Imaging Physics Research in Small Animal PET at BNL

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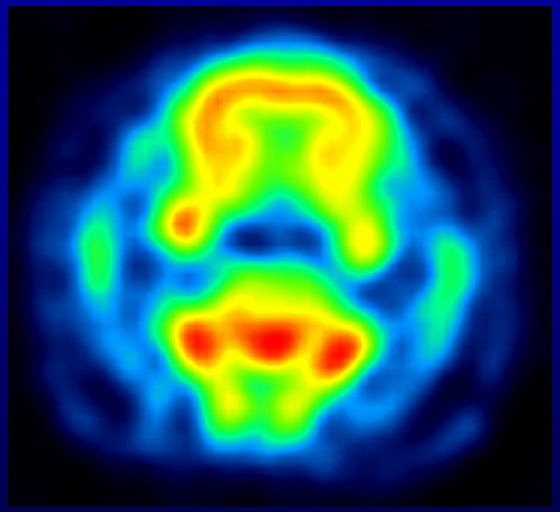


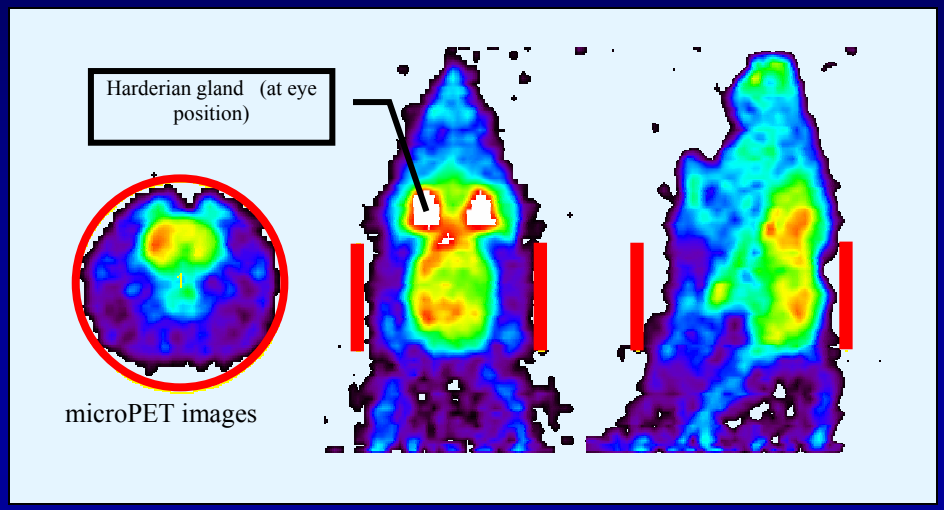
Why Image Small Animals?

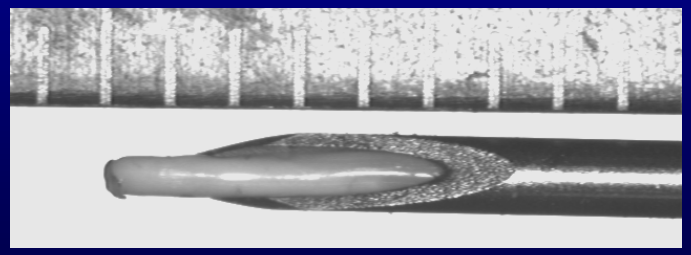
small animals = lab rats and mice

- Determine safety and efficacy before humans - “preclinical”
- Many rodent models of human systems and disorders available - “translational”
- Fewer subjects needed - “longitudinal”
- Cost-effective
- More cooperative

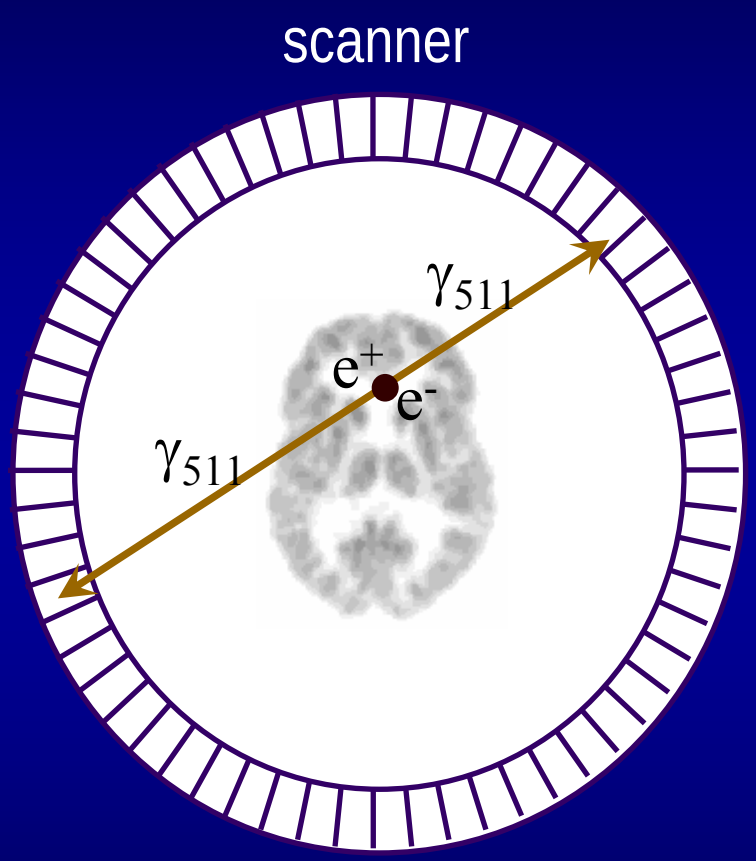
Small Animal PET Instrumentation Projects

- Awake animal imaging:
  - RatCAP
- Higher spatial resolution:
  - LSO/APD Anger Detector
  - CZT
- Related projects:
  - Simultaneous PET/MRI
  - Wrist detector
  - Motion tracking of awake animals
  - Beta probe





PET Basics



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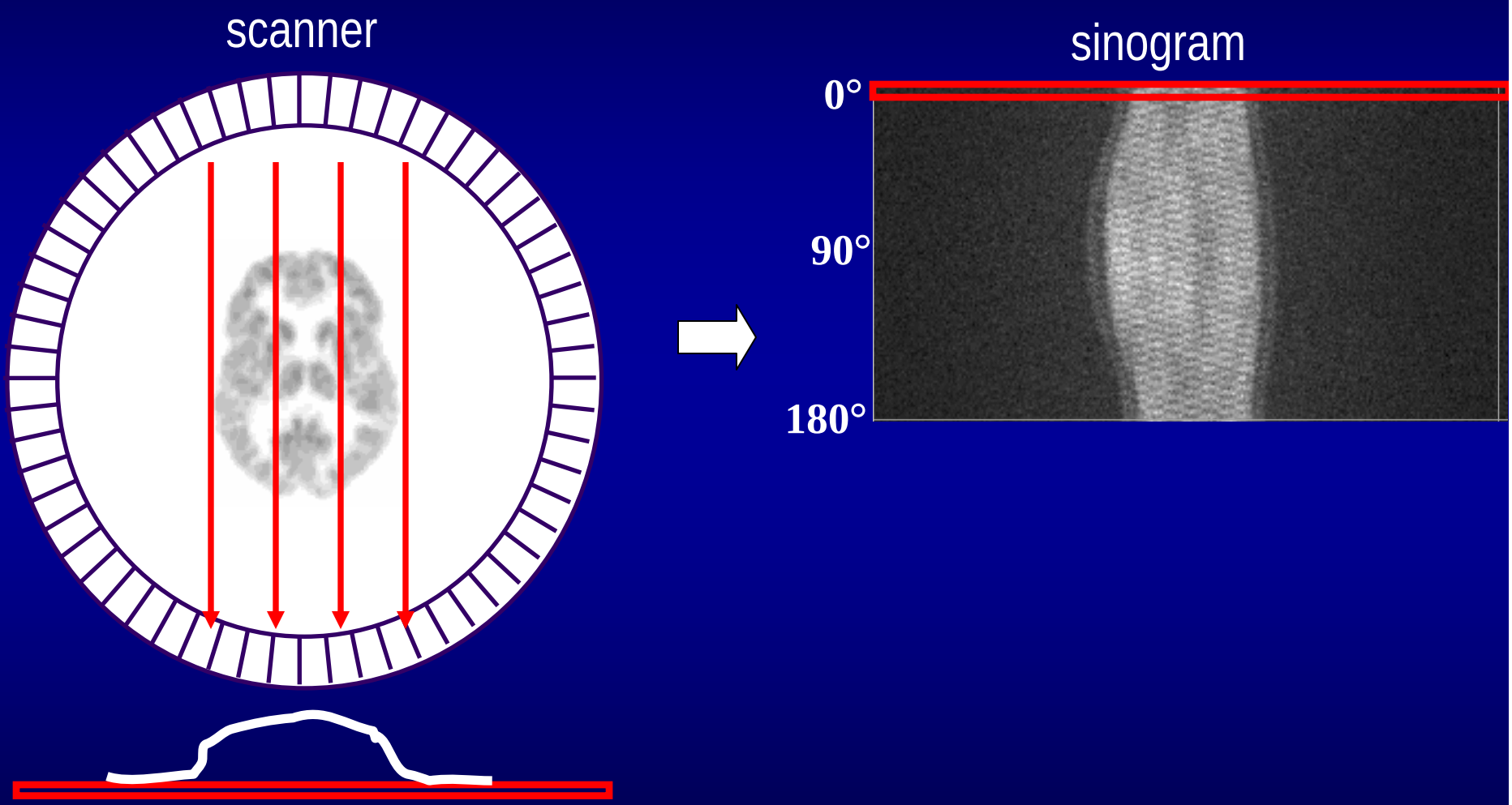

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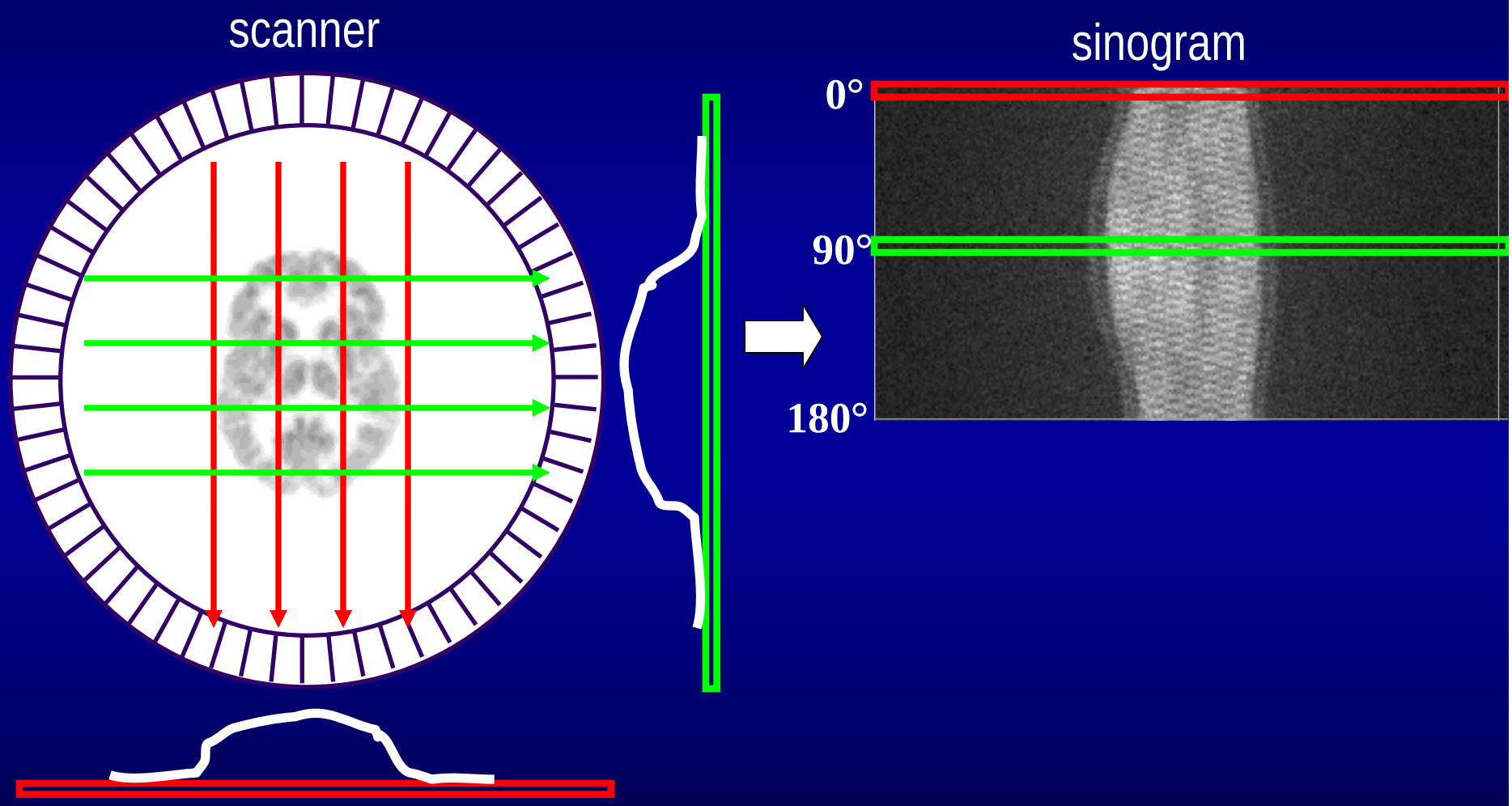
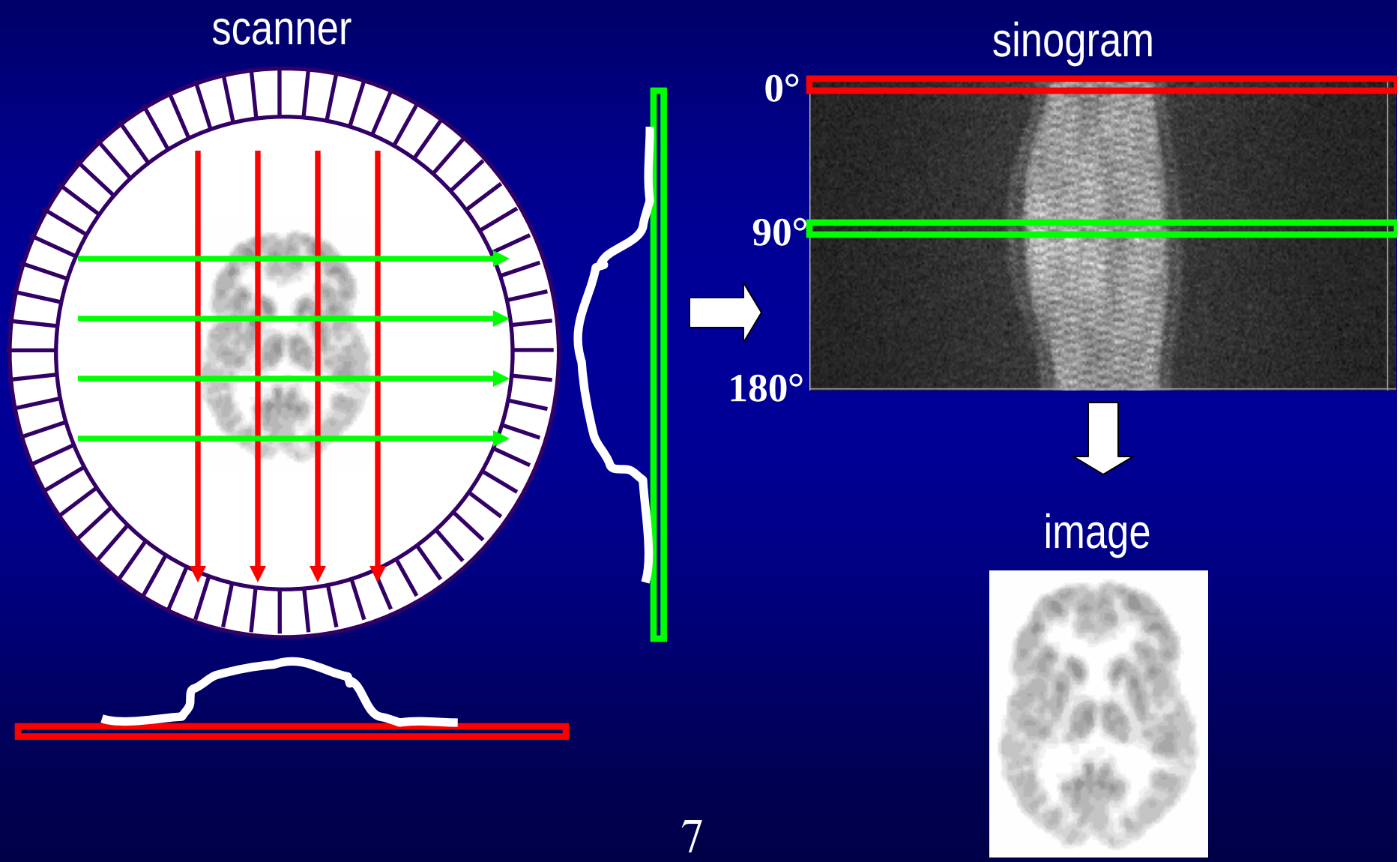
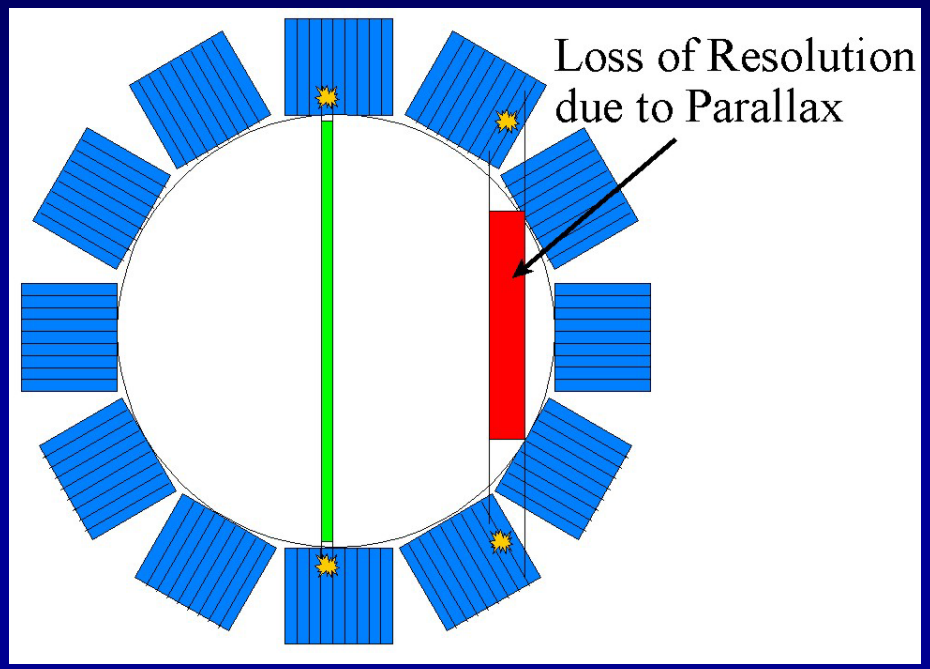


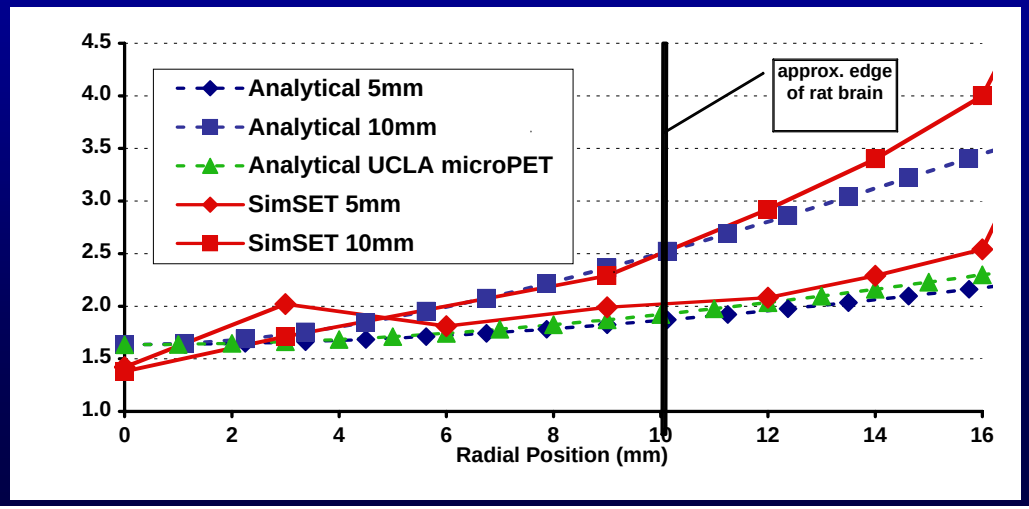
PET Basics



Requirements of Small-Animal PET

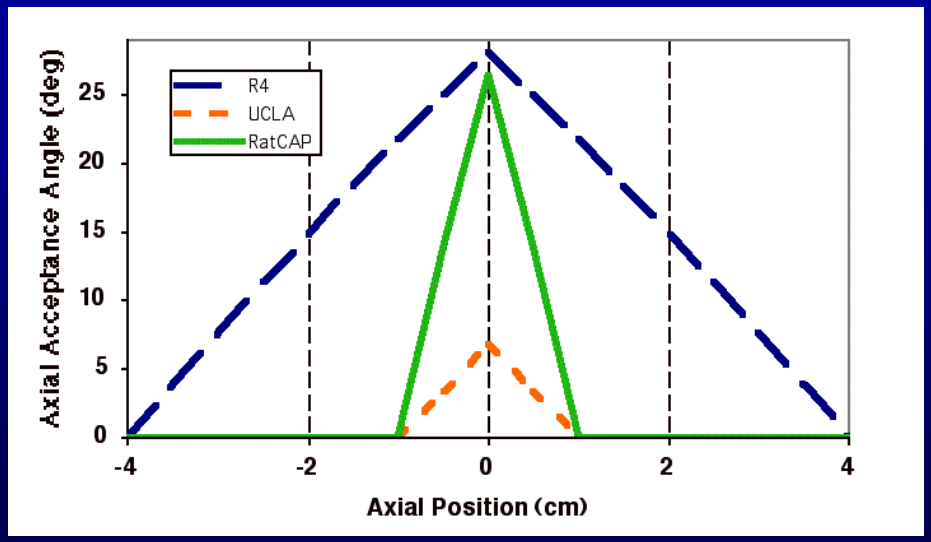
- High spatial resolution
  - Mainly crystal size
  - Radius/DOI
  - “fundamental” limits

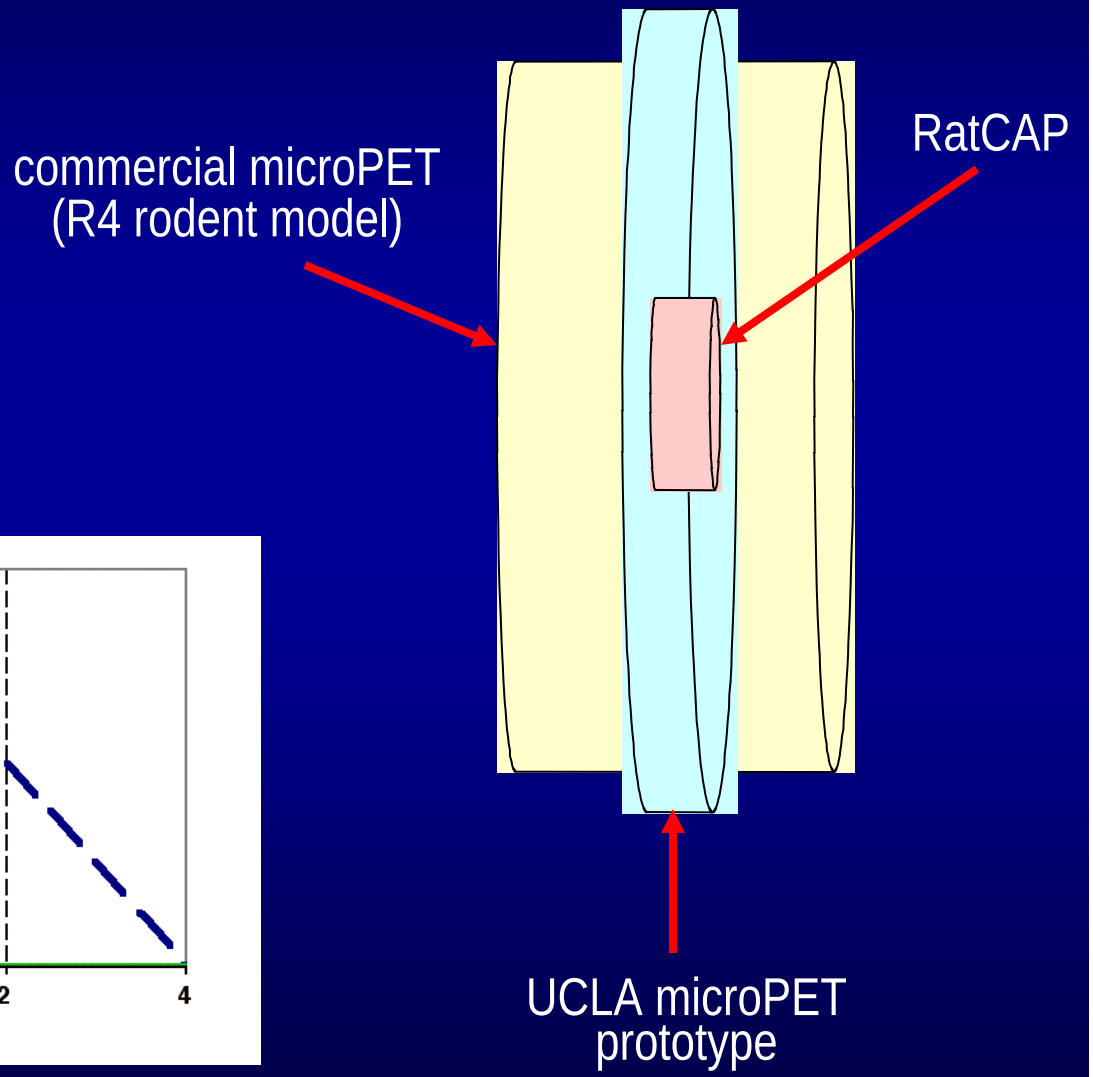




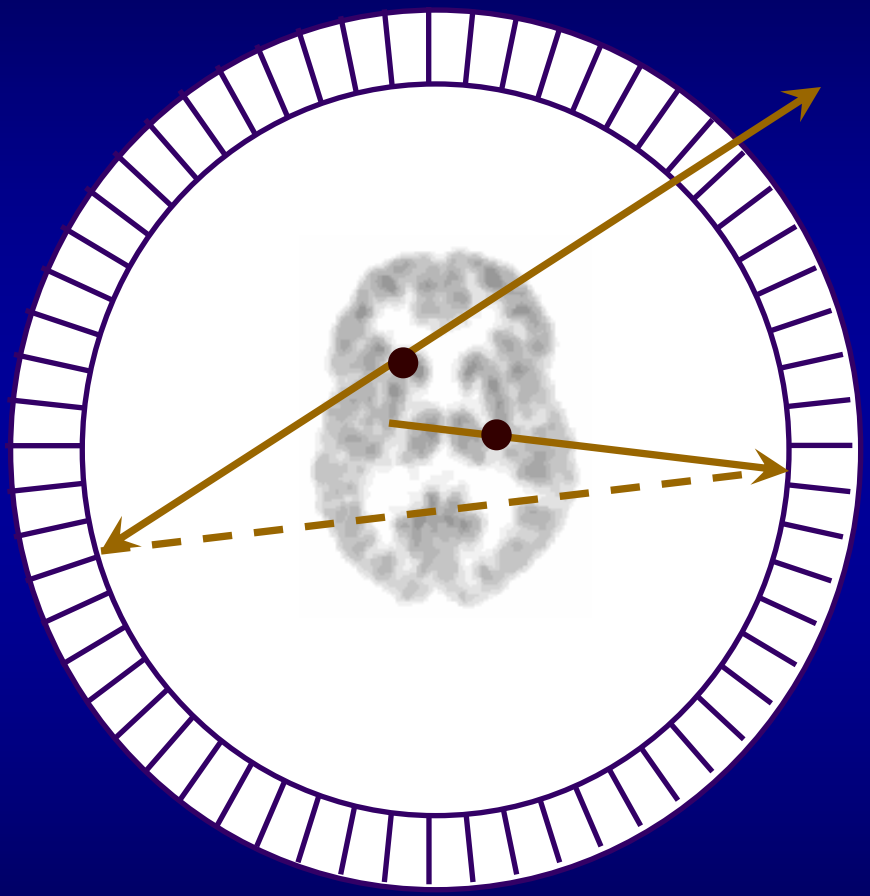
Requirements of Small-Animal PET

- High sensitivity
  - dose limited by
    - tracer principle
    - randoms
    - radiation damage
  - Solid angle
  - Detector efficiency

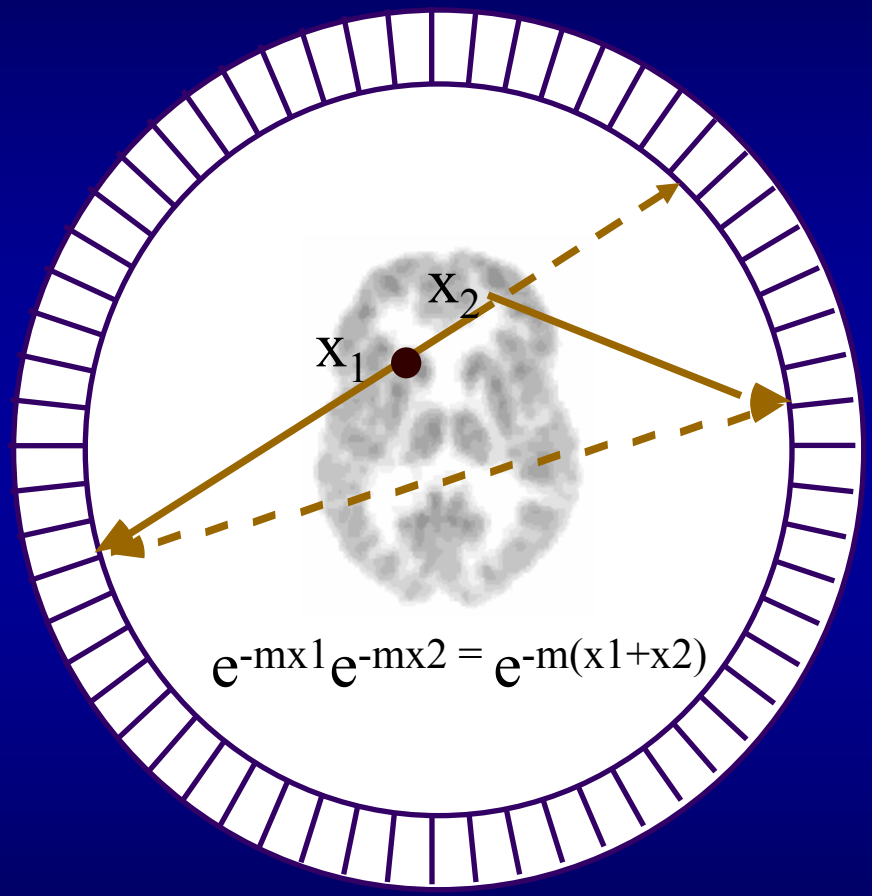




Randoms, Scatter, Attenuation



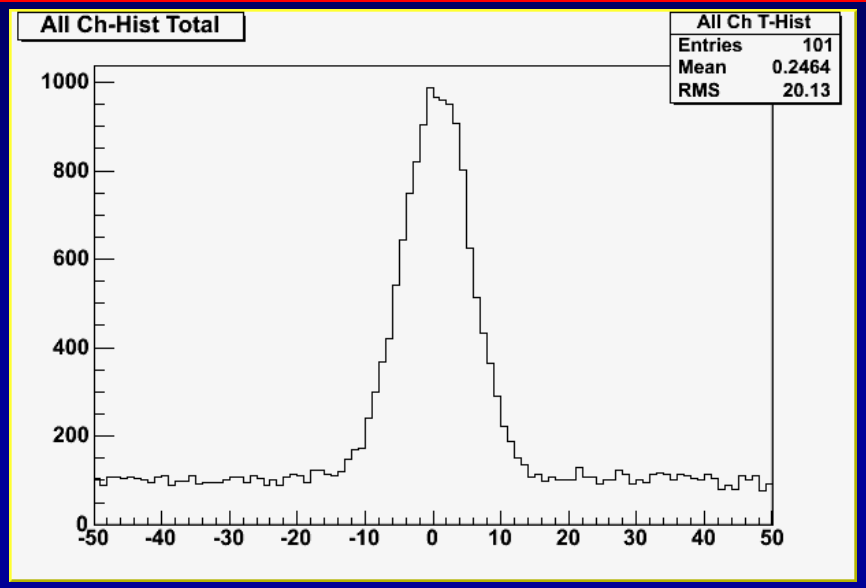
Random (accidental) coincidence



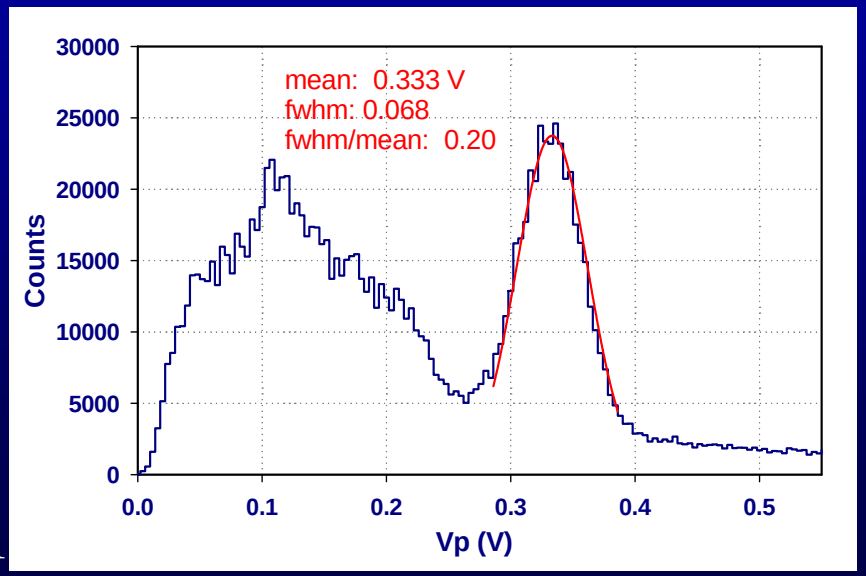
Scatter and Attenuation

Requirements of Small-Animal PET

- Time resolution
  - Randoms rejection
  - $R = 2\tau S^2$
  - $f_{randoms} \propto$ dose



- Energy resolution
  - Compton scatter
    - object: 170 - 511 keV
    - detector: 0 - 340 keV



RatCAP: Rat Conscious Animal PET

- Awake animal imaging
  - anesthesia disturbs neuro systems
  - prevents behavioral studies

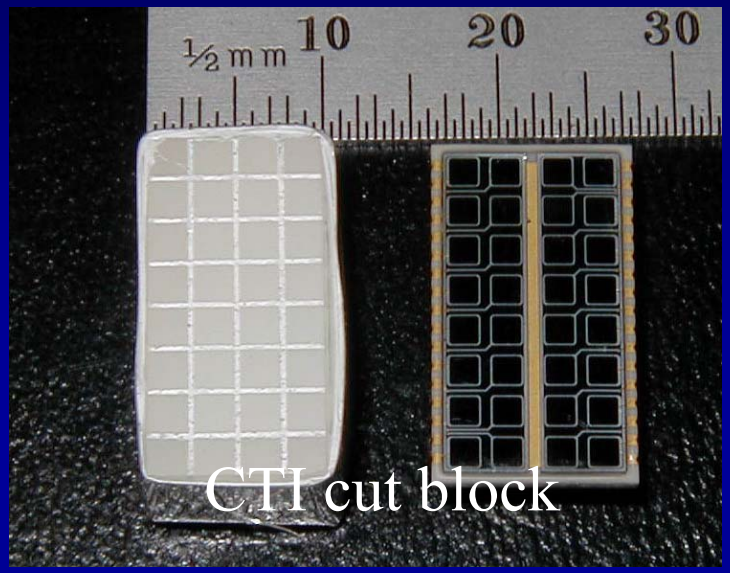
- High performance PET scanner w/ additional challenges:
  - compact!
  - low power ~ 1 W
  - minimize cabling
  - lightweight ~150 g

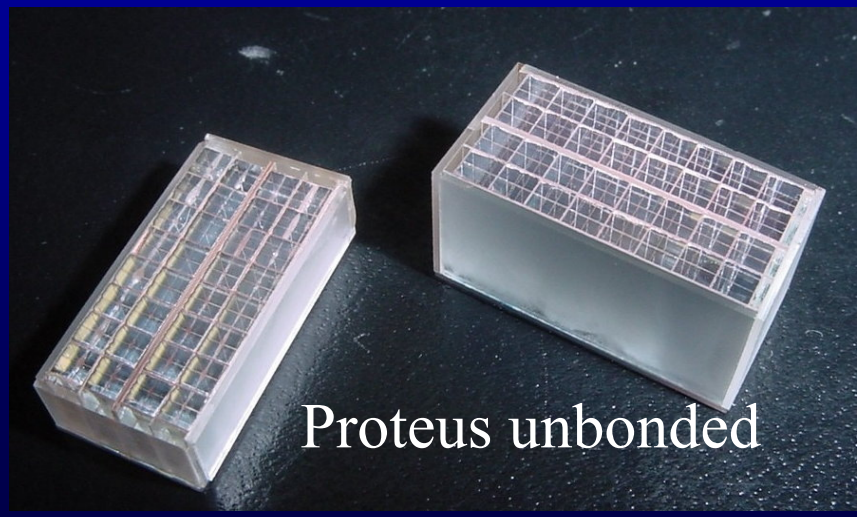
mockup on rat head

Scintillator and Photosensor

- LSO
  - 2.2 x 2.2 x 5 mm crystals
  - 4 x 8 array
- matching Hamamatsu S8550 APD array
  - gain ~50 at 370 V bias
  - capacitance ~10 pF
- ~5000 p-e/MeV

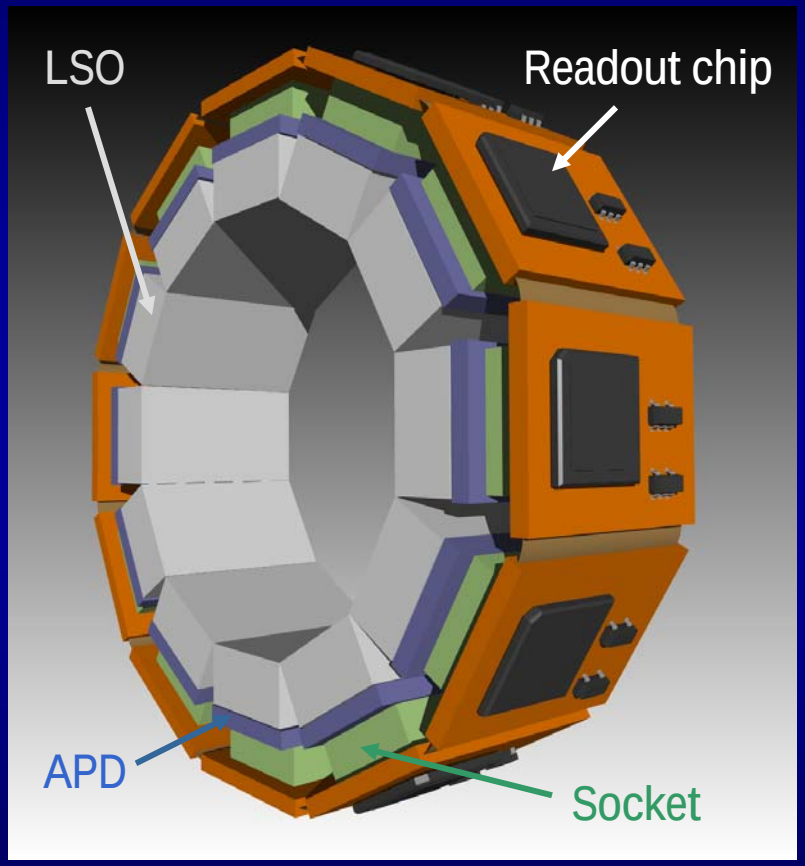
>> 1:1 coupling



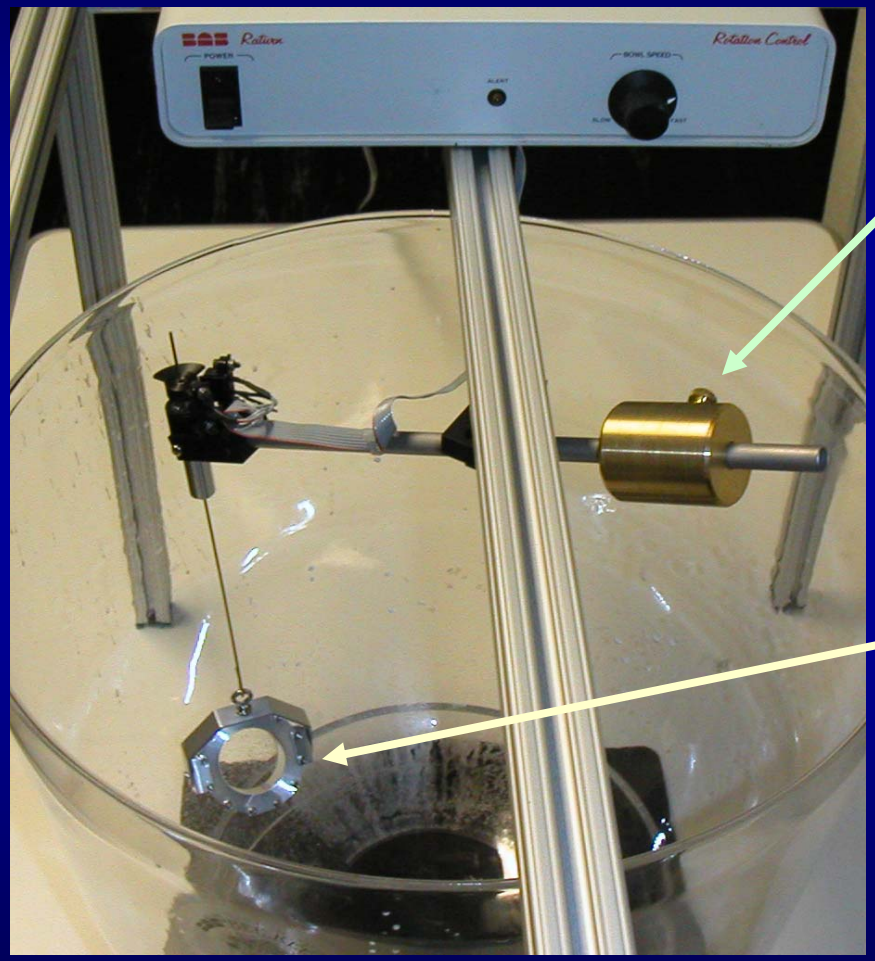


System Geometry

- 12 blocks
- 4 cm dia. x 2 cm axial FOV
- front-end electronics on detector, compact readout
- protective shield

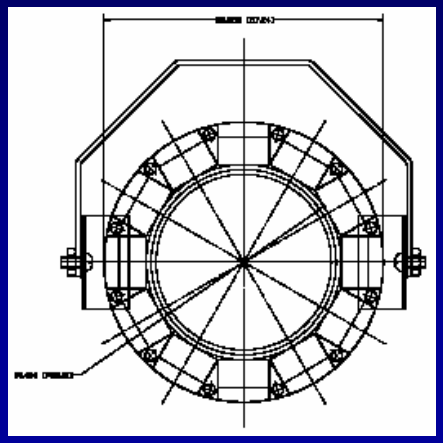


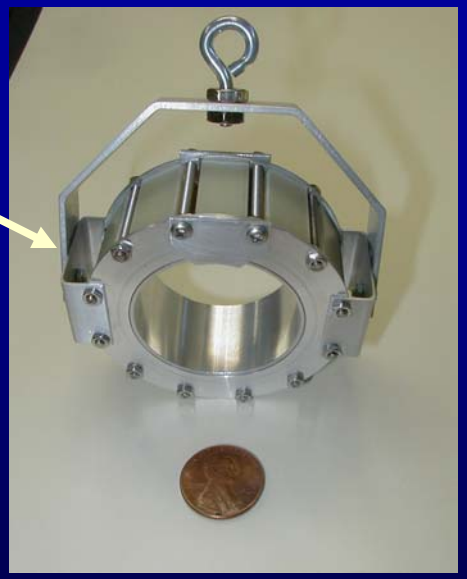
Support System



Weight is completely counterbalanced (animal only feels inertia)

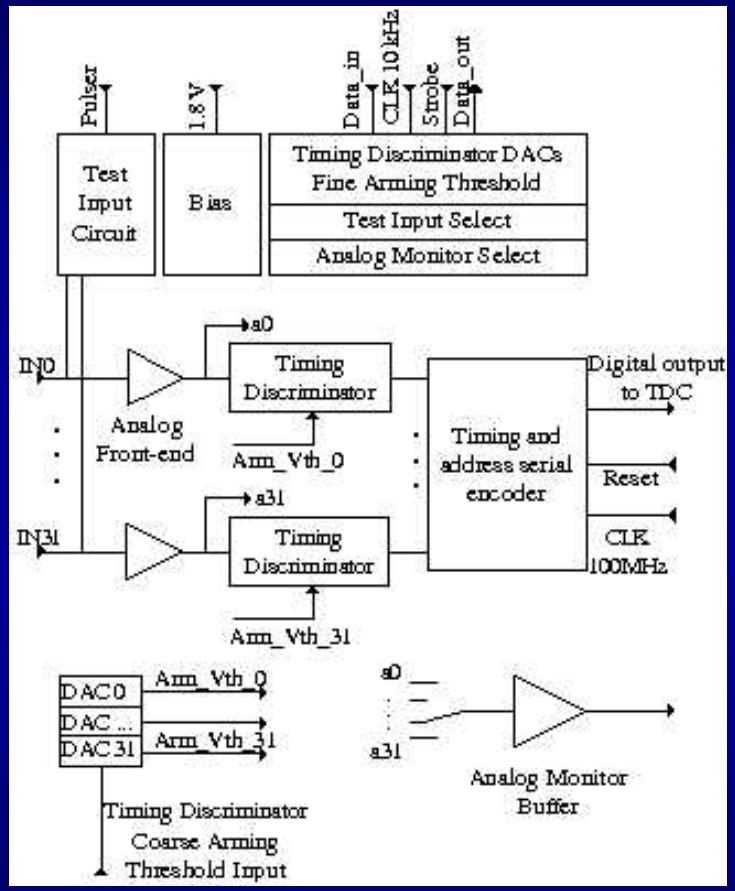
Gimbal ring allows head movement

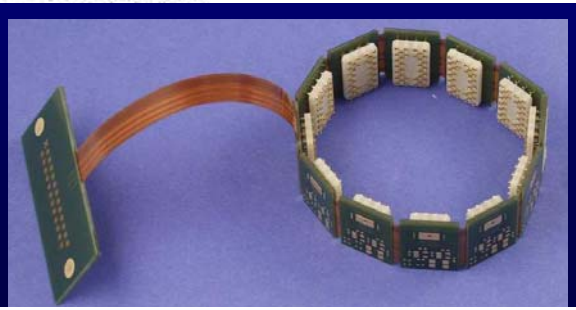




Front-end Electronics

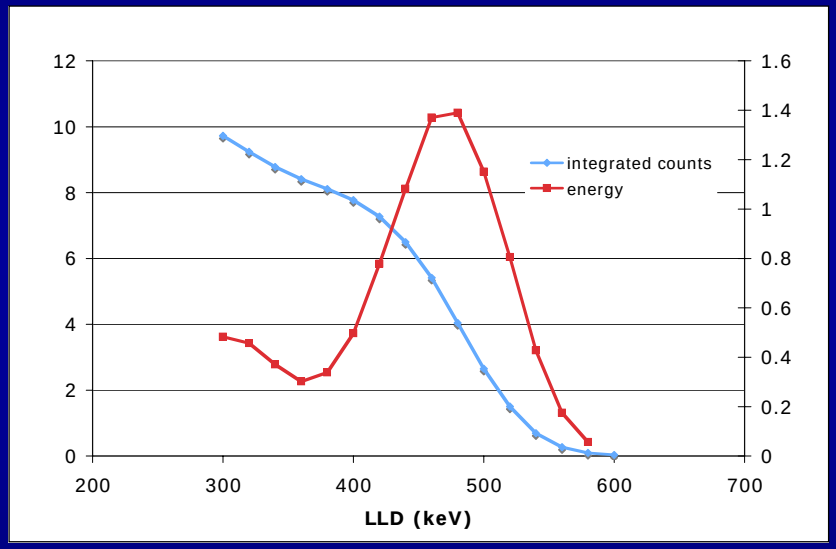
- Requirements
  - Good time and energy resolution
  - Low power
  - Minimal cabling
  - Rates ~ 100 kcps w/ low deadtime
- Solution: ASIC
  - 1 per block: 32 x preamp, shaper, ZCD
  - programmable threshold
  - serial encoder to single data line
    - only 12 lines total
  - interconnected by rigid flex PCB
  - 0.18 um CMOS
  - 125 mW power budget

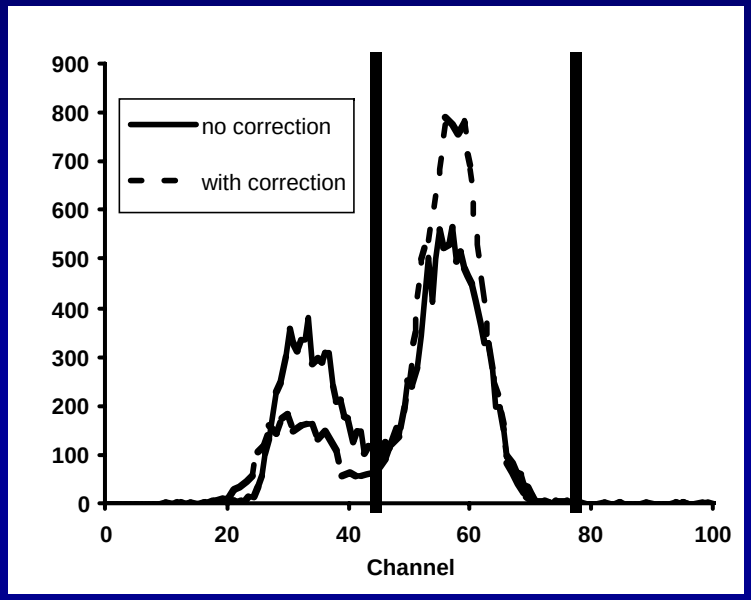




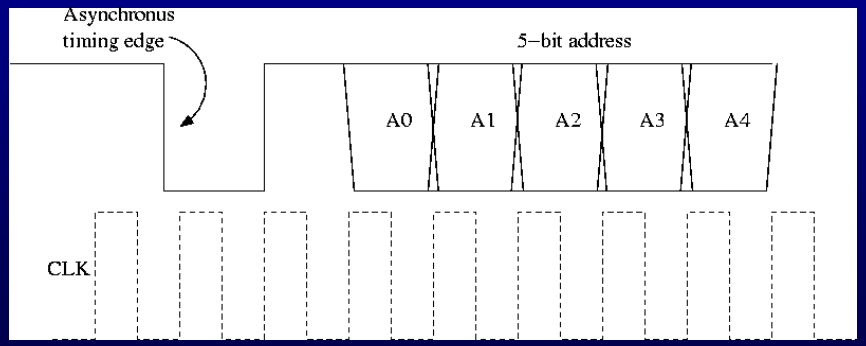
Front-end Electronics

- No ADCs?
  - not necessary w/ 1:1 coupling!



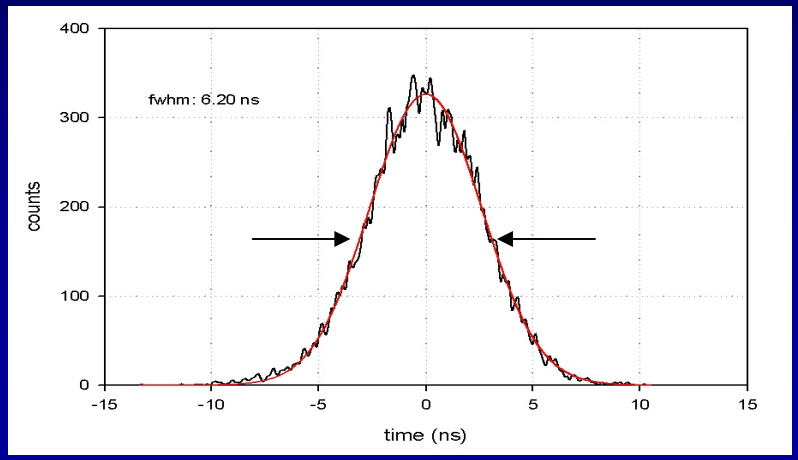


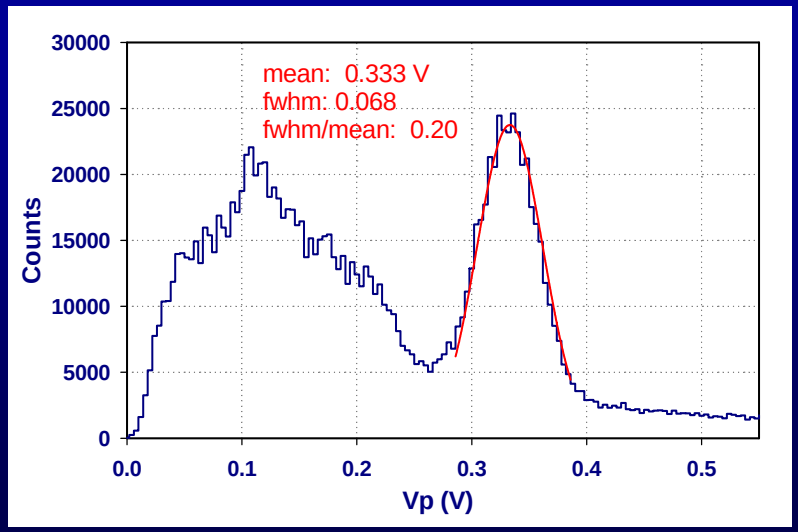
- Compact data stream for all 32 crystals
  - Asynchronous timing edge
  - 5 bit crystal address w/ 100 MHz clock



Front-end Electronics

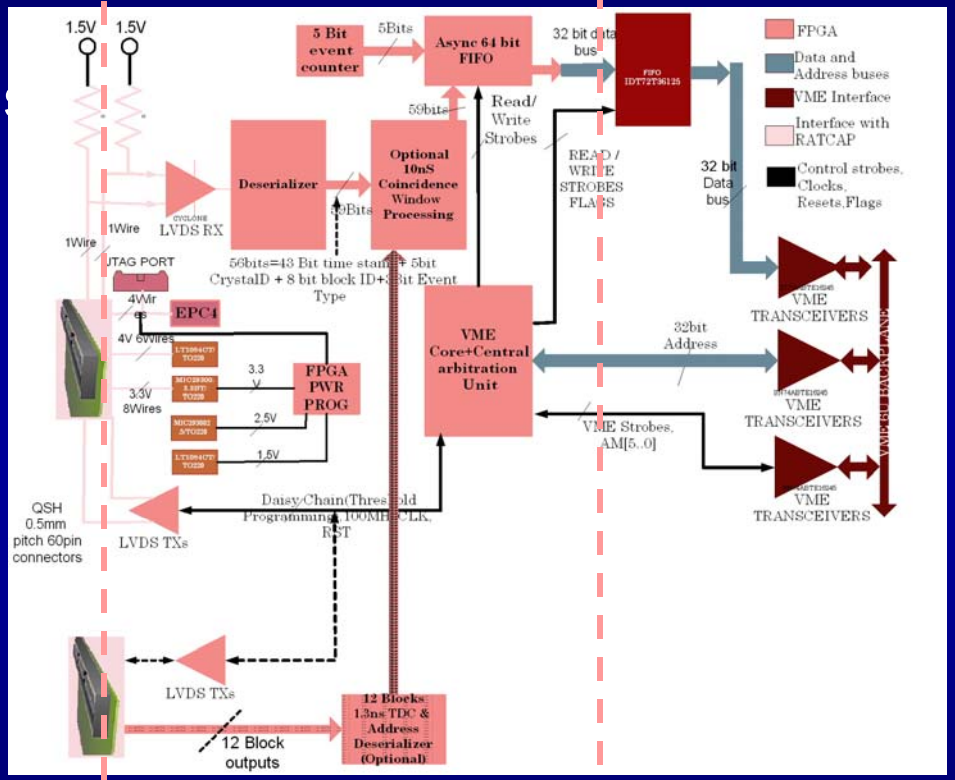
- First fully functional version:
  - Noise
    - 1000 rms e^-
  - Encoder tested
  - Time resolution
    - 6.2 ns FWHM measured vs. BaF_2
    - >> ~9 ns in coincidence >> 20 ns window
  - Energy resolution
    - 20% FWHM @ 511 keV
- Next version
  - DACs for LLD
  - Analog multiplexer
  - ESD protection





Data Acquisition

- COM module
  - FPGA time stamps and packages event into 64 bits
  - 1.3 ns bit resolution
- VME data acquisition
  - VxWorks running PDAQ
  - Up to 40 MB/s to linux box
- Online monitoring
  - Singles & coincidence rates
- Offline processing
  - Time and energy calibrations
  - Coincidence sorting
  - Randoms estimation
  - Efficiency normalization
  - Sinogram sorting



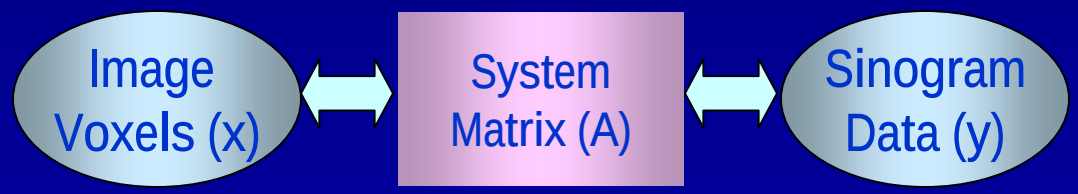
S.Junnarkar

FPGA

Image Reconstruction

Maximum Likelihood Expectation Maximization (MLEM) method

- proper statistical weighting of data
- accurate modeling of detection process



$$y = A\,x$$

A_{ij} is just the probability that a decay in image voxel x_j produces a count in projection y_i

system matrix can include many physical effects in the detector and object:

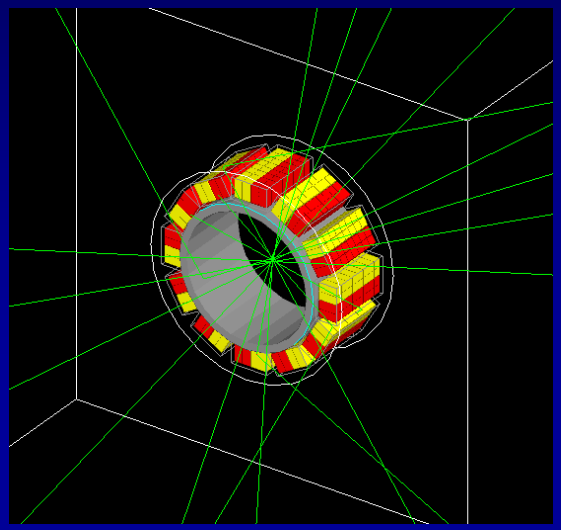
- scatter
- attenuation
- positron range
- electronics noise
- detector geometry
- detector efficiency

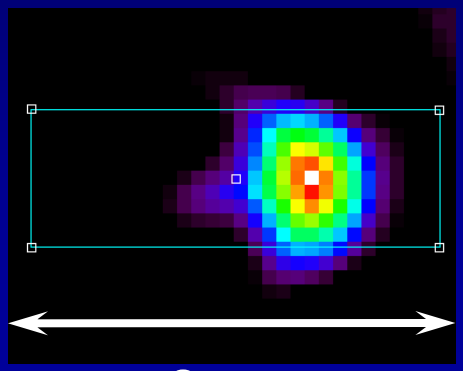
$$x_j^{(n+1)} = x_j^{(n)} \left[\sum_{i=1}^{n_d} a_{ij} \frac{y_i}{\left[Ax^{(n)} \right]_i} \right] \Big/ \left(\sum_{i=1}^{n_d} a_{ij} \right)$$

Shepp & Vardi, IEEE Trans. Med. Imaging (1982) 113-122

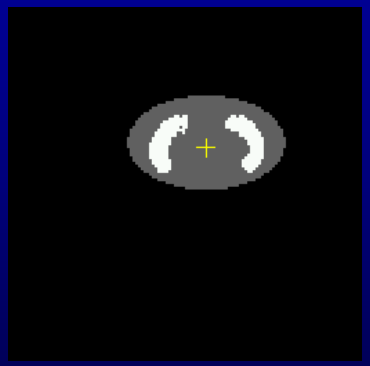
Image Reconstruction

- Full system matrix A
  - typically huge (TB's)
  - sparse
  - approximations needed

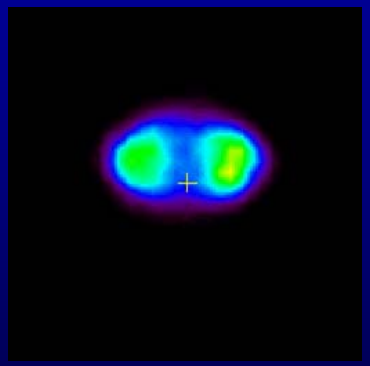




- RatCAP
  - Small FOV
  - 384 crystals
  - A = 2 GB
  - Simulate entire A, voxel by voxel
    - Include scatter and attenuation
    - Use PHENIX computing capacity to reduce to days

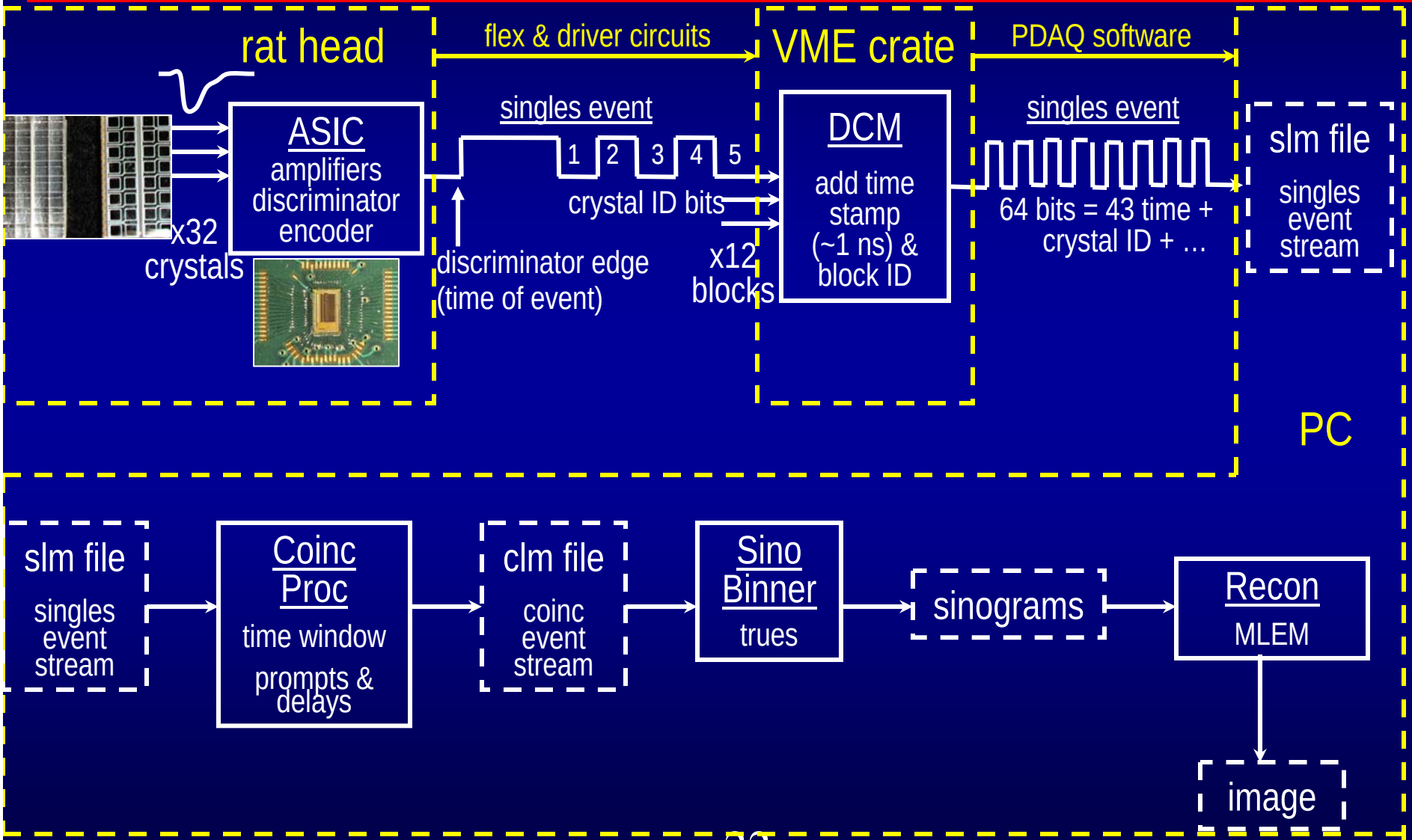


Input image



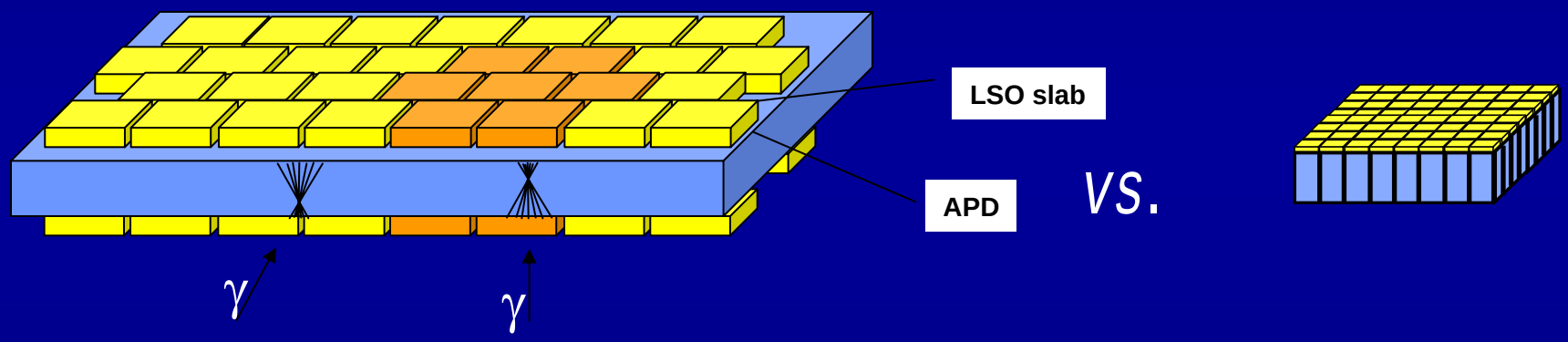
Reconstructed image

RatCAP Summary



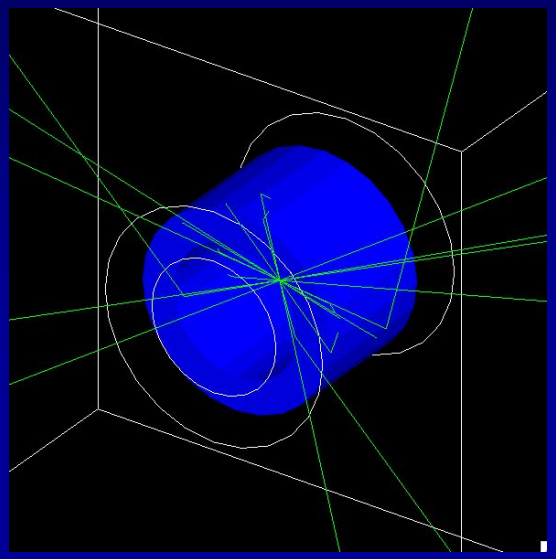
LSO/APD Anger PET Detector

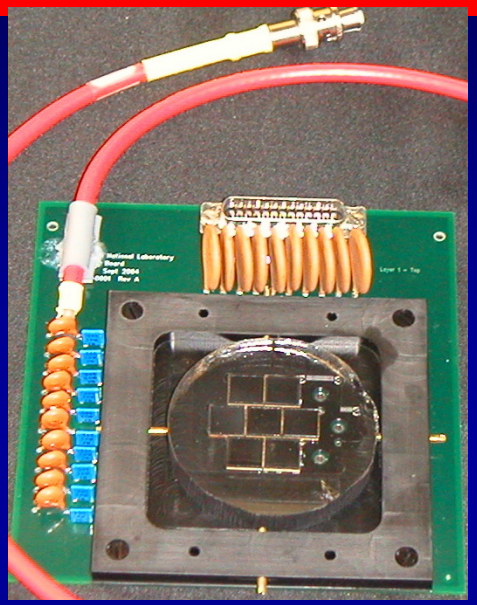
- Goal: ~1 mm FWHM spatial resolution but maintain high sensitivity
- Concept: a blend of old and new technologies
  - Anger camera
  - LSO and avalanche photodiodes (APDs)
  - New twists - photosensor on both sides for DOI, no lightguide necessary

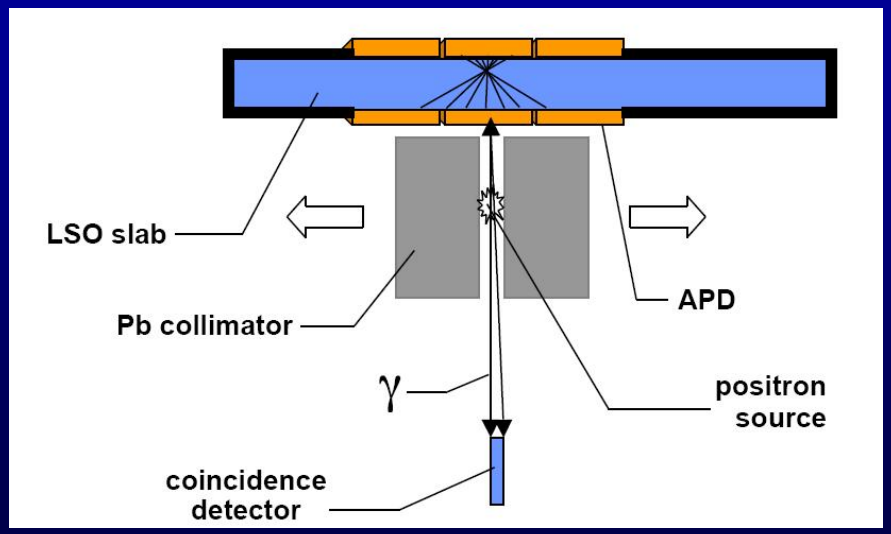


- Advantages over current small-crystal designs
  - Higher sensitivity - no gaps
  - Scalable to higher resolution - thickness determines resolution
  - Stackable to increase sensitivity
  - *Less expensive*
    - large slab vs. many individual crystals
    - fewer electronics channels
    - DOI means smaller radius possible

LSO/APD Anger PET Detector

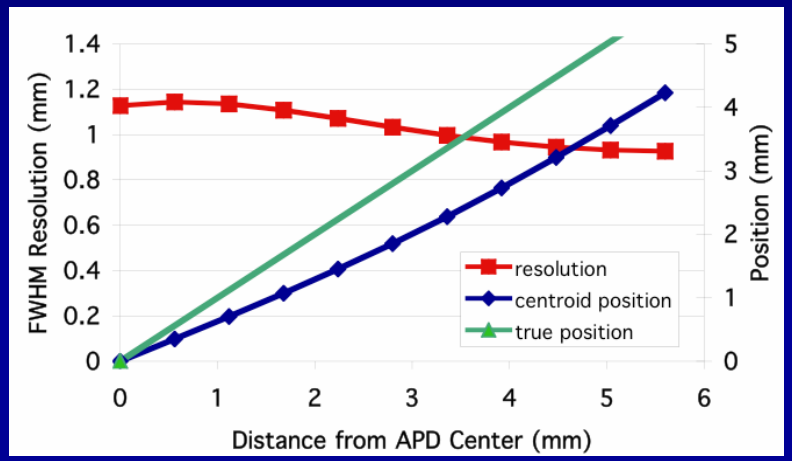


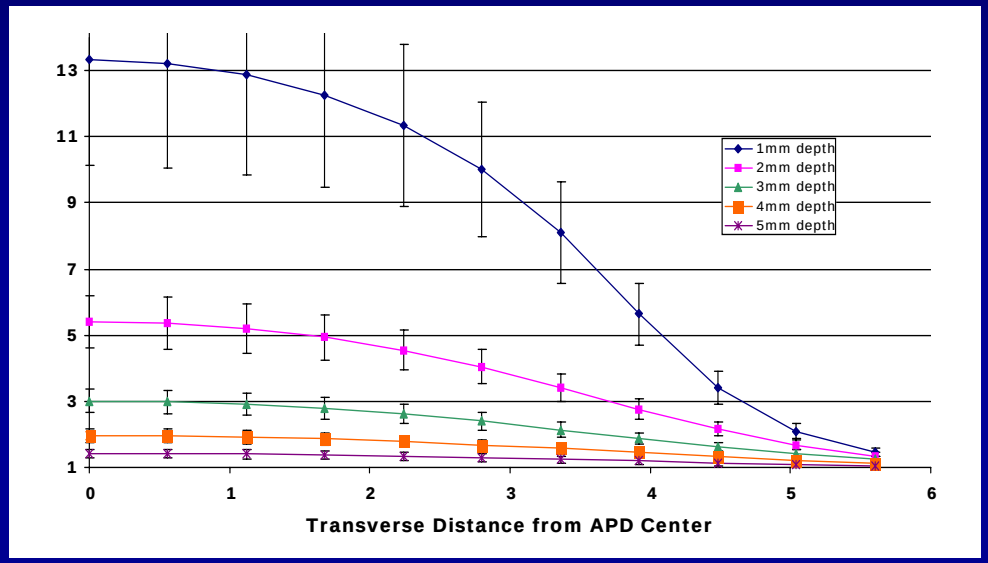




LSO/APD Anger PET Detector

- Simulations
  - 5000 rms electrons noise





$$\bar{x} = \sum_{i=1}^{14} x_i s_i \Big/ E$$

$$E = \sum_{i=1}^{14} s_i$$

$$\sigma_{\bar{x}}^{\ 2} = \sum_{i=1}^{14} (x_i - \bar{x})^2 \sigma_{s_i}^{\ 2} \Big/ E^2$$

- Spatial resolution data from full prototype soon
- Electronics improvement in next funding phase
  - Reduce noise = better spatial, energy, time resolution!
  - Fully digital or sample-and-hold?

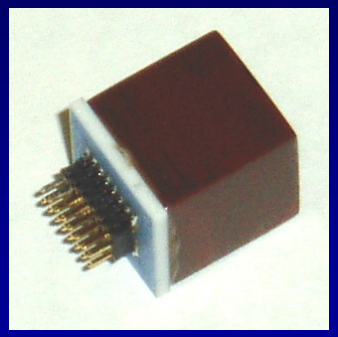
CZT for PET

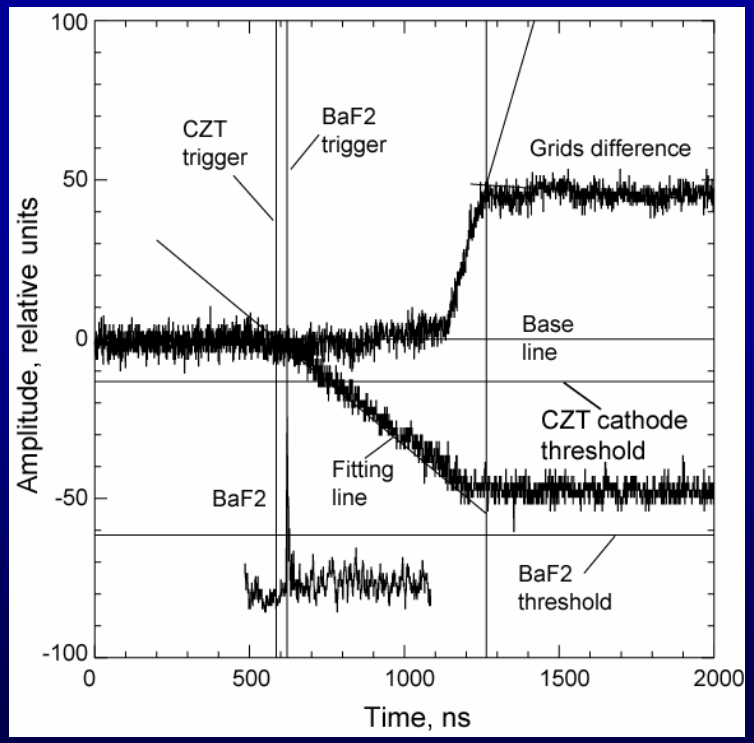
- New LDRD with Aleksey Bolotnikov, Gabriella Carini, Giuseppe Camarda, J-F Pratte, Avraham Dilmanian

- Advantages of CZT
  - High spatial resolution using block with pixel anodes: ~1 mm or less
  - High energy resolution: <3% at 511 keV
  - Compact

- Challenges
  - Timing
  - Stopping power
  - Sensitivity even with stacking

- Measurements
  - 15 x 15 x 7.5 mm CPG timing: 21 ns FWHM worst case
  - Next: 1 cm^3 block w/ 4 x 4 anodes on 2.5 mm pitch from eV





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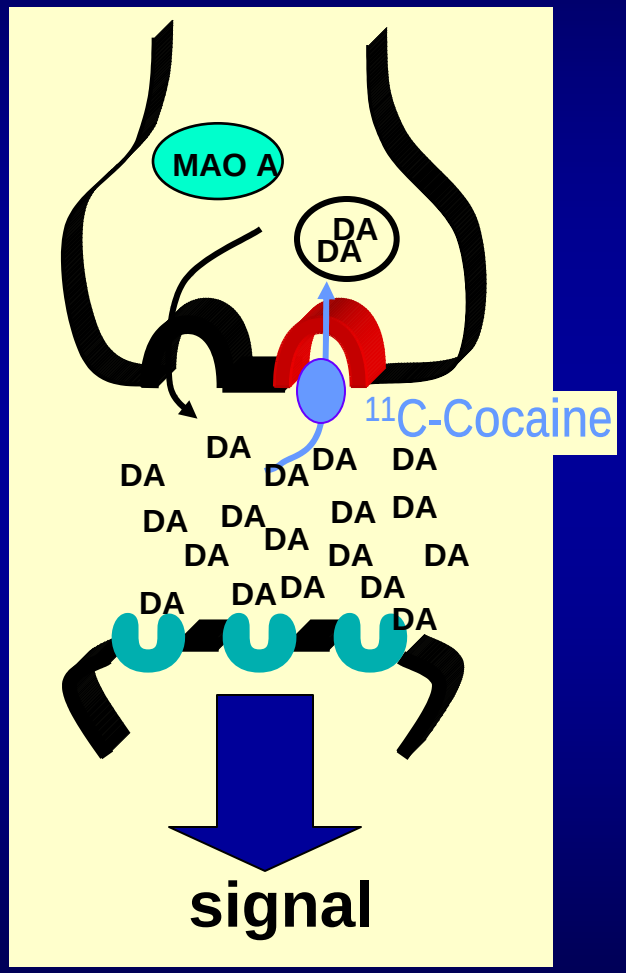
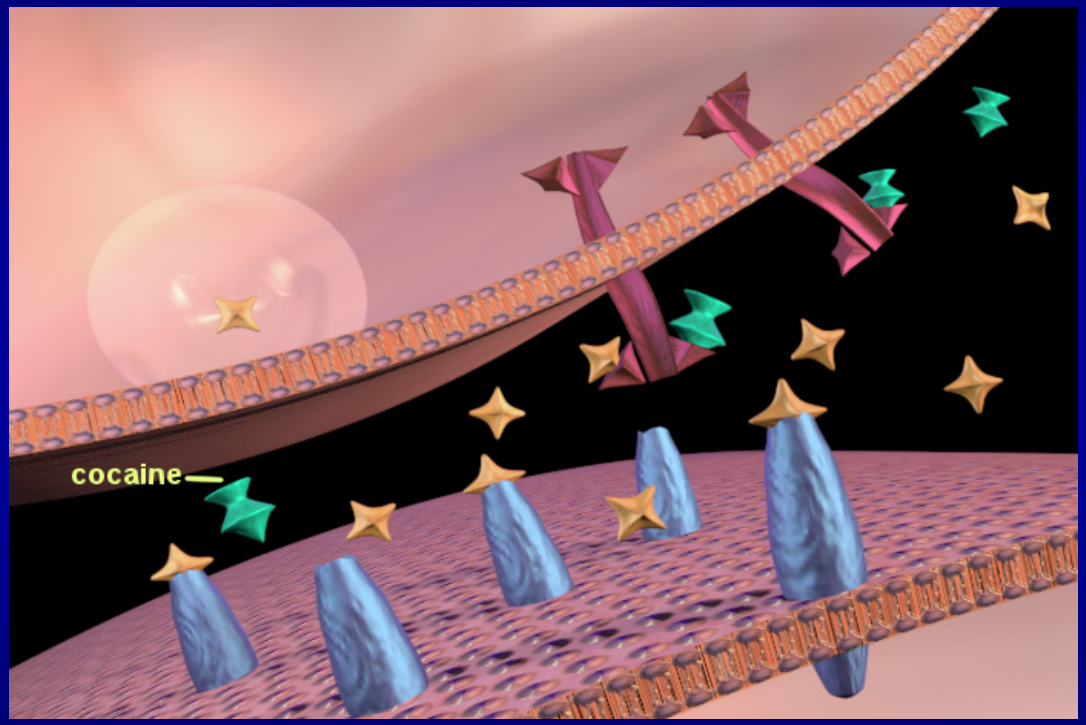
Dopamine System in Human (and Rat) Brain





RatCAP Team

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Veljko Radeka, Paul O'Connor, Jean-Francois Pratte, Bo Yu

Medical:
Paul Vaska, Nora Volkow

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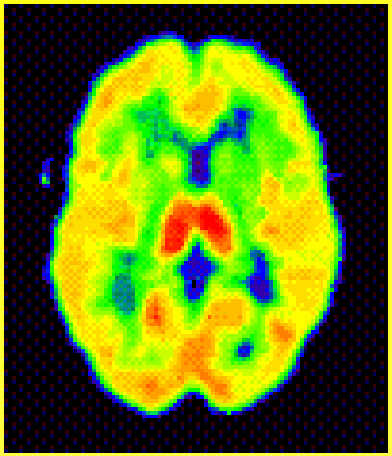
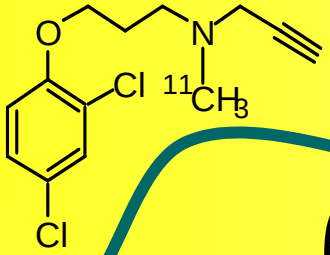
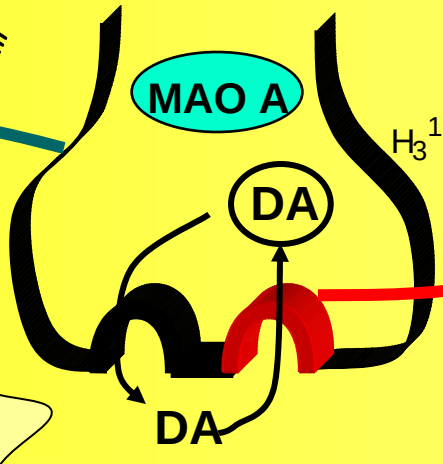
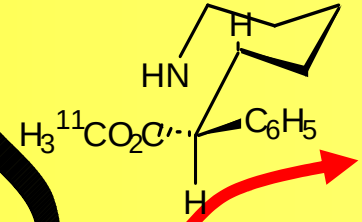
Molecular Imaging

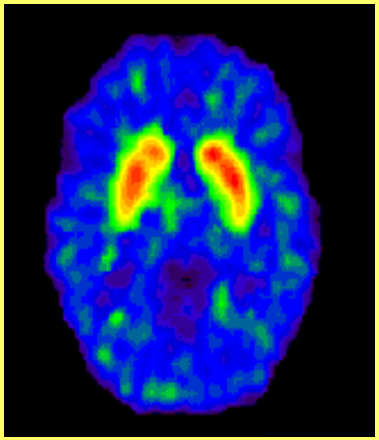


MAO A







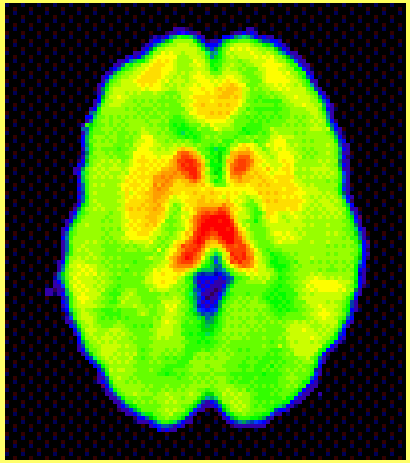


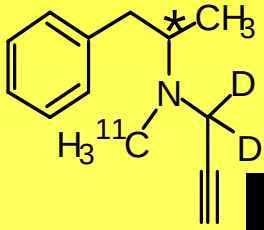
DA transporters

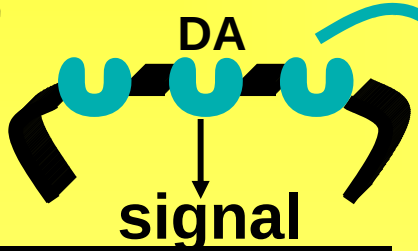
MAO B

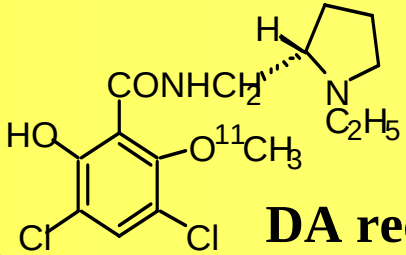
DA DA

MAO B

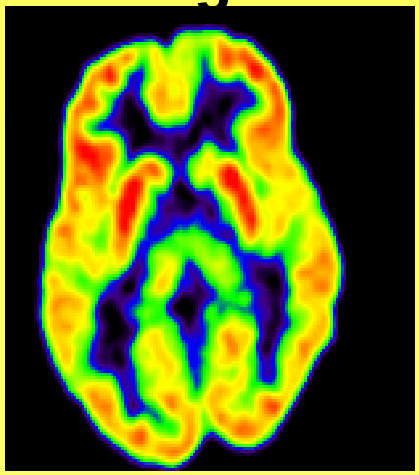


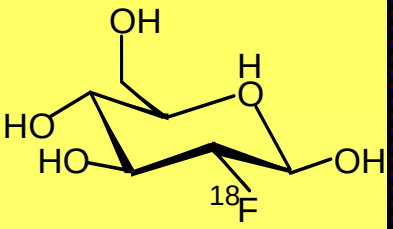


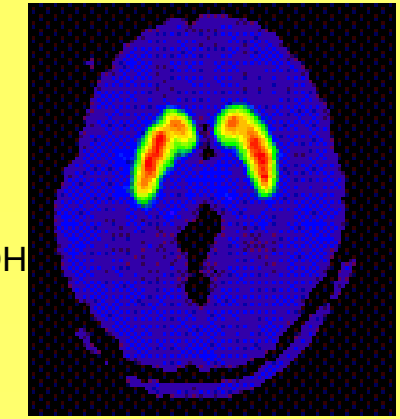




DA receptors

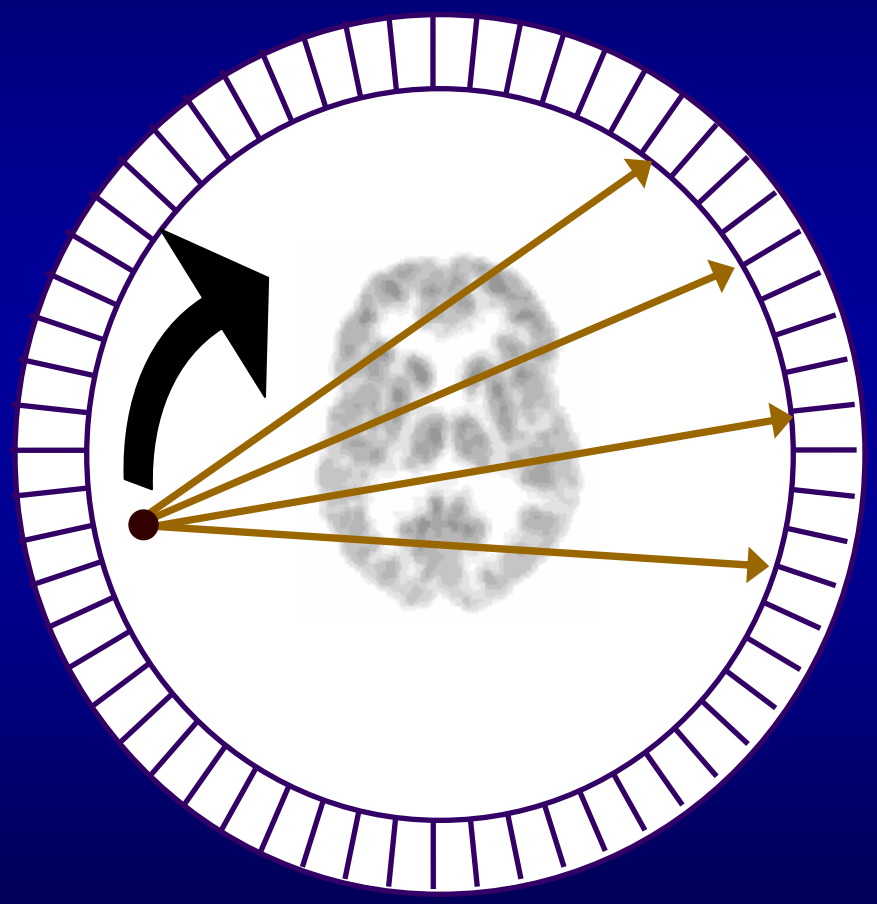




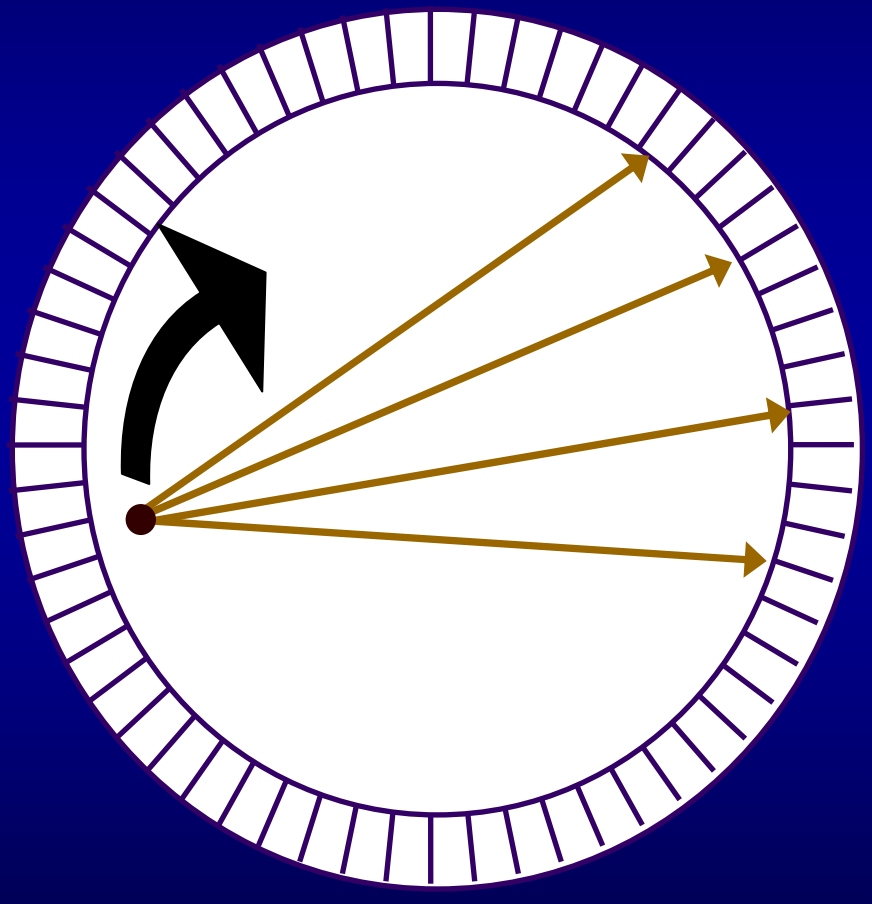


Measured Attenuation Correction

transmission scan

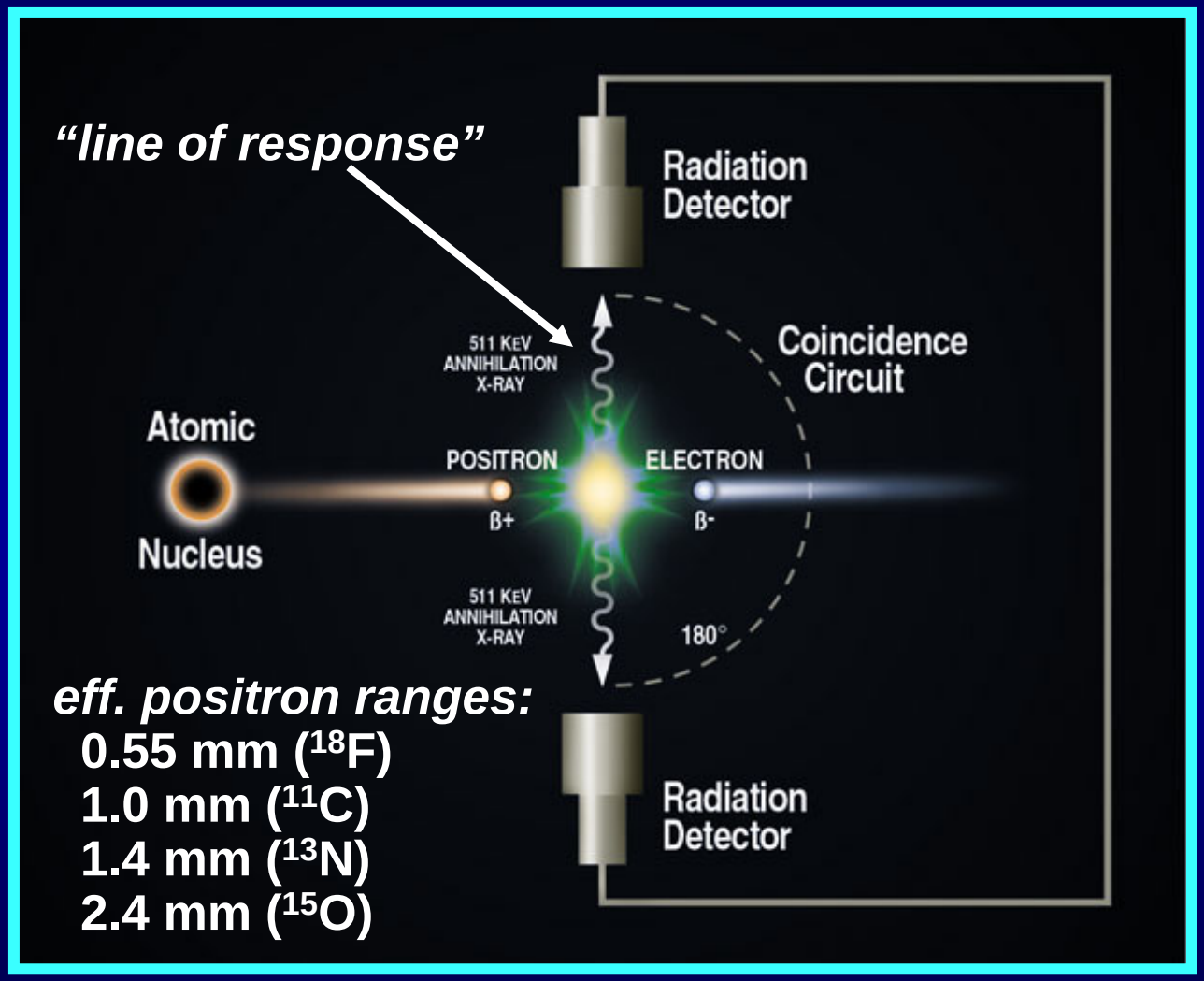


blank scan



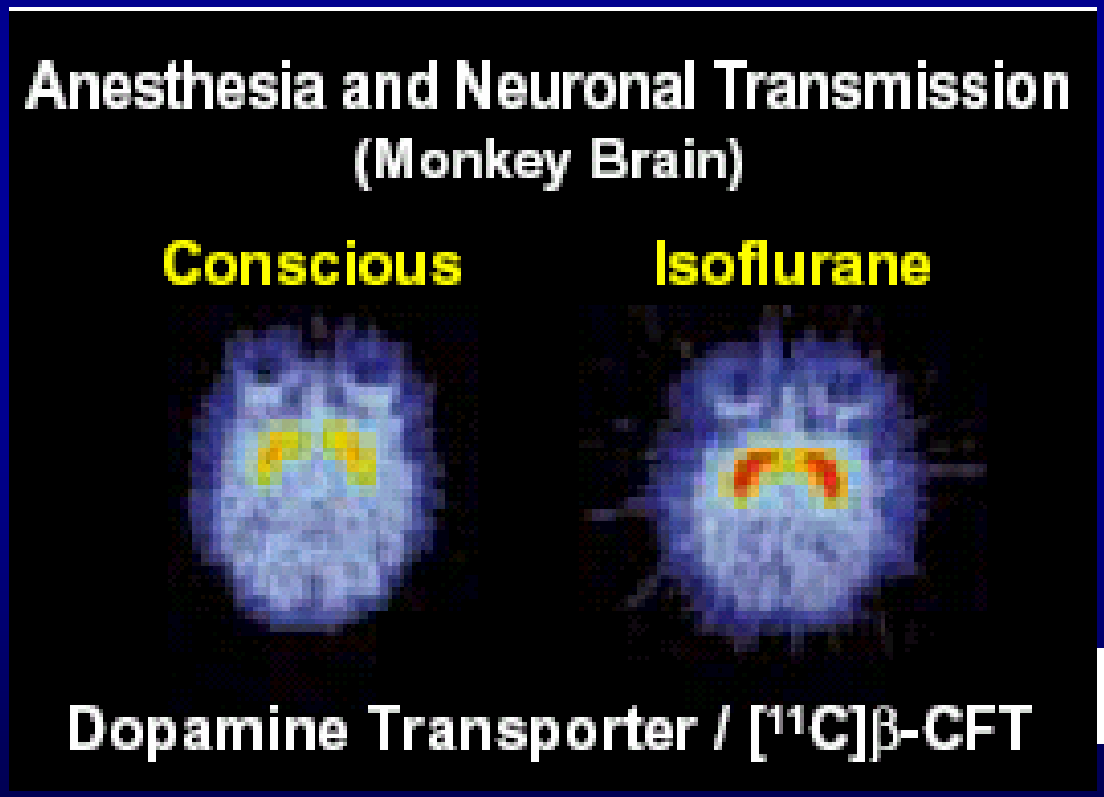
Positron Annihilation

- The positron collides with an atomic electron (anti-particle), giving back-to-back 511 keV gamma rays
- Positron range and noncollinearity ($\pm 0.25^0$) are ultimate limits on PET resolution



Effects of Anesthesia

Current small animal PET imaging instruments for rats are limited by the need to use anesthesia which can profoundly depress brain function.

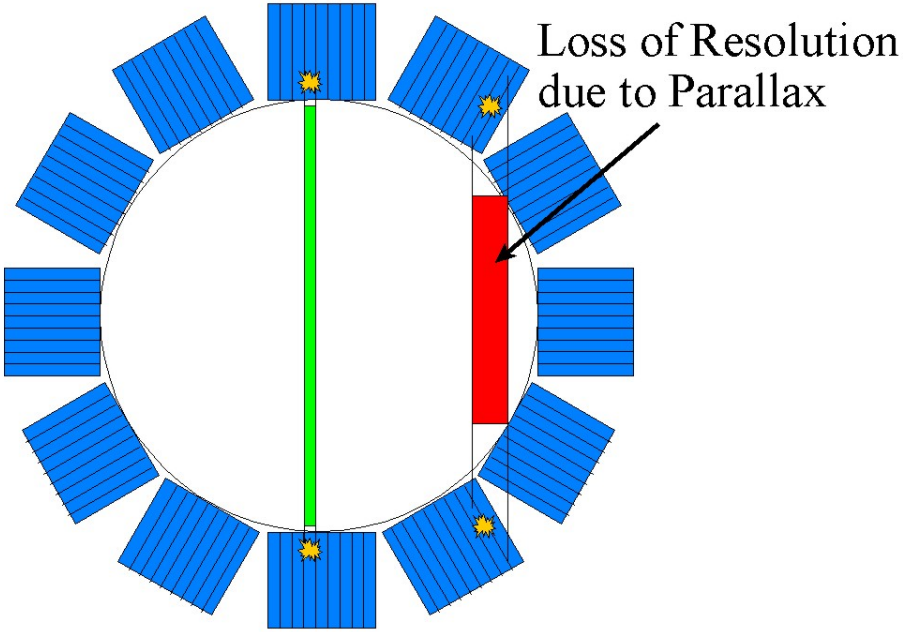


The effect of different anesthetics on the uptake of β-CFT on the dopamine transporter of the monkey brain.

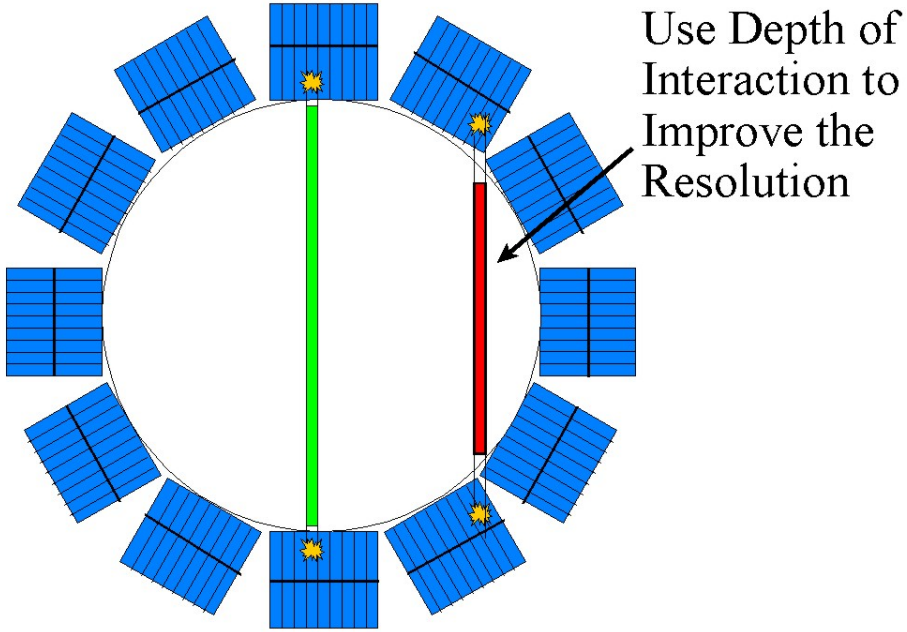
The 9th International Conference: Peace through Mind/Brain Science

RatCAP
Depth of Interaction Studies

In the small ring, parallax degrades the resolution



One layer of 10 mm Crystals

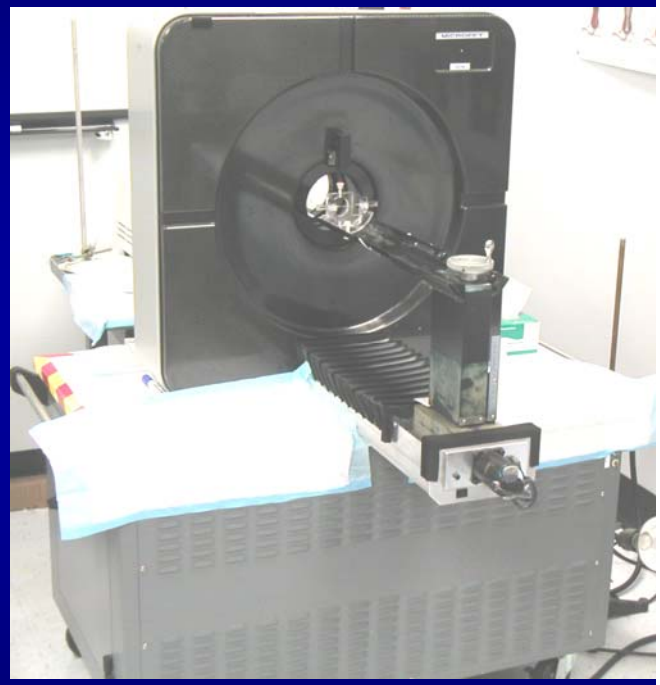


Two layers of 5 mm Crystals

This is a concern due to the fact that the rat brain occupies most of the ring diameter

RatCAP: Why image awake animals?

- To understand human function and disease, animal models are increasingly used
- PET is especially suited to measure brain function in humans and animal models
- To eliminate image blurring from motion, animals are anesthetized during PET imaging, BUT



  - Anesthesia can depress brain functions and affect the neurochemistry that one is trying to study
  - Cannot study animal behavior while under anesthesia

Design Requirements

- High spatial resolution and sensitivity for quantitative brain studies
- Size and weight small enough to allow reasonable freedom of movement
  - Light weight detectors (~ 150 g total weight)
  - Light weight electronics with low power consumption

    $\Rightarrow$ New custom electronics chip
- High count rate capability to handle large background
- Rugged to withstand activity of the rat

Image Processing Projects

- Sinogram Corrections: Development & Validation
  - scatter
  - attenuation
  - normalization
  - LSO radioactivity analysis

- Image Reconstruction Algorithms:
  Comparisons & Optimization
  - FBP
  - OSEM
  - MAP
  - post-smoothed ML-EM

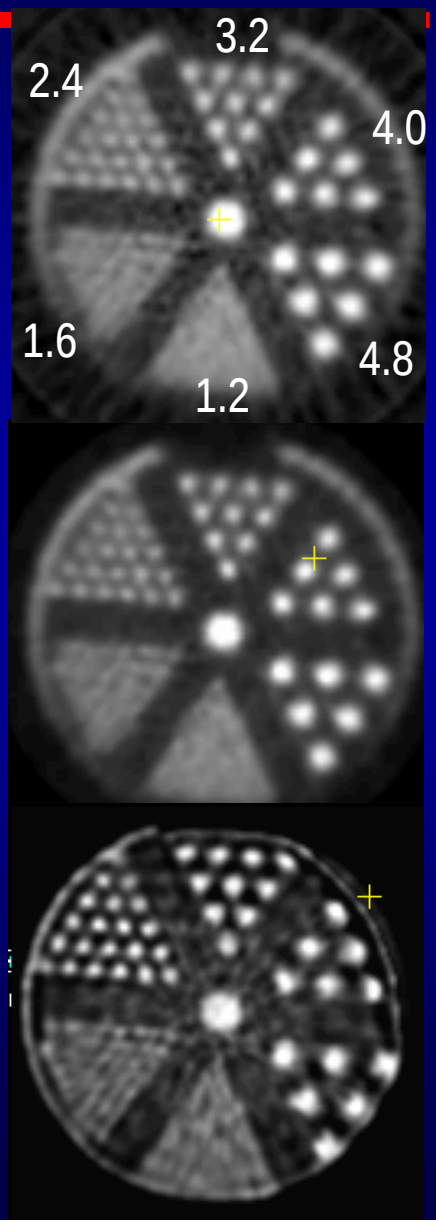
- Image Coregistration
  - provides anatomical identification of regions

- Partial Volume Correction
  - for ultimate quantitation in small regions

FBP

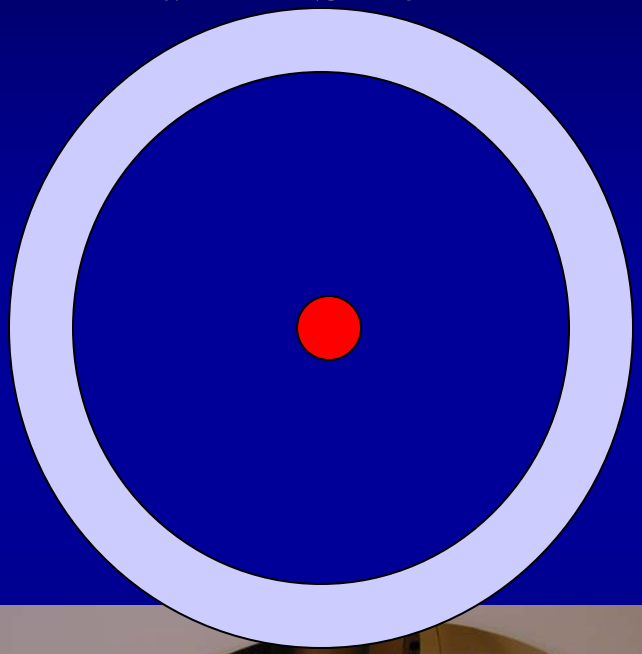
OSEM

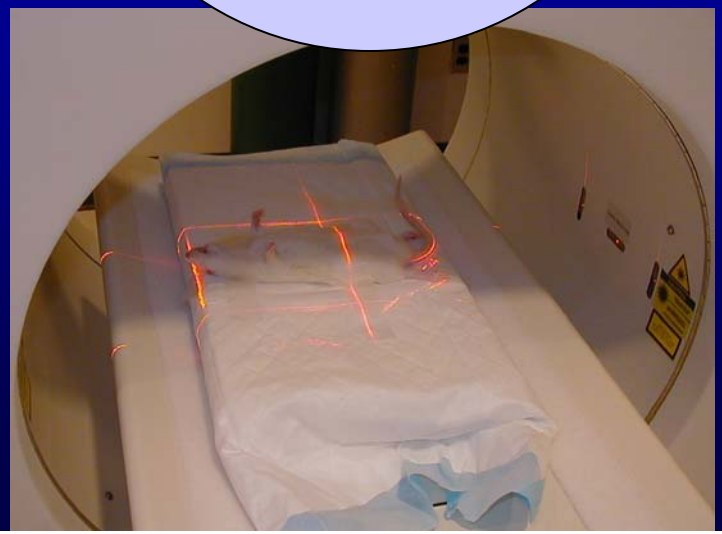
MAP



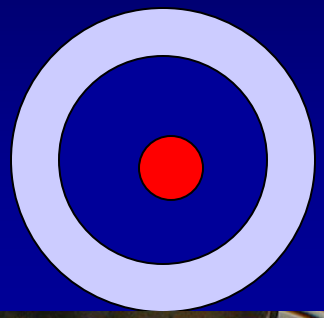
RatCAP
The Parallax Problem

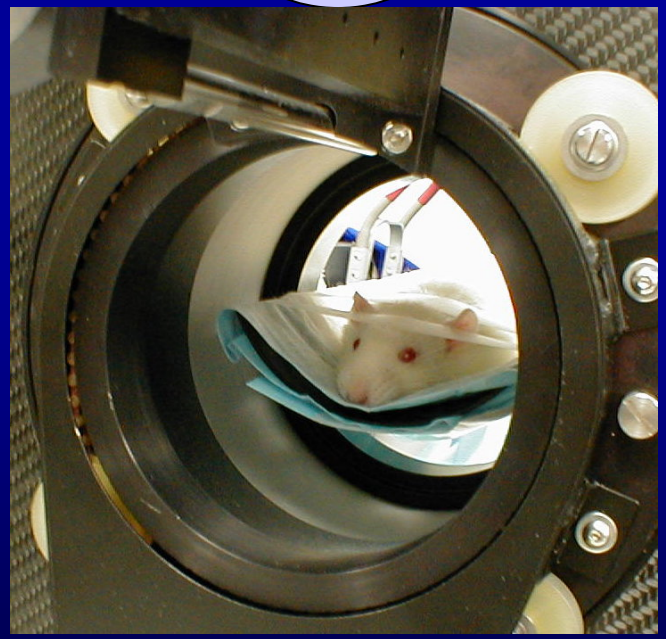
Human Size PET



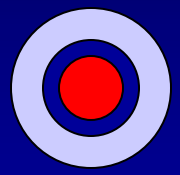


MicroPET



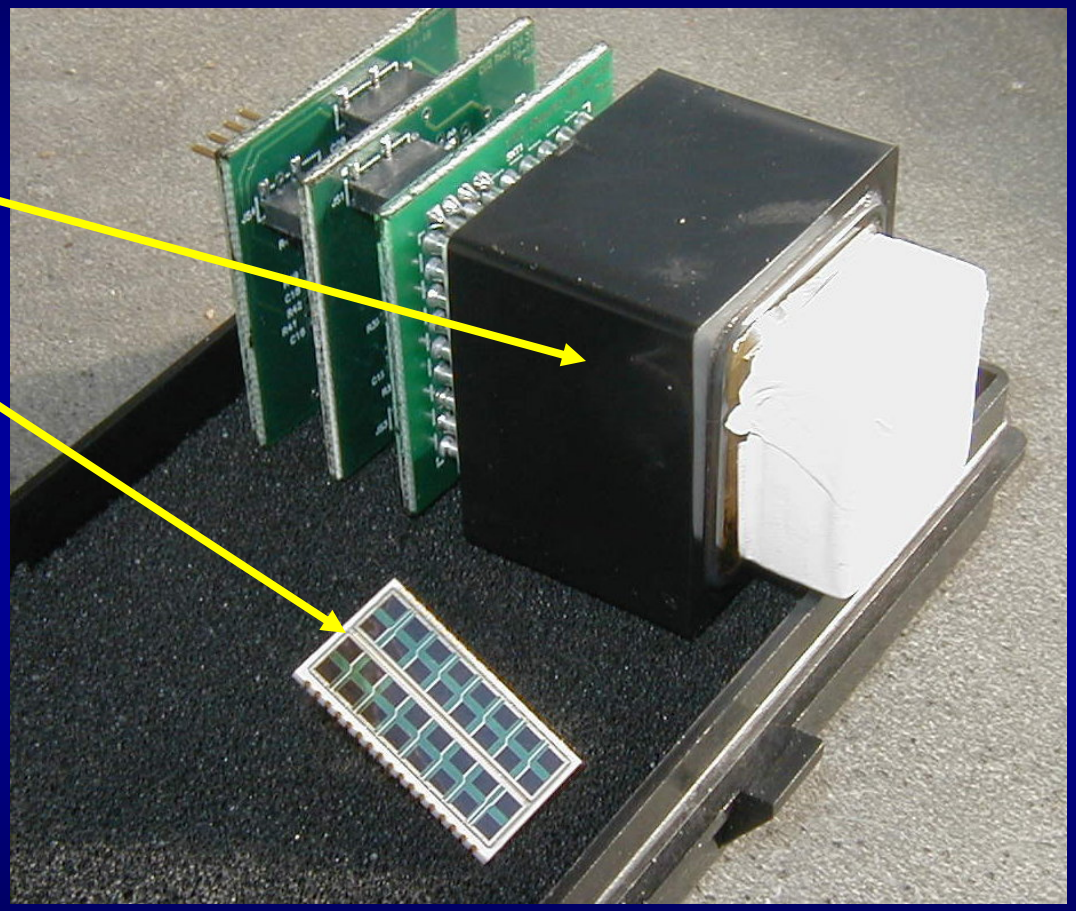


RatCAP



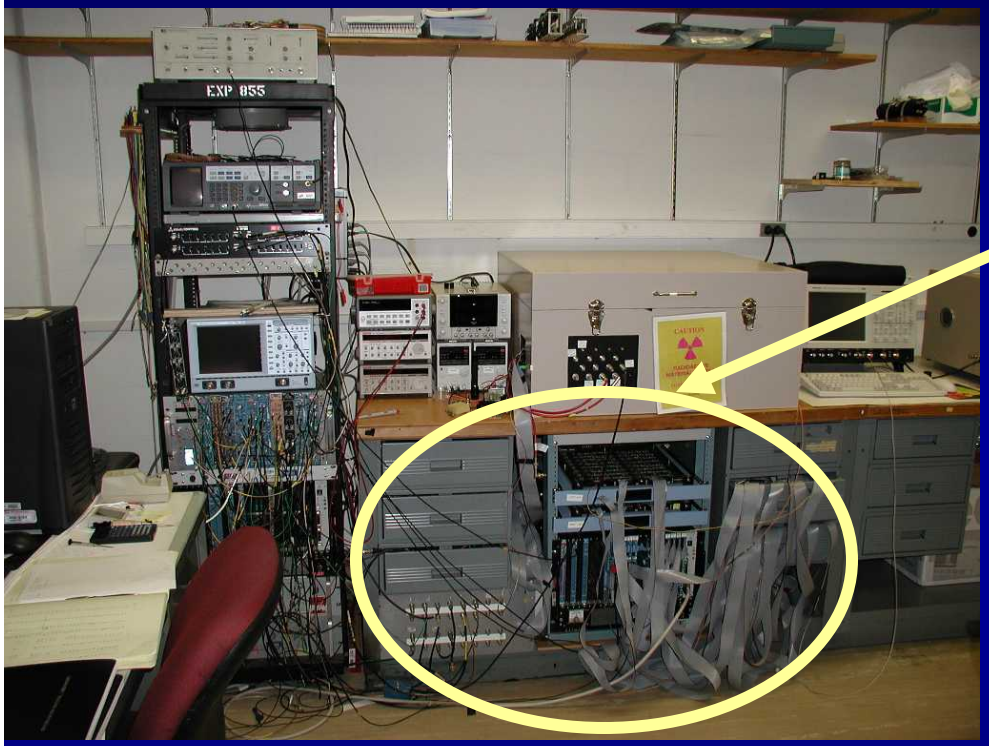
Light Sensor Miniaturization

- The light sensor can be a photomultiplier tube
- Or it can be a Avalanche Photodiode Array (APD) which matches the crystal array



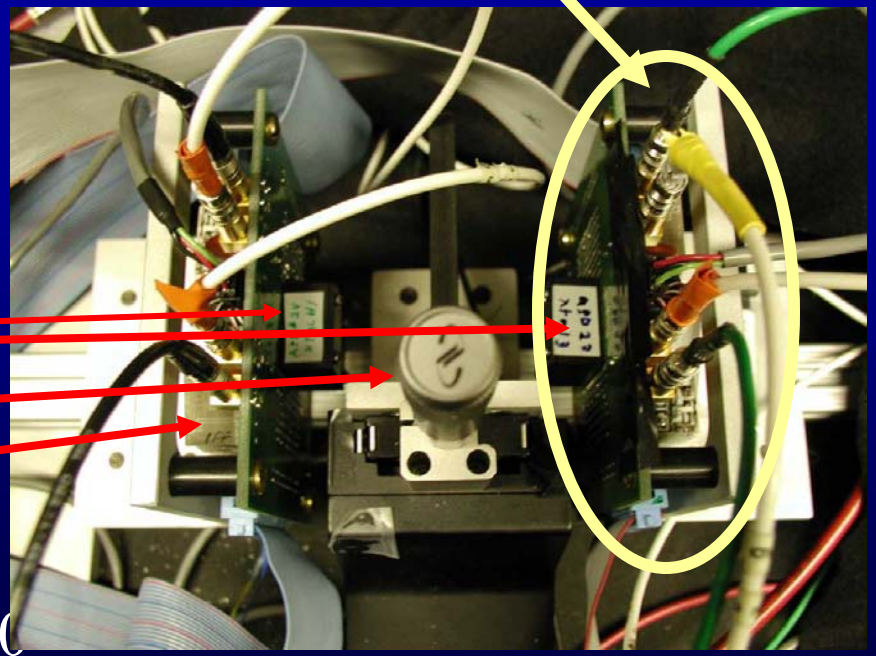
Craig Woody
Sean Stoll
Paul Vaska

RatCAP
Electronics Challenge



Two arrays of 4x8 APDs and crystals

- Need to get 6 times these electronics on the head of the rat



LSO and APD's

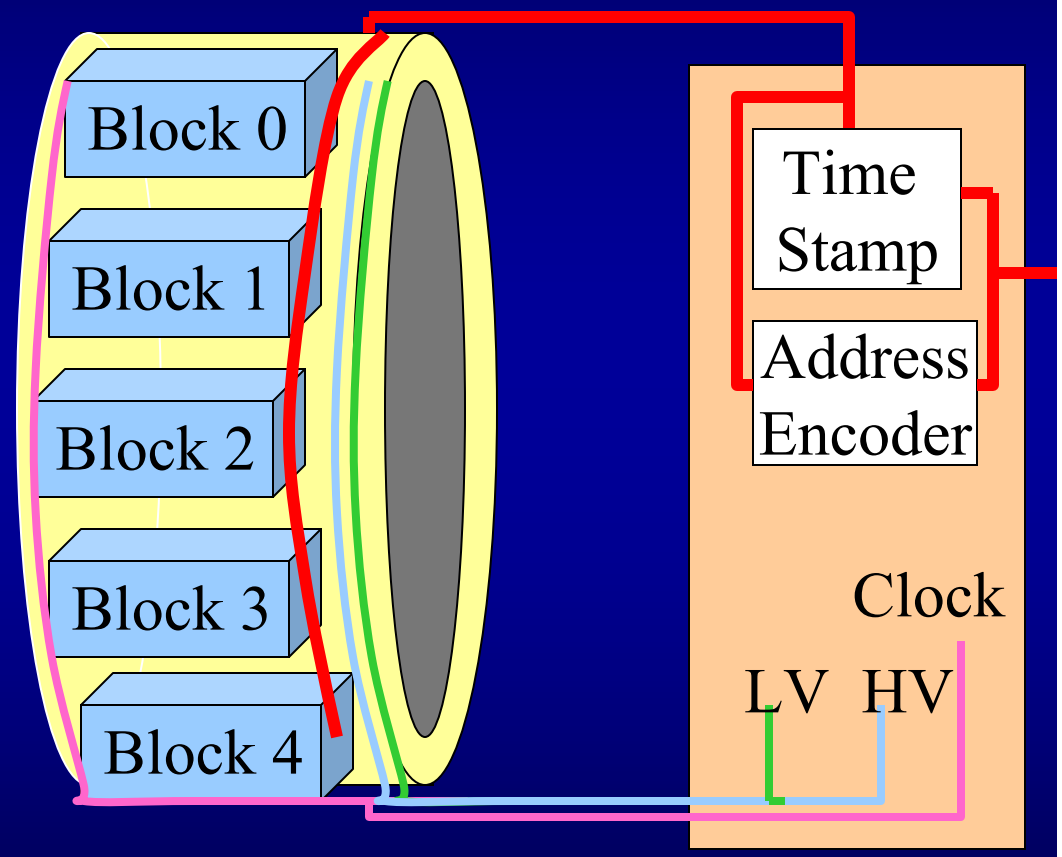
Positioning platform

Preamplifier

Craig Woody's lab in Physics

RatCAP
Electronic Development

- Simple electronics
- All the voltages, clock signal come in and data comes out on a single tether
- All the coincidence processing is done on the side of the cage
- Power consumption is low enough that we don't need additional cooling



1.5 watts power

On the Rat

3-10 watts power

On the Cage