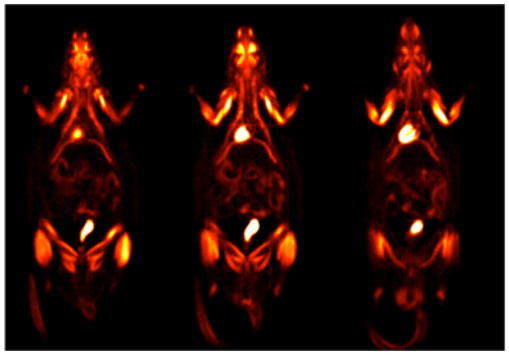
HIGH RESOLUTION GAMMA RAY DETECTORS FOR IN VIVO IMAGING

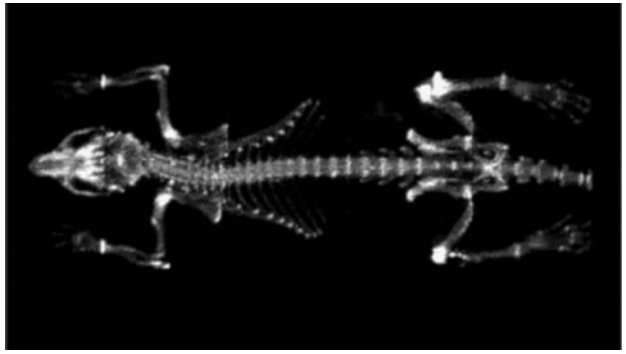
Simon R. Cherry, Ph.D.

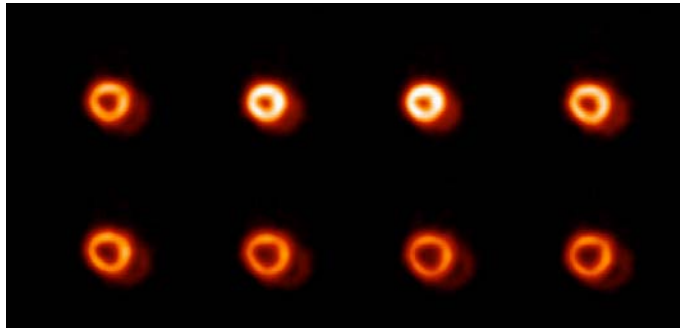
Department of Biomedical Engineering

University of California, Davis

RDC Seminar
May 24th, 2005







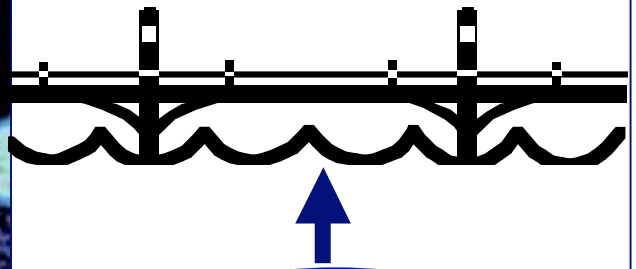
Outline

- why *in vivo* small animal PET imaging?
- design and performance of a small animal PET scanner “microPET II”
- limitations in spatial resolution and sensitivity
- APD-based depth-encoding scintillation detectors
- simultaneous PET-MRI imaging

In Vivo Animal Imaging - Bridging the Divide

IN VITRO, EX VIVO

DRUG DISCOVERY GENOMICS



In Vivo Small Animal Imaging

IN VIVO

MEDICAL DIAGNOSTICS AND THERAPEUTICS

Why *In Vivo* Small Animal Imaging?

- in vivo ≠ in vitro
- non-destructive - repeat studies in the same animal
- each animal serves as its own control
- can efficiently survey whole animal
- provides bridge from animal to human studies

In Vivo Small-Animal Imaging

Anatomic | Physiologic | Metabolic | Molecular

optical imaging

x-ray CT | **CT+probe**

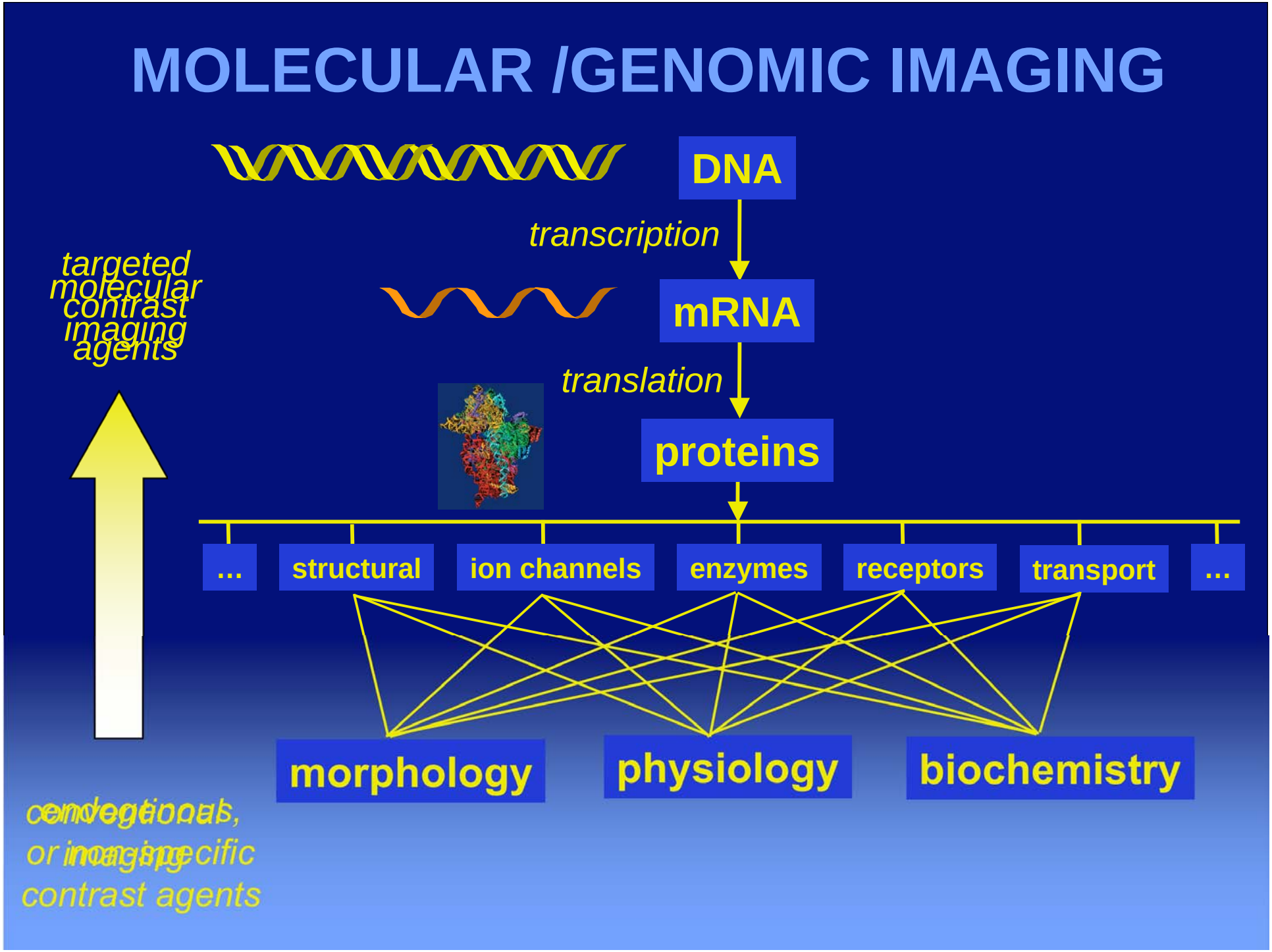
PET/SPECT

MRI | **MR Spectroscopy** | **MR+probe**

fMRI

ultrasound | **ultrasound+probe**

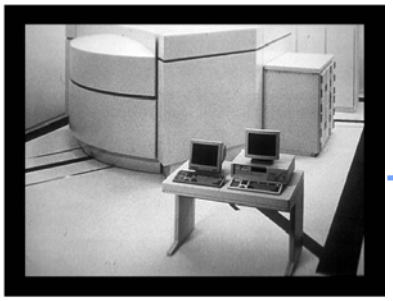
MOLECULAR /GENOMIC IMAGING



Positron-Emitting Radionuclides

Isotope	Halflife	β^+ fraction	Max. Energy	range(mm)	production
C–11	20.4 mins	0.99	0.96 MeV	0.4 mm	cyclotron
N–13	9.96 mins	1.00	1.20 MeV	0.7 mm	cyclotron
O–15	123 secs	1.00	1.74 MeV	1.1 mm	cyclotron
F–18	110 mins	0.97	0.63 MeV	0.3 mm	cyclotron
Cu–62	9.74 mins	0.98	2.93 MeV	2.7 mm	generator
Cu-64	12.7 hours	0.19	0.65 MeV	0.3 mm	cyclotron
Ga–68	68.3 mins	0.88	1.83 MeV	1.2 mm	generator
Br-76	16.1 hours	1.00	1.90 MeV	1.2 mm	cyclotron
Rb–82	78 secs	0.96	3.15 MeV	2.8 mm	generator
I–124	4.18 days	0.22	1.50 MeV	0.9 mm	cyclotron

PET-labeled Probes for Molecular Imaging

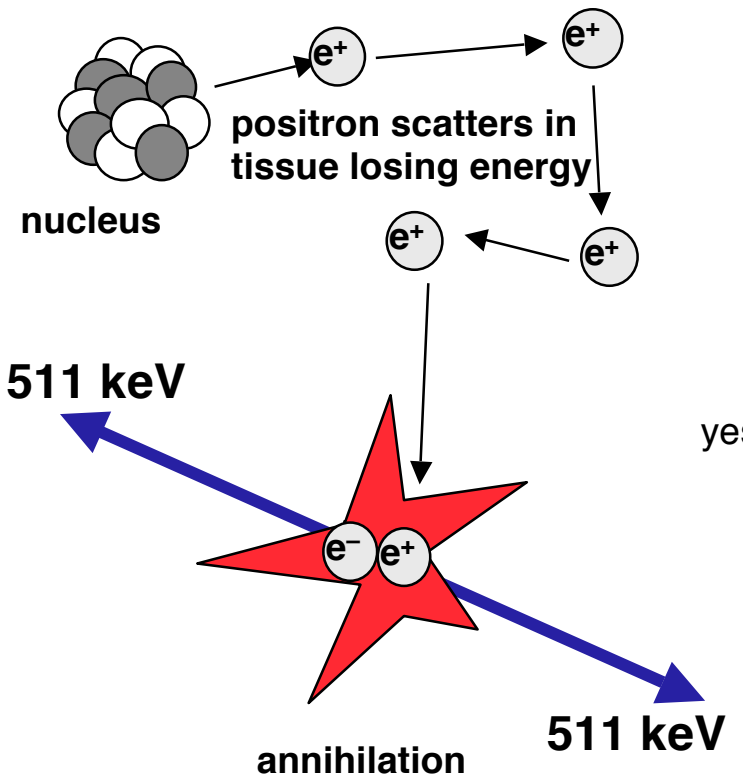


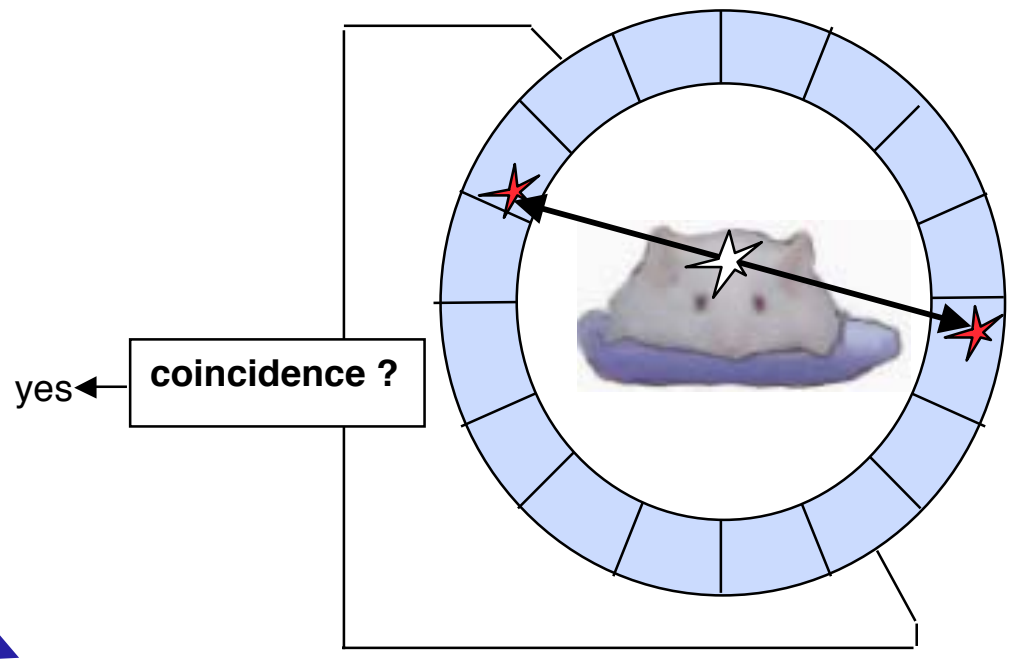
cyclotron
^{11}C, ^{13}N, ^{15}O, ^{18}F

- hemodynamic parameters ($H_2{}^{15}O$, ^{15}O-butanol, ^{11}CO, $^{13}NH_3$.....)
- substrate metabolism(^{18}F-FDG, $^{15}O_2$, ^{11}C-palmitic acid....)
- protein synthesis (^{11}C-leucine, ^{11}C-methionine, ^{11}C-tyrosine)
- enzyme activity (^{11}C-deprenyl, ^{18}F-deoxyuracil...)
- drugs (^{11}C-cocaine, ^{13}N-cisplatin, ^{18}F-fluorouracil...)
- receptor affinity (^{11}C-raclopride, ^{11}C-carfentanil, ^{11}C-scopalamine)
- neurotransmitter biochemistry (^{18}F-fluorodopa, ^{11}C-ephedrine...)
- gene expression (^{18}F-penciclovir, ^{18}F-antisense oligonucleotides...)
- .....

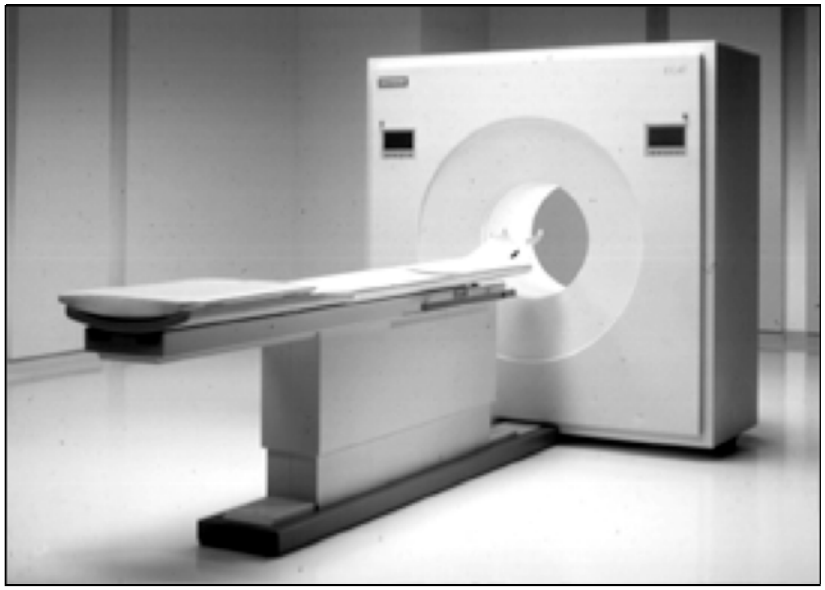
PET can detect and image sub nanomolar levels of these tracers in vivo

Positron Emission Tomography





Clinical PET Scanners



Siemens ECAT EXACT HR+
20,000 scintillator detectors
ring diameter ~ 80 cm
4 mm (64 μL) spatial resolution
(typically 6-12 mm in clinical practice)

^{18}FDG
coronal sections through whole body

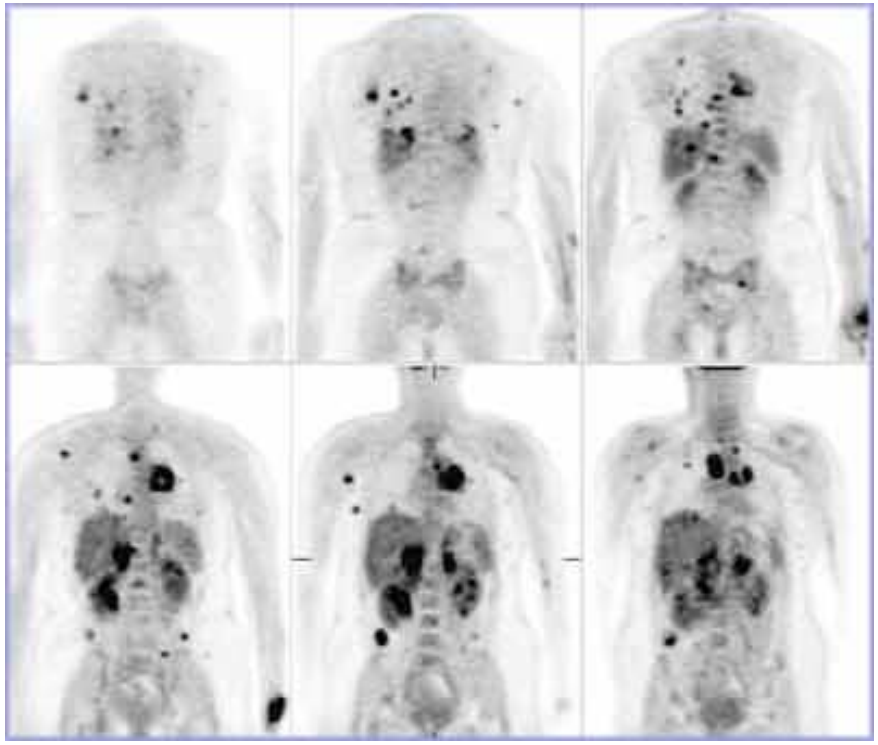
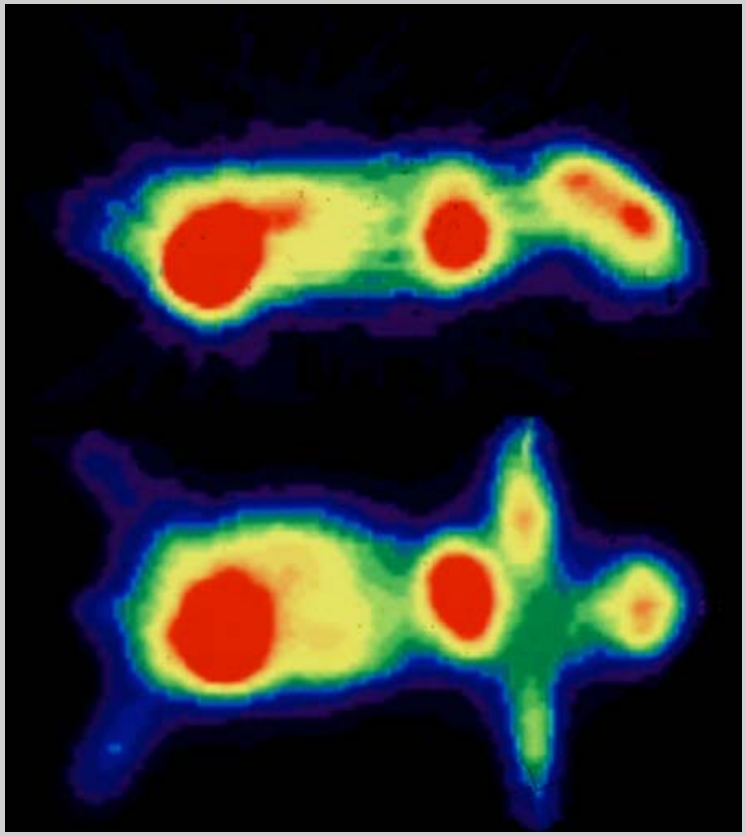


Image courtesy of GE Healthcare

PET Imaging of Mouse on Clinical PET Scanner



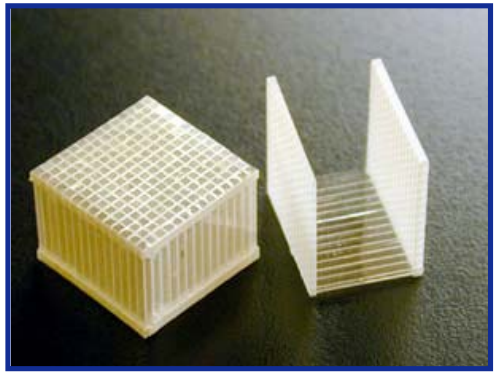
^{18}F-FDG images of tumor bearing mouse

image resolution ~ 4 mm

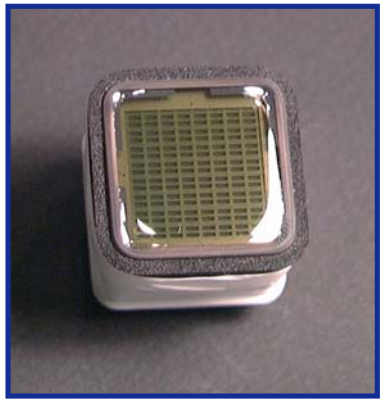
microPET II
Small Animal PET System

microPET II Detector Design

LSO crystal array

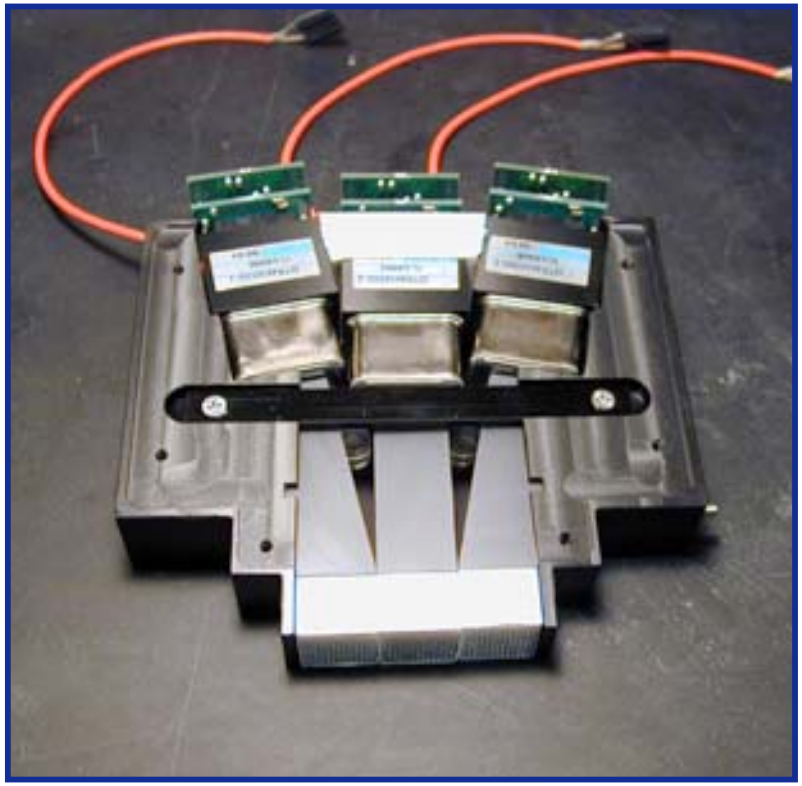


Glass fiber bundle



Hamamatsu H7546
64 channel MC-PMT

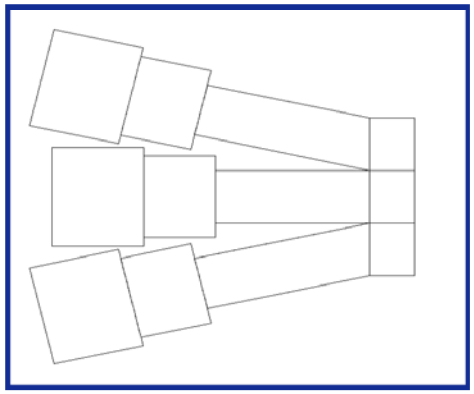
Detector Cassette
(3 modules)

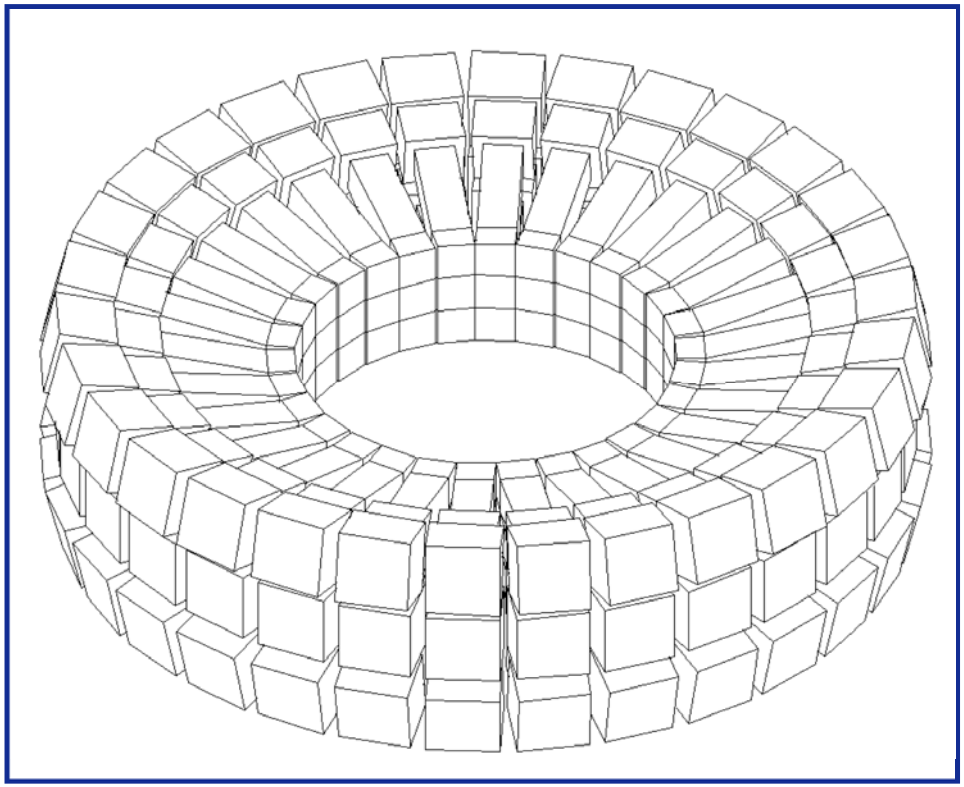


System Geometry

- 90 detectors in 3 rings
- Inner diameter: 16.0 cm
- Transverse FOV: 8.0 cm
- Axial FOV: 4.9 cm

30 x

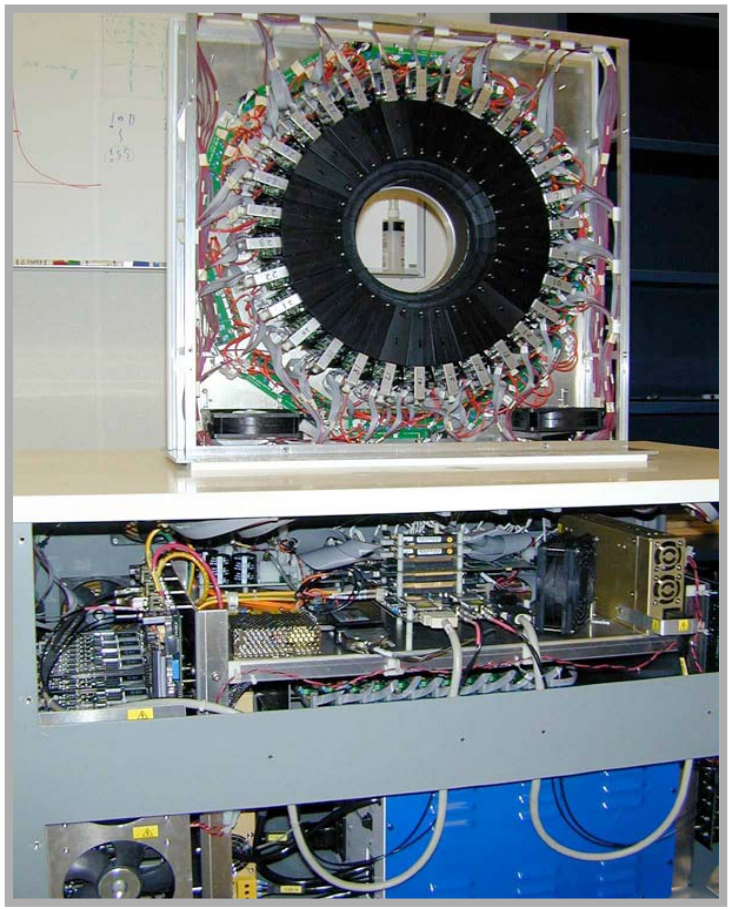




microPET II System

Tai, Chatziioannou, Yang, Cherry et al, Phys Med Biol, 2003

- 14 × 14 LSO crystal array
- 90 detector modules in 3 rings
- 17640 LSO detector elements
- Inner diameter: 16.0 cm
- Axial FOV: 4.9 cm
- Transaxial FOV: 8.0 cm
- Custom built gantry: 62 × 62 cm
- Number of LORs: 51,861,600
- # sinograms (3D): 1764
- # image planes: 83
- 3D dataset size: 200 MB

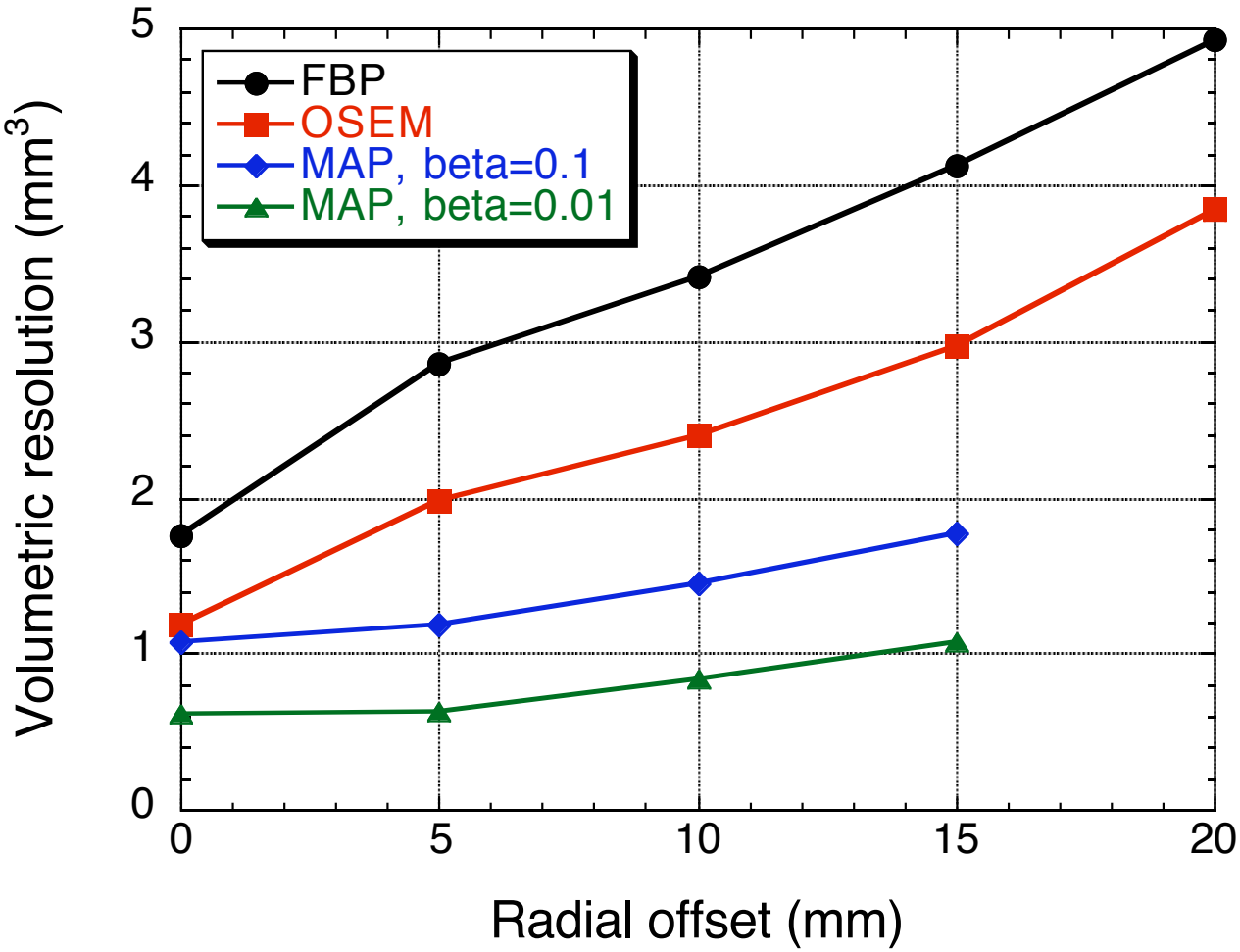


Volumetric Image Resolution

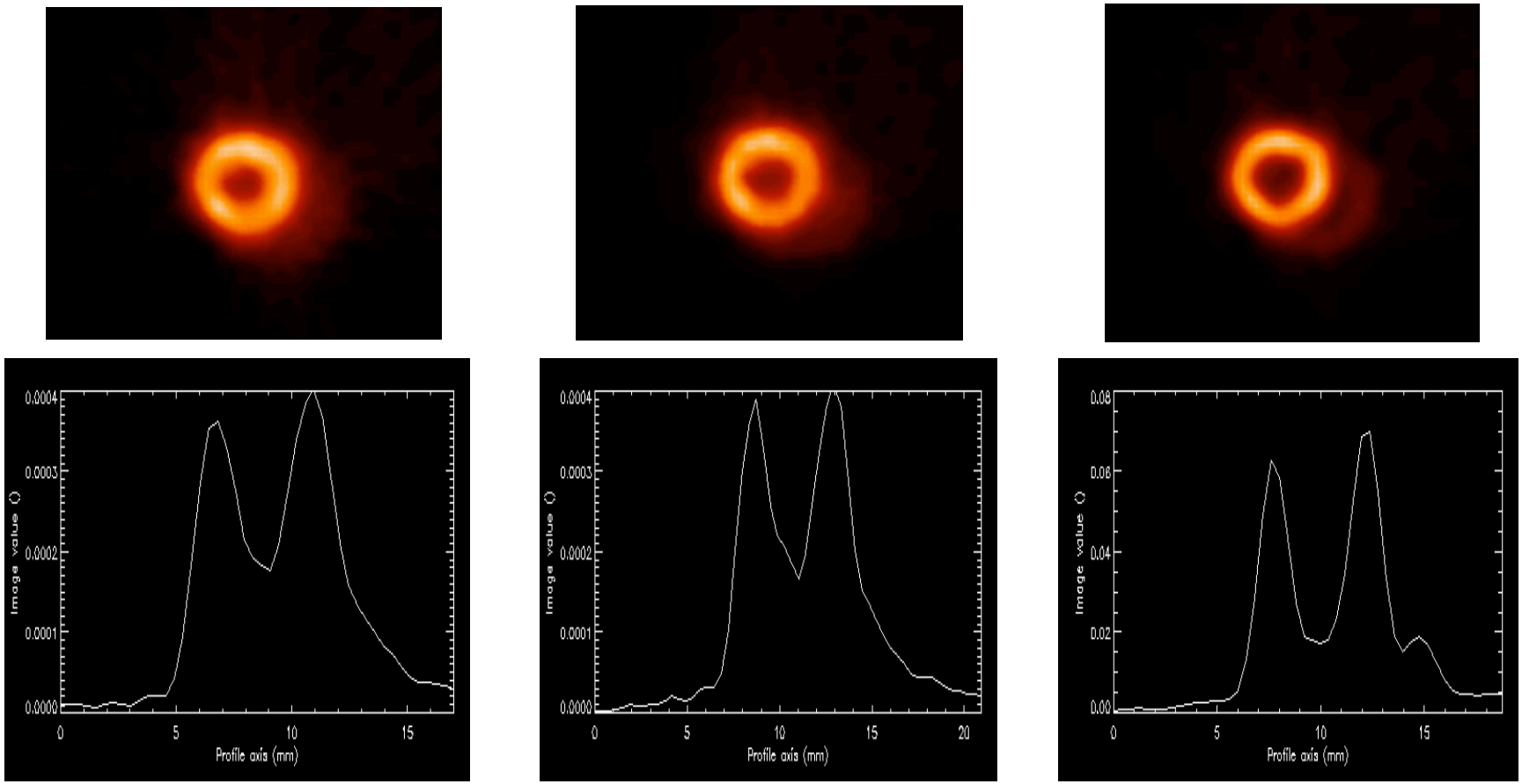
Average volumetric image resolution for central 30 mm FOV (size of mouse)

1.4 μL

for MAP, β=0.1

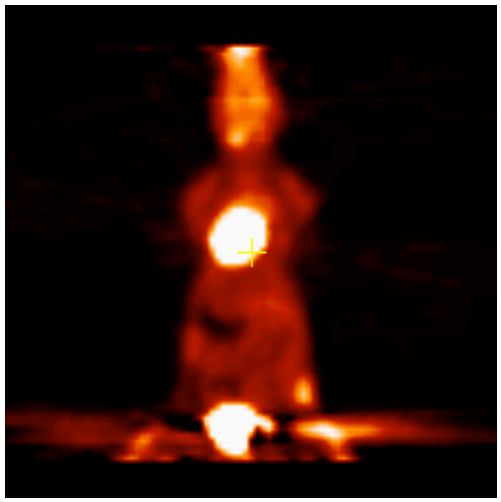


Mouse Heart Imaging - FDG

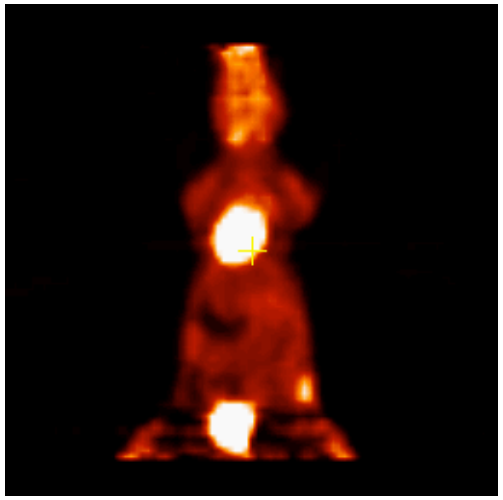


FORE + 2D FBP | OSEM 2D | MAP

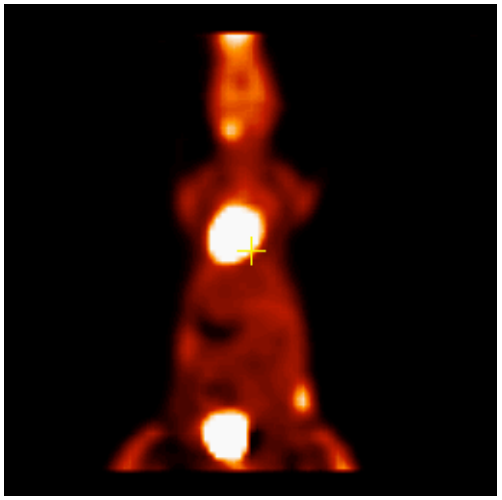
Bladder Artifacts



FORE + 2D FBP



OSEM 2D



MAP

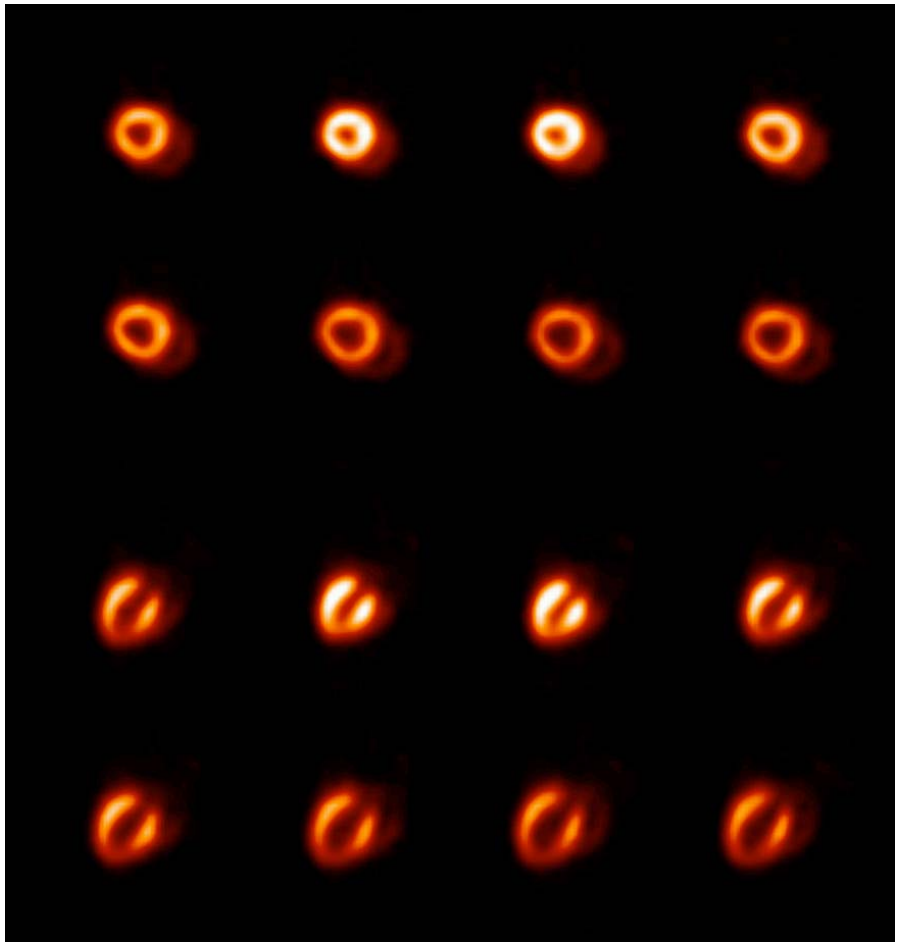
Cardiac Gated FDG: Mouse

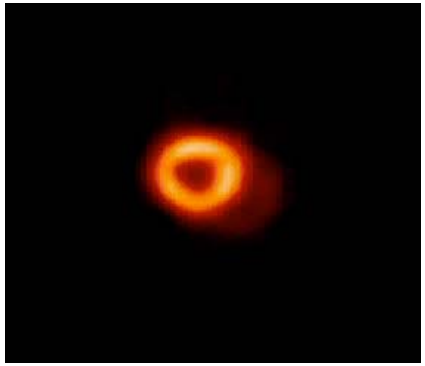
Injected Dose: 0.6 mCi; Imaging Time: 60 mins

transverse

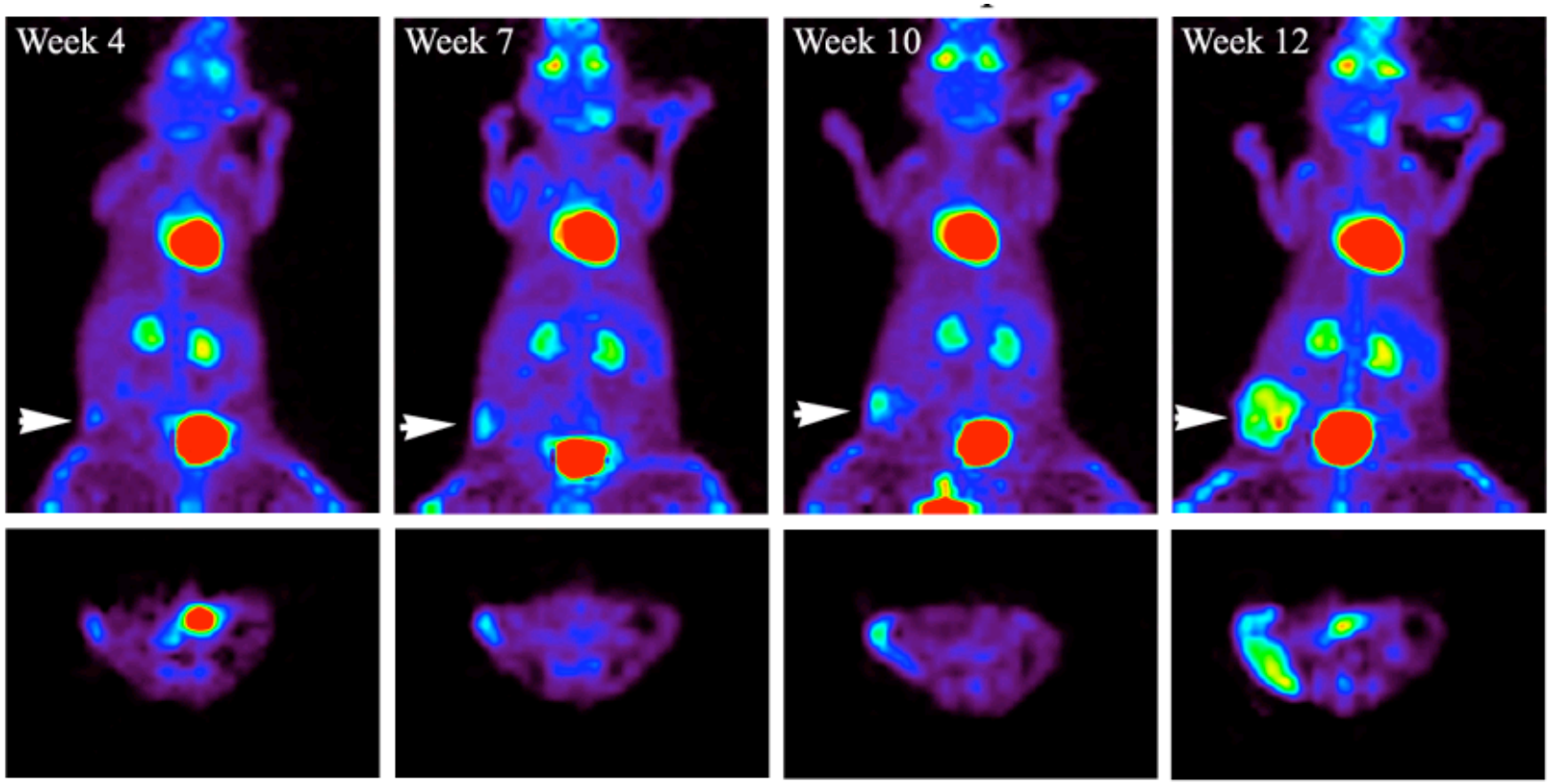
time resolution
25 msecs

coronal





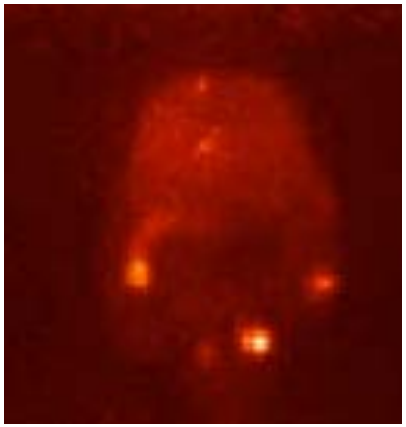
Mouse Model of Breast Cancer

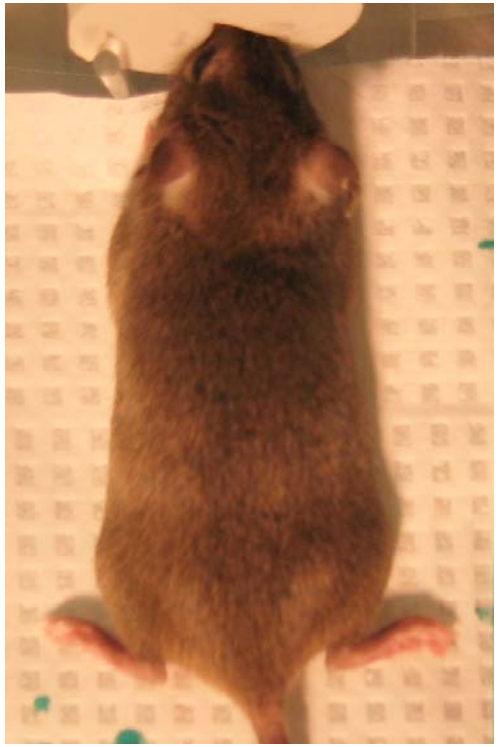


Craig Abbey, Robert Cardiff, Sandy Borowsky, et al, UC Davis, PNAS, 2004

Imaging of Cell Trafficking

microPET image
8.5 hrs p.i.
15 min scan





PET with ^{64}Cu radiolabeled T cells reveals sites of T cell accumulation and provides temporal information about T cell trafficking

Bernd Pichler, Ph.D., University of Tuebingen

Detection Limits

Detection of objects smaller than resolution of scanner

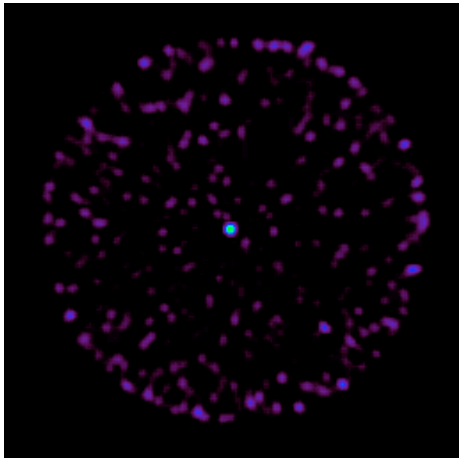
Point source in air

30 minute scan

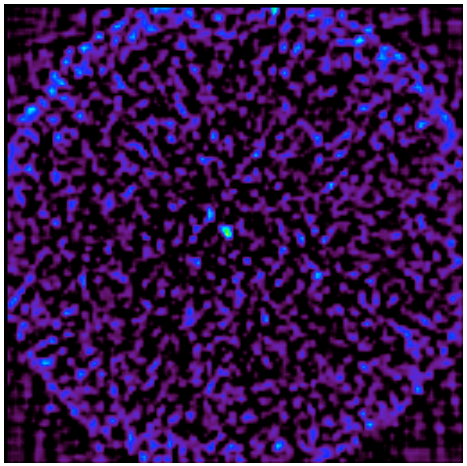
No subtraction of LSO background

Detection limit (CNR=4) is 0.25 nCi (9 Bq)

0.9 nCi (33 Bq)



0.39 nCi (14 Bq)



Detection Limits

Detection of objects much larger than resolution of scanner

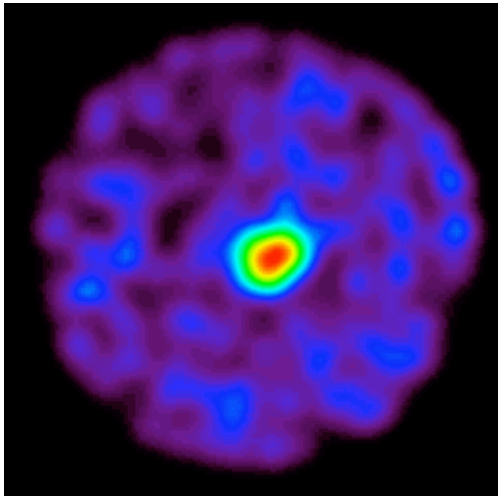
Uniform 1 cm cylinder

30 minute scan

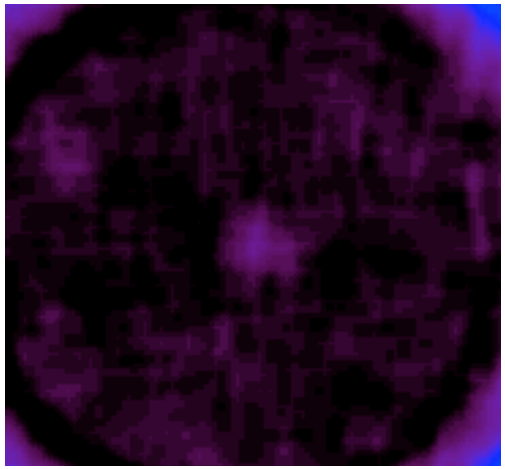
No subtraction of LSO background

Detection limit (CNR=4) is 5.6 nCi/cc (208 Bq/cc)

28 nCi/cc (1 kBq/cc)



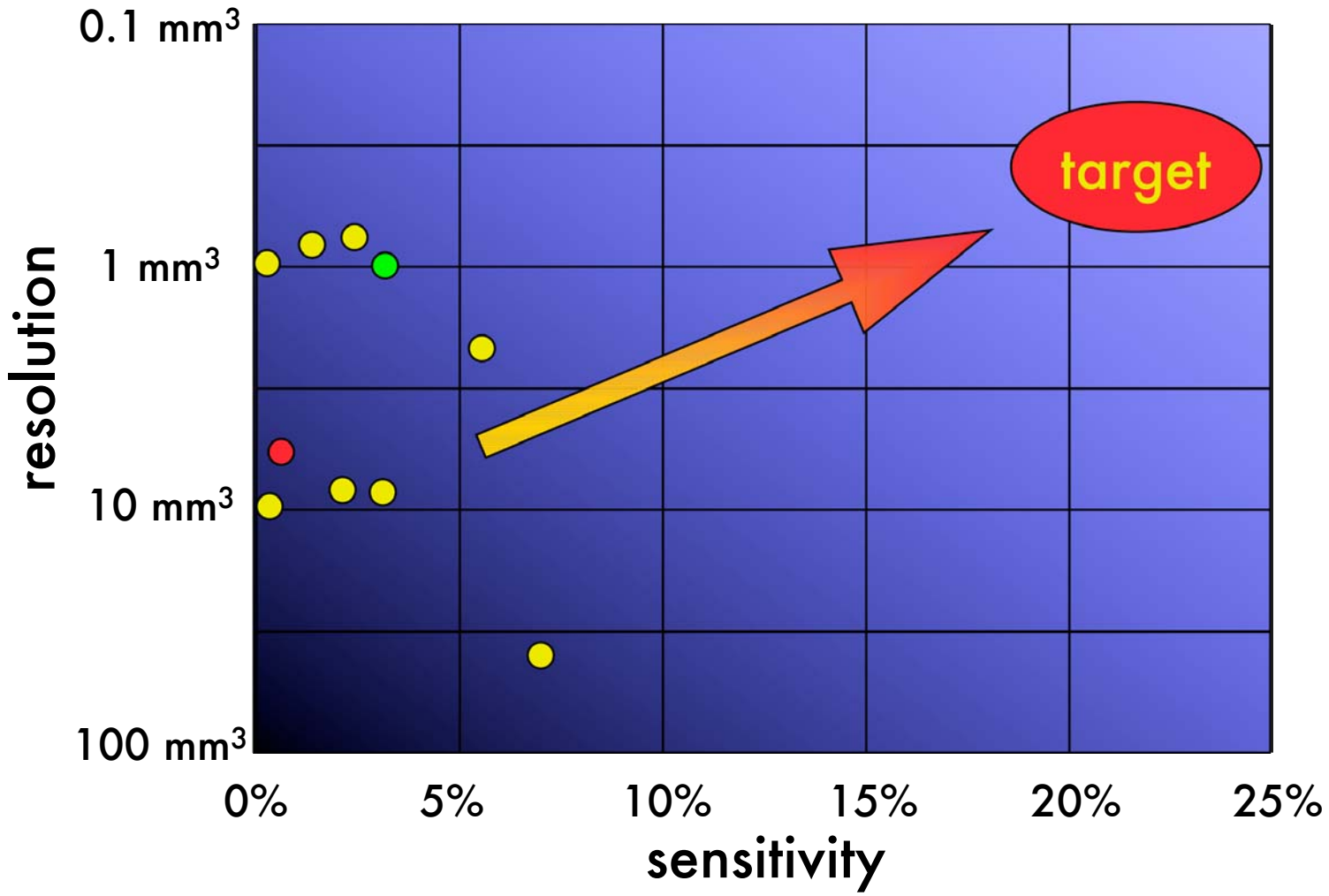
5.6 nCi/cc (208 Bq/cc)



Detection Limits - Cell Trafficking

- ^{64}Cu-PTSM at 0.25 - 1 pCi per cell
- can detect as few as ~ 1000-5000 cells localized in a small region
- can detect distributions of cells in an organ at a concentration of 30-150 cells per mm^3

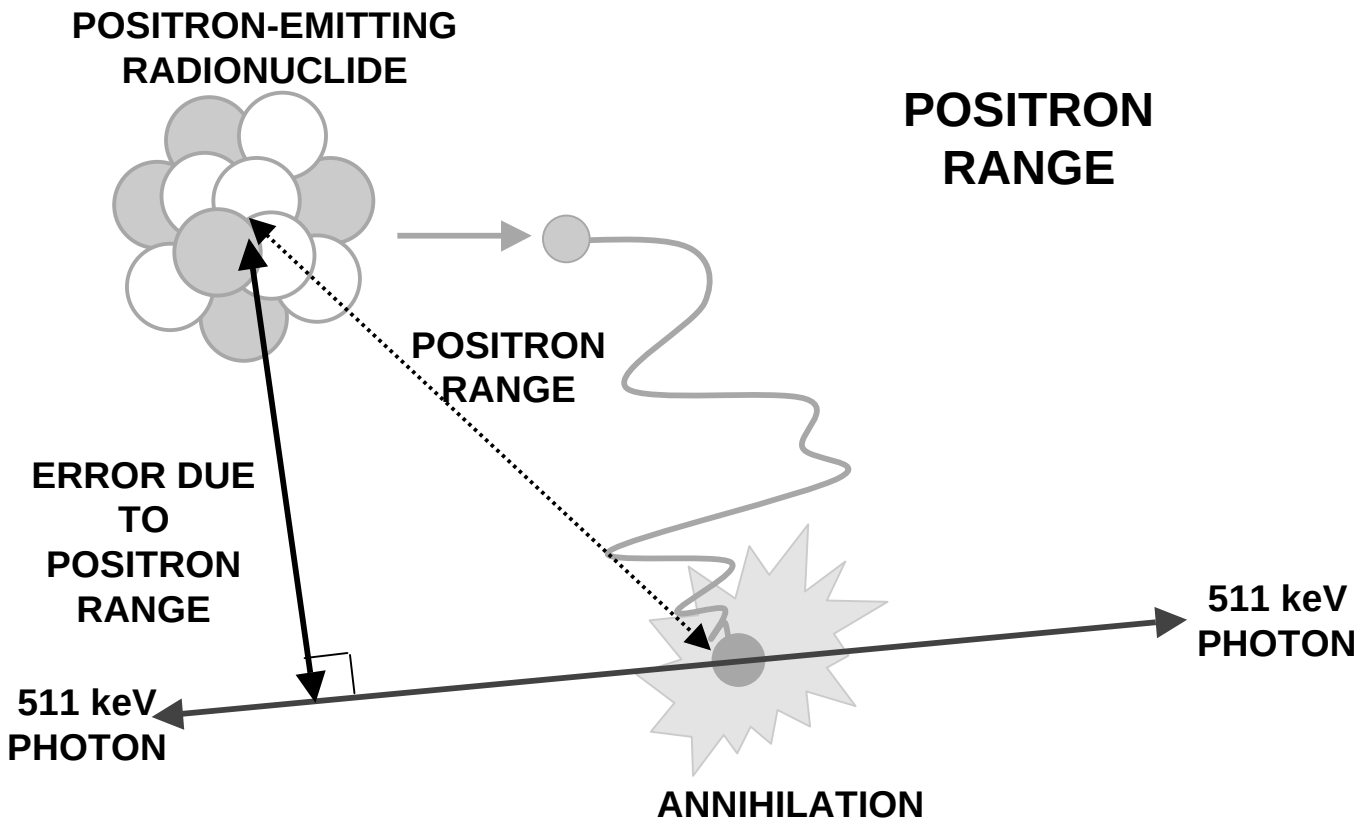
Sensitivity - Resolution



Resolution Limitations

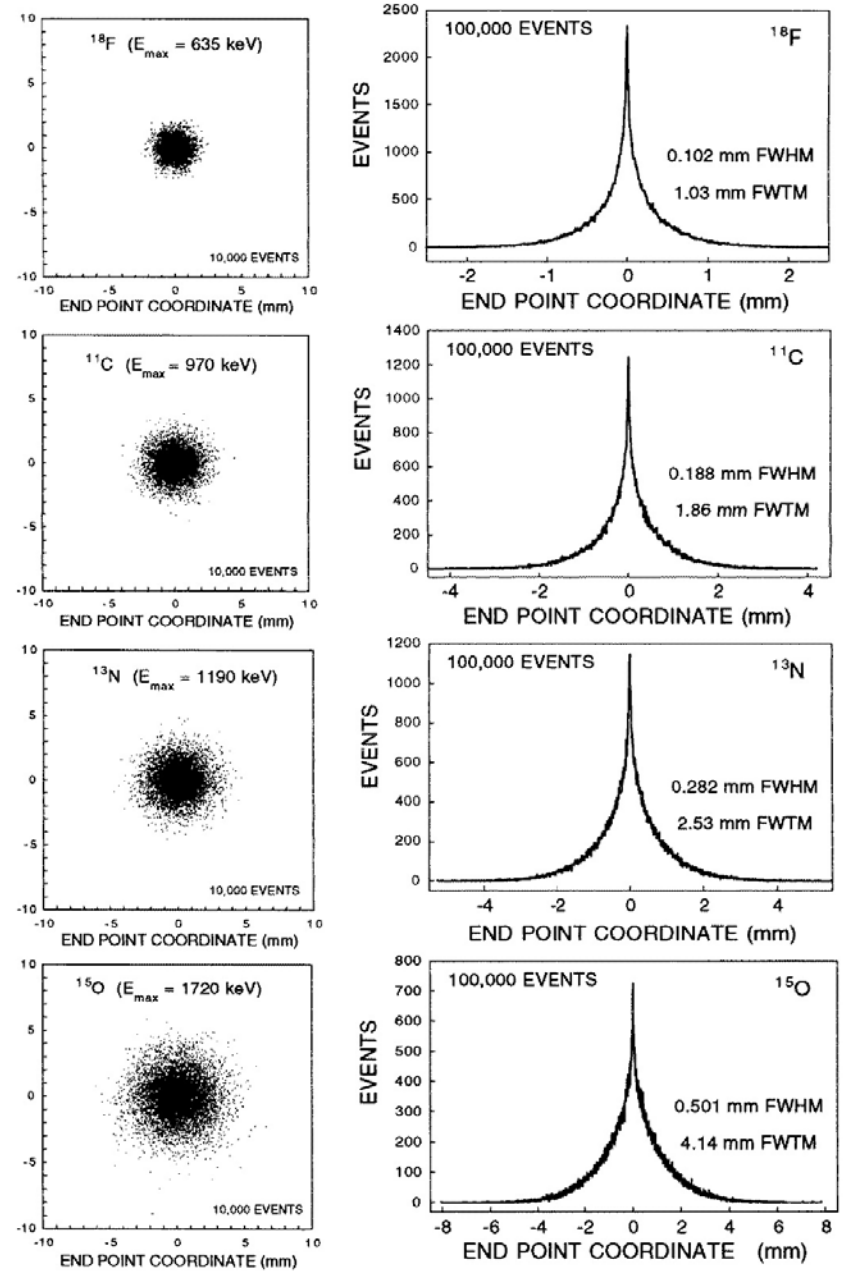
- Positron range
- Non-colinearity
- Geometry
  - Detector dimensions (~d/2)
  - Depth of interaction effects
- Detector interaction physics
  - Compton scatter within detectors
  - Spatial distribution of interaction products

Positron Range



Positron Range

- Depends on E_{max} of emitted positrons
- Exponential shape
- Root mean square (rms) range a better descriptor than FWHM
  - ^{18}F rms = 0.23 mm
  - ^{11}C rms = 0.39 mm
- Range is inversely proportional to absorber density

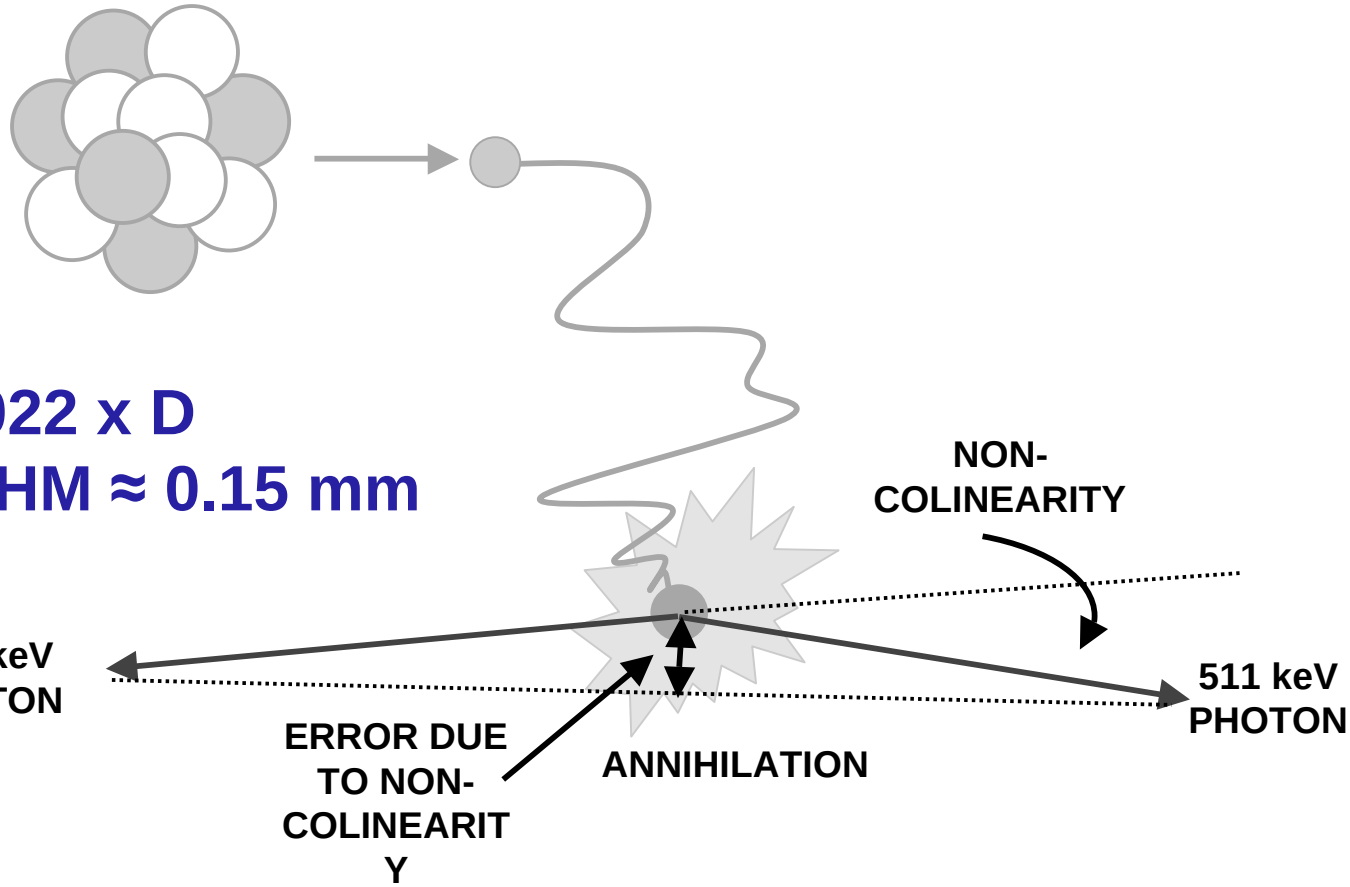


From Levin et al, Phys Med Biol, 1999

Positron Range

- To minimize effects:
  - **Use low-energy positron emitters**
    - ^{18}F, ^{64}Cu, ^{11}C
  - **Place in high magnetic field**
    - Wirrwar et al, IEEE Trans Nucl Sci 44;184-9(1997)
    - PET/MRI, Shao et al, IEEE Trans Nucl Sci 44;1167-71(1997)
  - **Model in iterative reconstruction algorithm**

Non-Colinearity



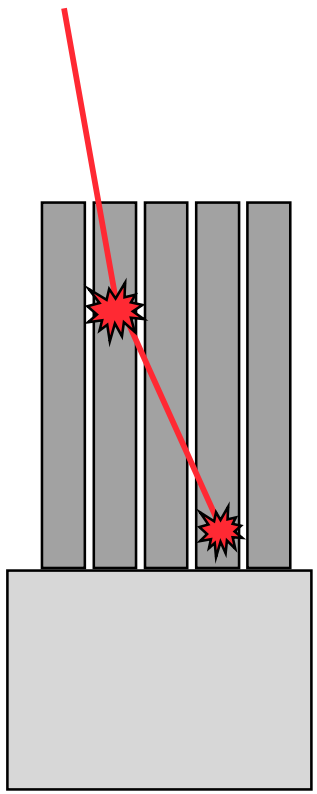
FWHM = 0.0022 x D

D= 8 cm, FWHM ≈ 0.15 mm

Non-Colinearity

- To minimize
  - bring detectors close together
    - Separation of 4 cm possible for mouse imaging
    - Also good for sensitivity
- Problems
  - parallax (depth of interaction) errors

Detector Interactions



- **Multiple interactions in crystal array**
  - Compton Scatter
  - Leads to loss of resolution (unless individual interactions can be resolved)
- **Interaction products**
  - Photoelectrons, recoil electrons, char. x-rays, Auger electrons etc…
- **Possible solutions**
  - Stacks of thin detectors

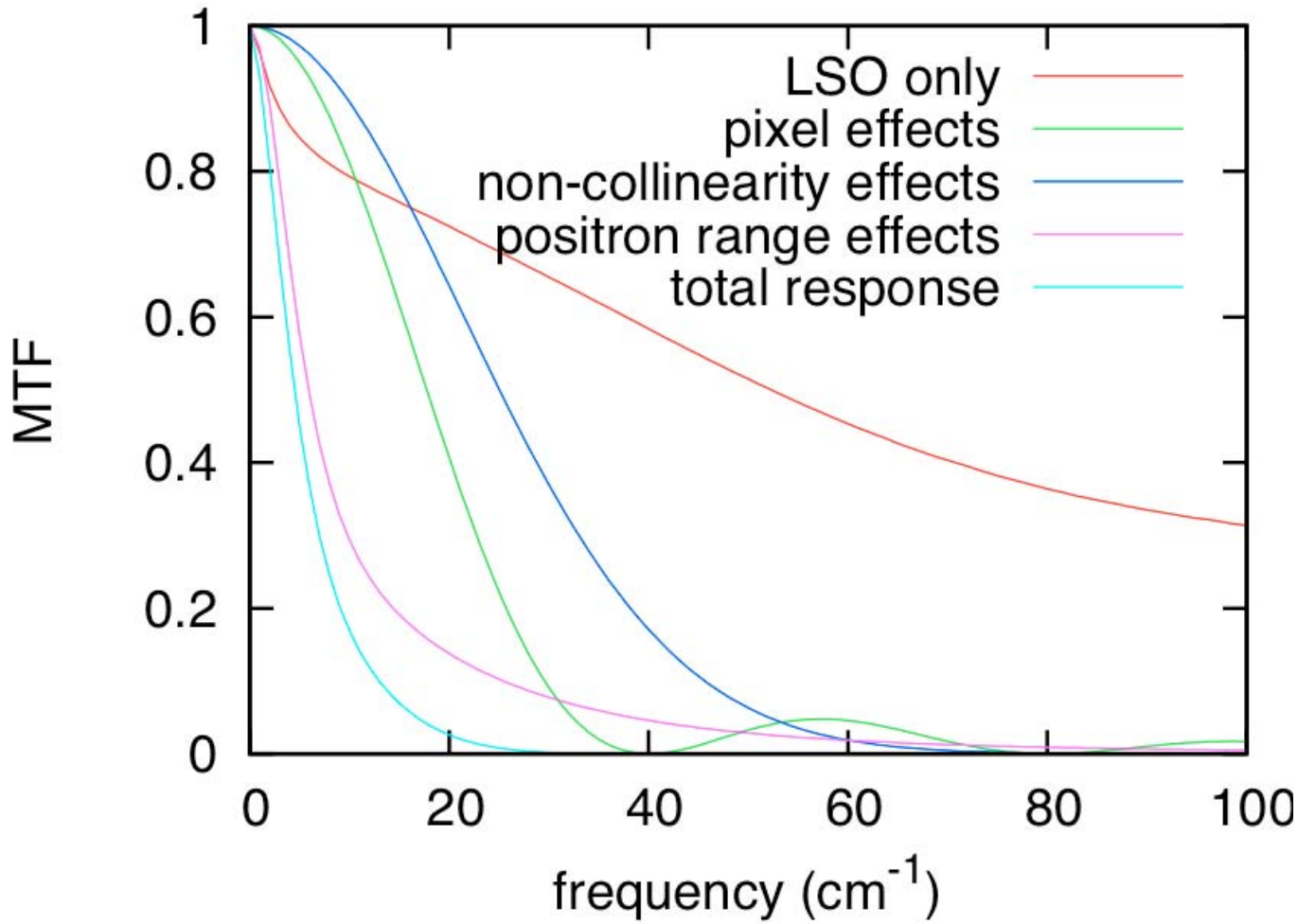
Resolution Components

^{18}F tracer

8 cm diameter scanner

500 µm pixels

2.7 mm thick LSO

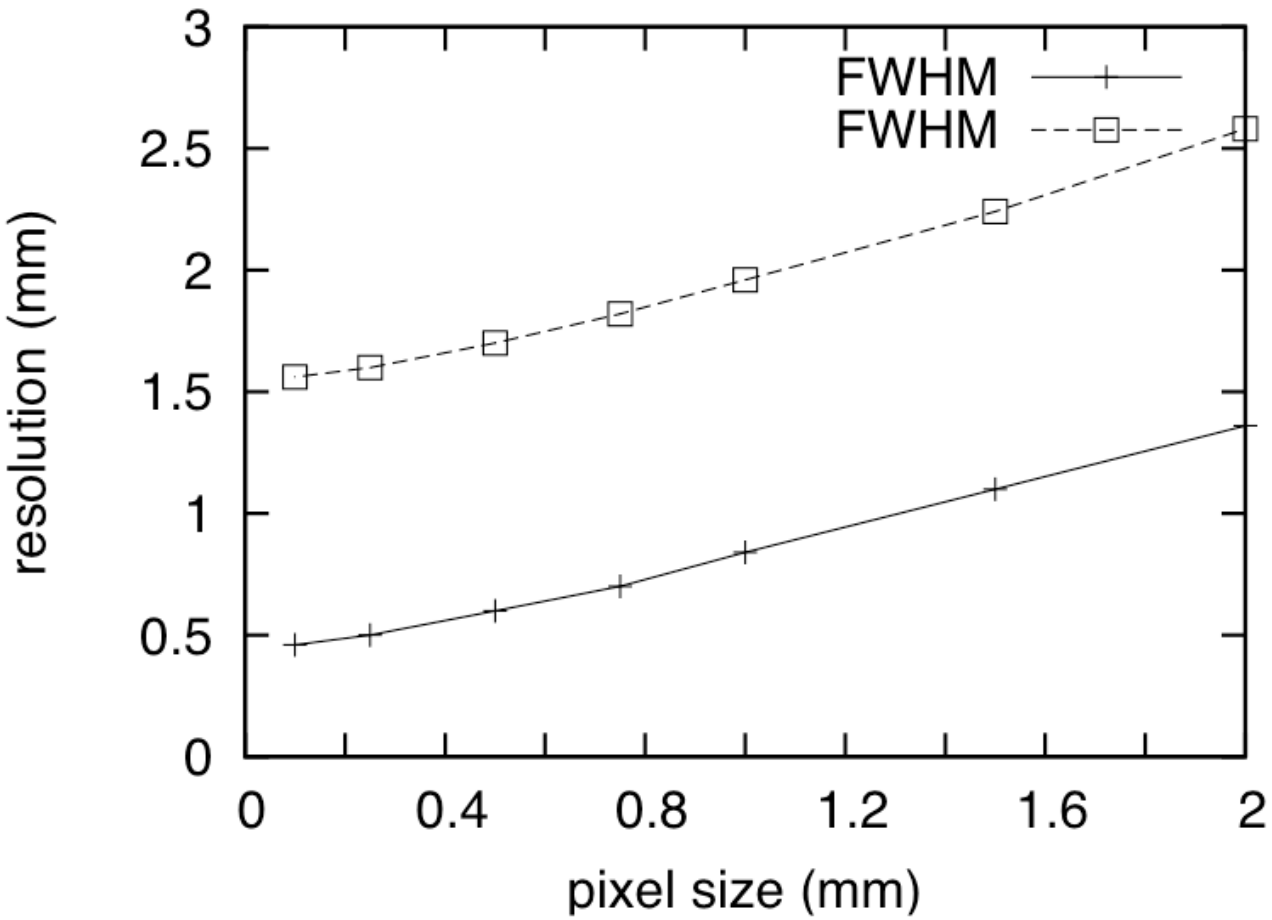


Resolution versus "Detector Size"

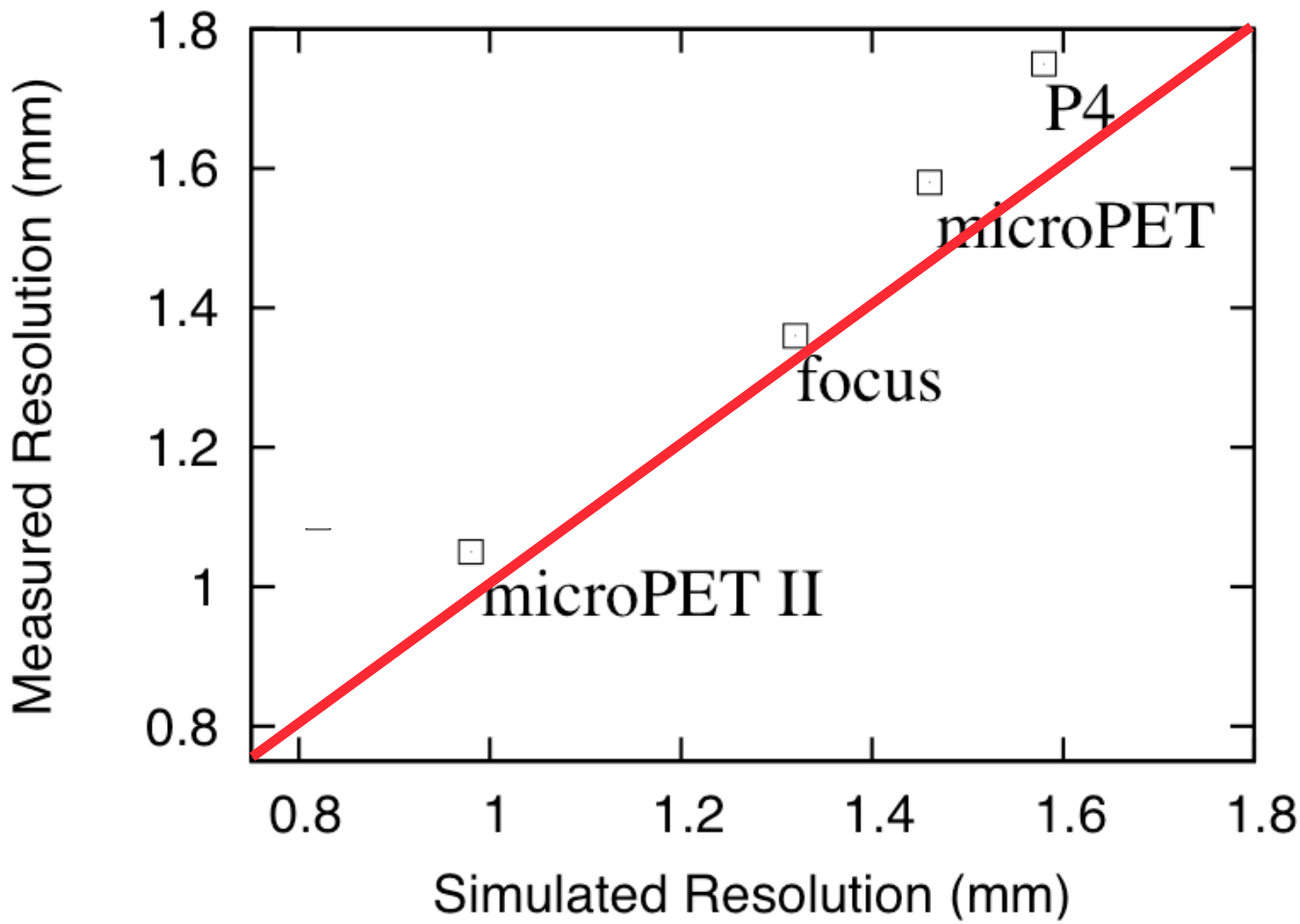
^{18}F tracer

8 cm diameter scanner

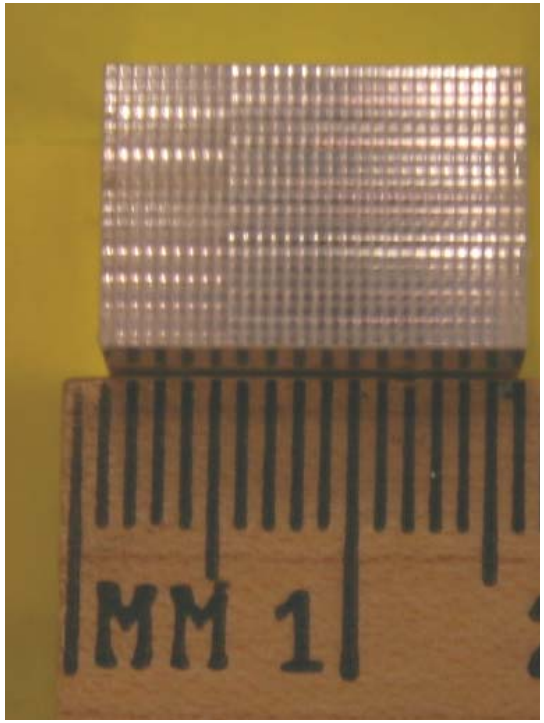
2.7 mm thick LSO

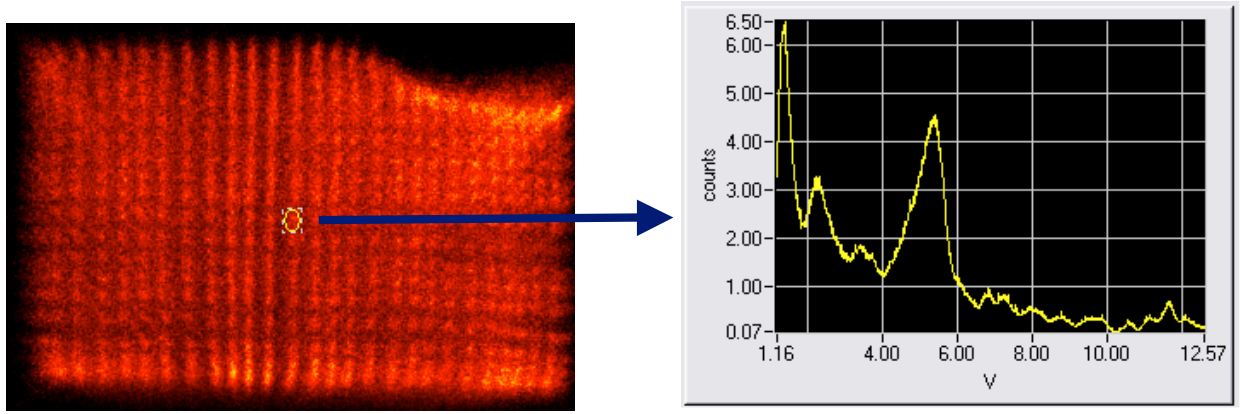


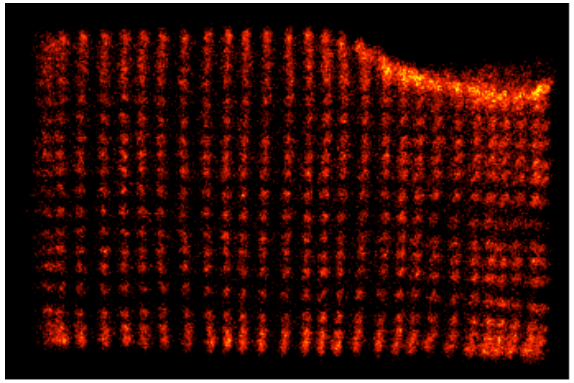
Comparison with Experimental Data



0.5 mm LSO Detector Array



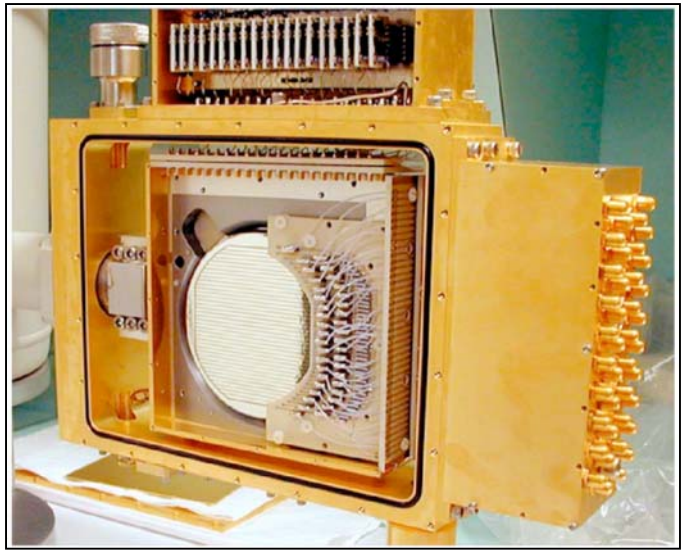


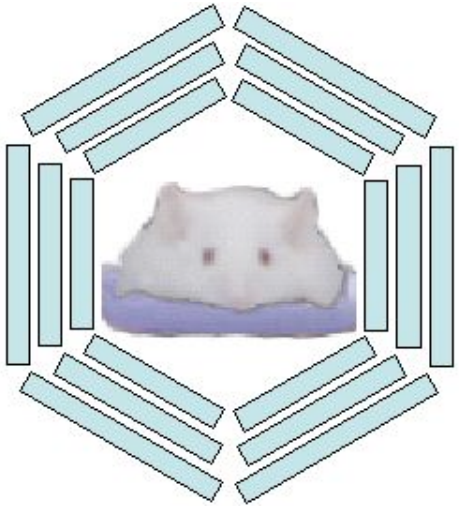


20 x 40 array of
0.5 x 0.5 x 10 mm
LSO crystals

Ge Detectors for Small-Animal PET

in collaboration with Klaus Ziock (LLNL)





- Stacks of Ge strip detectors for high resolution, high sensitivity imaging of 511 keV gamma rays

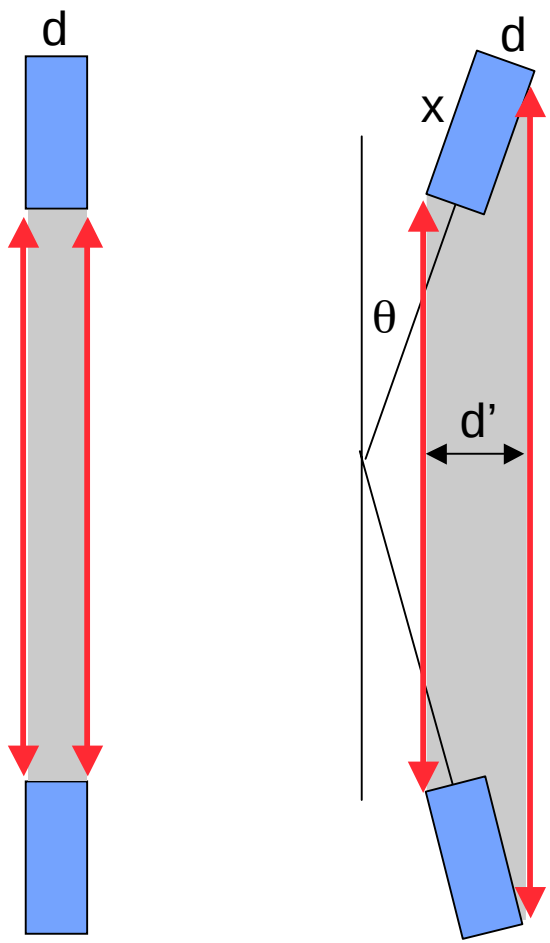
Sensitivity

- Solid Angle Coverage
  - Surround animal with detector material
    - Huber et al, IEEE Trans Nucl Sci 46;498-502(1999)

- (Detector Efficiency)^2
  - Dense detector material
  - Sufficient total thickness for high absorption probability
  - Efficient use of all interacting events

- Current systems typically have sensitivities < 5%

Depth of Interaction Effects



$$d' = d\cos\theta + x\sin\theta$$

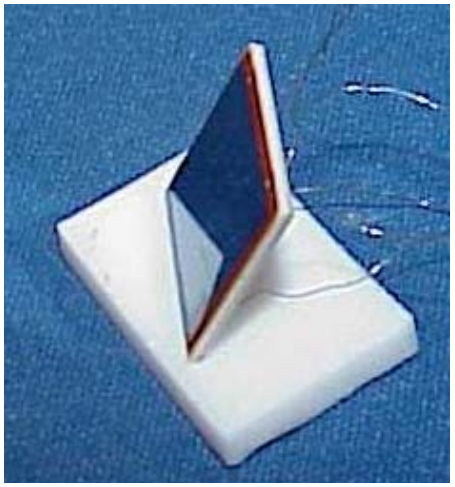
$$R_{\text{int}}' \approx \frac{d'}{2} \approx \frac{d}{2} \times [\cos\theta + \frac{x}{d}\sin\theta]$$

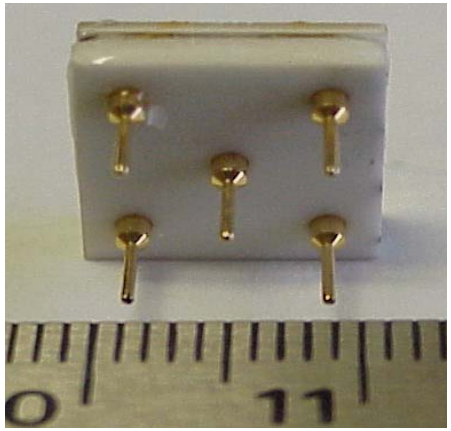
$$R_{\text{int}}' \approx R_{\text{int}} \times [\cos\theta + \frac{x}{d}\sin\theta]$$

Depth of Interaction

- Solutions:
  - “thin” detectors
    - poor sensitivity
  - DOI capable detector
    - Phoswich detector
    - Dual-ended readout
    - Many other schemes…

Position-Sensitive Avalanche Photodiodes





Active area: 8x8 or 14x14 mm

Gain ~ 1000 at 1750 V

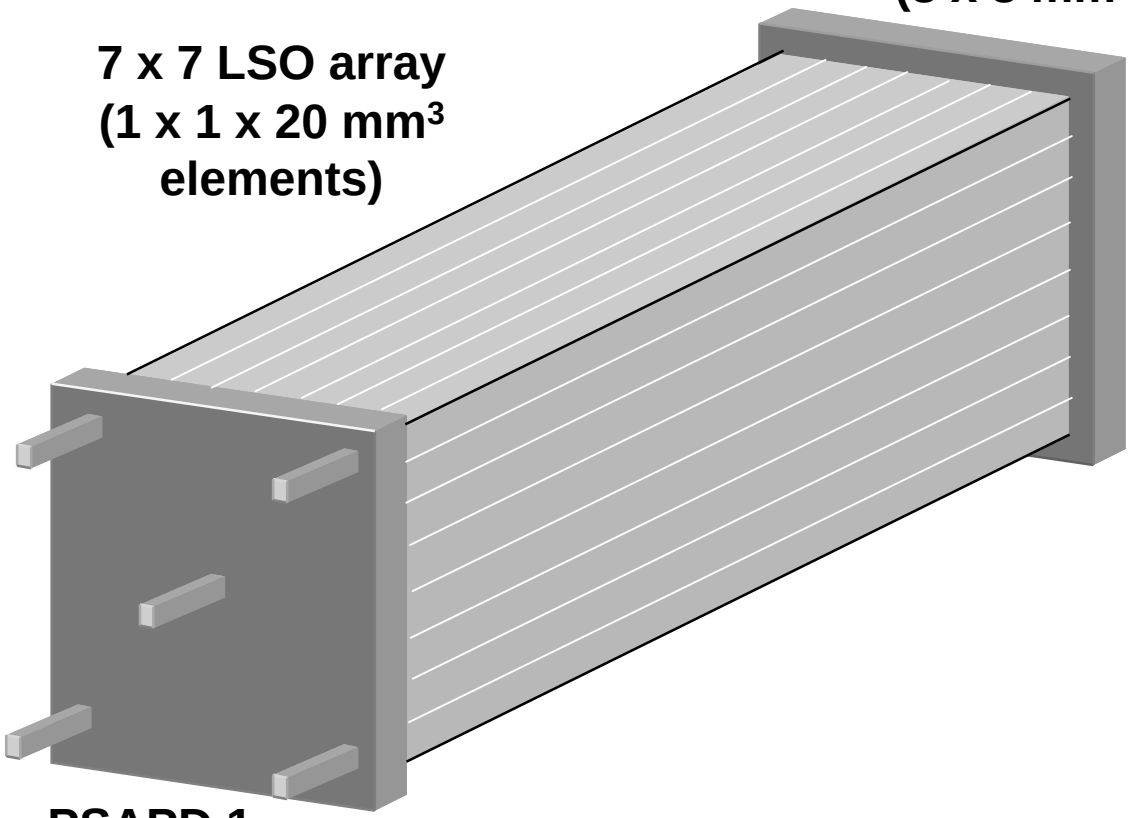
Noise = 200 e^- (FWHM)

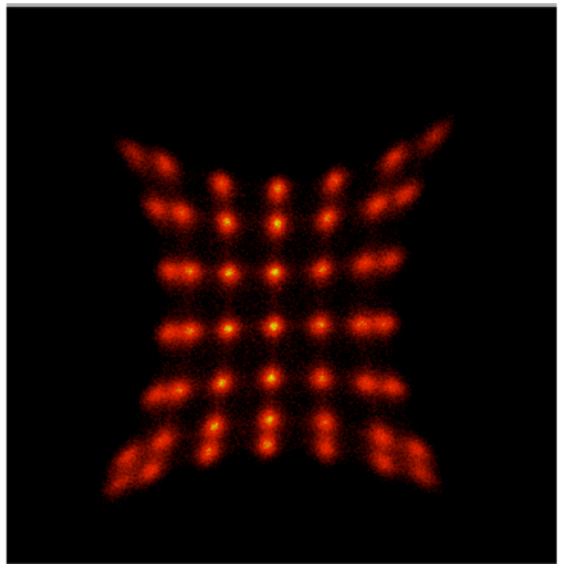
Q. E. ≥ 60 % (400-700 nm)

Rise time ~ 1 ns

Capacitance 0.7 pf/mm^2

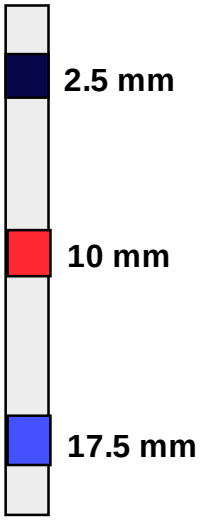
3-D Avalanche Photodiode Detector

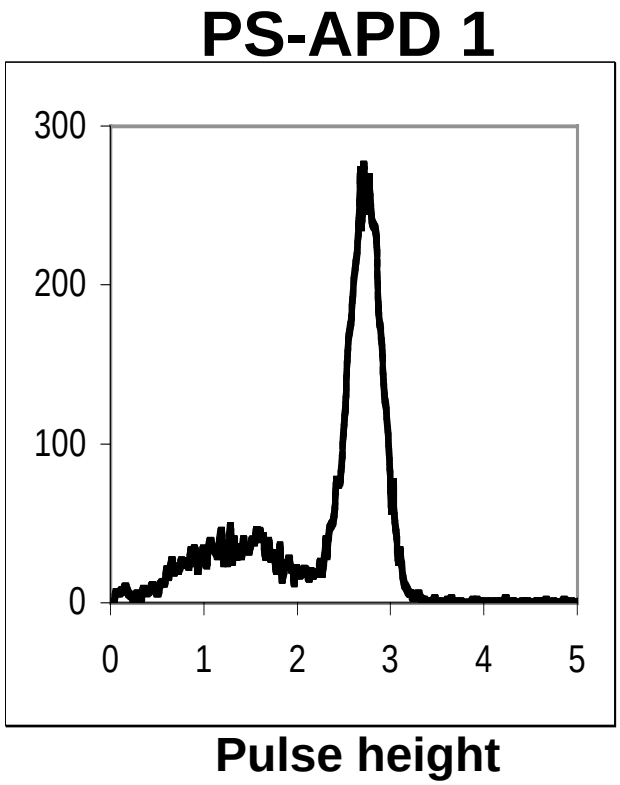


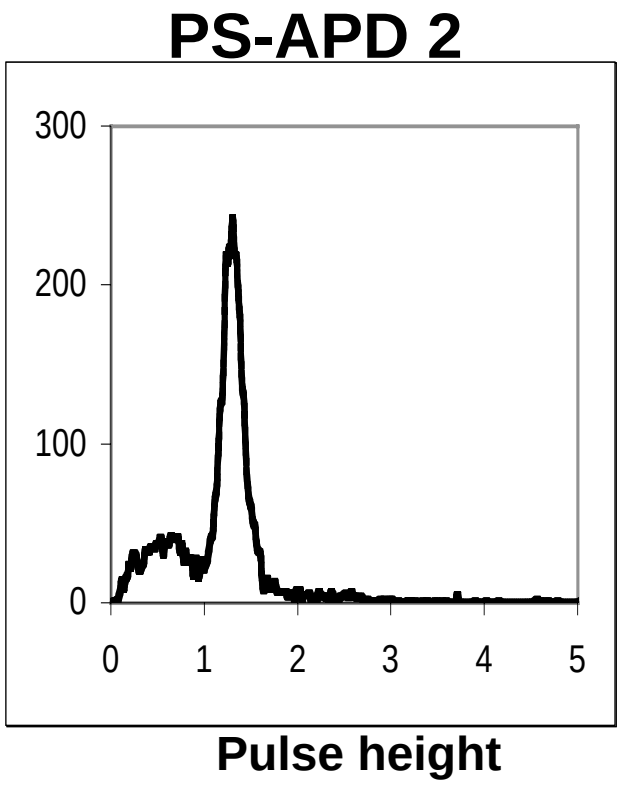


Depth-Dependence of Signals

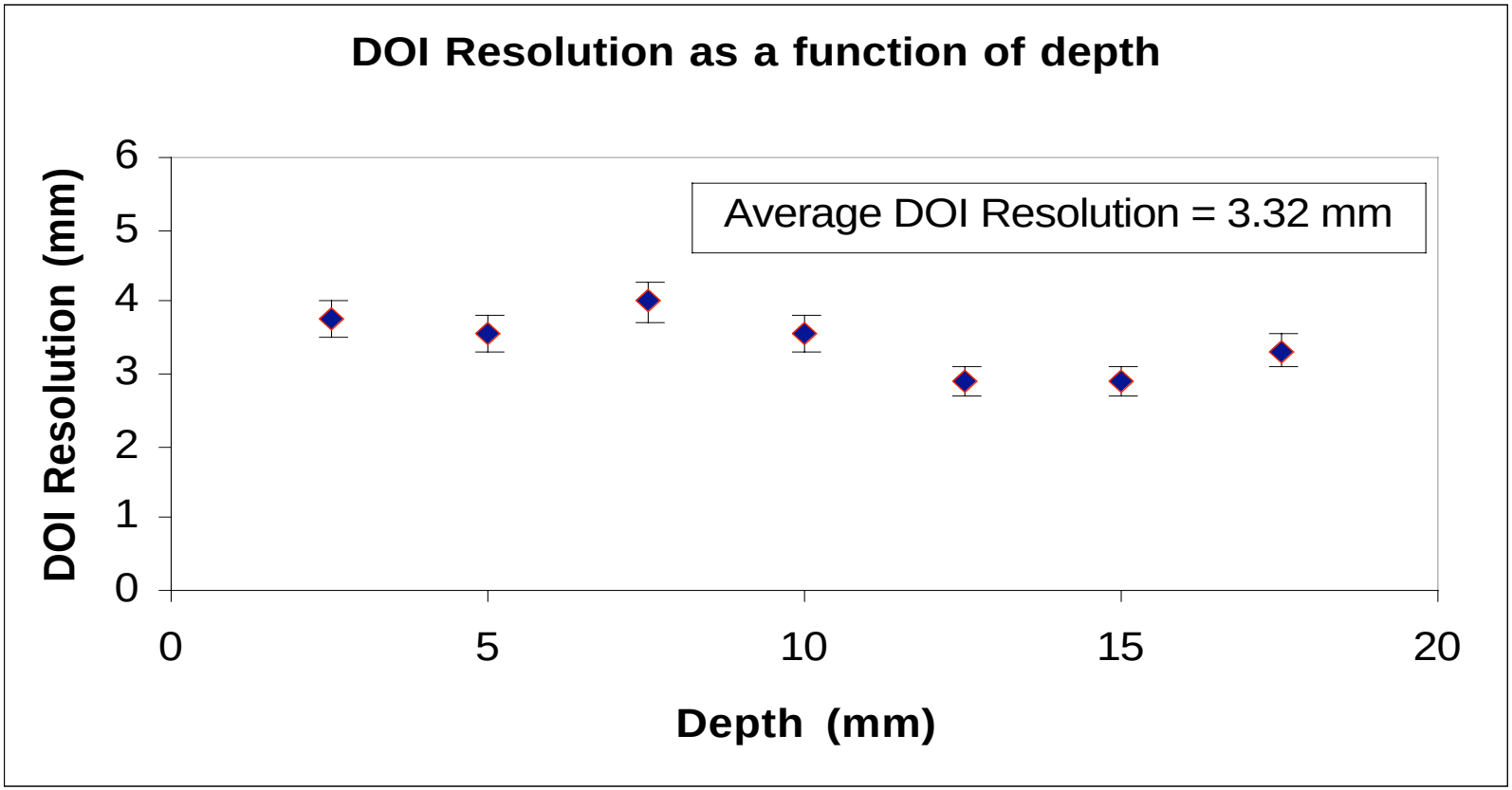
1 mm saw-cut LSO



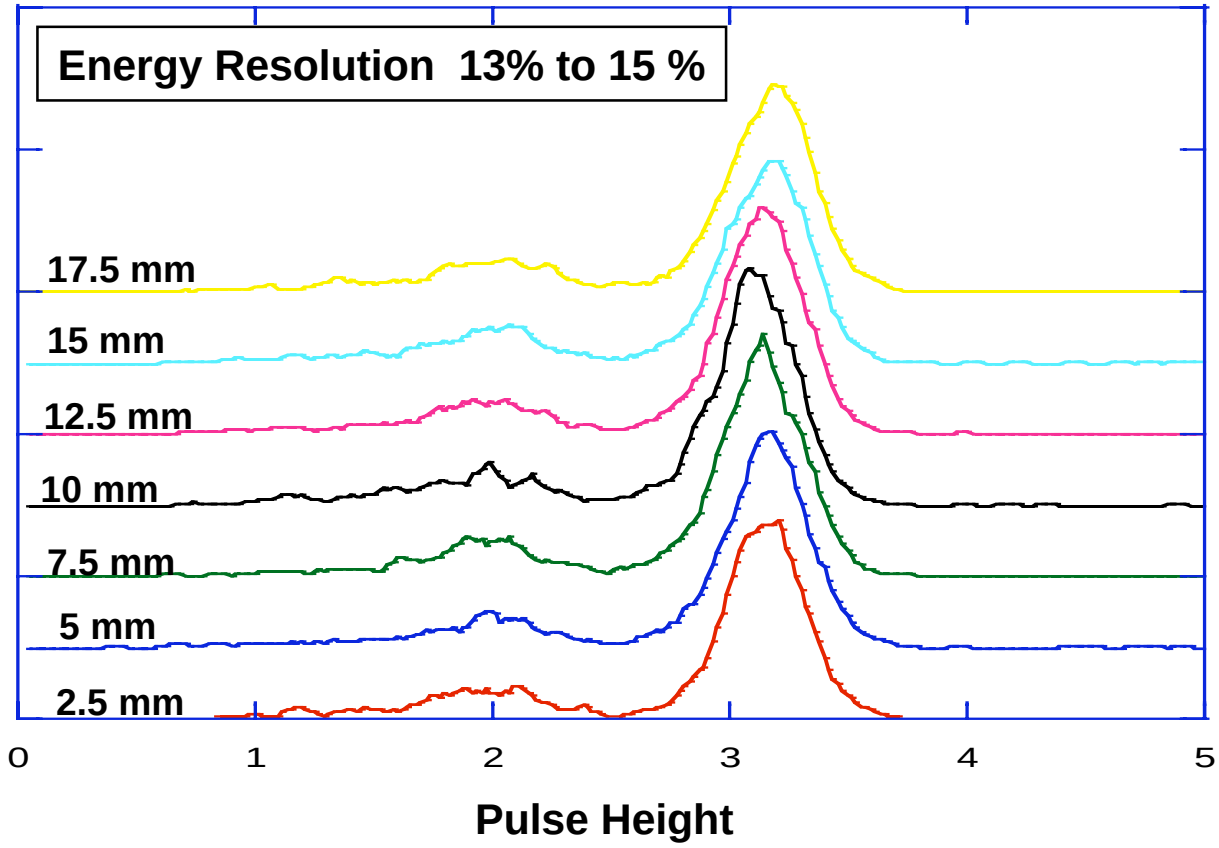




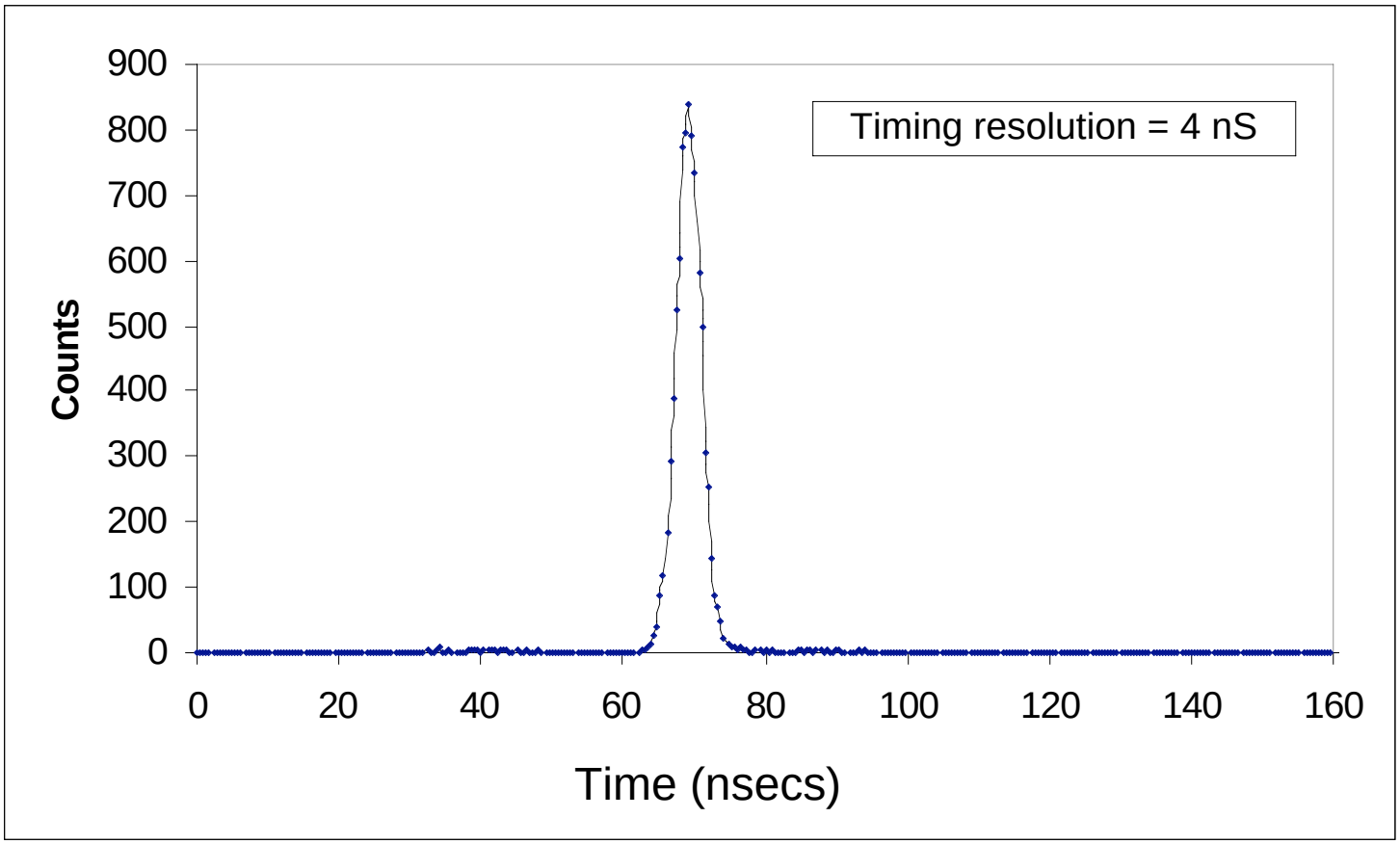
Z (depth) Resolution



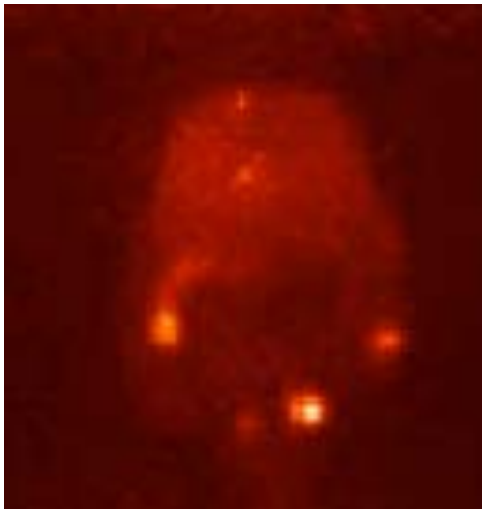
Uniformity of Light Collection



Timing Resolution



Integrated PET/MRI System

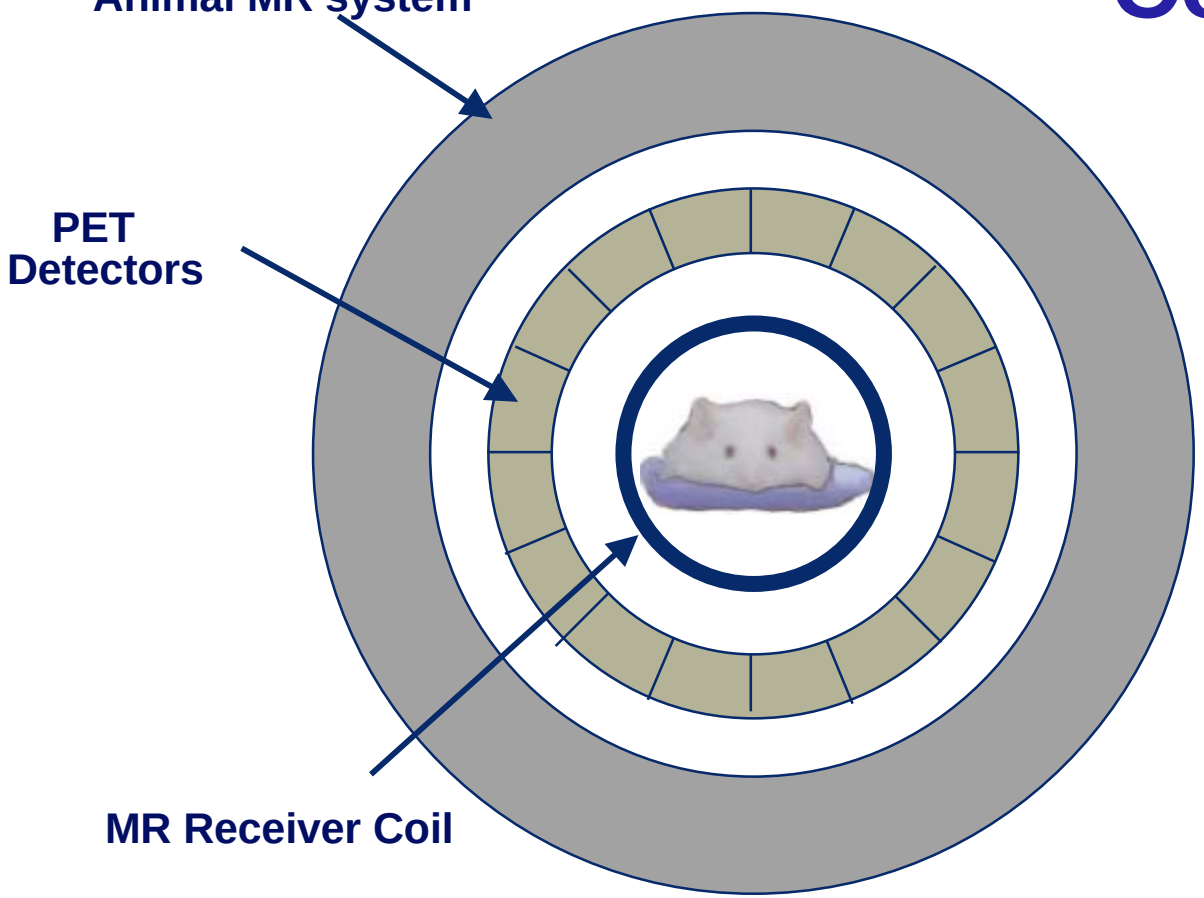


Opportunities:

- direct and accurate registration of molecular PET signal with high resolution anatomy
  - Anatomically guided analysis of PET data
  - Improved quantification of PET data
- time correlation of PET and MRI or MRS signal
  - Interventional, therapeutic studies
  - Dual-labeled agents (^{64}Cu, Gd)

MR Compatible PET System

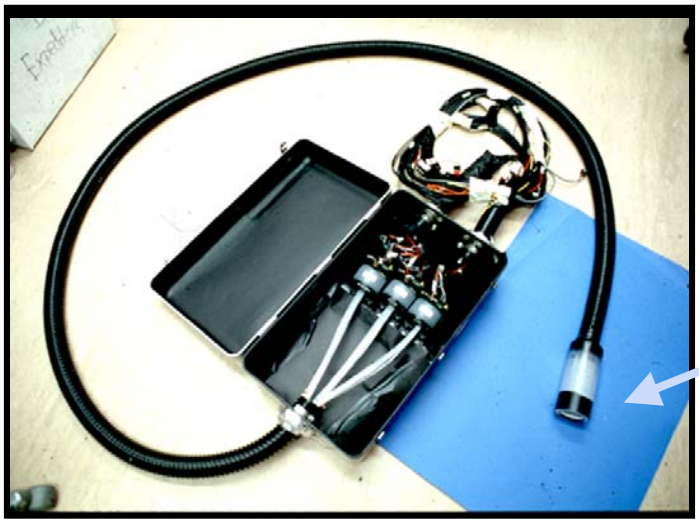
Concept

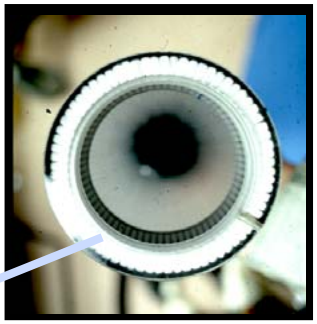


Two Approaches

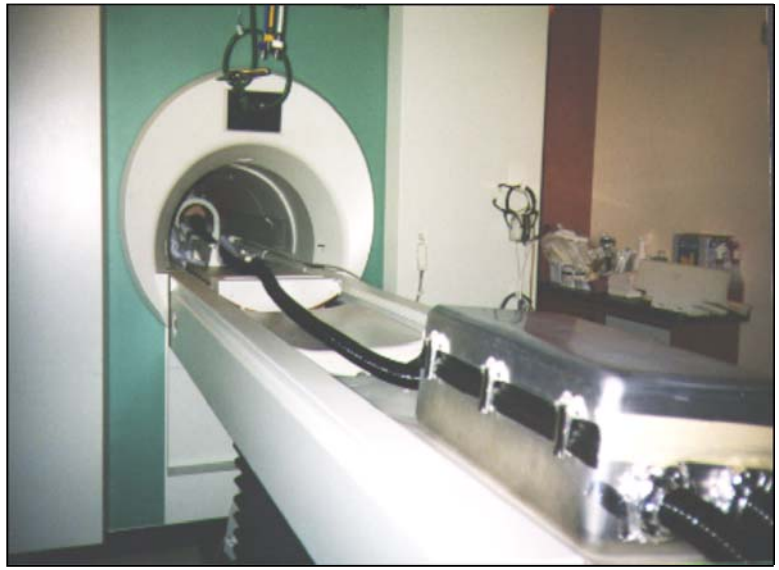
- Fiber-optically coupled scintillation detectors
  - Minimal interference
  - Practical limits due to bulk of optical fiber
  - Likely best performance from MR perspective
- Avalanche-photodiode based scintillation detectors
  - Compact system
  - Interference more likely
  - Better performance from PET perspective

Simultaneous PET/MRI Imaging



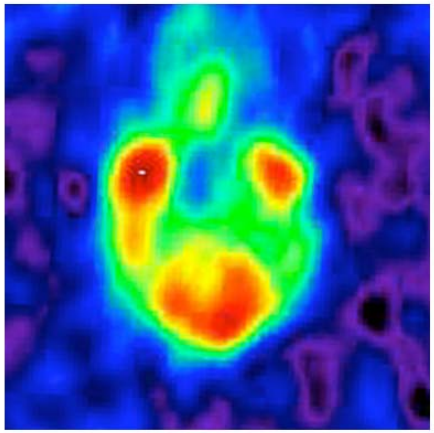


56 mm ring diameter
72 2x2x25 mm LSO scintillators

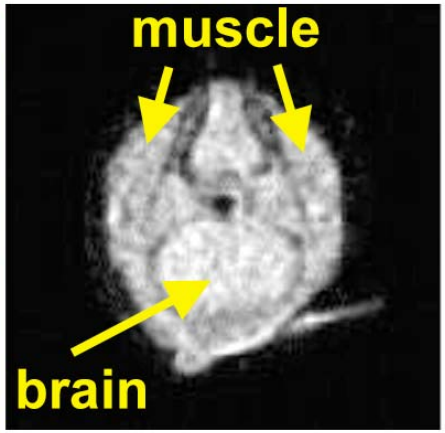


Simultaneous PET/MRI Images

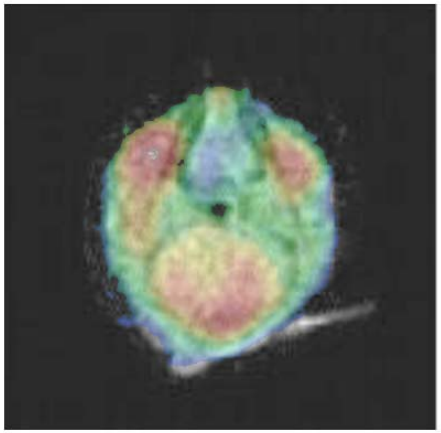
200 g Rat - ^{18}F-FDG Brain Study



PET



MRI

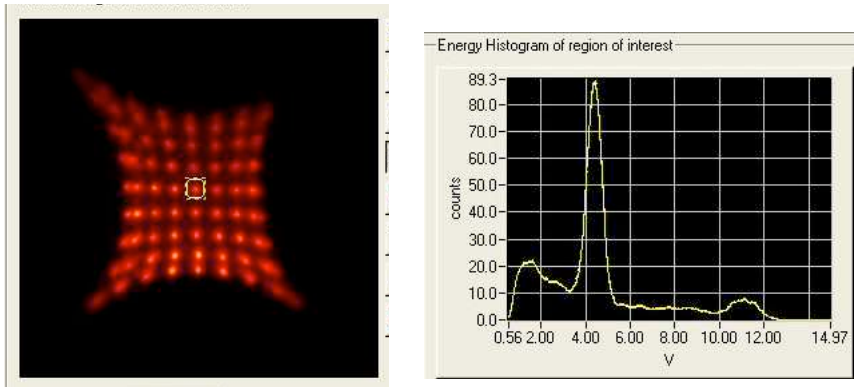


fused PET/MRI

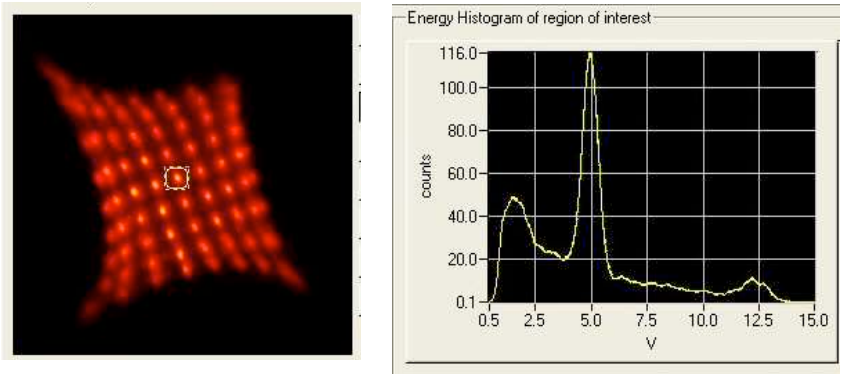
PET
1.3 mCi ^{18}F-FDG
imaging time 30 mins
slice thickness ~ 2mm

MRI
TE=12 msec, TR=280 msec
continuous 75 secs
acquisitions during PET study
slice thickness 4 mm

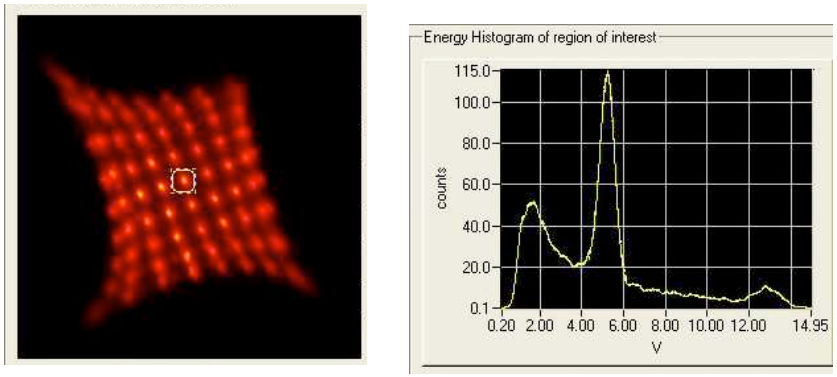
APD-PET Detector in MRI



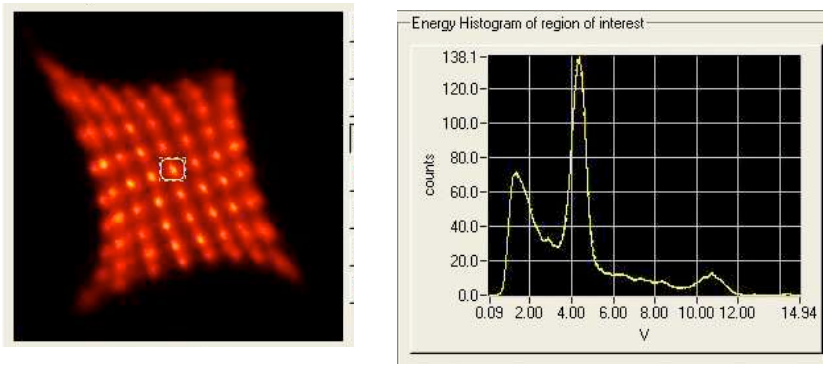
Outside Magnet



Inside Magnet

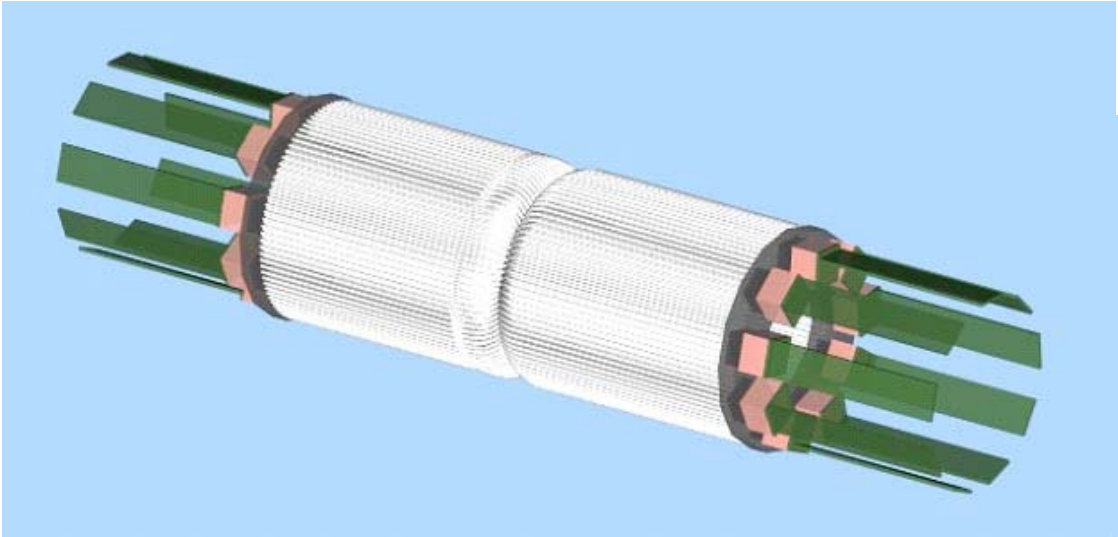


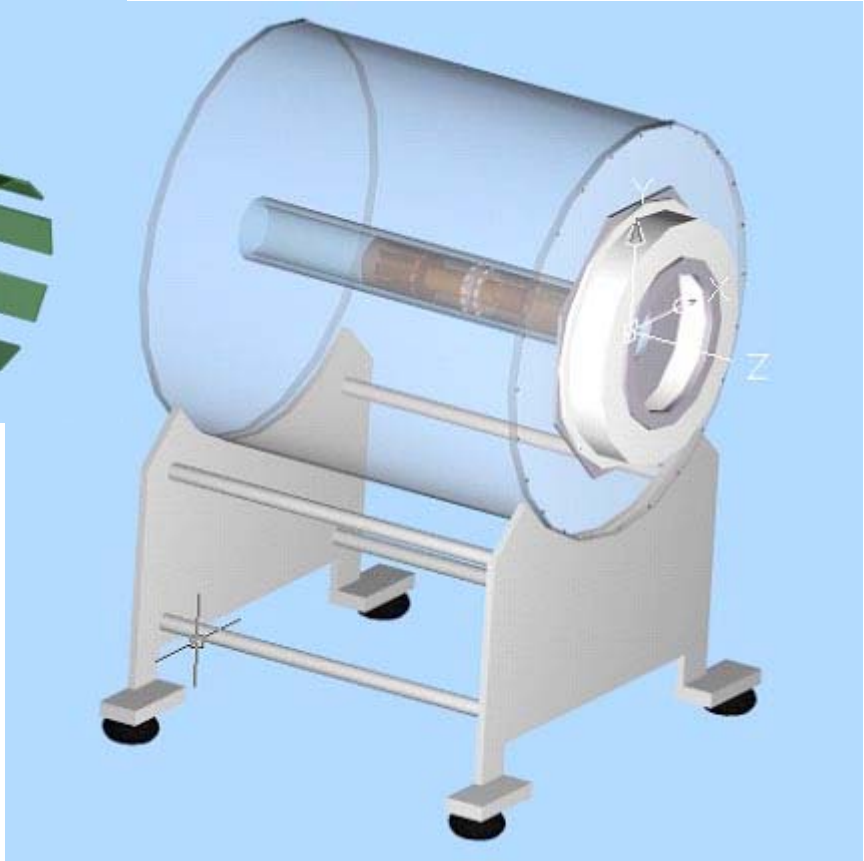
Inside Magnet - Spin Echo



Inside Magnet - Gradient Echo

Integrated PET/MRI System





- APD/LSO PET insert for existing magnets
- Short optical fibers to minimize interference
- PET performance better than first generation animal PET scanners

New Technologies

"New directions in science are launched by new tools much more often than by new concepts.

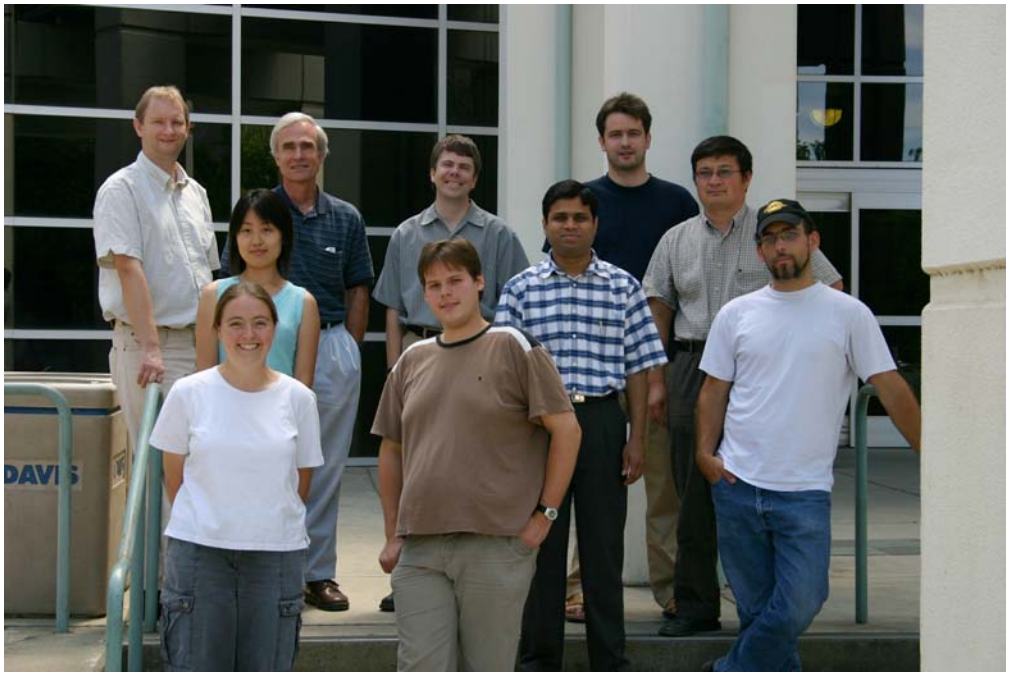
The effect of a concept-driven revolution is to explain old things in new ways.

The effect of a tool-driven revolution is to discover new things that have to be explained."

Freeman Dyson, Imagined Worlds

Acknowledgments

NIH R01 EB000561, R01 EB000230, DOE



Yongfeng Yang
Jennifer Stickel
Hongjie Liang
Stephen Rendig
Martin Judenhofer
Bernd Pichler
Ciprian Catana
Purushottam Dokhale
Ulli Weisser
Huini Du

Prior Members of the Group
Yuan-Chuan Tai
Arion Chatziioannou
Robert Silverman
A. Ken Meadors
Randal Slates
Yiping Shao

UC Davis
Julie Sutcliffe-Goulden
Jinyi Qi
Angie Louie

University of Southern California
Richard Leahy
Bing Bai
Quanzheng Li

Collaborators:
Russell Jacobs (Cal Tech)
Paul Marsden (King's College)
CTI Concorde Microsystems