Oxford Summer School "Intelligent Front-End Signal Processing for Frontier Exploitation in Research and Industry" July 9-13, 2013

Molecular Imaging Modalities and Technologies III

Technologies for < 1 millimeter resolution PET

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Molecular Imaging Program at Stanford

MIPS Molecular Imaging Program at Stanford

Stanford University Department of Radiology & BIO-X, School of Medicine

Instrumentation and algorithms for 1 millimeter resolution clinical PET

Outline of Talk:

- Brief review of positron emission tomography (PET)
- Is 1 mm resolution PET possible?
- Why 1 mm resolution rather than 2, 3, or 4 mm?
- What are the challenges of achieving 1 mm resolution clinical PET?
- What is the basic design to achieve 1 mm resolution?
- How do we achieve this 1 mm resolution design?
- New algorithms for this 1 mm resolution design
- Summary

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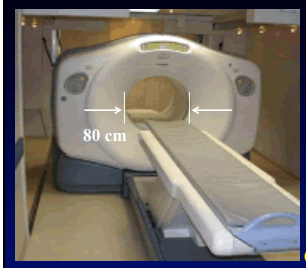
Limitations of the Standard PET/CT Camera



- Large and awkward for imaging a specific organ of interest at close proximity
- Accepts activity from outside organs
- Low photon sensitivity (~1%)
- Poor spatial resolution (7-10 mm)
- Poor energy resolution (>15-20%)
- Limited contrast resolution
- Long study durations
- Relative high cost per study
- Not portable

Can we improve the technology?

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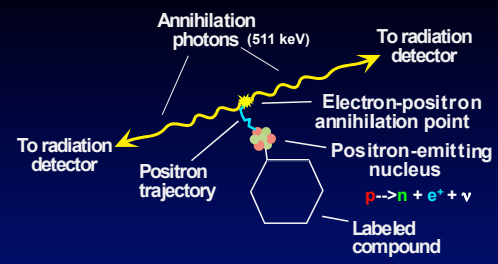
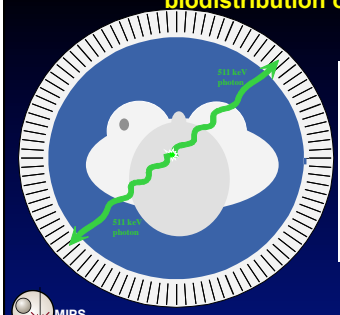
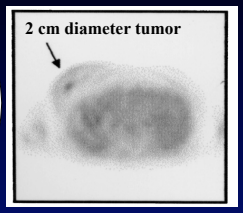
•Brief review of PET

Basic principles of PET



Reconstruction of cross-sectional slices through biodistribution of probe





Is 1 mm resolution clinical PET possible?

Limitations on PET Spatial Resolution

- Positron Range
- Annihilation Photon Non-collinearity
- Detector Element Width

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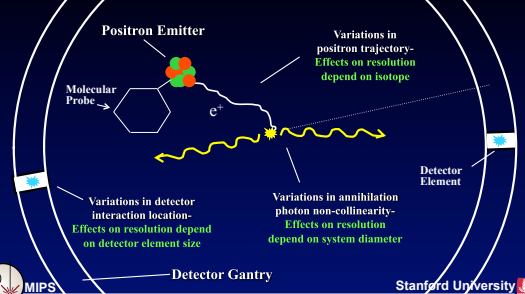
Limitations on PET Spatial Resolution



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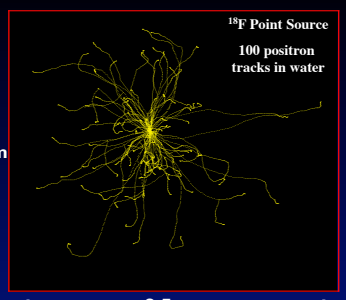
Simulated Positron Trajectories



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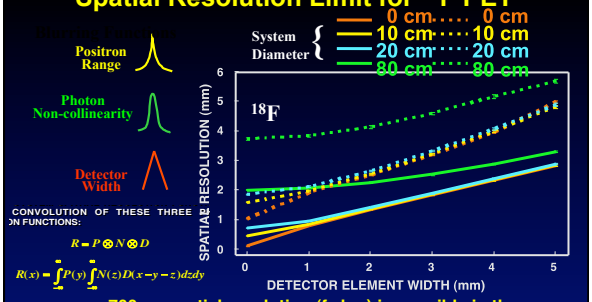
Spatial Resolution Limit for ^{18}F PET



~700μm spatial resolution (fwhm) is possible in theory

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Levin *et al* Phys. Med. Bio. 1999
Stanford University School of Medicine Department of Radiology

Why 1 mm resolution rather than 2, 3, or 4 mm?

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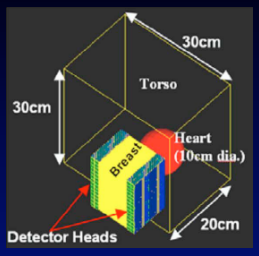
Monte Carlo simulations of dual-head PET system



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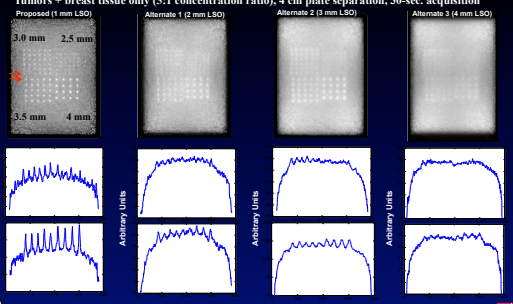
Lesion visualization in water-equivalent tissue

Tumors + breast tissue only (5:1 concentration ratio), 4 cm plate separation, 30-sec. acquisition



Zhang *et al*, Medical Physics 2007

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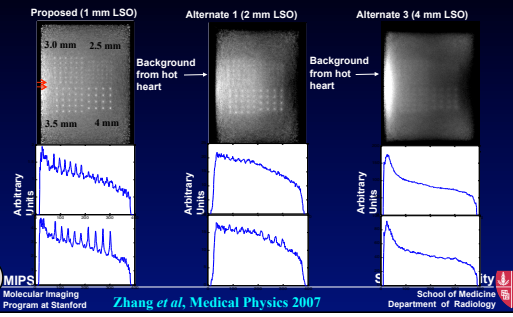
Lesion visualization with hot heart/warm torso

Tumors + breast tissue + heart + torso (5:1:5:1 activity concentration ratio), 4 cm plate separation, 30-second acquisition time



Zhang *et al*, Medical Physics 2007

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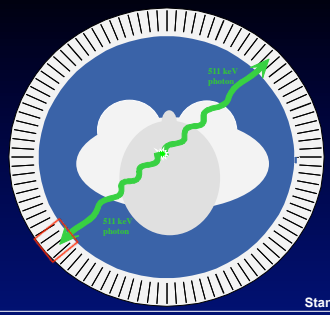
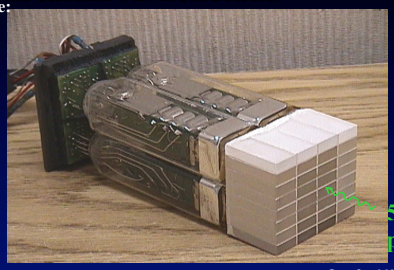
What are the challenges of achieving 1 mm resolution for clinical PET?

A PET system is a ring of 511 keV photon detectors



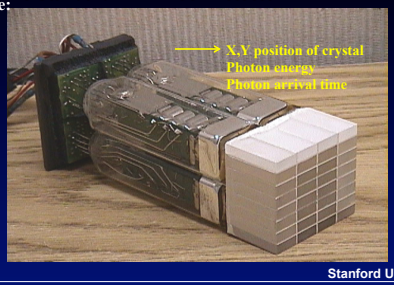
Standard PET detector technology

Example: The Standard PET Block Detector



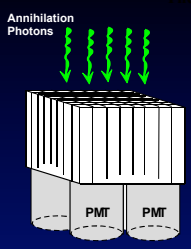
Standard PET detector technology

Example: The Standard PET Block Detector

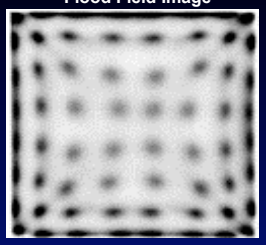


Resolving crystals in PET Detectors

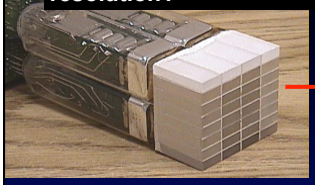
The "Block Detector"

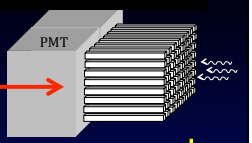


Flood Field Image



What are the challenges of achieving 1 mm resolution?





- Photons/crystal element ↓
- Scintillation light signal ↓
- Dispersion of light signal ↑
- Number of photosensors ↑
- Complexity ↑

Limitations of the Standard PET/CT Camera

- Large and awkward for imaging a specific organ of interest at close proximity
- Accepts activity from outside organs
- Low photon sensitivity (~1%)
- Poor spatial resolution (7-10 mm)
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What is the basic design to achieve 1 mm resolution?

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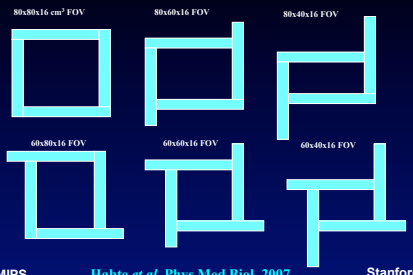
High photon sensitivity whole body clinical PET system design with patient-selectable FOV



Up to ~10-fold increase in photon sensitivity is possible

Habte *et al*, Phys Med Biol, 2007

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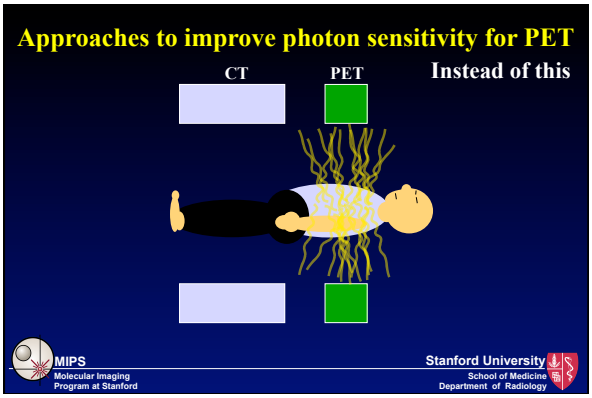
Approaches to improve photon sensitivity for PET
CT
PET
Instead of this
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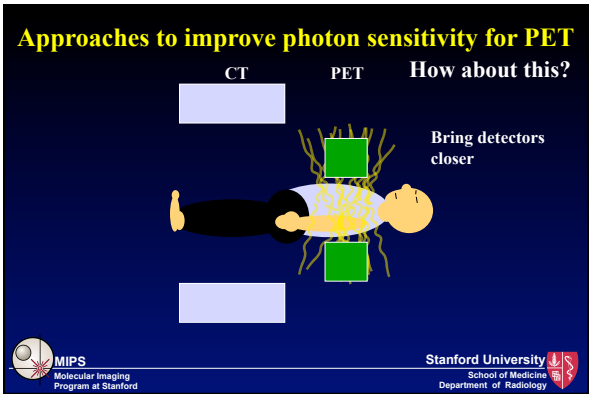
Approaches to improve photon sensitivity for PET
CT
PET
How about this?
Bring detectors
closer
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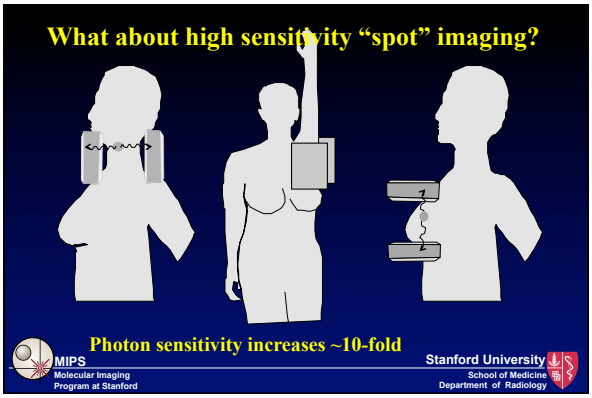
What about high sensitivity "spot" imaging?
Photon sensitivity increases ~10-fold
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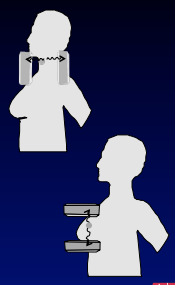
What are potential roles for a "spot" PET imager

An adjunct to existing methods for:

- Earlier detection ???
- Evaluation of indeterminate cases?
- Reducing rate of false positives??
- Guiding biopsy?
- Guiding surgical procedures?
- Staging of nearby nodes?
- Monitoring for local recurrence?
- Monitoring/guiding therapy?



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How do we achieve this 1 mm resolution system design?

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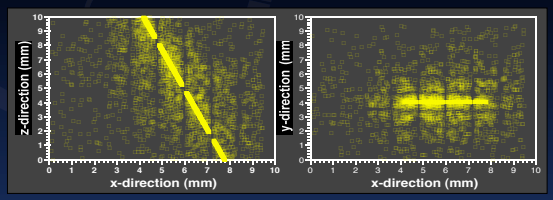
511 keV photon penetration in crystals

Side view of array | Top view



Levin et al. *Proc. IEEE*. 2008

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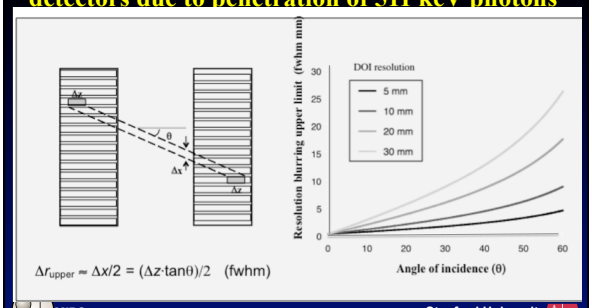
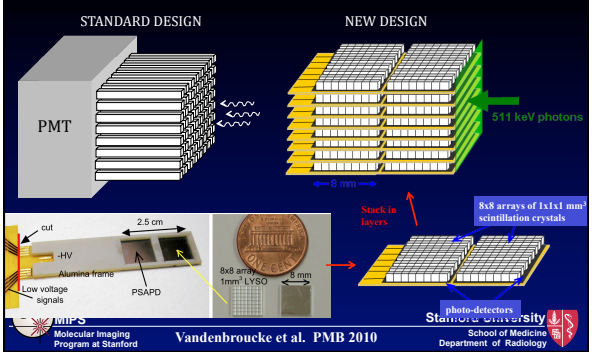
But…this requires "depth-of-interaction" detectors due to penetration of 511 keV photons

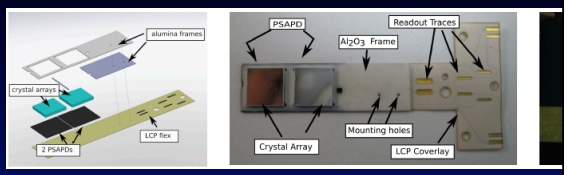


New 3-D positioning detector design

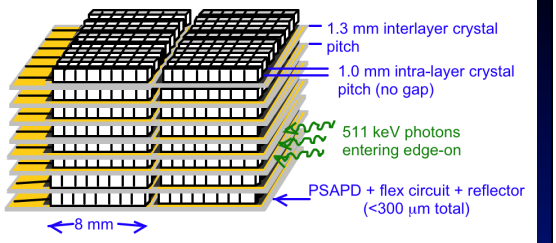


Vandenbroucke et al. PMB 2010

Detector modules….



New 3-D positioning PET detector design



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New 3-D positioning parking lot design

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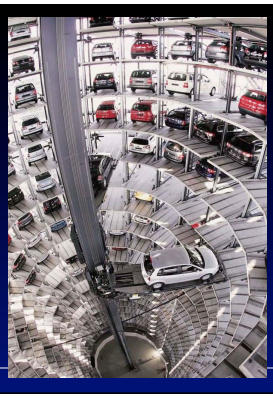
Large axial FOV!



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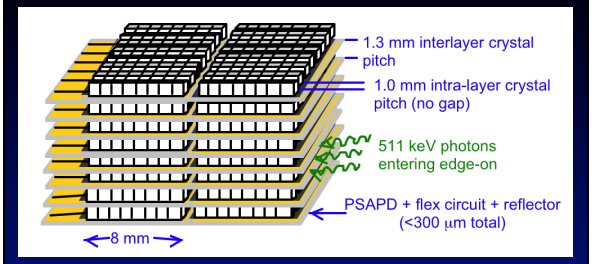
New 3-D positioning PET detector design



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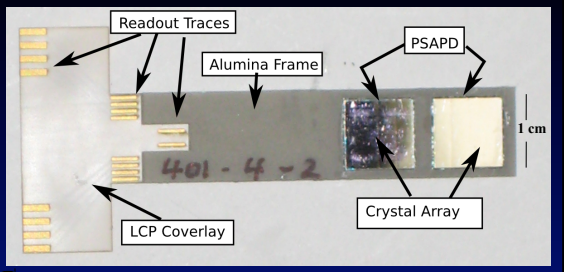
Performance of "dual-LYSO-PSAPD-flex modules"



Vandenbroucke et al. PMB 2010 (in press)

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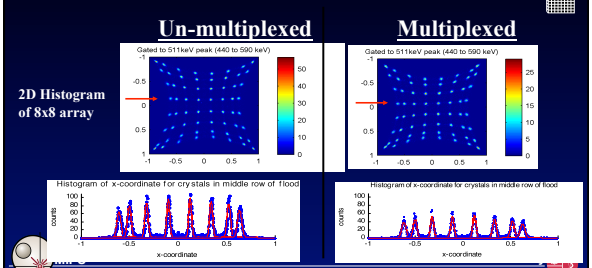
Verification of Multiplexed Performance:

1) Crystal Identification

- The ability to separate events from each 1mm^3 crystal in the 8x8 array is important for good spatial resolution



Lau et al. PMB 2010 (in press)

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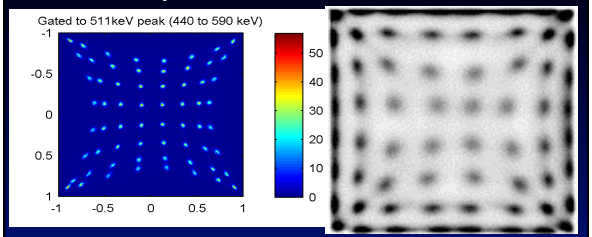
New 1 mm, 3-D positioning 511 keV photon detector

1 mm crystals | **6 mm crystals**



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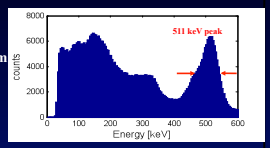
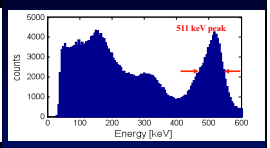
Verification of Multiplexed Performance:

2) Energy Resolution

- Good energy resolution necessary to reject scattered events

	Un-multiplexed	Multiplexed
Na-22 Energy Spectrum		
Energy Resolution of 511keV peak	14.6% ± 0.8% (at full-width-half-max)	14.4% ± 0.8% (at full-width-half-max)

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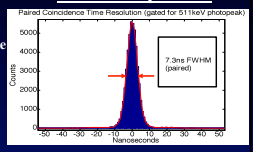
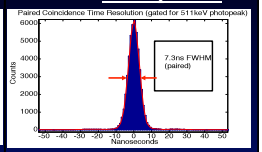
Verification of Multiplexed Performance:

3) Coincidence Time Resolution

- Good time resolution necessary to find coincident pairs

	Un-multiplexed	Multiplexed
Coinc. Time Resolution Histogram		
Time Resolution	7.3 ± 0.2 ns (at full-width-half-max)	7.3 ± 0.2 ns (at full-width-half-max)

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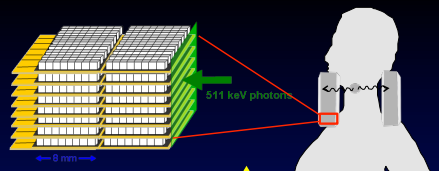
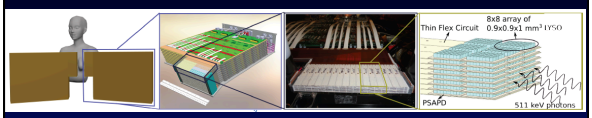
Close proximity + new 3-D positioning detector design

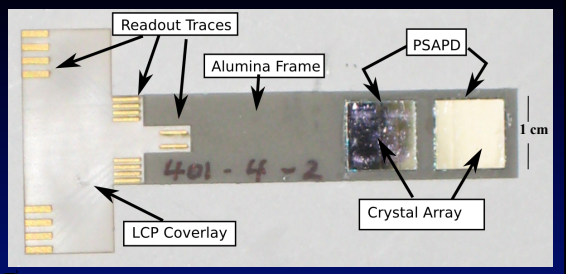


- Photons/crystal element ↑
- Scintillation light signal ↑
- Dispersion of light signal ↓
- Number of photosensors ↑
- System complexity ↑

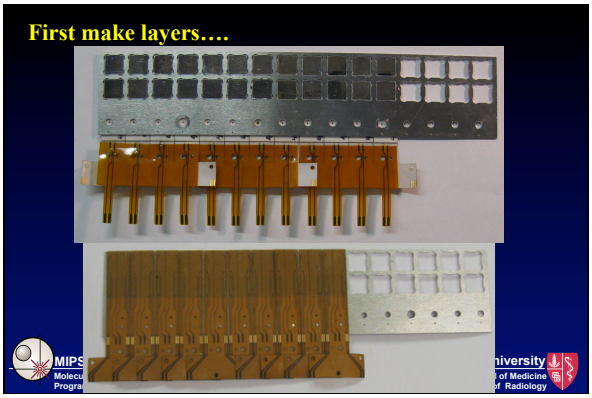
Top down view of 1 mm resolution system design

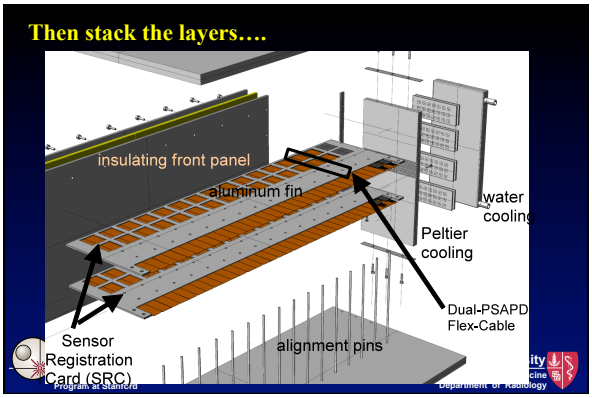


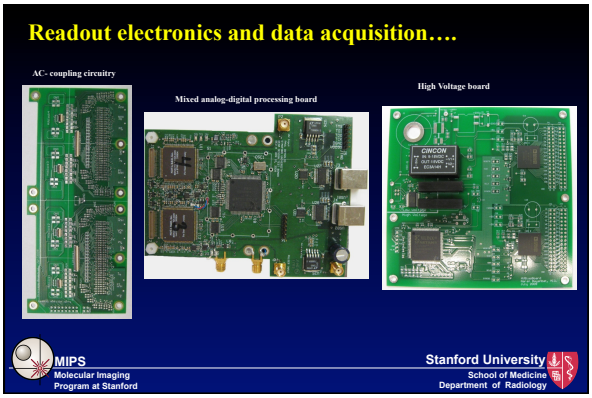
Form stacks of these dual-LYSO-PSAPD-flex modules



Vandenbroucke et al. PMB 2010 (in press)


First make layers….


Then stack the layers….
insulating front panel
aluminum fin
water cooling
Peltier cooling
Dual-PSAPD Flex-Cable
Sensor Registration Card (SRC)
alignment pins


Readout electronics and data acquisition….
AC- coupling circuitry
Mixed analog-digital processing board
High Voltage board
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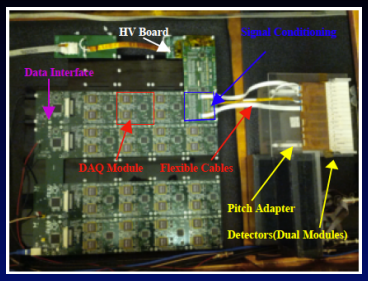
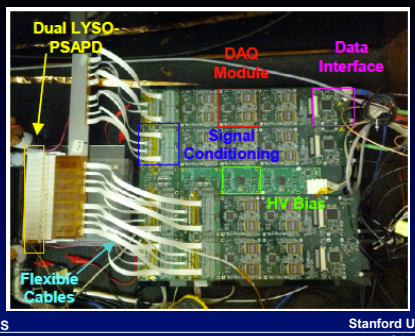
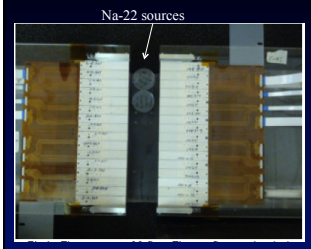
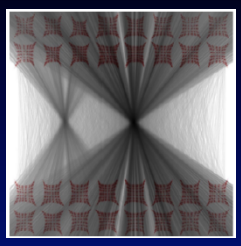
Readout electronics and data acquisition….



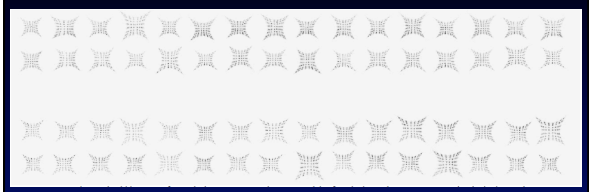


Measured response lines for one detector layer from the two panels





Crystal histograms for one layer from the two panels



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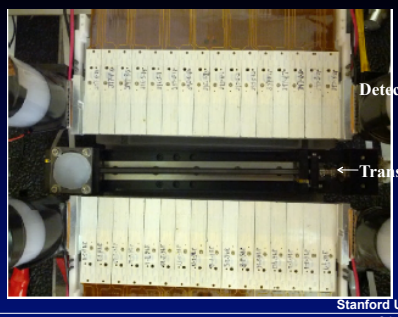
Point spread function measurements



Detector panel

←Translation stage

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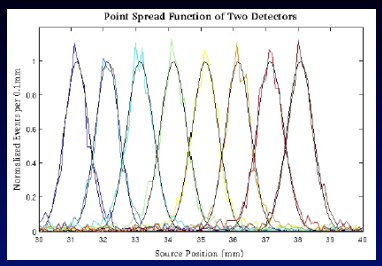
Point spread function measurements



0.90 ± 0.03 mm
FWHM

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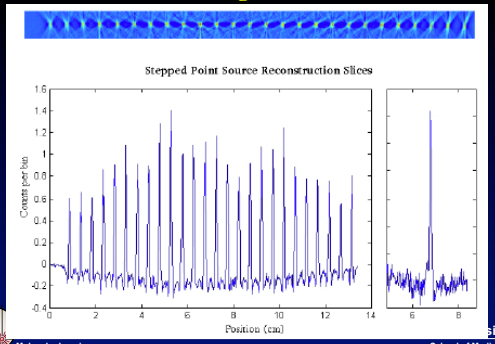
Point source image reconstruction



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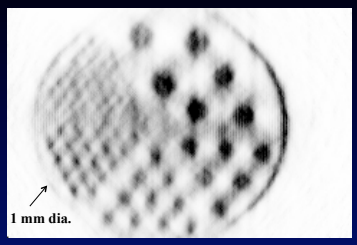
First phantom image reconstruction



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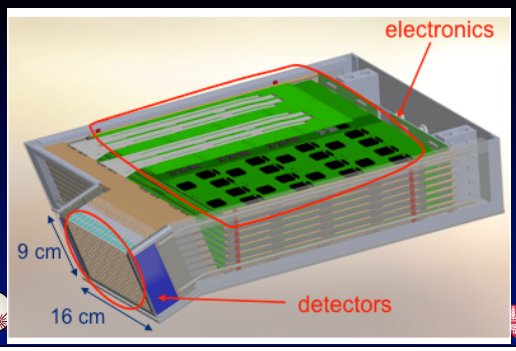
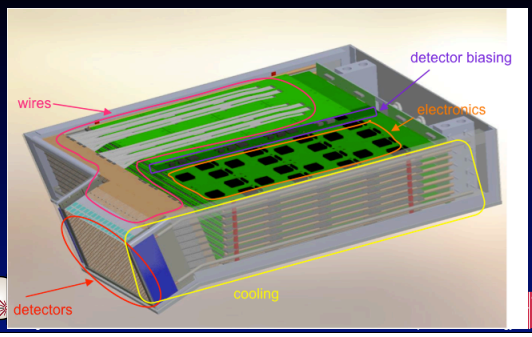
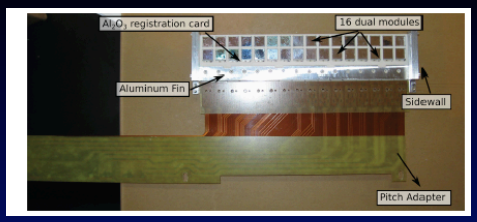
Currently scaling up the number of detector layers….



System components….





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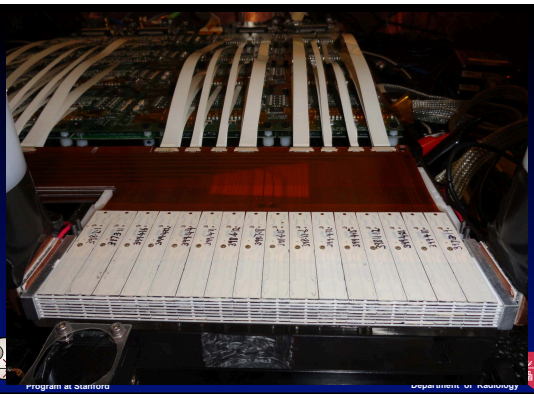

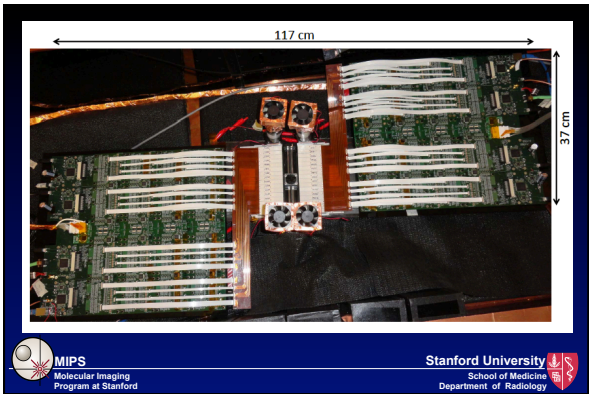
117 cm
37 cm
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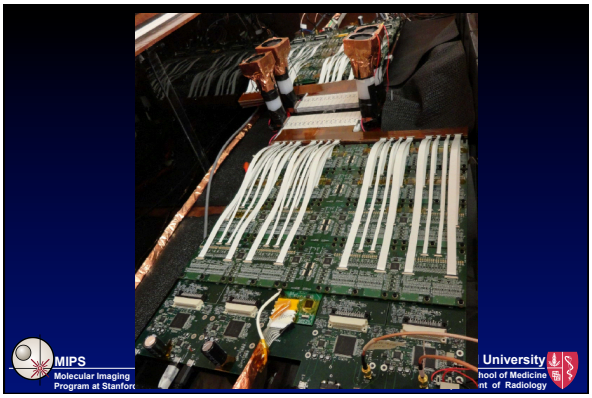
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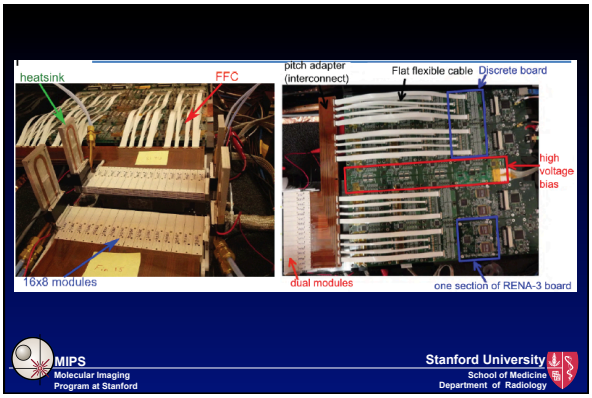
heatsink
FFC
pitch adapter
(interconnect)
Flat flexible cable
Discrete board
high
voltage
bias
16x8 modules
dual modules
one section of RENA-3 board
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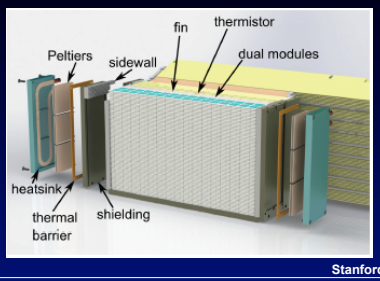
Thermal management system….



List of circuit boards and elements in each cartridge

Component name	#	Description
Dual Module	128	2 LYSO arrays/2 PSAPDs each
Sensor Registration Card	8	16 dual modules each
Flat flexible cable	64	HV/LV interconnect
High Voltage Bias Board	1	4 32 channel DAC
Discrete board	8	LC[a] and temperature sensing Signal conditioning/AC coupling
RENA board	4	8 RENA-3 chips each 4 Xilinx FPGA each
DAQ board	1	4 Spartan FPGA chips
Electronic Channels	1024	8 per dual module

Summary of system performance goals

Parameter	Design Goal
System wide E_{res}	<11% FWHM
System wide coincidence t_{res}	<10 ns FWHM
Crystal misidentification probability	<1% on average
Intrinsic spatial resolution in 3-D	< 1mm
Identifiable phantom rods	≤ 1mm
DAQ throughput rate	$>10^6$ events/sec
System photon sensitivity	>10% (absolute)
Active PSAPDs	>90%
Front-end temperature and stability	22 ± 0.5 °C

System Performance So Far

(2-cartridges, 512 dual-LYSO-PSAPD modules)

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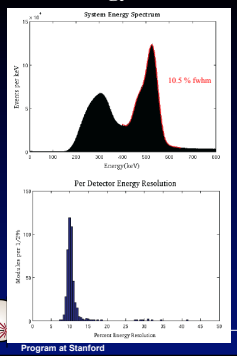
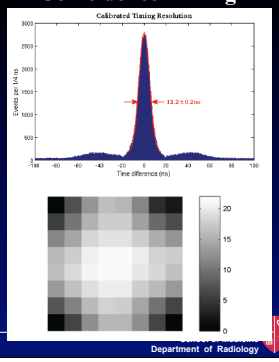
Energy



Coincidence Timing



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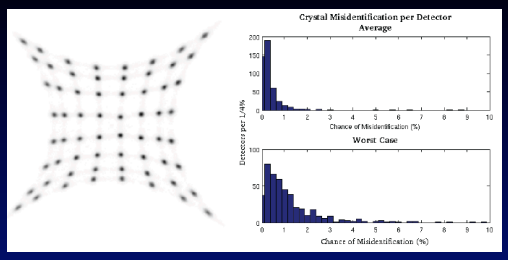
Event crystal identification



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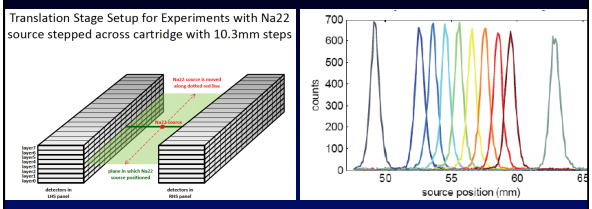
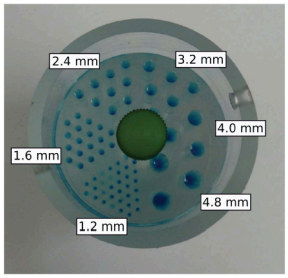
Point spread function measurements

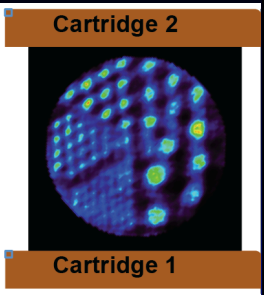
Translation Stage Setup for Experiments with Na22 source stepped across cartridge with 10.3mm steps



0.84+/-0.02 mm FWHM

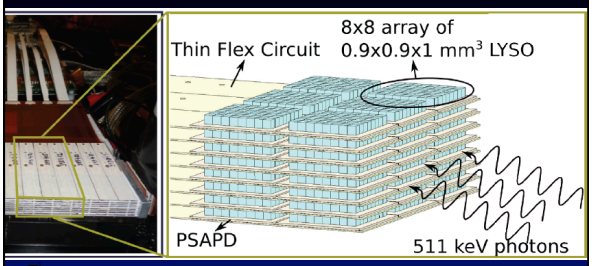
Reconstructed image of a resolution phantom





New event processing algorithms for this 1 mm resolution design

3-D position sensitive scintillation detector



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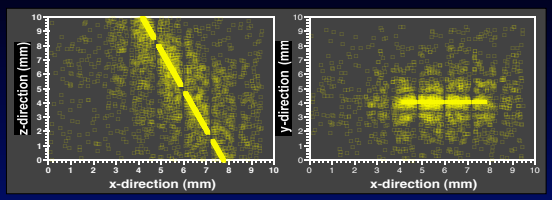
511 keV photon scatter in crystals

Side view of array

Top view



C.S. Levin, *Proc. IEEE*, 2008

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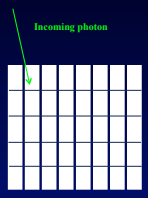
Advantages of 3-D positioning photon detectors:

Intelligent positioning algorithms for photons that scatter in crystals

--->Better estimate of first interaction location



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Advantages of 3-D positioning photon detectors:

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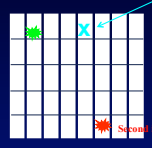


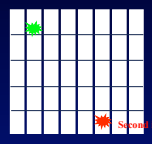
Conventional PET detectors:
Energy-weighted mean of
interaction locations
(in two-dimensions only)

Advantages of 3-D positioning photon detectors:

Intelligent positioning algorithms for photons that scatter in crystals

--->Better estimate of first interaction location

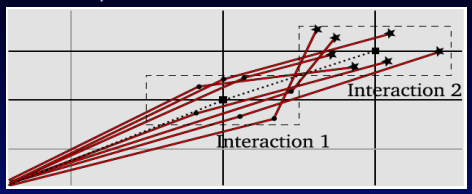
How does one position
this photon event?



Intelligent positioning algorithms for photons that scatter in crystals

--->Better estimate of first interaction location

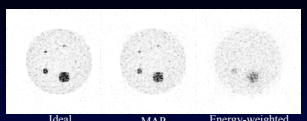
Generate multiple realizations of trajectories; Seek the sequence of interactions that has the greatest statistical consistency with the observations



Pratx *et al*, Phys Med Biol, 2009

MAP Sequencing: Comparison

Sphere phantom
Activity ratio 10:1



Ideal positioning | MAP | Energy-weighted centroid

Energy resolution	0%	3%	12%
Full sequencing accuracy			
1 x 1 x 1 (mm)	95%	86%	66%
1 x 1 x 5	89%	78%	57%
Positioning first interaction			
1 x 1 x 1	97%	90%	77%
1 x 1 x 5	90%	84%	71%

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Advantages of 3-D positioning photon detectors:

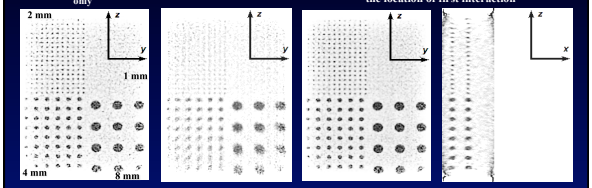
Intelligent algorithms to determine the sequence of multiple interactions

--->Better estimate of first interaction location---required to visualize smaller lesions

1 Positioning each photon using photopeak events only

2 Positioning each photon using energy weighted mean over all interactions

3 Positioning each photon using ML algorithm that estimates the location of first interaction



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Gu *et al*, Phys Med Biol 2010

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Benefits of 3-D positioning detectors

By resolving individual photon interactions in the detector, can:

- Correct parallax positioning errors (maintain uniform spatial resolution
- Reject background coincidence events

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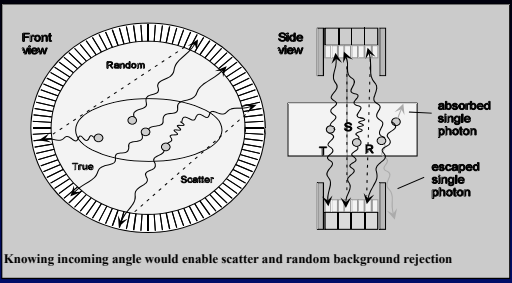
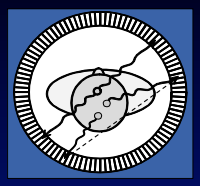
Filtering out background events in PET

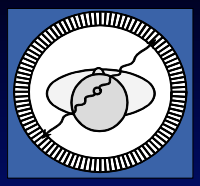


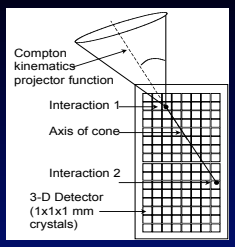
Knowing incoming angle would enable scatter and random background rejection

Angular collimation to reject random coincidences

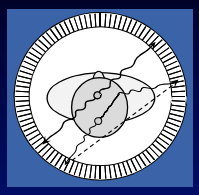


Angular collimation to reject random coincidences

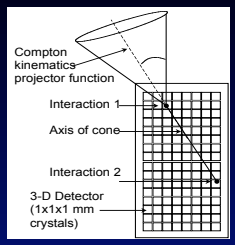


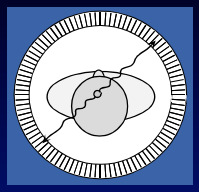


Angular collimation to reject tissue scatter coincidences



Angular collimation to reject tissue scatter coincidences





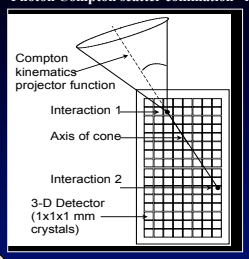
Benefits of 3-D positioning detectors

By resolving individual photon interactions in the detector, can:

- Correct parallax positioning errors (maintain uniform spatial resolution
- Reject background coincidence events
- Include events normally rejected from the data set

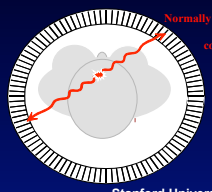
Exploiting 3-D positioning detectors to include single photon events (usually rejected)

"Photon Compton scatter collimation" in 3-D positioning detectors



With an intelligent algorithm can:

- Include single photons in data set for image reconstruction



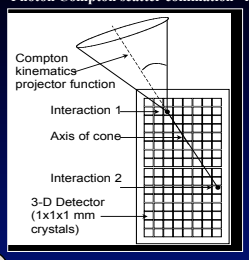
MIPS Molecular Imaging Program at Stanford

Chinn *et al*, IEEE Med Im Conf Rec. 2006

Stanford University School of Medicine Department of Radiology

Exploiting 3-D positioning detectors to include single photon events (usually rejected)

"Photon Compton scatter collimation" in 3-D positioning detectors



With an intelligent algorithm can:

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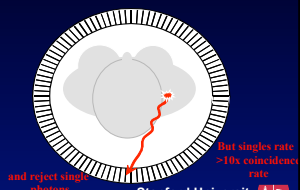

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Chinn *et al*, IEEE Med Im Conf Rec. 2006

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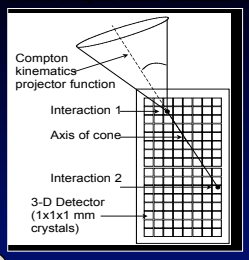
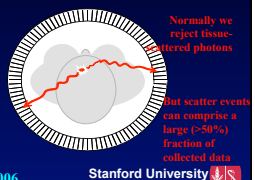
Exploiting 3-D positioning detectors to include tissue scatter events (usually rejected)

"Photon Compton scatter collimation" in 3-D positioning detectors



With an intelligent algorithm can:

- Include single photons in data set for image reconstruction
- Use tissue-scattered photons in image reconstruction



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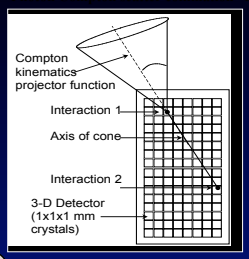
Chinn *et al*, IEEE Med Im Conf Rec. 2006

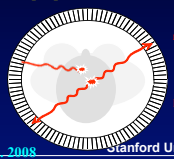
Stanford University School of Medicine Department of Radiology

Exploiting 3-D positioning detectors to include multiple photon events (usually rejected)



With an intelligent algorithm can:

- Include single photons in data set for image reconstruction
- Use tissue-scattered photons in image reconstruction
- Extract true coincidences from multiple photon coincidences



Normally we reject multiple photon coincidences

But multiples happen a lot for high sensitivity systems

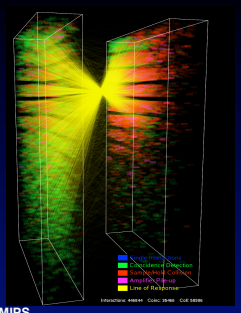
Chinn *et al*, IEEE Med Im Conf Rec, 2008

Benefits of 3-D positioning detectors

By resolving individual photon interactions in the detector, can:

- Correct parallax positioning errors (maintain uniform spatial resolution
- Reject background coincidence events
- Include events normally rejected from the data set

This system has billions of detector response lines!



Example data acquisition visualization of an event based simulation of a point source between two panels

- Detected Line of Response
- Detected Singles
- Detected Coincidence
- Sample-Hold Collision
- Shaper Pileup

Olcott et al, IEEE NSS-MIC proceedings, 2007

Must use list-mode iterative image reconstruction: Computationally intensive

List-mode 3D-OSEM algorithm

$$\lambda_j^{m,l} = \frac{\lambda_j^{m,l-1}}{\sum_{i=1}^{I} w_{ii} p_{ij}} \sum_{k \in S_i} p_{i_k j} \frac{1}{\sum_{b=1}^{J} p_{i_k b} \lambda_j^{m,l-1}}$$

C B A

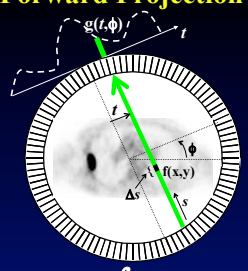
A= forward projection on the LOR i_k of the current voxel space

B=back-projection of every event i_k that goes through voxel j weighted by 1/A

C (via w_{ij}) = normalization factors that take into account the detector efficiencies, LOR geometry, and photon tissue attenuation coefficients

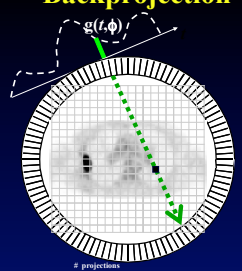
Pratx *et al.* Trans Med. Imag. 2009

Forward Projection



$$g(t,\phi) = \int_{FOV} f(x,y)\,ds$$

Backprojection



$$bp(x,y) = \sum_{k=0}^{\#\text{ projections}} g(t_k, \phi_k)\Delta\phi$$

Computing hardware

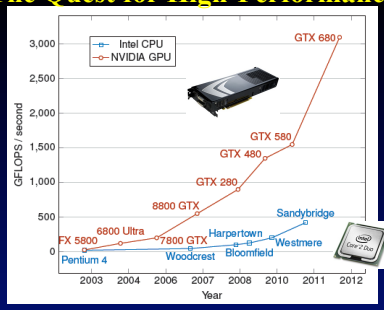
Central Processing Unit (CPU)

Graphics Processing Unit (GPU)

1. Slow growth in clock frequency and instructions-per-clock
2. Multi-CPU cluster costly

1. Highly parallel, multi-threaded processor
2. Low cost (~ $500)

The Quest for High-Performance



GPU ≈ (Moore's law)$^{1.6}$

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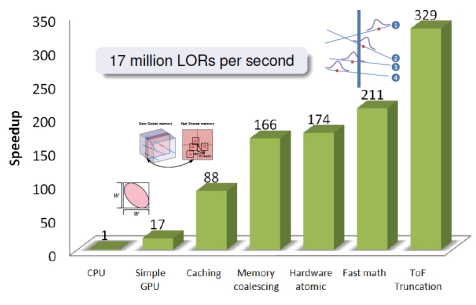
Speedup breakdown



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Cui *et al*, Medical Physics, 2011

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Summary

- With new geometries and special detectors, 1 mm resolution clinical PET is possible
- 1 mm resolution enables substantial abilities to visualize and quantify smaller lesions above background signal
- We are currently constructing a dual-panel "spot imager" for cancer that uses 3-D positioning detectors and novel electronics
- The 3-D positioning detectors allow us to better position events as well as enable an estimate of the incoming photon direction opening new possibilities for processing PET photon events
- GPUs can help to realize practical image reconstruction
- If successful, we can explore new roles of PET in disease management

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Department of Radiology

Stanford Molecular Imaging Scholars (SMIS) Program
Postdoctoral Training in Molecular Imaging of Cancer
Stanford University, Stanford, CA, USA

Program Director:
Craig Levin, PhD

Co-Program Director:
Sanjiv Sam Gambhir, MD, PhD

The Stanford Molecular Imaging Scholars (SMIS) Program is a diverse training program bringing together more than thirteen Departments, predominantly from the Stanford Schools of Medicine and Engineering, in order to train the next generation of interdisciplinary leaders in molecular imaging. Oncologic molecular imaging is a rapidly growing area within molecular imaging which combines the disciplines of chemistry, cell/molecular biology, molecular pharmacology, physics, bioengineering, imaging sciences, and clinical medicine to advance cancer research, diagnosis, and management. SMIS fellows will conduct innovative research in cancer imaging under the supervision of two faculty mentors from complementary fields, in a comprehensive, integrated, flexible program (up to 3 years). Funding is available for stipend, supplies, and travel.

Application Deadline:
May 13, 2013
for a start date in September 2013

Applicants must have a PhD or MD.

Inquiries to Sofia Gonzales
(650) 724-9139, sofiaas@stanford.edu

More information: http://mips.stanford.edu/grants/smis/

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