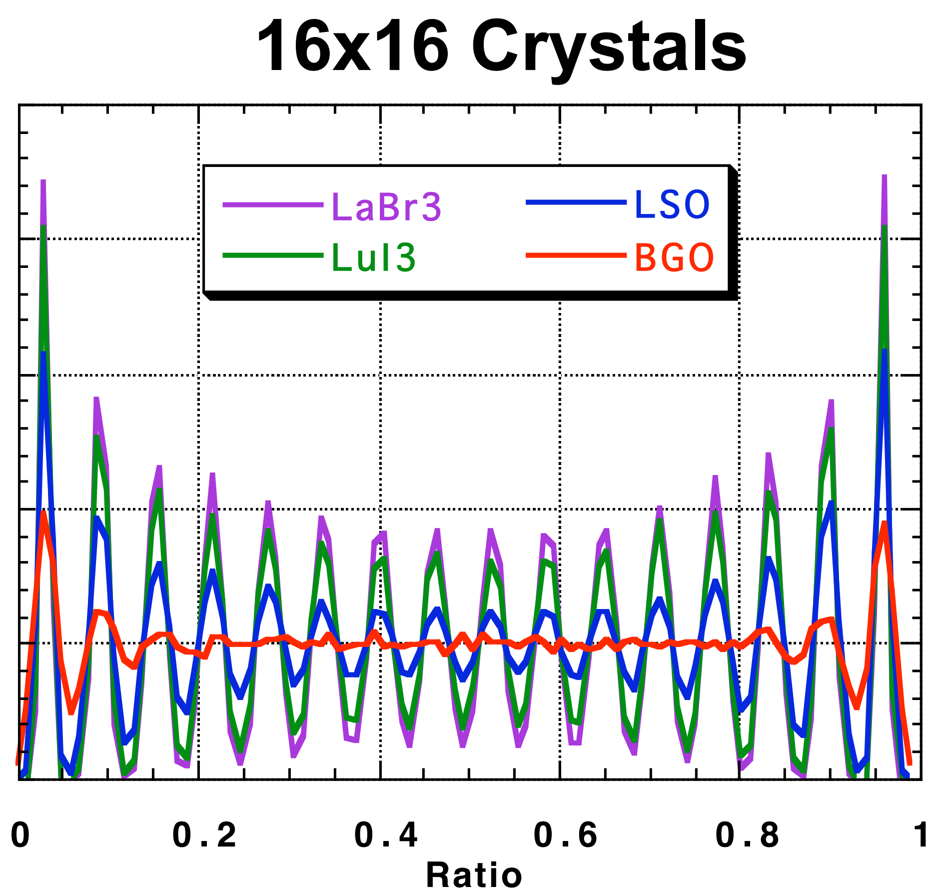




- Little Degradation with LuAP, LuYAP, LPS, or LuI_3
- Significant Degradation with RGB, $LaBr_3$, and $LaCl_3$

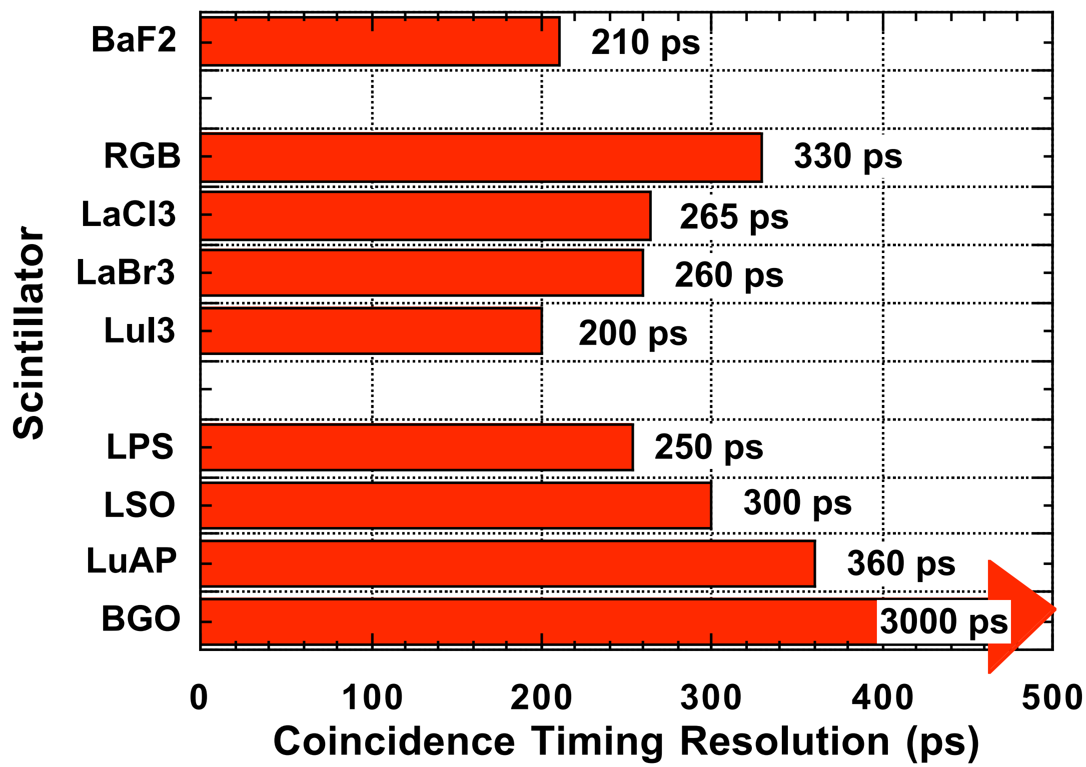
Crystal Decoding vs. Scintillator Type





Can Decode 256 Crystals with $LaBr_3$ and LuI_3

Coincidence Timing Resolution



- All New Scintillators are Capable of Time-of-Flight
- 500 ps Resolution $\Rightarrow$ 5x Reduction in Noise Variance

Several Promising Scintillators for PET...

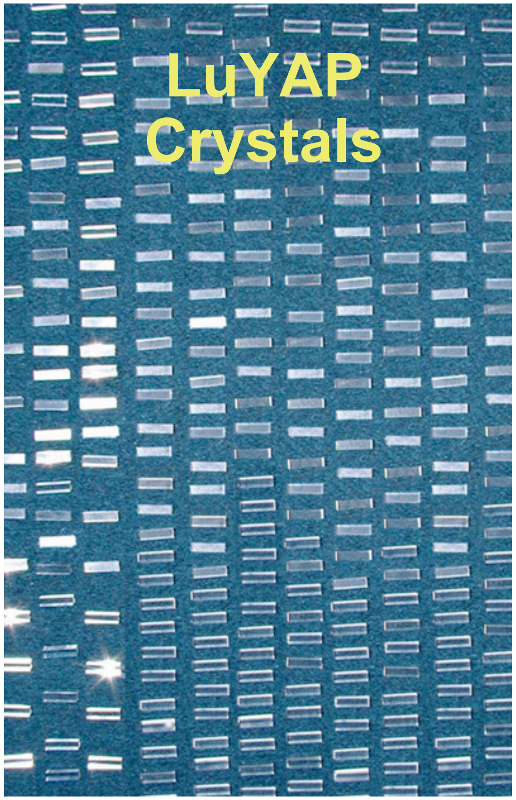


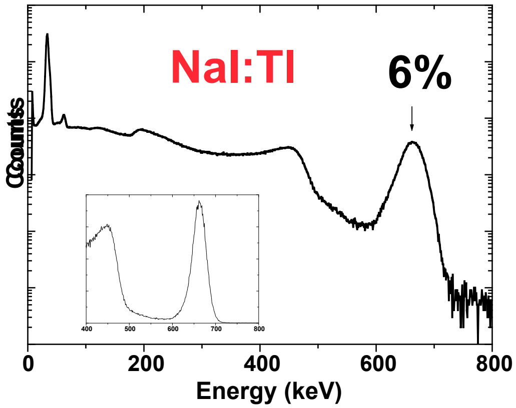
*Image courtesy of C. Kunter, CERN

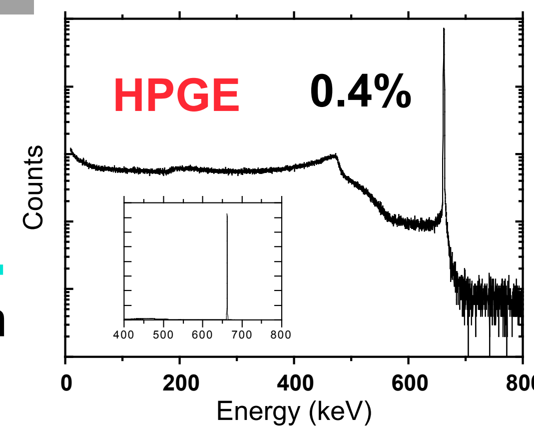
Compared to LSO:

- **LuAP, LuYAP**
  very similar, but lower light output
- **LPS**
  very similar
- **$LaBr_3$**
  better energy resolution & light output
  worse spatial resolution & efficiency
- **LuI_3**
  better energy resolution & light output
  slightly worse spatial resolution

- **Some Advantages, Some Disadvantages**
- **Economical Growth Needed (5000 liters / year)**

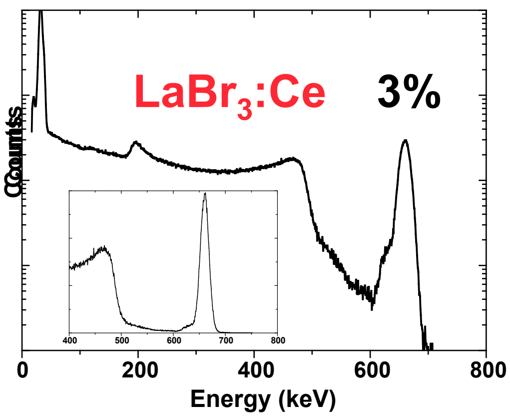
Solid-State Detectors





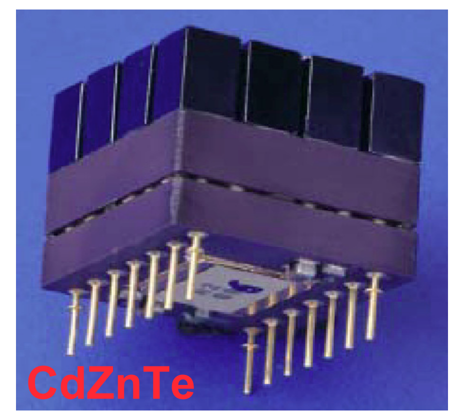
Advantages

- *Much* Improved Energy Resolution
- Improved Stability



Disadvantages

- *Much* Higher Cost
- Lower Photofraction?
- Worse Timing Resolution
- Difficult to make in the sizes / volumes necessary



Best Theoretical Energy Resolution with Solid State

Position-Sensitive PMTs and Scintillator

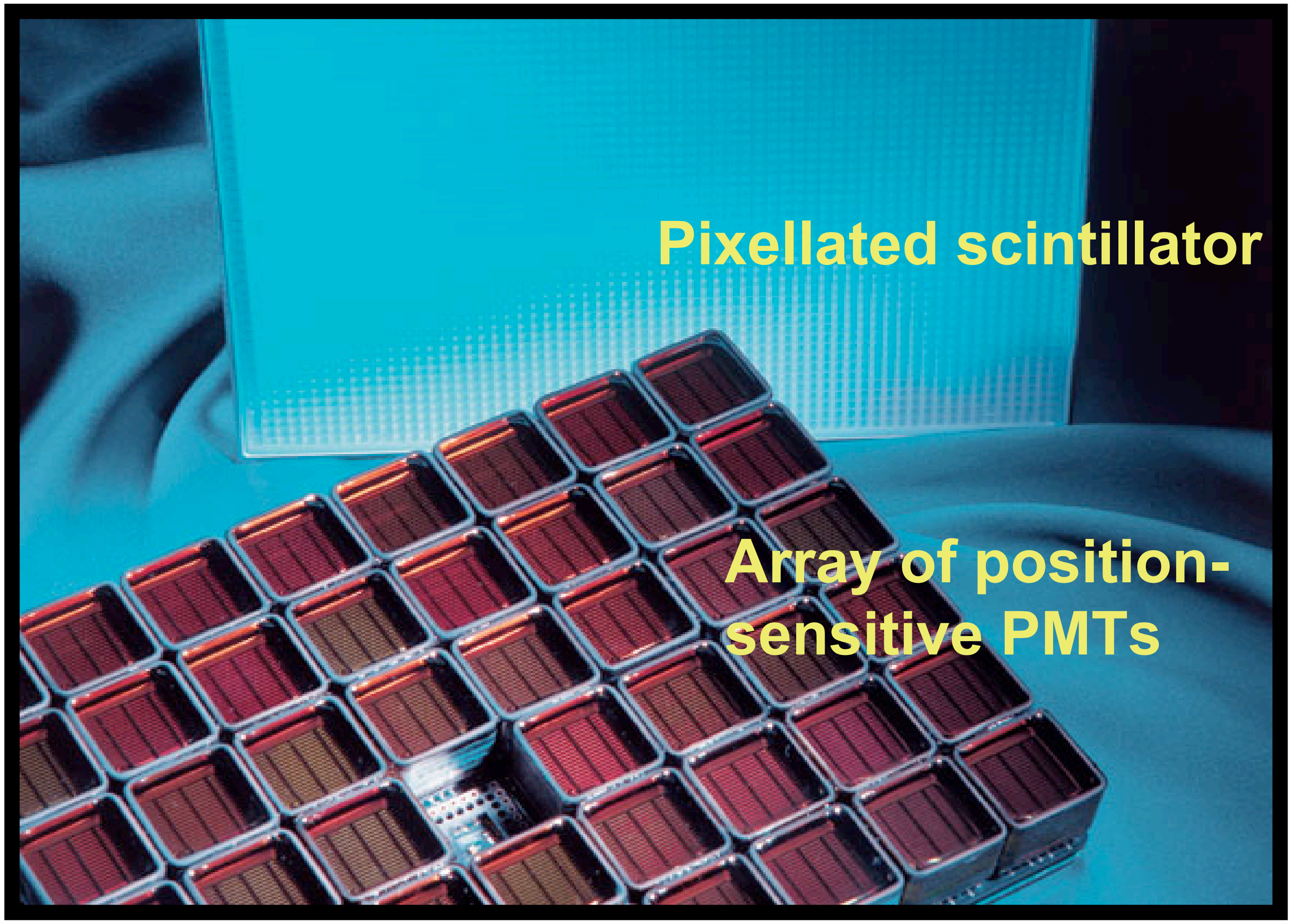
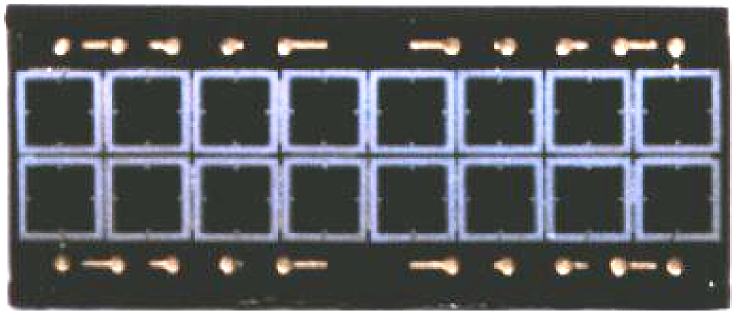


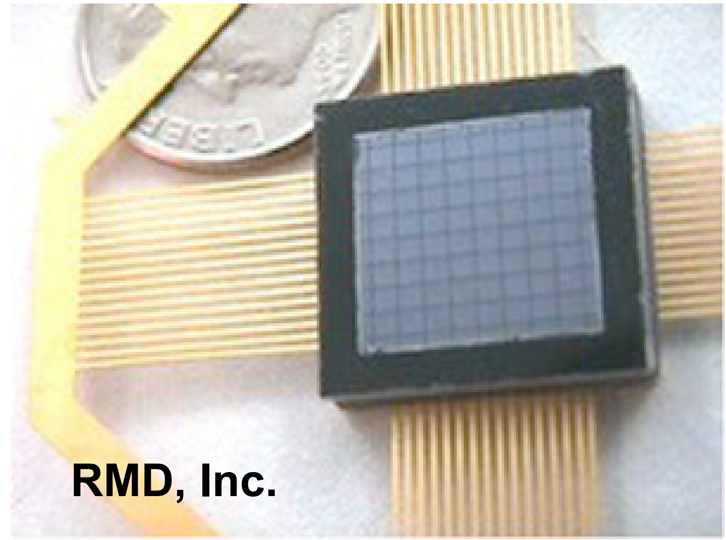
*Image courtesy of M. Smith, JLab.

Easier, But Higher Cost per Area

Avalanche Photodiode Arrays



Hamamatsu Photonics



Advantages:

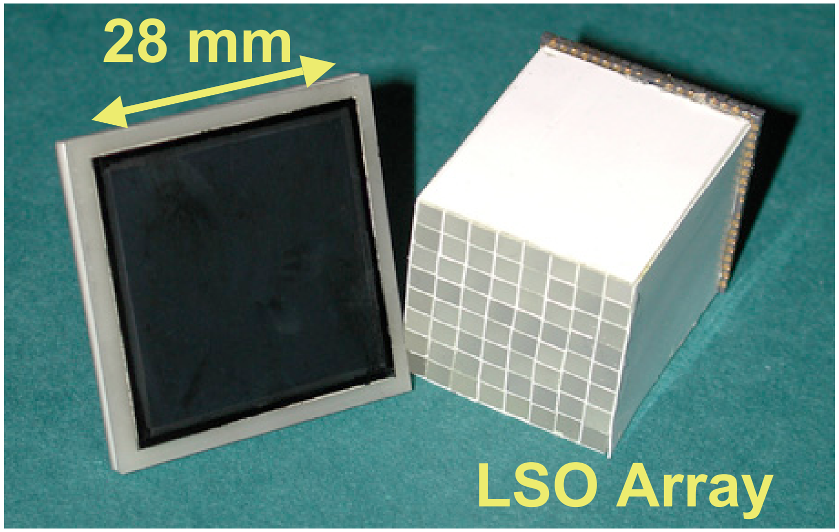
- High Quantum Efficiency ⇒ Energy Resolution
- Smaller Pixels ⇒ Spatial Resolution
- Individual Coupling ⇒ Spatial Resolution

Challenges:

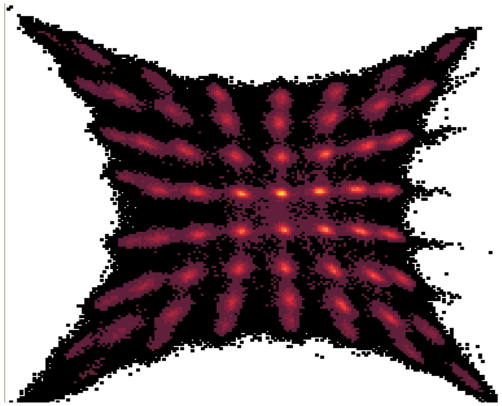
- Dead Area Around Perimeter
- Signal to Noise Ratio
- Reliability and Cost
- # of Electronics Channels

Steady Progress Being Made

Position-Sensitive APD (PSAPD)



Flood Map,
–20° C



- 15% fwhm Energy Resolution
- 3 ns fwhm Timing Resolution

APD Analog of a Position-Sensitive PMT

*Data and image courtesy of K. Shah, RMD, Inc.

Electronics $\Rightarrow$ Custom ICs

Common:

- TDCs
- Charge-Sensitive Preamps
- Pixel Detector Readout
- Strip Detector Readout
- Higher Level HEP Readout

Uncommon:

- CFDs
- PMT Amplifier
- APD Amplifier
- Nuclear Medicine ICs
- Multi-Anode PMT Readout

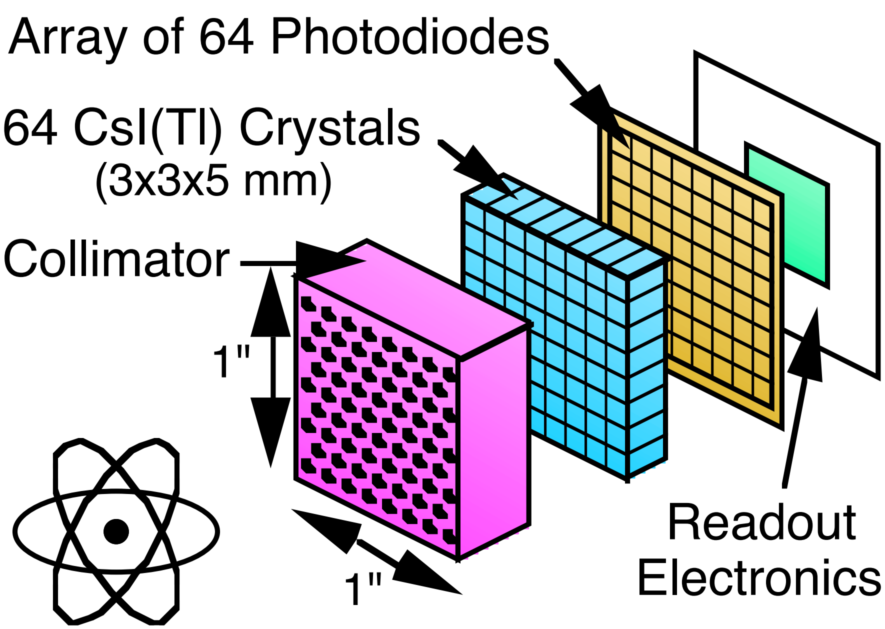
High-Density Packaging

How to Attach Detectors to ICs?

- Often as Difficult as Detectors and Electronics
- Large Numbers of Channels in Small Area
- Tiled Arrays with Minimal Dead Area
- Thermal Management

Often Overlooked…

Single Photon Detector Module



Collimator:
Only passes gammas that are perpendicular to imaging plane

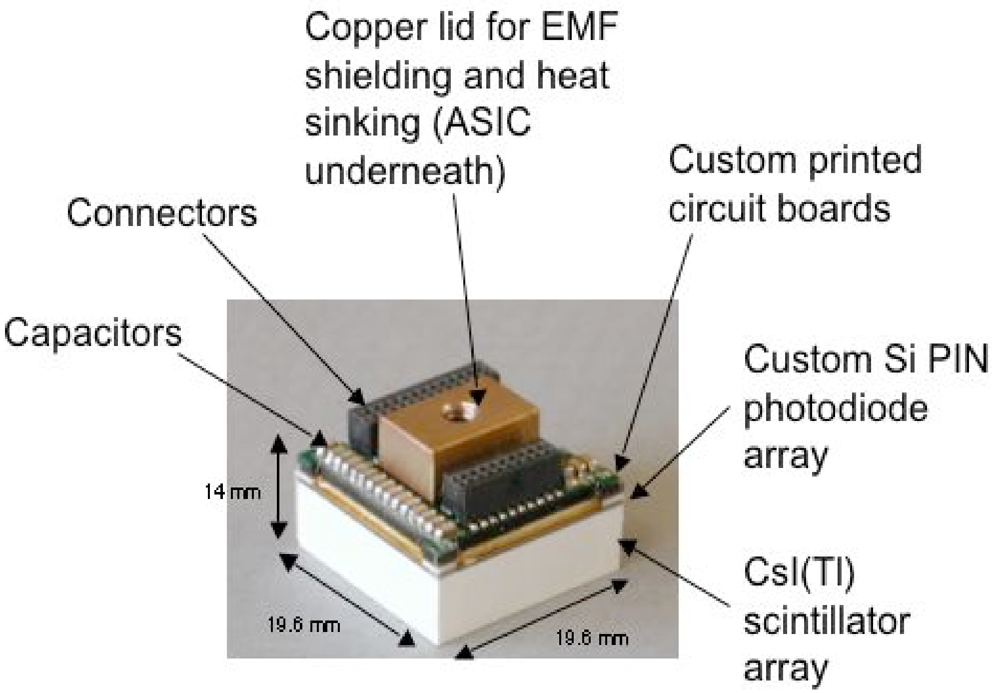
CsI:Tl Array:
Convert gammas to visible light

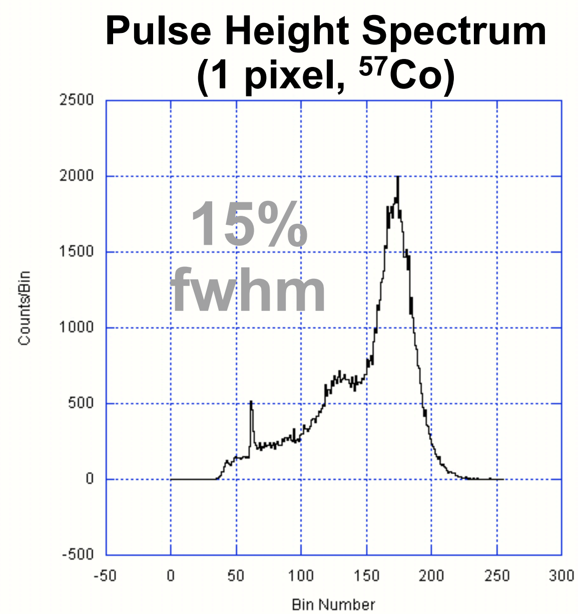
Photodiode Array:
Convert light to electrical signal

Custom IC & Readout Electronics:
Amplify electrical signal and interface to computer

- **Much More Compact than Anger Camera**
- **Allows Small, Hand-Held Probes**

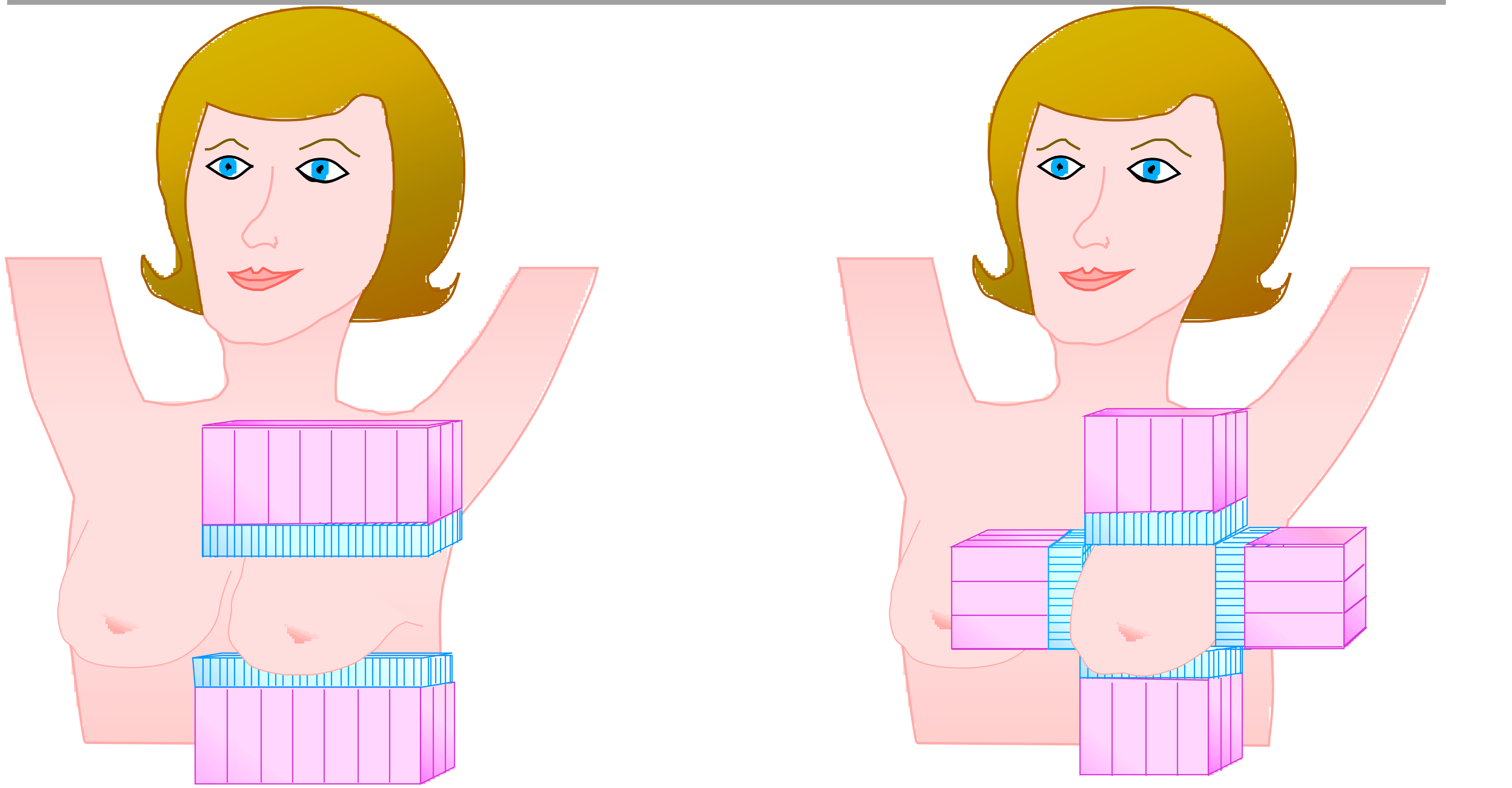
64-Pixel Detector Module





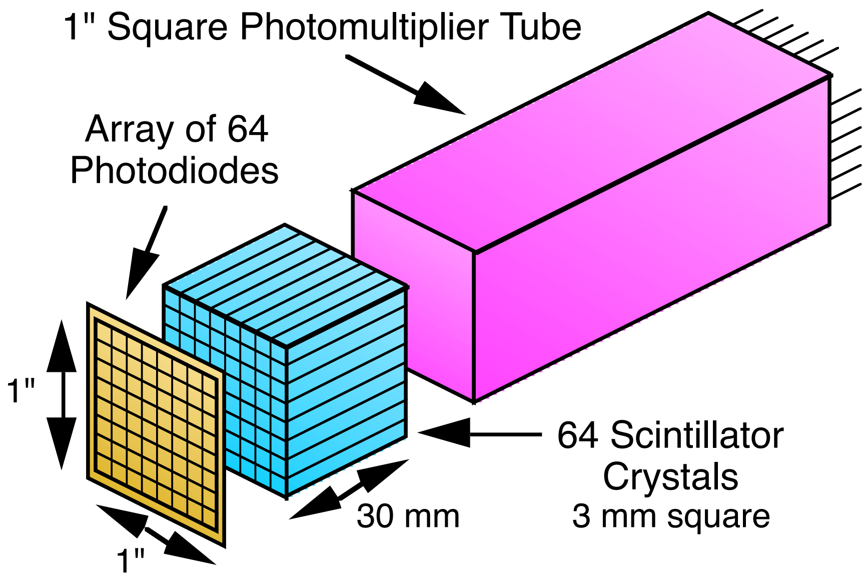
- Photodiode Array Developed by LBNL Microsystems Lab
- Custom ASIC Developed by LBNL IC Design Group
- Technology Licensed to Digirad and Capintec
- Similar Technology in SNAP CCD

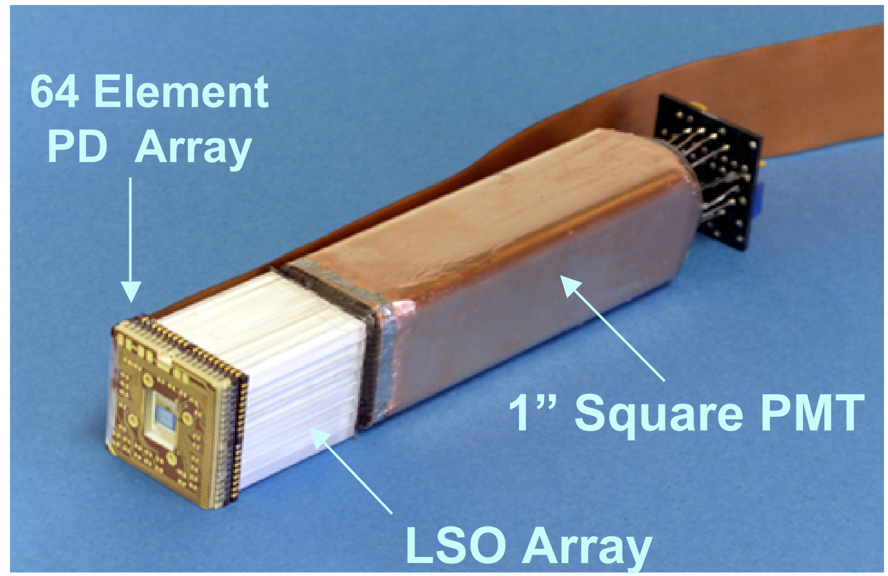
Positron Emission Mammography



- PET Cameras Optimized to Image the Breast
- Reduced Field of View
  - ⇒ Lower Cost (10x)
  - ⇒ Higher Performance (2x – 30x)

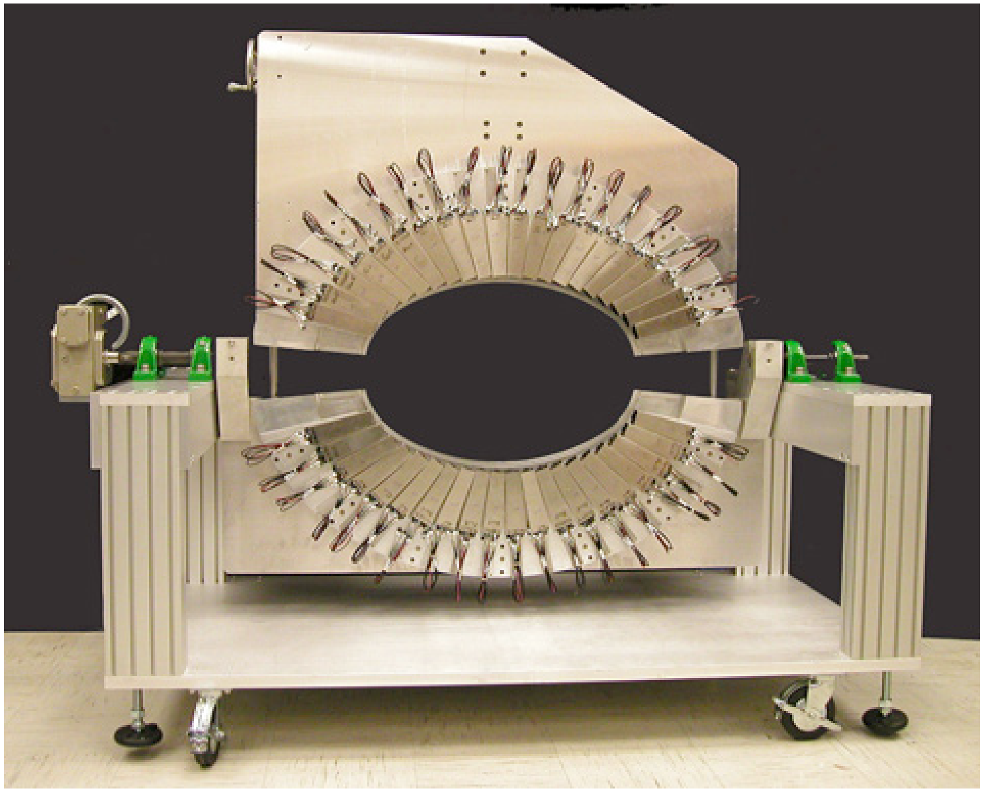
LBNL PET Detector Module





- PMT Provides Timing Pulse
- PD Array Identifies Crystal of Interaction
- PD+PMT Provides Energy Discrimination
- PD / (PD+PMT) Measures Depth of Interaction

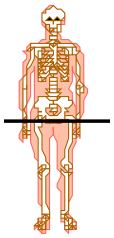
Prostate PET Camera



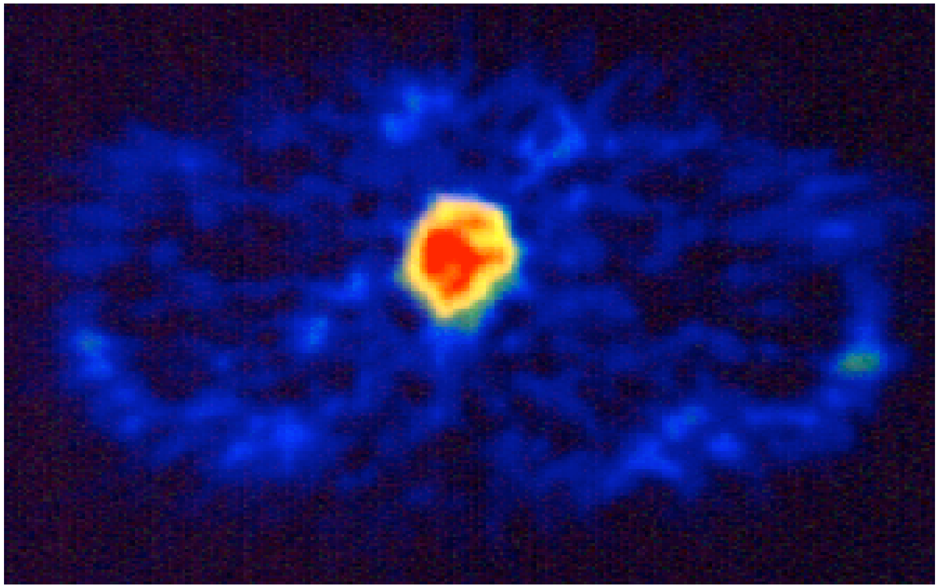
- Uses Commercial Detector Modules & Electronics
- Compared to Conventional PET Cameras:
  - + 1/4 the number of detector modules (*i.e.*, cost)
  - + Greater than 2x the sensitivity

*Photo courtesy of J.S. Huber, LBNL

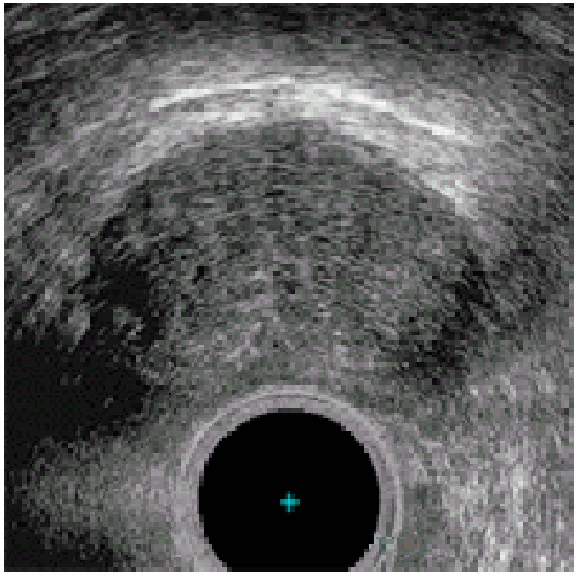
Dual Modality Imaging: PET & Ultrasound



^{11}C-Choline PET Image

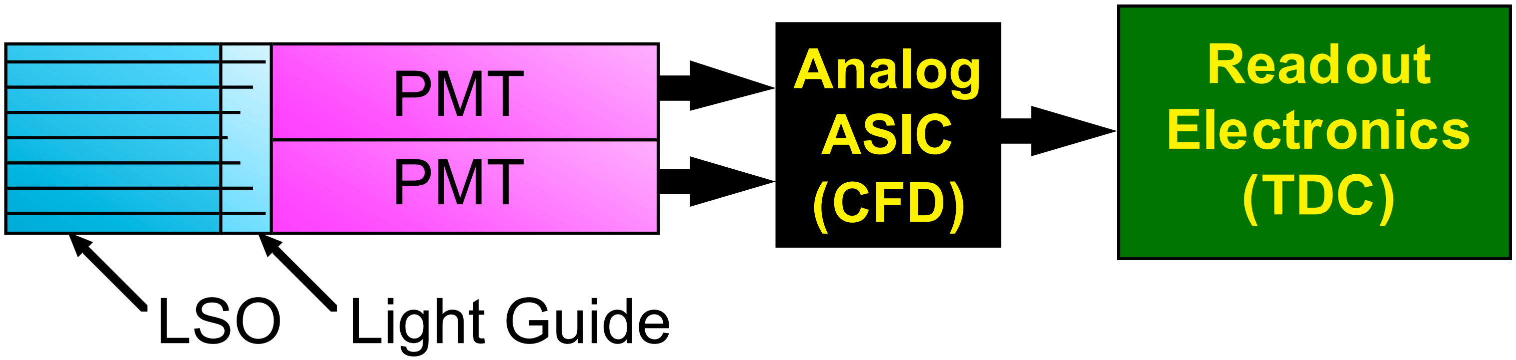


Transrectal US Image



- **Co-Register PET with Transrectal Ultrasound?**
- **Guide Biopsy?**

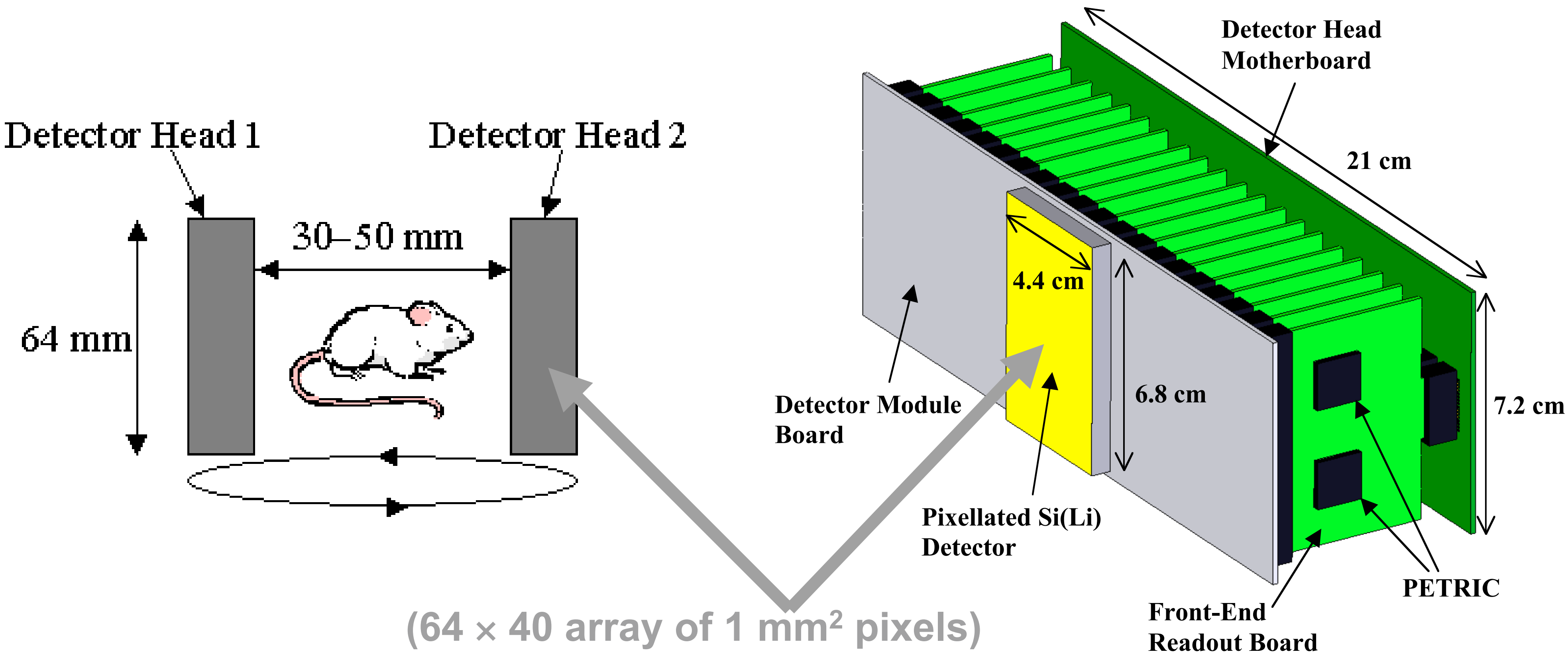
Time-of-Flight in Commercial PET Camera?



- **Recently developed scintillator material (LSO) is capable of <300 ps timing resolution (in optimal conditions)**
- **TOF with 300 ps would give large performance gain**
- **First commercial PET camera has ~3 ns timing resolution**
- **Which components limit the timing resolution?**
- **How much can they be improved?**

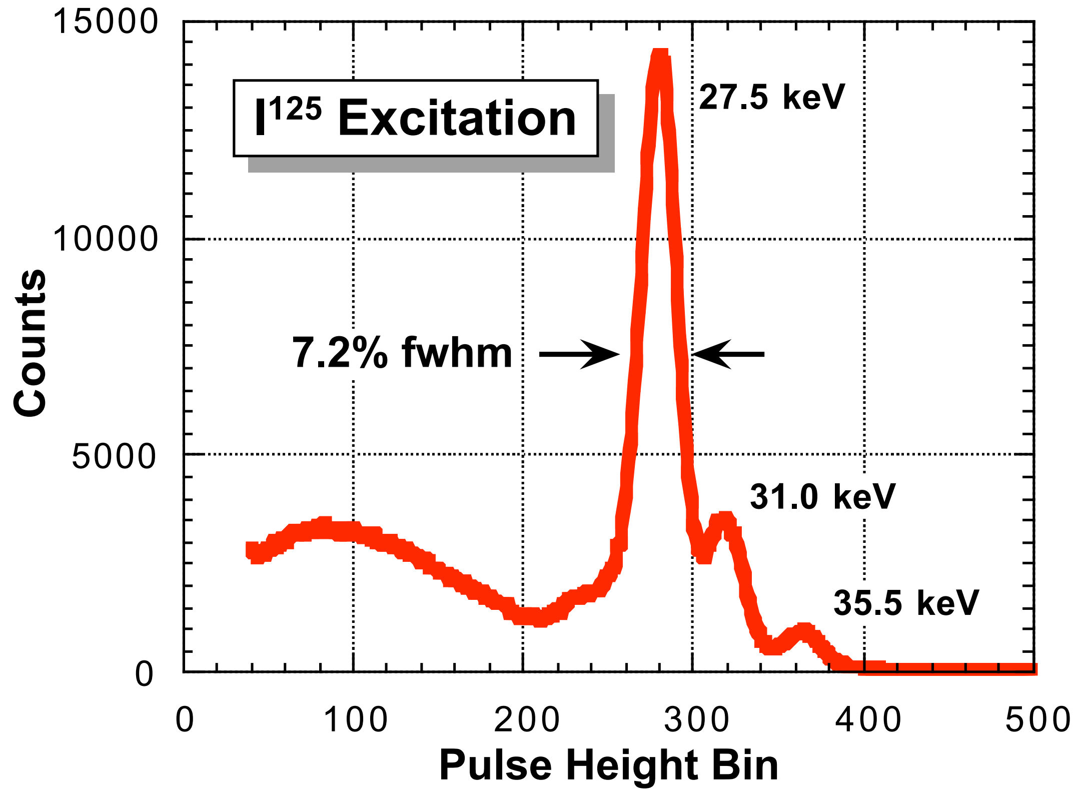
- **Measure Timing Performance of Each Component**
- **Develop Modifications to Achieve TOF Capability**

Camera for ^{125}I SPECT Imaging in Mice



- Mice Used *Extensively* in Disease and Genomic Studies
- Many ^{125}I-Labeled Pharmaceuticals Available (30 keV)
- Use Lithium-Drifted Silicon (Si:Li) for Detector

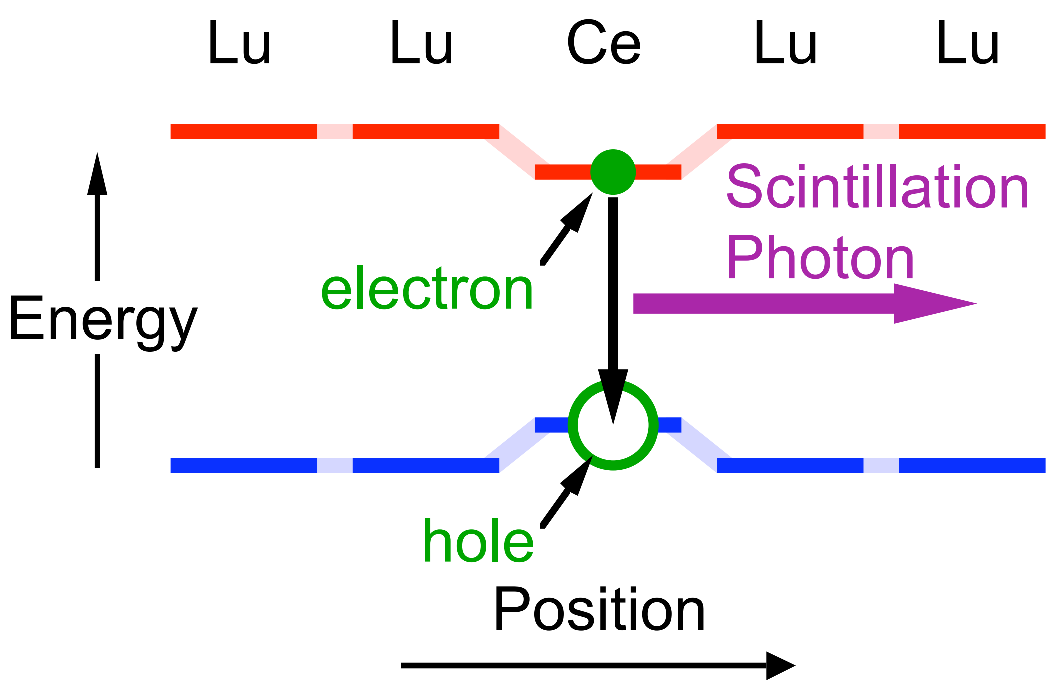
Si(Li) for I^{125} Animal SPECT?



- **Well-Matched to ~30 keV Gamma Imaging**
- **New Use for an Old Material?**

*Data courtesy of W.-S. Choong, LBNL

“Classical” Scintillation Mechanism

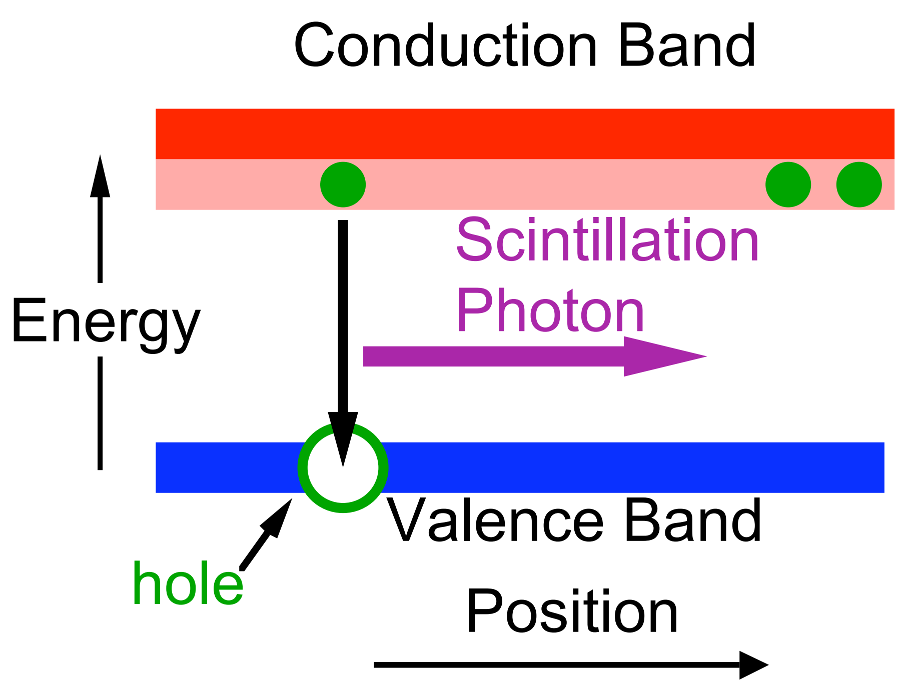


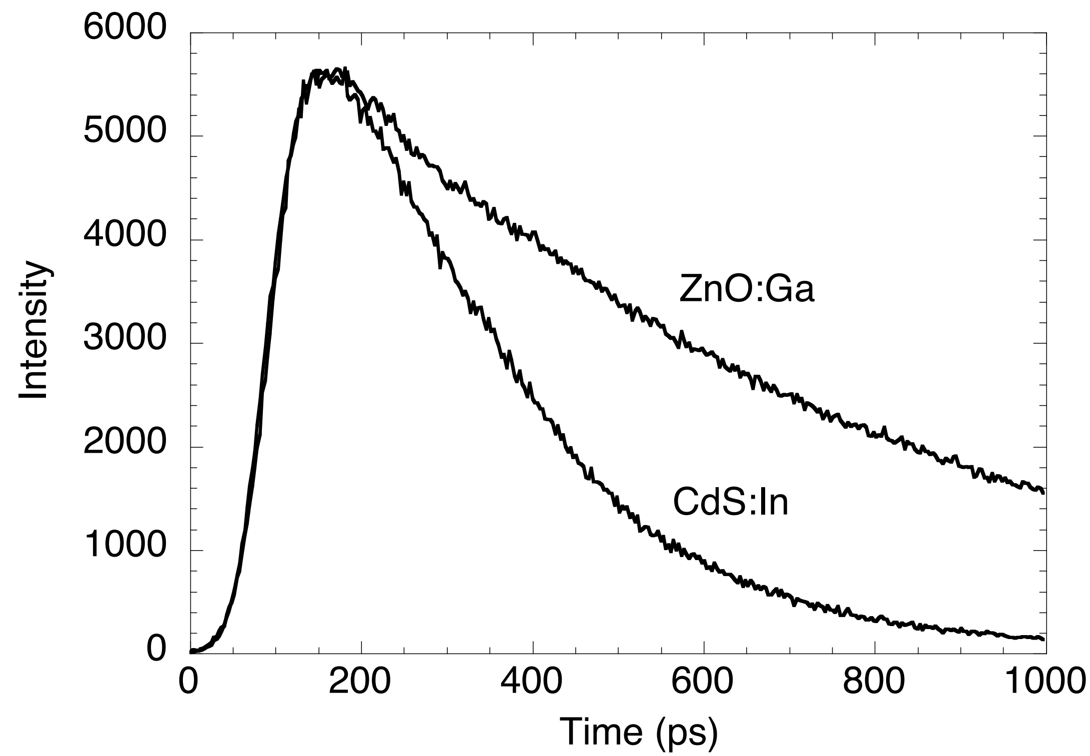
Why Ce^{3+}?

- **Spin / Parity Allowed**
- **Single Optical Electron**
- **Good Size Match**

Ionic Bonding / Transitions Dominate

"Semiconductor" Scintillator Mechanism





*Data courtesy of S. Derenzo, LBNL

- Covalent Bonding / Transitions Dominate
- Allows *Many* More Hosts & Dopants

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