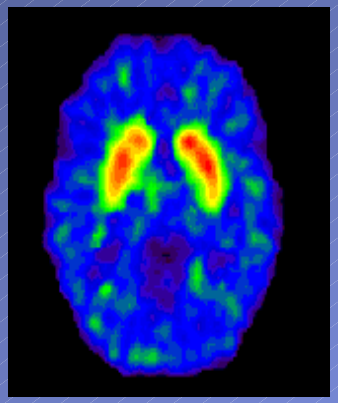
New Detectors for PET Imaging of Small, Awake Animals

- RatCAP
- Non-invasive wrist monitor
- Beta microprobe

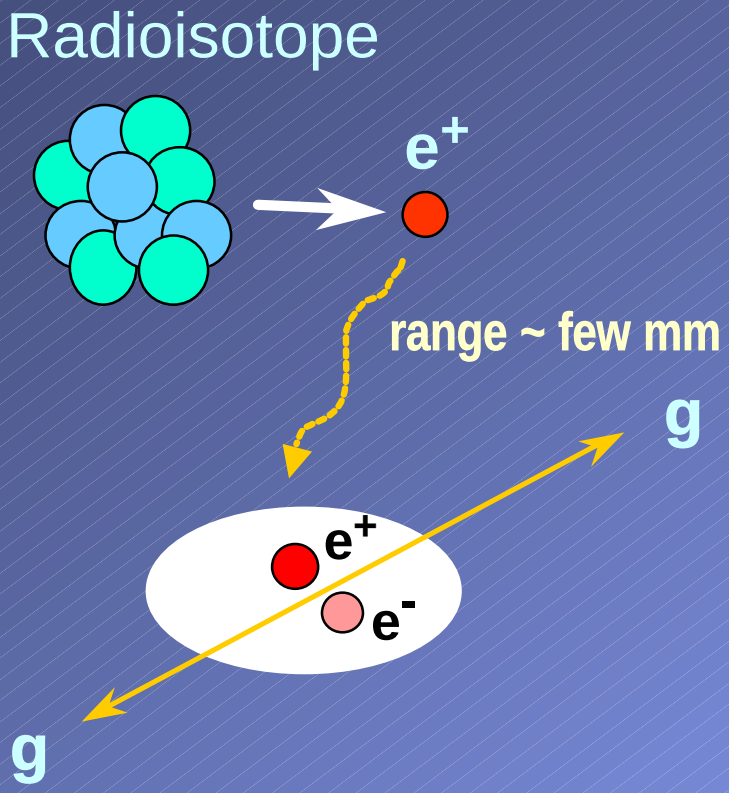


Craig Woody

Instrumentation Seminar

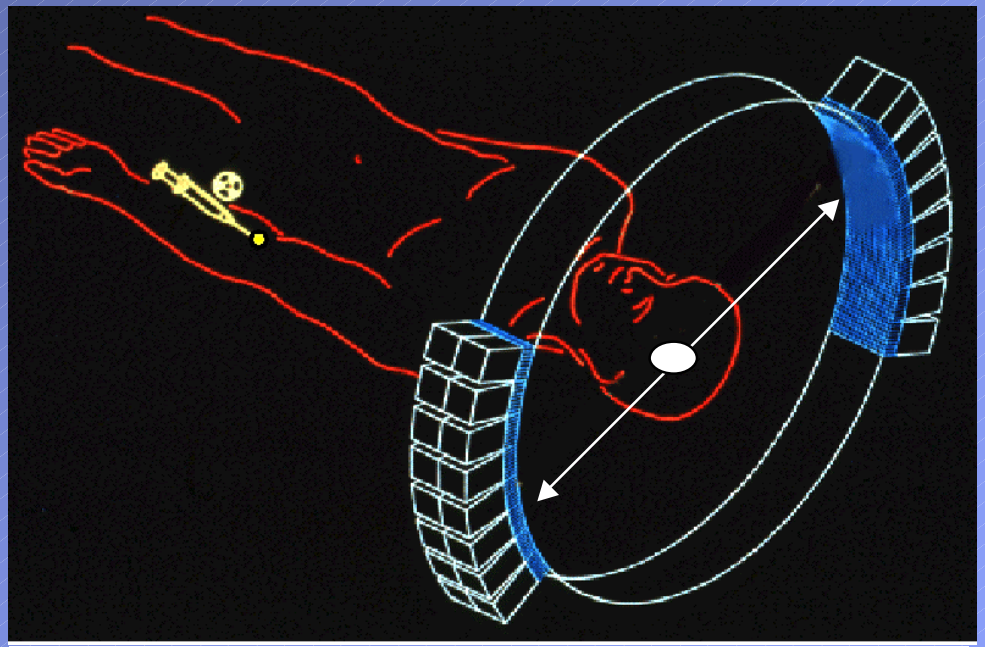
March 12, 2003

Positron Emission Tomography



Isotopes emit positrons with energies of a few hundred keV

PET detects coincident 511 keV gamma rays



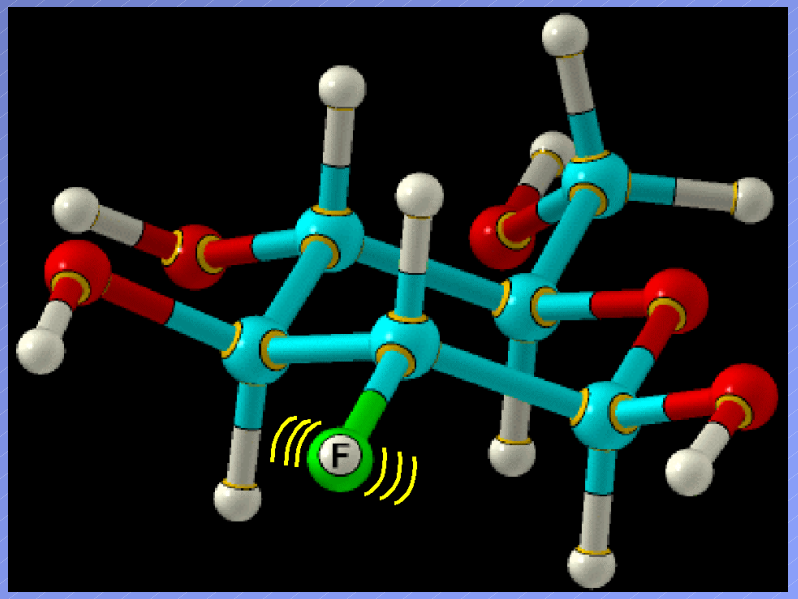
PET Scanner

Positron Emitting Radiotracers

SHORT-LIVED POSITRON EMITTERS

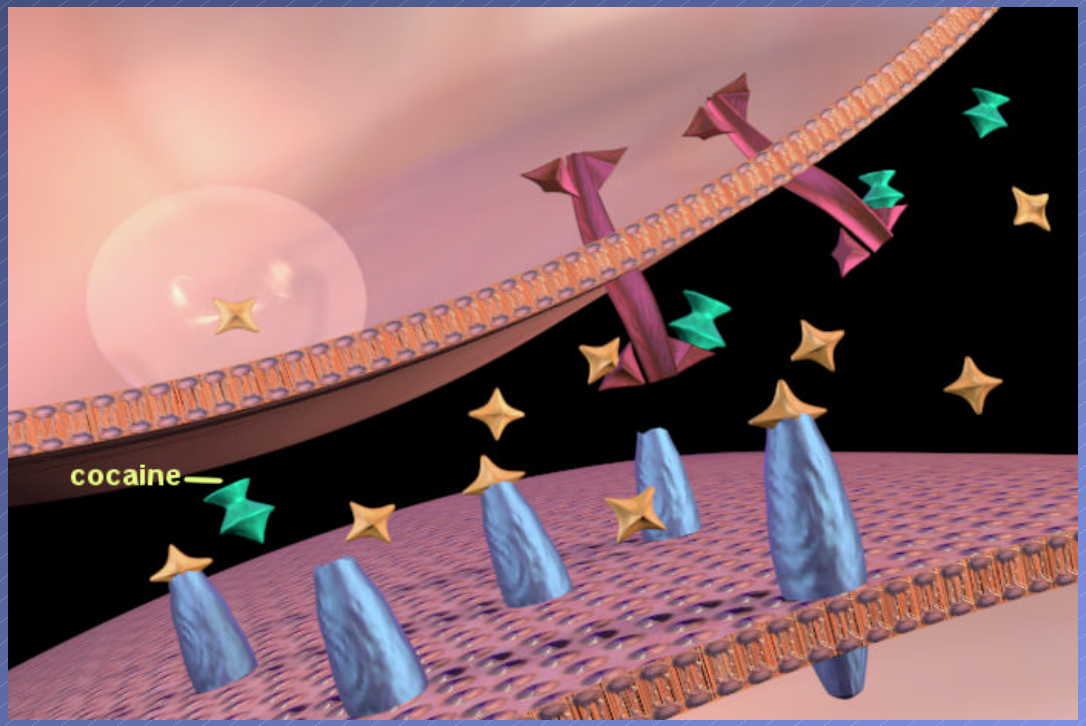
Isotope	Half-Life	Decay Product
carbon-11	20.4 min	boron-11
fluorine-18	110 min	oxygen-18
nitrogen-13	10 min	carbon-13
oxygen-15	2 min	nitrogen-15

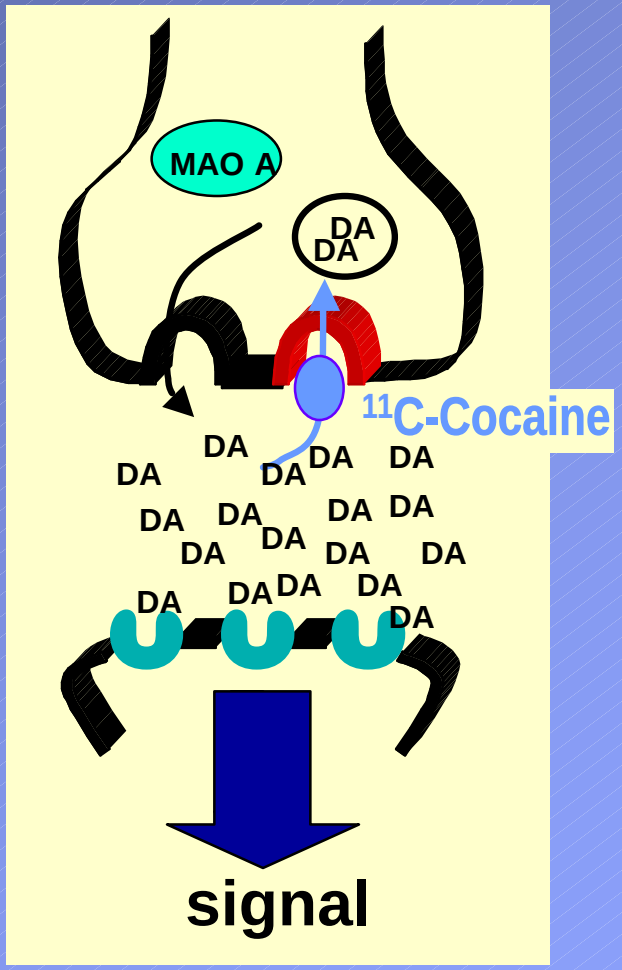
Organic molecules are labeled with positron emitting isotopes and used as tracers



Tracers can be used to study neurotransmitter activity in the brain

Neurotransmitter Activity in the Brain





Drugs like cocaine can block the re-uptake sites for neurotransmitters like dopamine which upsets the normal equilibrium and can cause effects of addiction

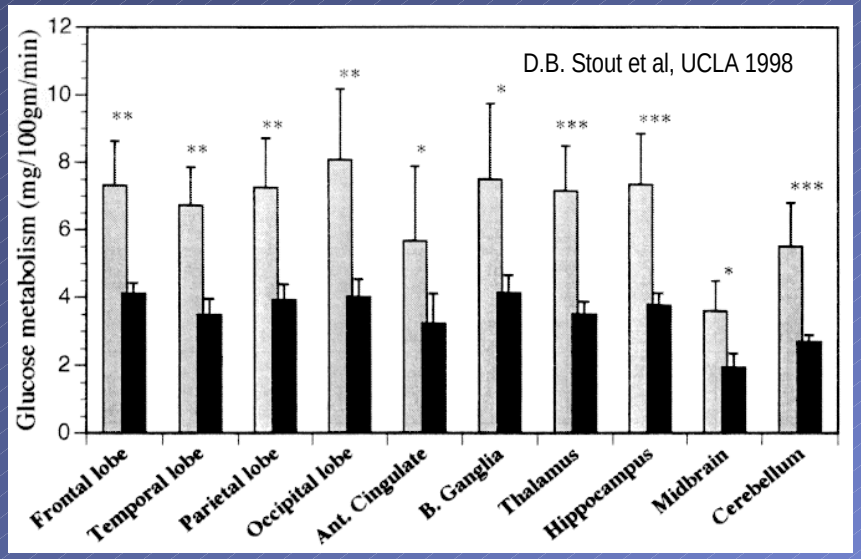
The Problem

One wants to use PET to study the neurophysiological activity and behavior in laboratory animals in order to understand and treat these effects in humans.

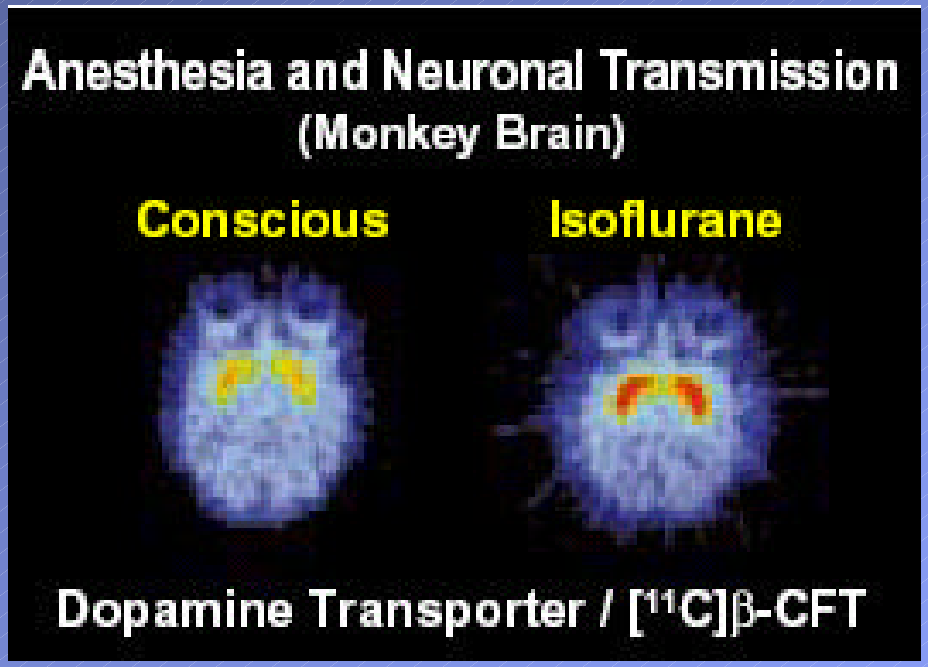
However, animals currently need to be anesthetized during PET imaging.

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

Effects of Anesthesia



H.Hideo et.al., Synapse 42 (2001) 273-280



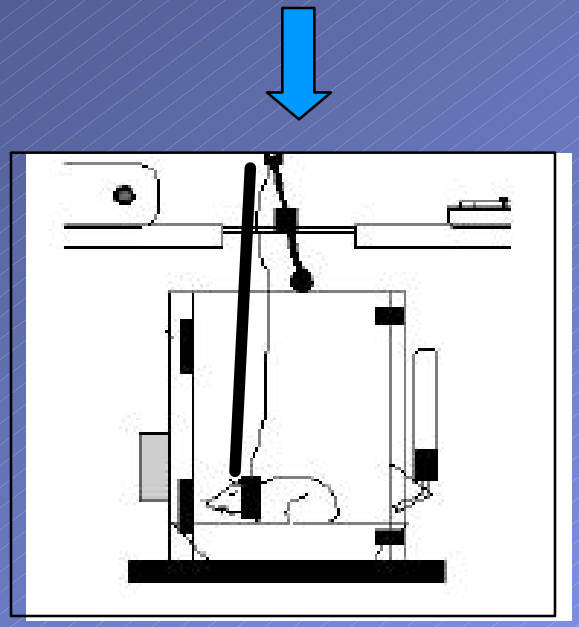
Reduction in glucose metabolism with isoflurane in humans

Similar effects are seen in the rat

The effect of anesthesia on the uptake of ß-CFT on dopamine transporters in the monkey brain.

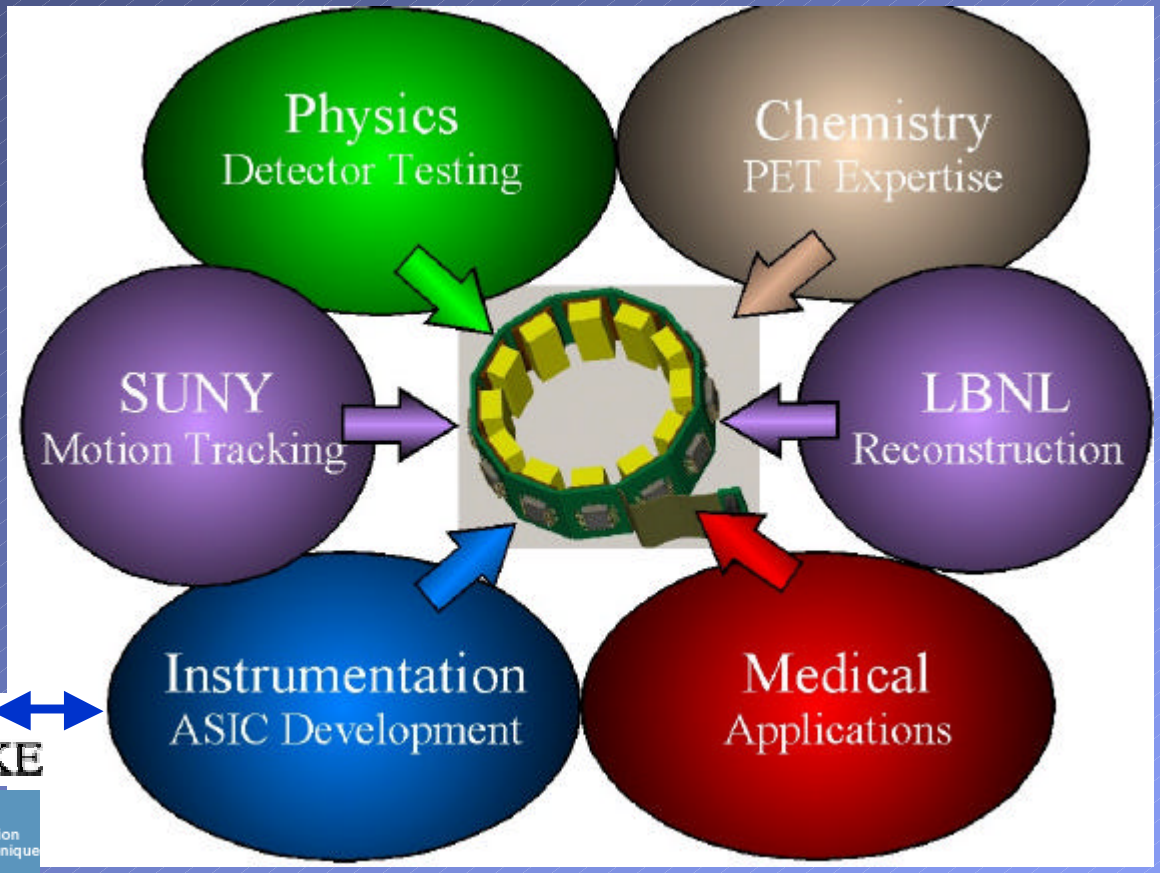
RatCAP: Rat Concious Animal PET

A septa-less, full-ring tomograph with a diameter of 4 cm and an axial extent of 2 cm, suspended by a tether, which would allow nearly free movement of the awake animal



Mockup of the portable ring on the head of a rat

The Collaboration



UNIVERSITÉ DE SHERBROOKE

Canadian Microelectronics Corporation
Société canadienne de micro-électronique

Part of a larger project for Imaging The Awake Animal also involving motion tracking in both PET and MRI

The People

Chemistry
David Schlyer
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Mike Schueller
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Physics
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Sean Stoll
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Instrumentation
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Bo Yu

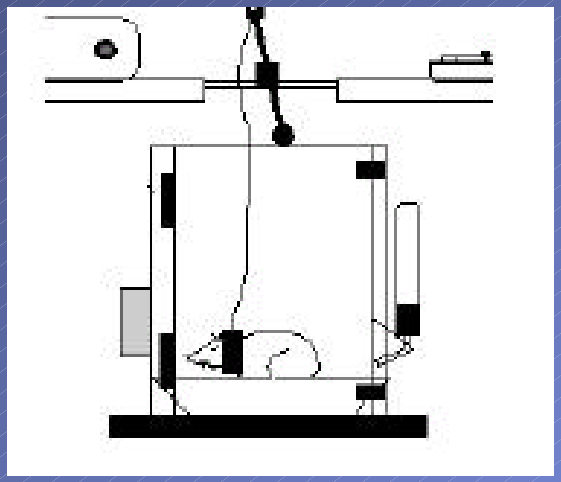
SUNY Stony Brook
Sepideh Shokouhi
Azael Villanueva
Aarti Kriplani

Design Requirements

- The tomograph ring must be light enough to be supported by the rat and allow reasonable freedom of movement
- Light weight detectors (~ 125 g total weight)
- Light weight electronics with low power dissipation
  $\Rightarrow$ New custom ASIC
- High data rates and large singles background
- Small field of view and large parallax effects
- Limited sampling due to space and weight requirements
- Must be rugged enough withstand activity of the rat

Support Structure

Similar support structures are used in microdialysis experiments



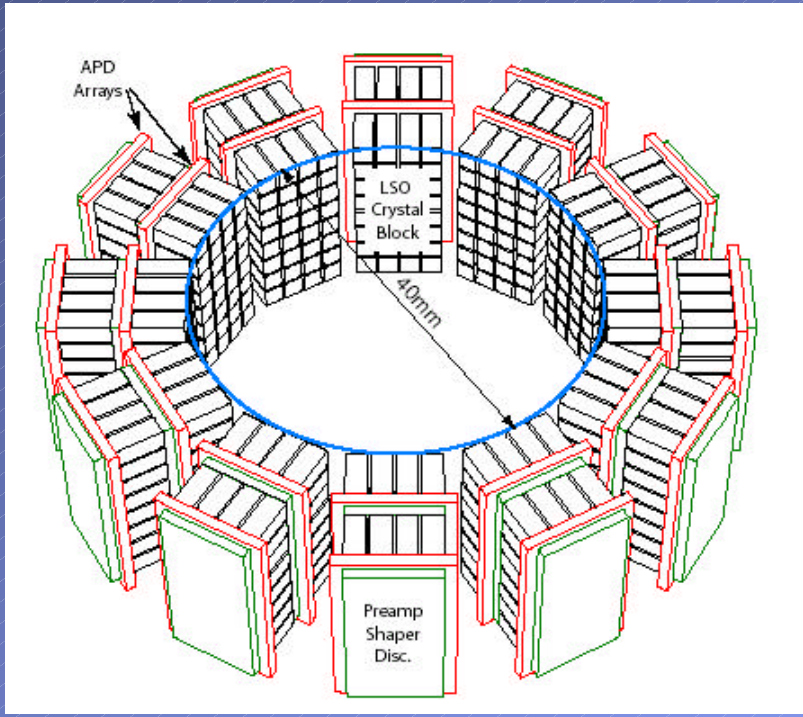
"Ratturn Bowl"

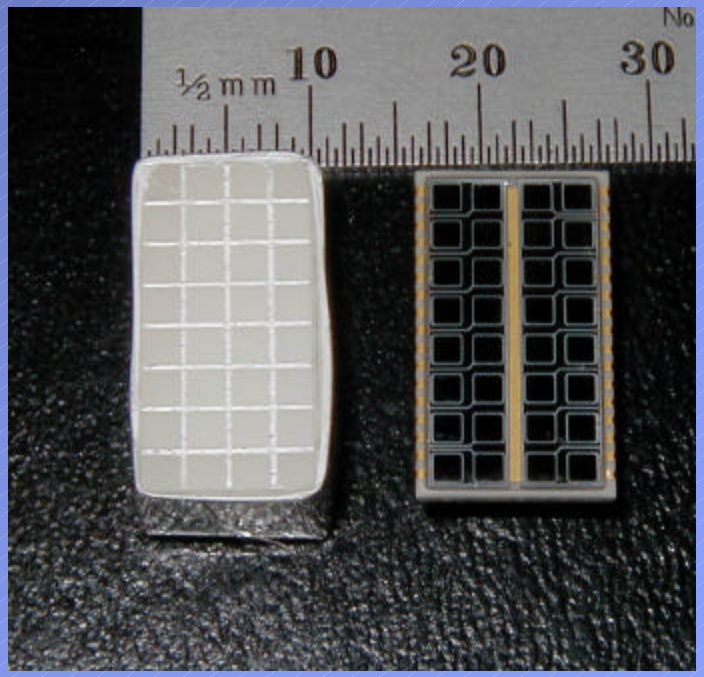
Prototype support tether

Tomograph Ring

Ring containing 12 block detectors
Up to two layers of 5 mm deep crystals with APDs and integrated readout electronics

2x2 mm^2 LSO crystals read out with APD arrays



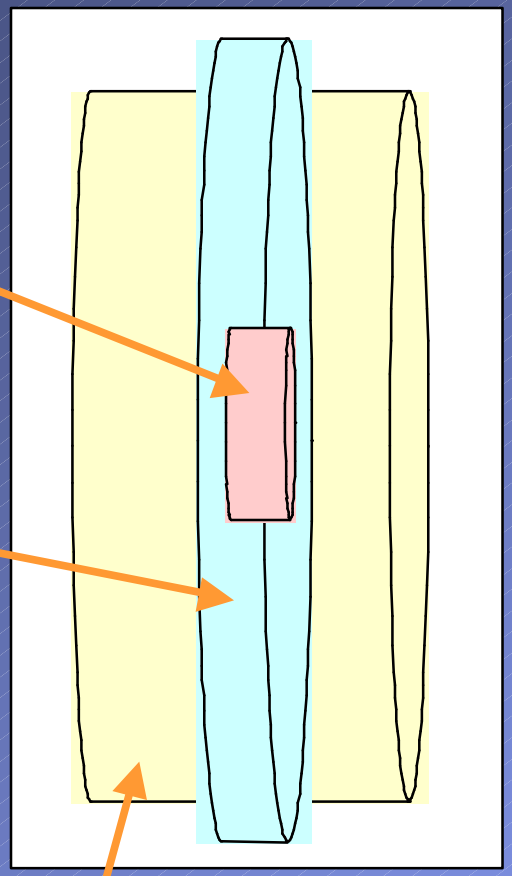


Sensitivity

BNL RatCAP
4 cm Ø x 2 cm

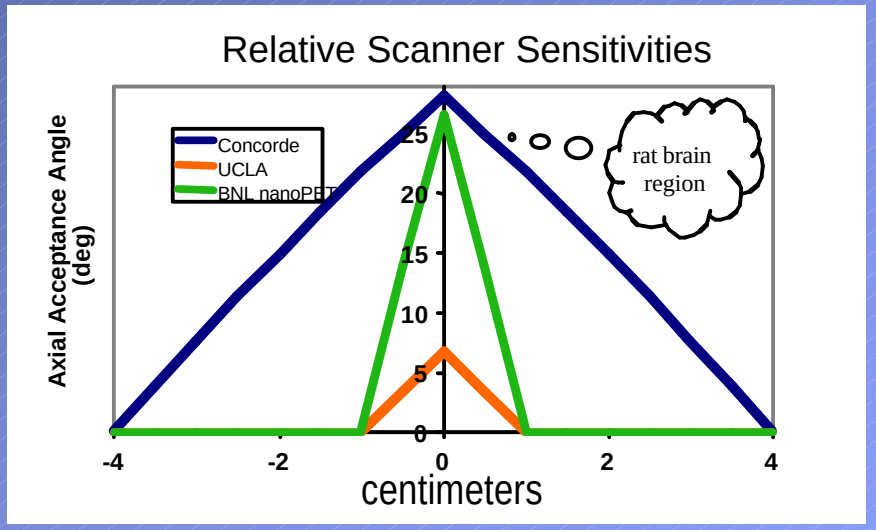
UCLA mPET
17 cm Ø x 2 cm

Concord mPET R4
15 cm Ø x 8 cm



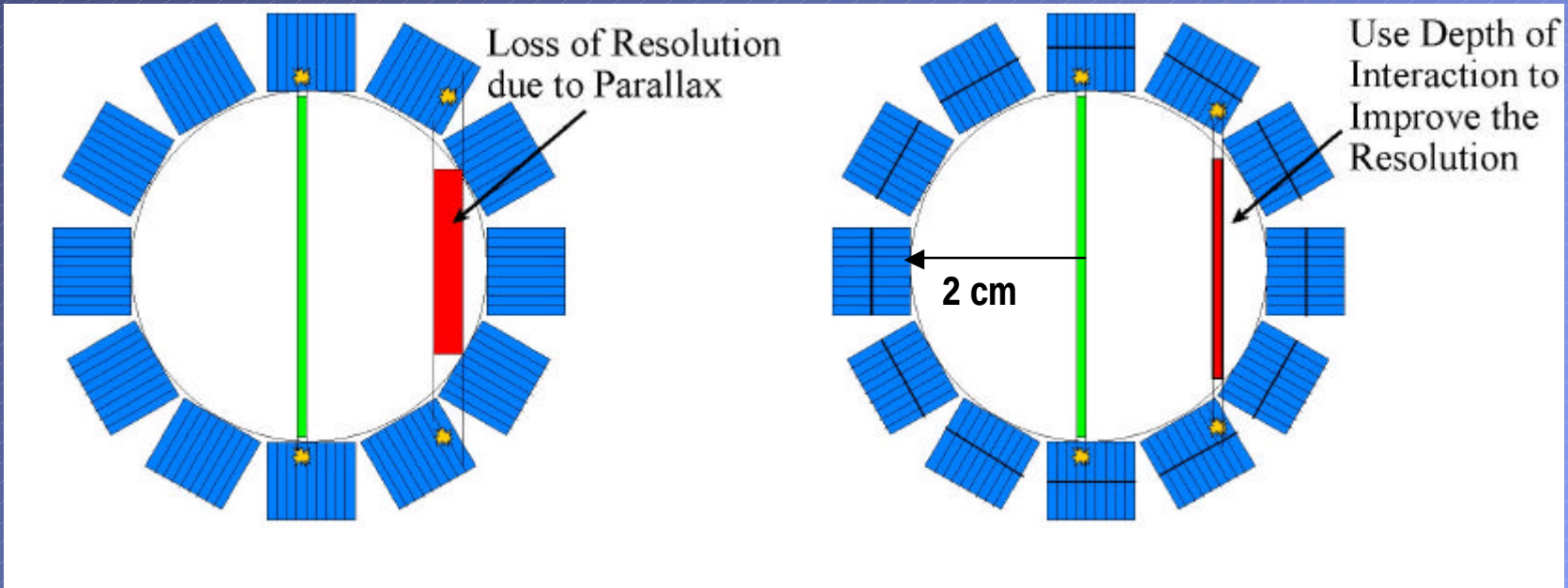
P.Vaska

Comparison of sensitivity with other small animal PET scanners



- Intrinsic detector sensitivities are essentially the same
- Coincidence sensitivities are proportional to axial acceptance

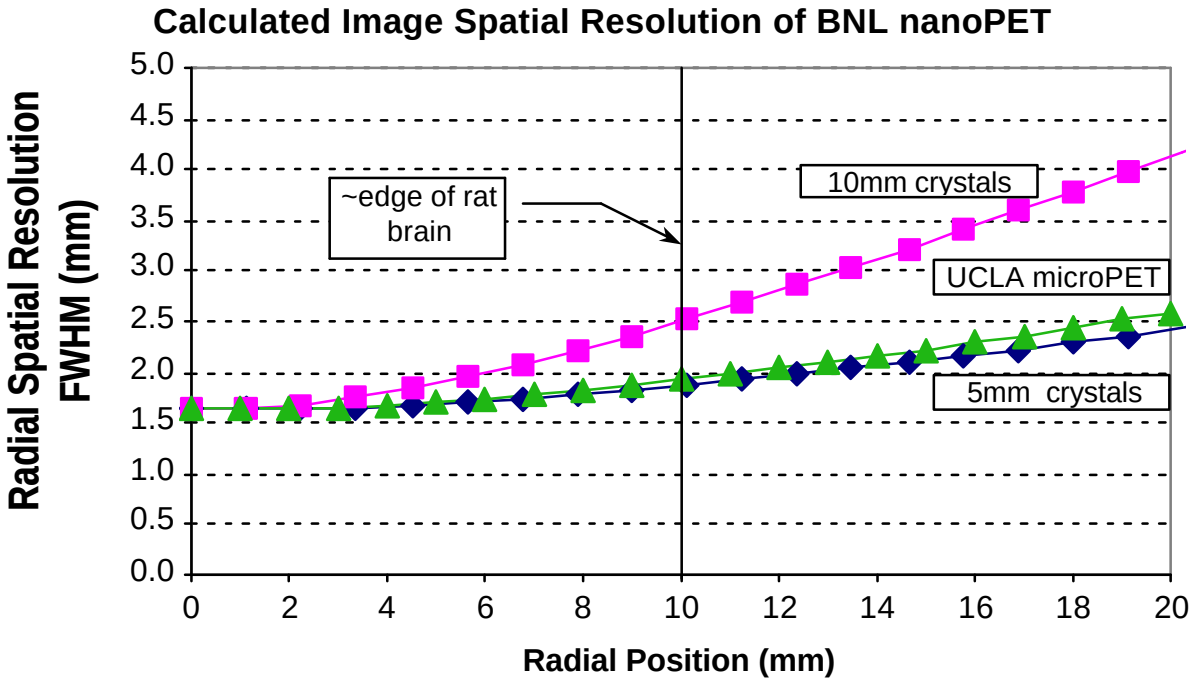
Parallax Effects



Due to the small diameter of the ring, the parallax error is a major factor in determining the spatial resolution

Spatial Resolution and Field of View

P.Vaska



Resolution at the edge of the rat brain

Single layer - 10 mm
~ 2.5 mm
Double layer - 5 mm
~ 1.9 mm

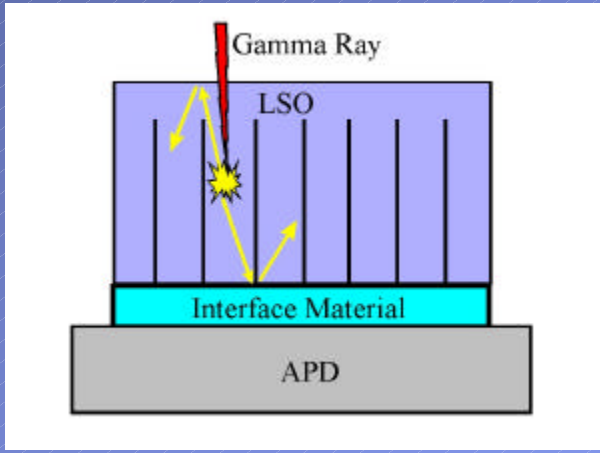
First prototype will be a single layer of 5 mm crystals
Will sacrifice sensitivity for improved spatial resolution

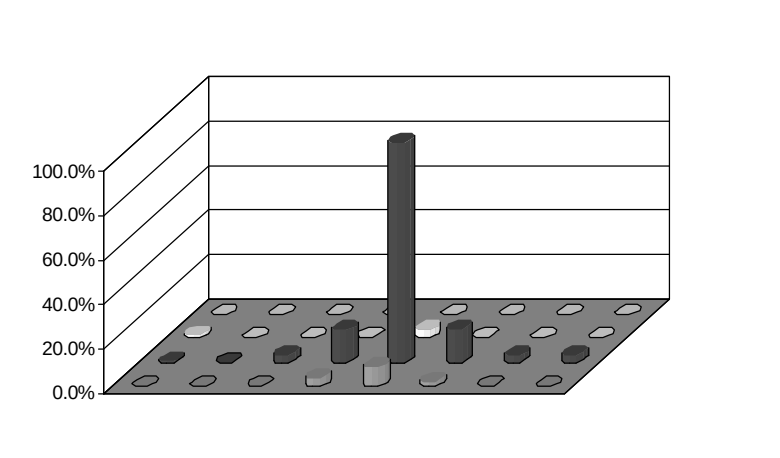
Inter-Crystal Scatter and Cross Talk

Energy information in each crystal could be used to recover Compton events and correct for cross-talk between pixels

Collected data with ADC information and compared energy, position, time resolution and sensitivity :

- **D**E (FWHM) : 21% → 19%
- time & position resolution ~ same
- ~25% increase in coincidence sensitivity



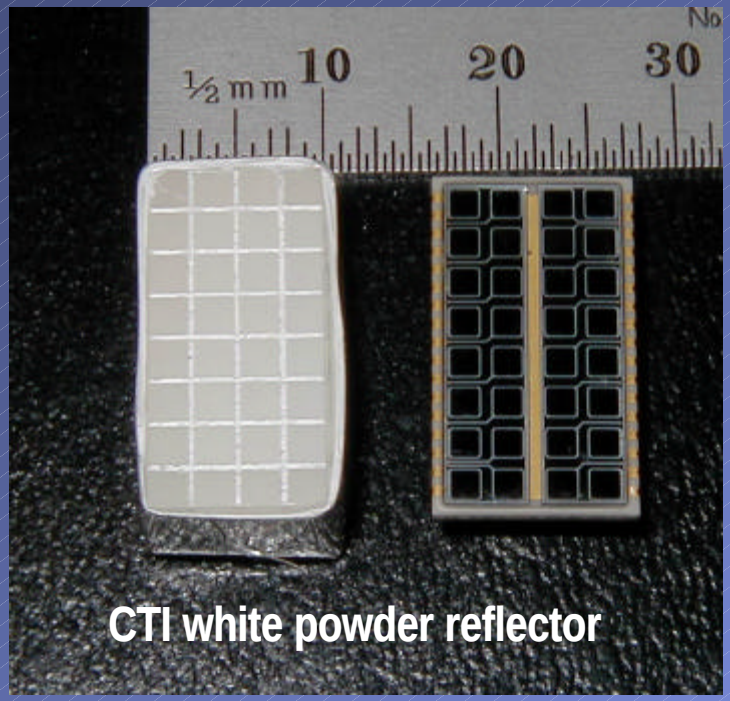


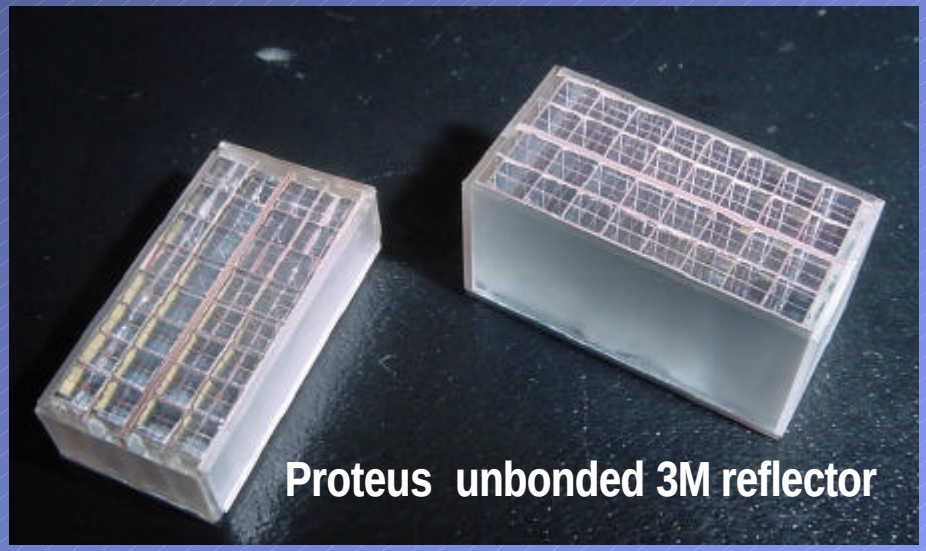
Conclusion:

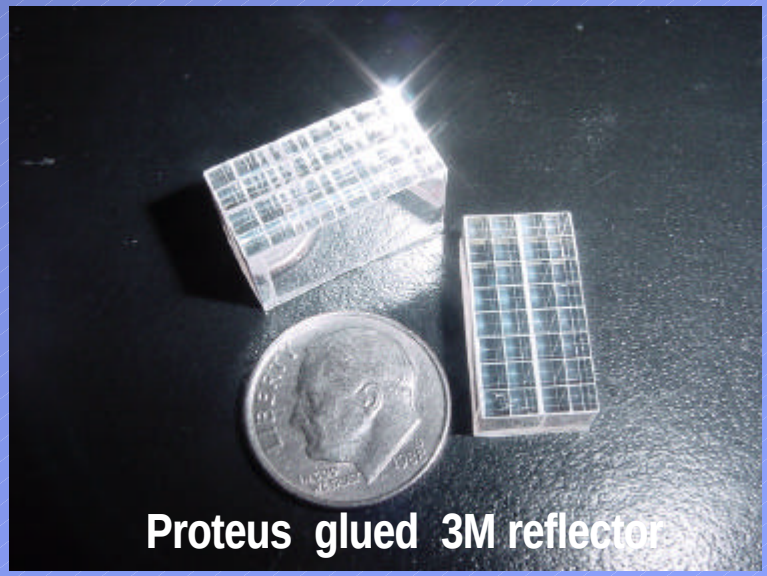
The slight improvement in resolution and increased sensitivity does not justify the added complexity in the ASIC

P.Vaska et.al., 2002 MIC, to be published in IEEE TNS

Light Output and Energy Resolution







Studying different types of crystal arrays to optimize light output and energy resolution

Contributions to Energy Resolution

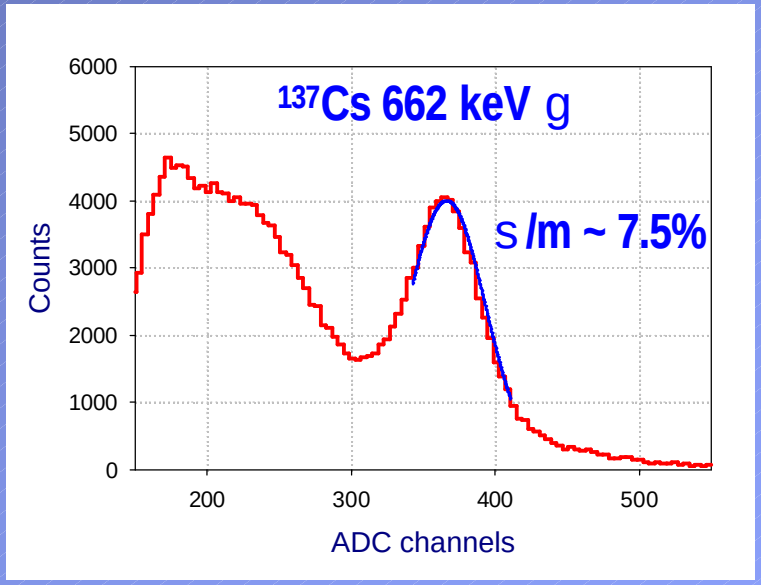
$$\left(\frac{\Delta E}{E}\right)^2 = \left(\frac{\Delta N_{sc}}{N_{sc}}\right)^2 + \left(\frac{\Delta N_{col}}{N_{col}}\right)^2 + \left(\frac{\Delta N_{e-h}}{N_{e-h}}\right)^2 + \left(\frac{d_{noise}}{N_{e-h}}\right)^2$$

N_{sc} = Number of scintillation photons produced

N_{col} = Number of photons collected

$N_{e\text{-}h}$= Number of electron-hole pairs produced in APD

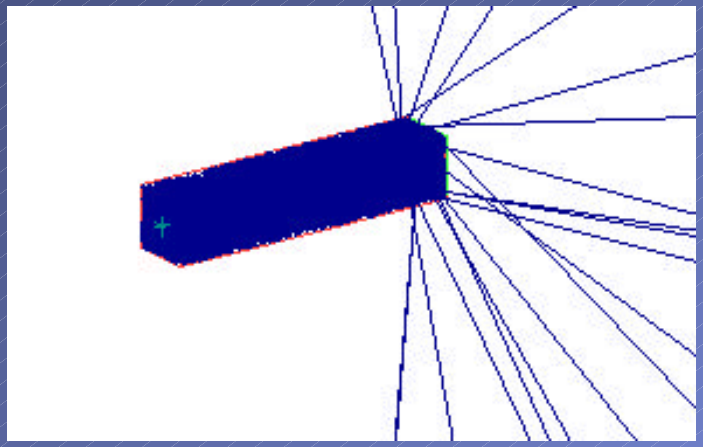
$\mathbf{d}_{noise}$ = Dark current noise



S.Stoll

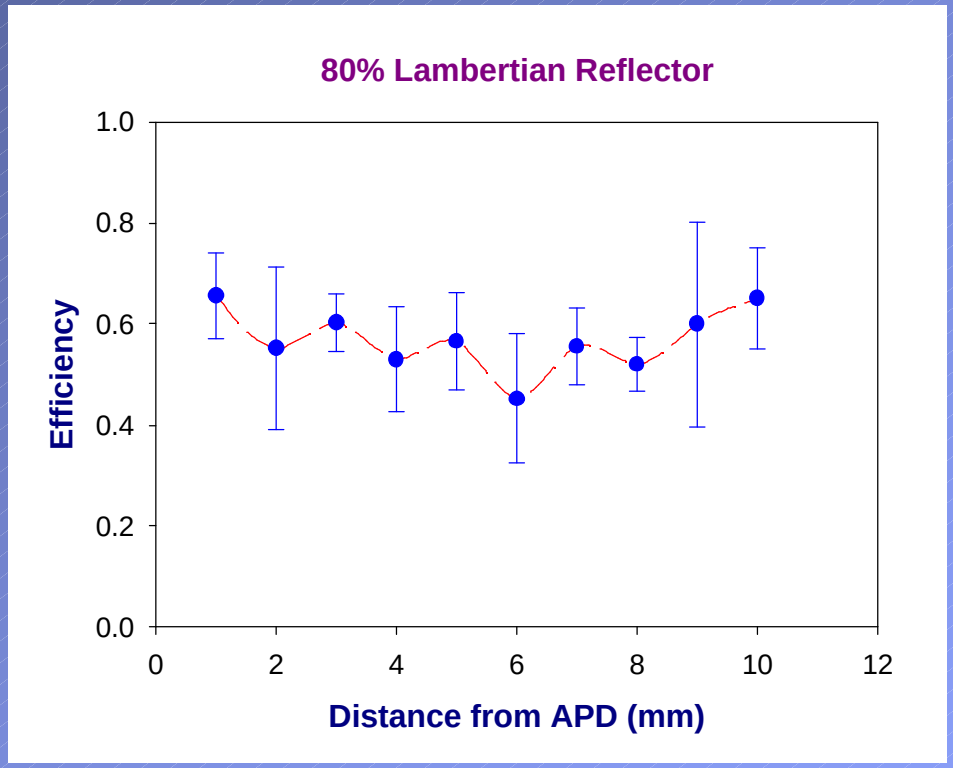
Monte Carlo Study of Light Collection

OPTICAD Program



Maximum light collection near ends of crystal

Very dependent on geometry and reflector properties



S.Shokouhi

Comparison of Light Output and Energy Resolution of Different Crystals

Average Light Output and Resolution of 4x8 LSO arrays

FWHM

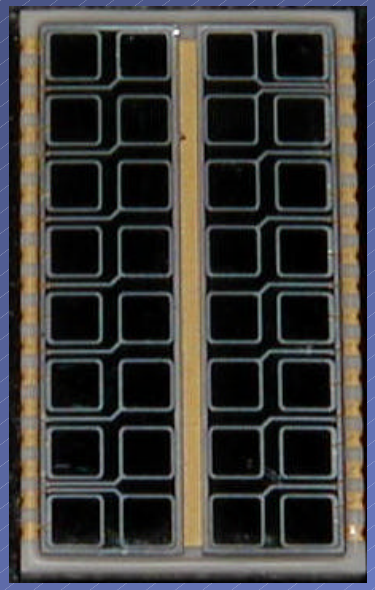
manufacturer	length		# meas.	pe/MeV	resolution
CTI	8mm	slotted block	3	2512	0.23
Proteus	5mm	glued	2	1402	0.18
3M Reflector	10mm	glued	2	2272	0.17
Proteus	5mm	not glued	1	2265	0.12
3M Reflector	10mm	not glued	1	2660	0.13

S.Stoll

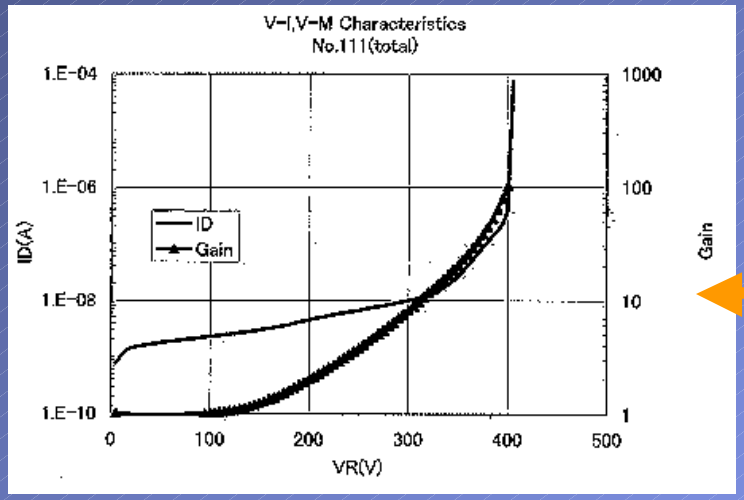
Conclusion: Crystals wrapped with 3M reflector and air gap give the highest light output and best energy resolution

Avalanche Photodiodes

Hamamatsu S8550



4x8 array
1.6 x 1.6 mm^2
active pixel area
C_T~ 10 pF



Improvements in Gain and Dark Current

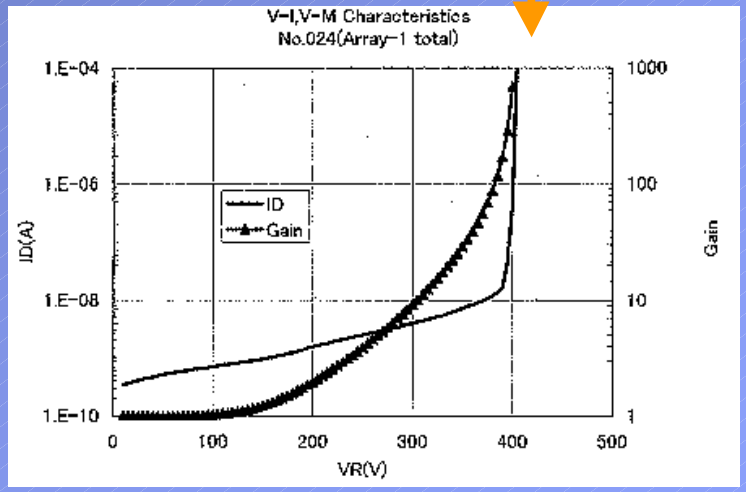
Jan '01

Jan '02

Typical G ~ 50
N_{pe} ~ 1200

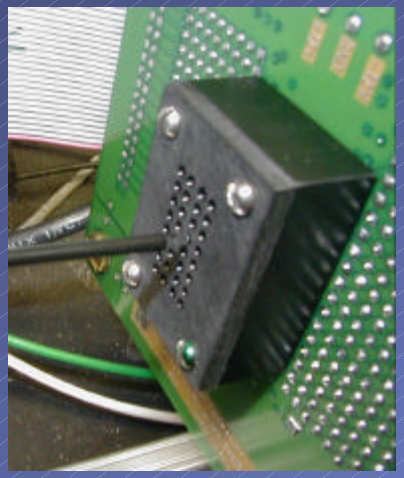
$\Rightarrow$ ~ 60K signal electrons

Expected noise in final ASIC
~ 500-600 e's



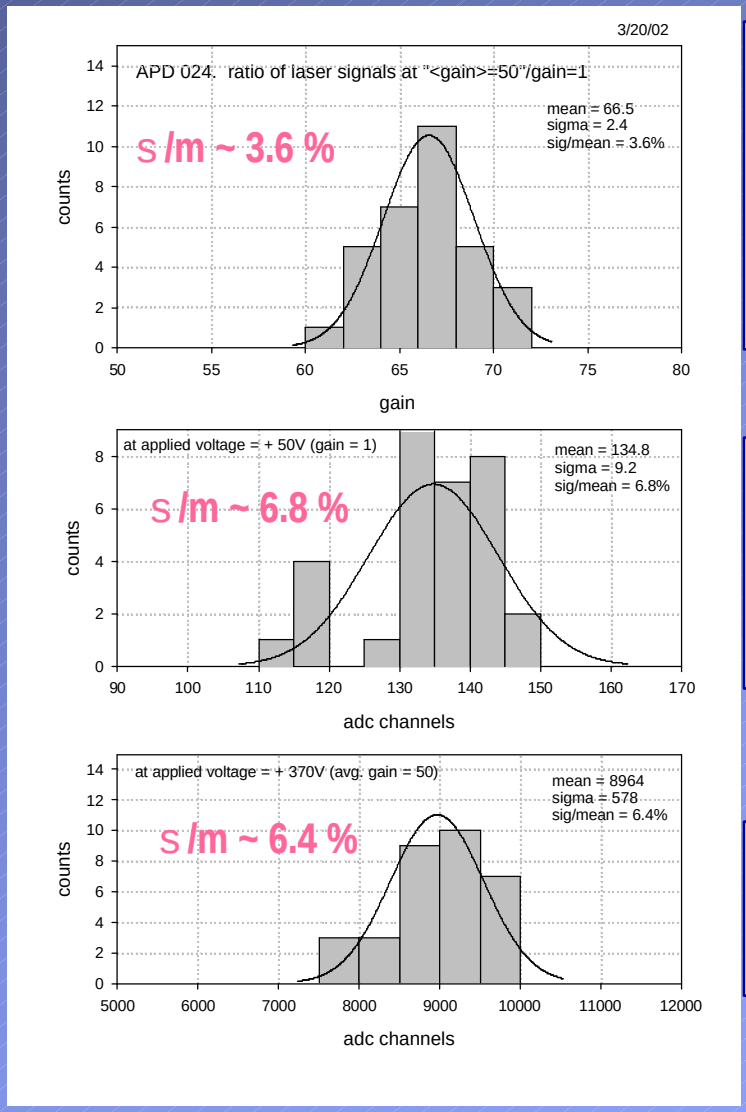
Gain and Quantum Efficiency Variation

Measured with N_2 laser + optical fiber



1.01	1.08	1.14	1.18
1.00	1.00	1.14	1.12
1.00	1.02	1.07	1.04
0.97	0.96	1.02	0.99
0.92	0.94	1.01	0.99
0.94	0.96	1.00	0.98
0.95	1.00	0.94	0.95
0.92	0.93	0.90	0.93

Channel to channel differences dominated by quantum efficiency variation



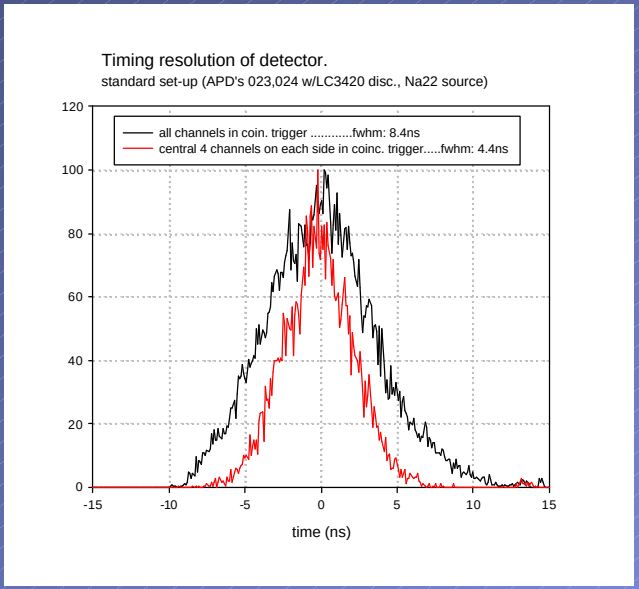
Channel to channel gain variation

Quantum efficiency variation

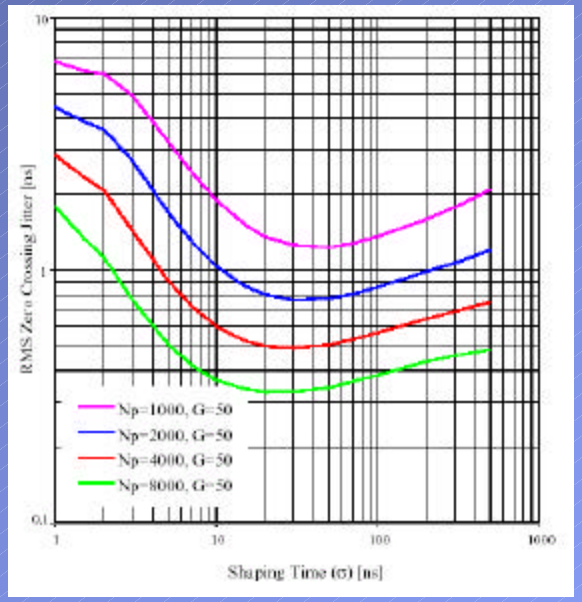
Gain + QE variation

Timing Resolution

Need good time resolution (~ few ns) for coincidence timing to reject singles background



S.Stoll



B.Yu

1 ns

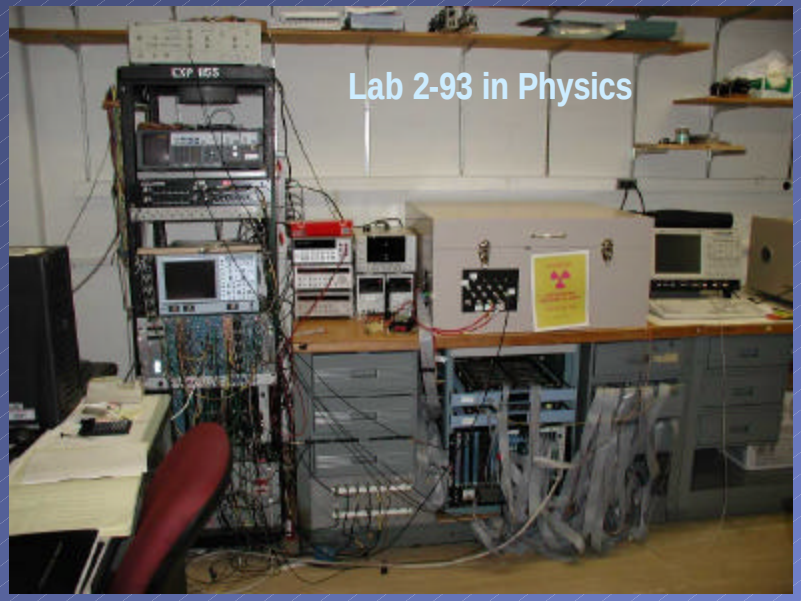
t ~ 70 ns

DT~ 5 ns fwhm

Presently dominated by noise in electronics setup

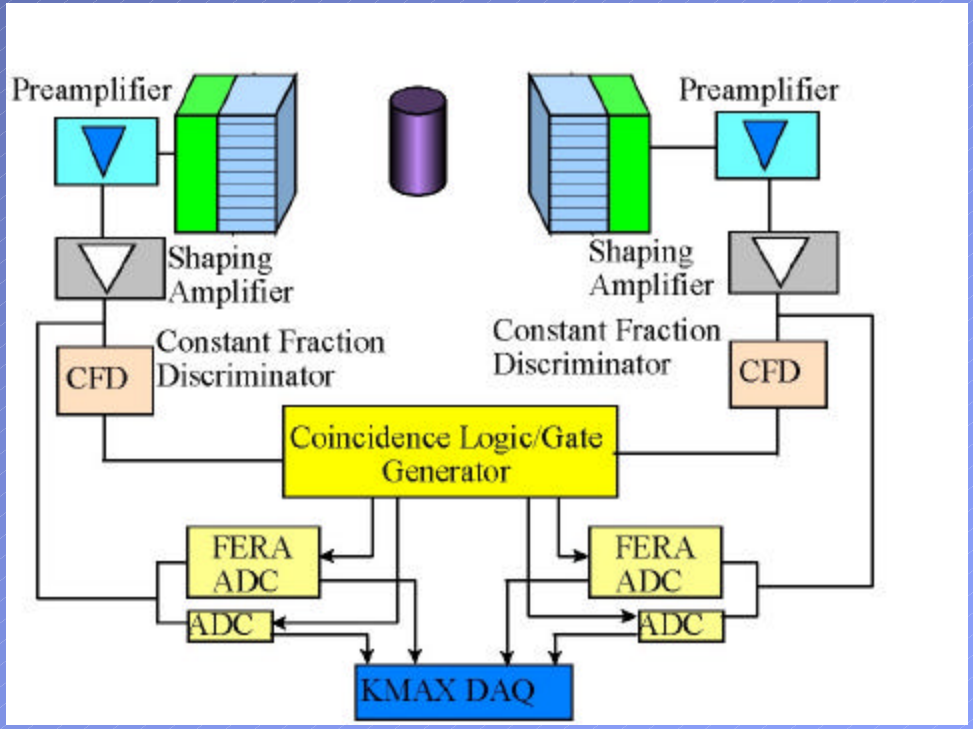
Expect time resolution to improve considerably with new ASIC

Test Setup with Crystal and APD Arrays

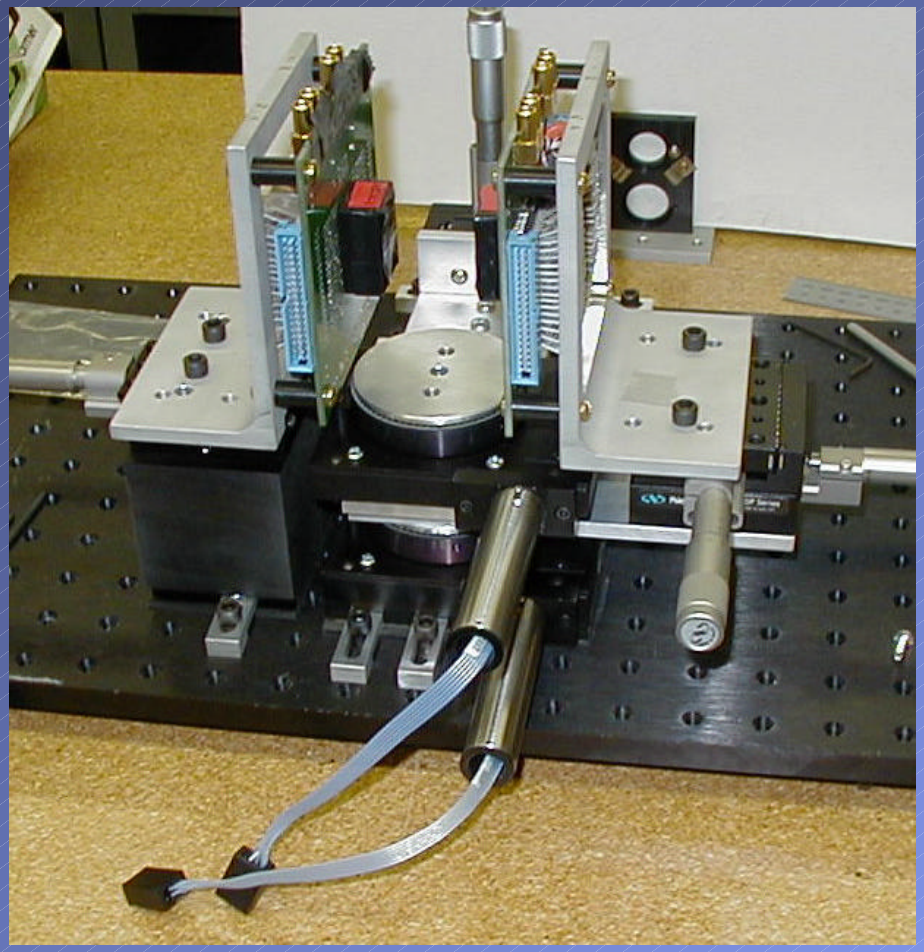


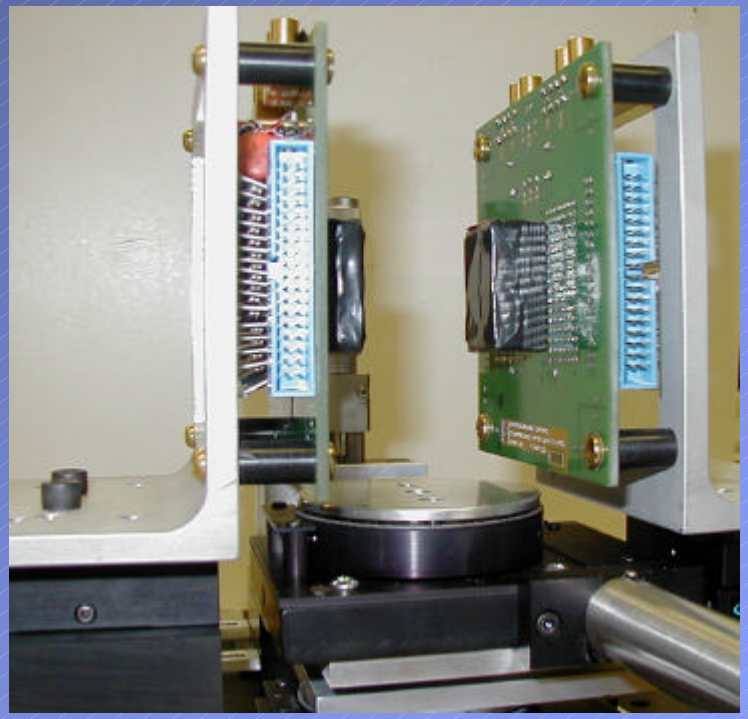
Challenge is to put all of this on a chip !

Two arrays of 4x8 APDs and crystals using hybrid preamps and shapers and CAMAC DAQ system



Rotatable Stage for Taking Tomographic Data



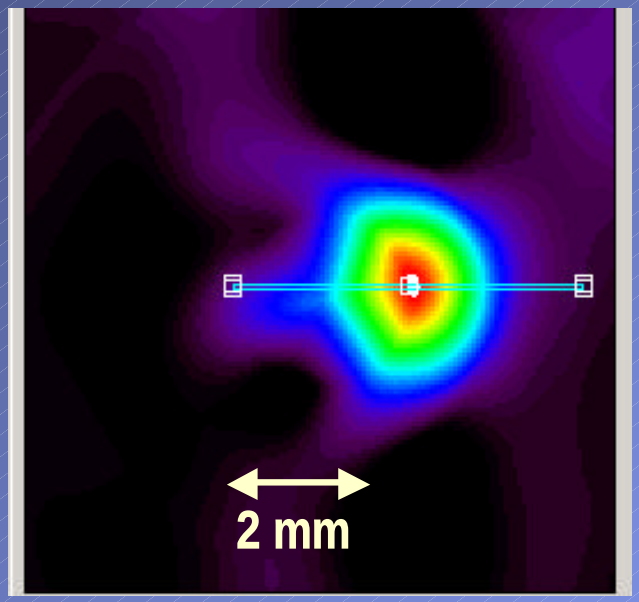


Source phantoms mounted on rotatable stage to simulate full tomographic ring

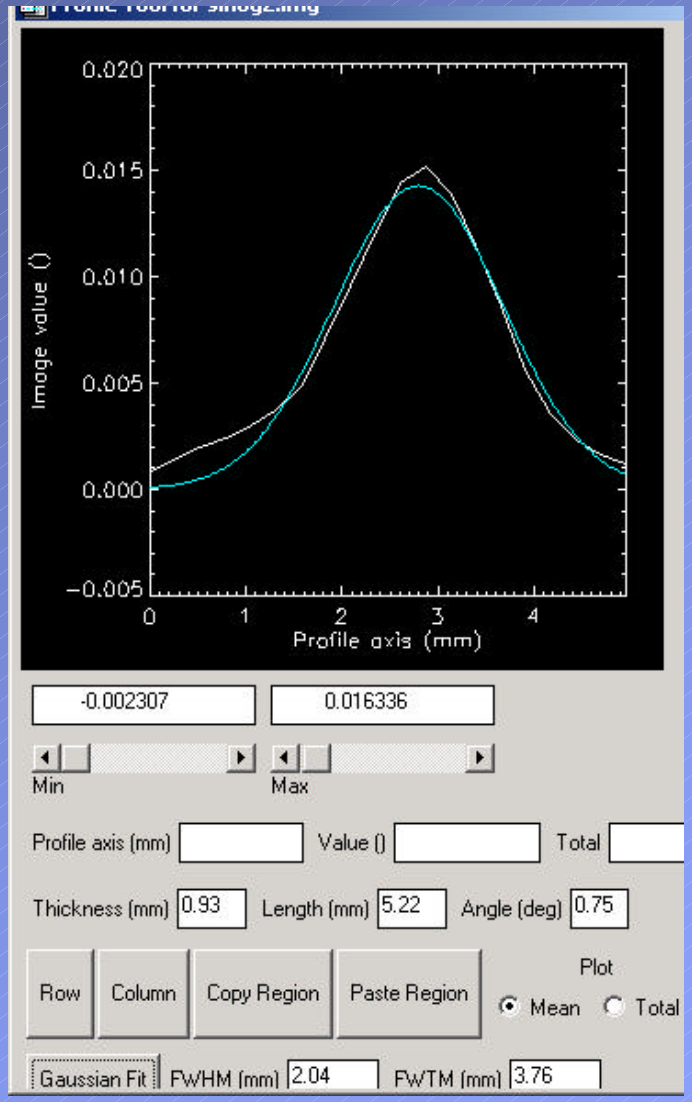
Tomographic Images

Measured with a ~2 mm diameter ^{68}Ge point source and two gamma coincidence

52 samples (6.9 degrees)



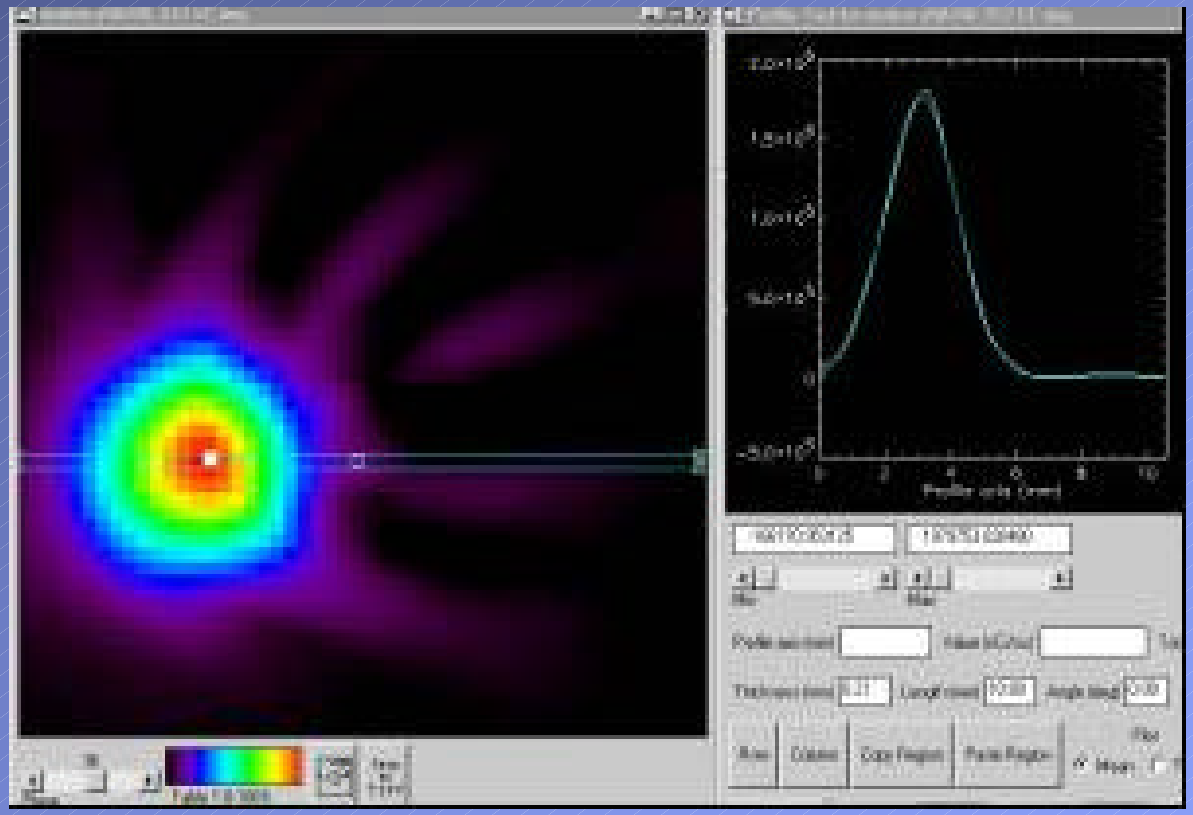
S.Shokouhi



Spatial resolution is 2.1 mm FWHM

Comparison with MicroPET

MicroPET resolution measured with the same ~ 2 mm point source



Spatial Resolution

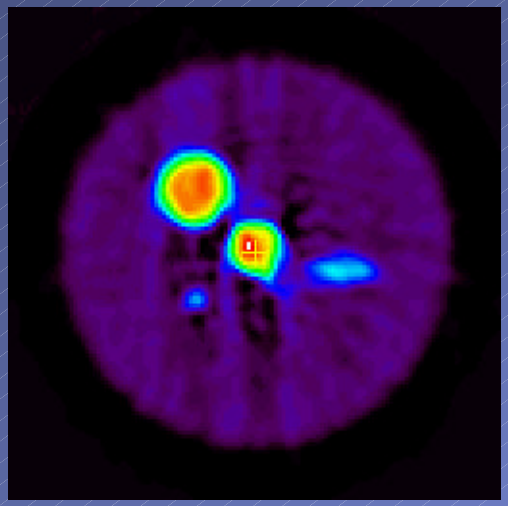
MicroPET ~ 2.7 mm

RatCAP ~ 2.1 mm

P.Vaska & S.Shokouhi

Modeled Reconstructed Images

Reconstruction Simulations using SimSet



Fully sampled image of four circular point sources

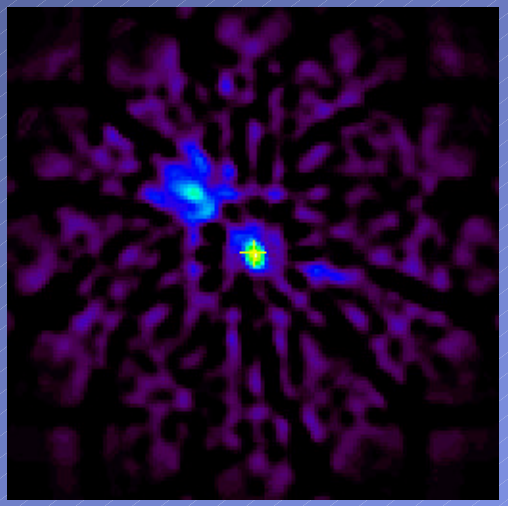


Image reconstructed using incomplete data set

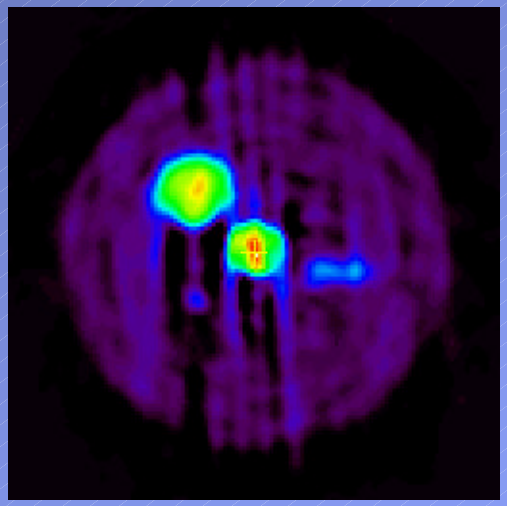
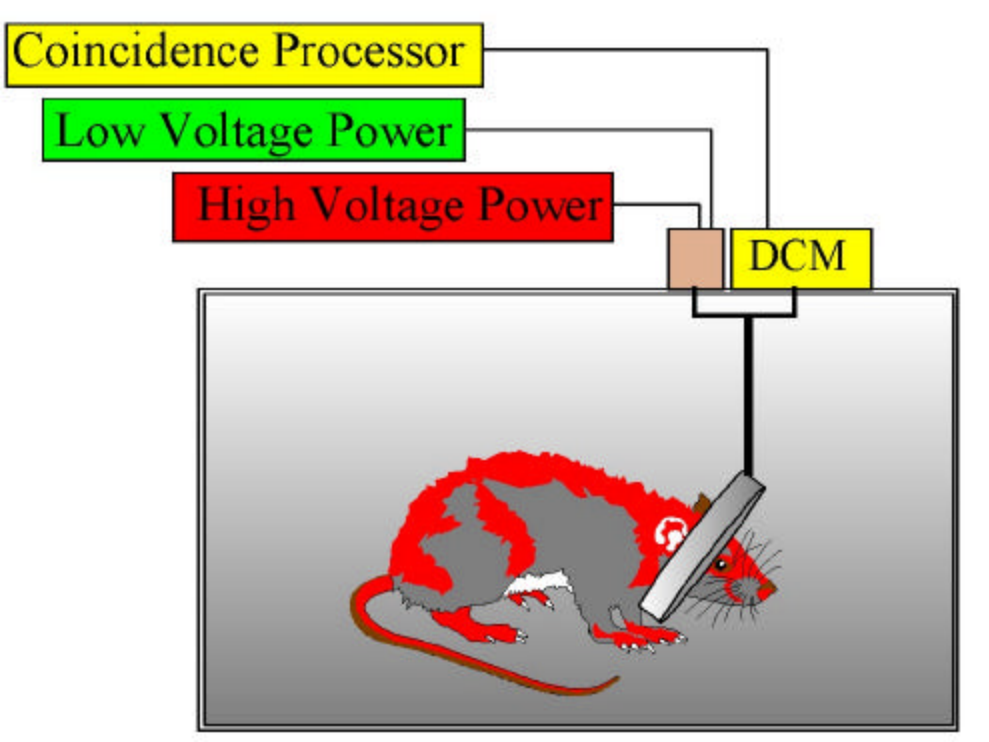


Image reconstructed using incomplete data set with interpolation

S.Shokouhi

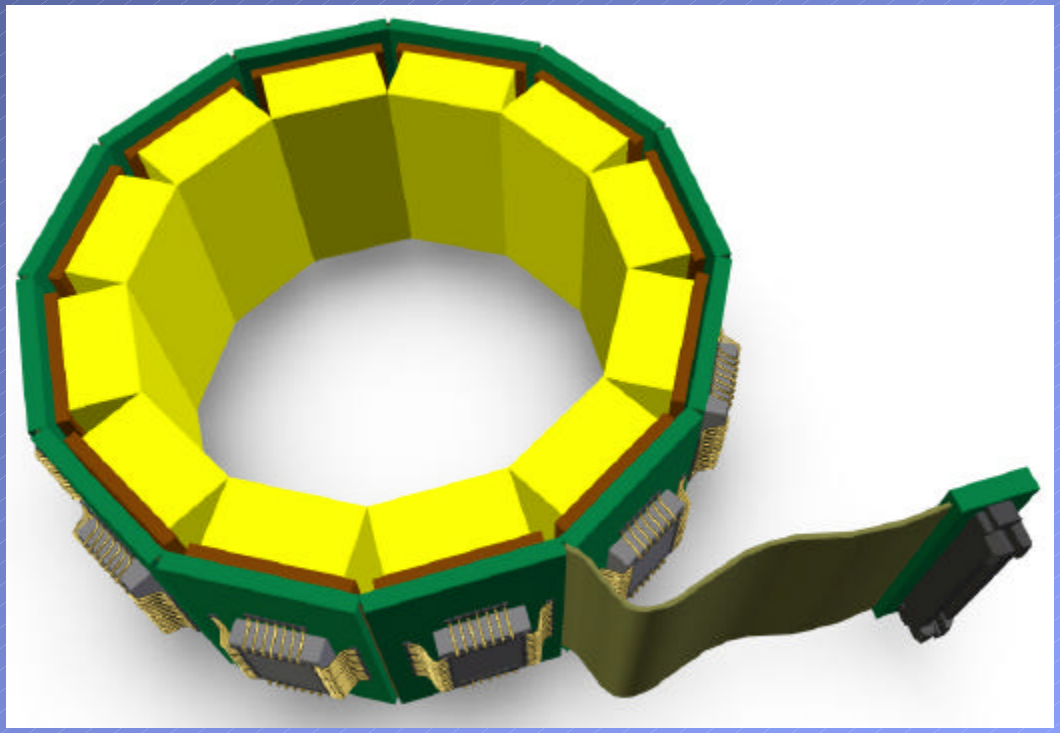
Electronics & Readout System

- Tomograph ring with detectors and front end readout electronics are mounted to the head of the rat
- Tether carries discriminator pulses, encoded addresses, high and low voltage power to a Data Collection Module which adds time stamp information



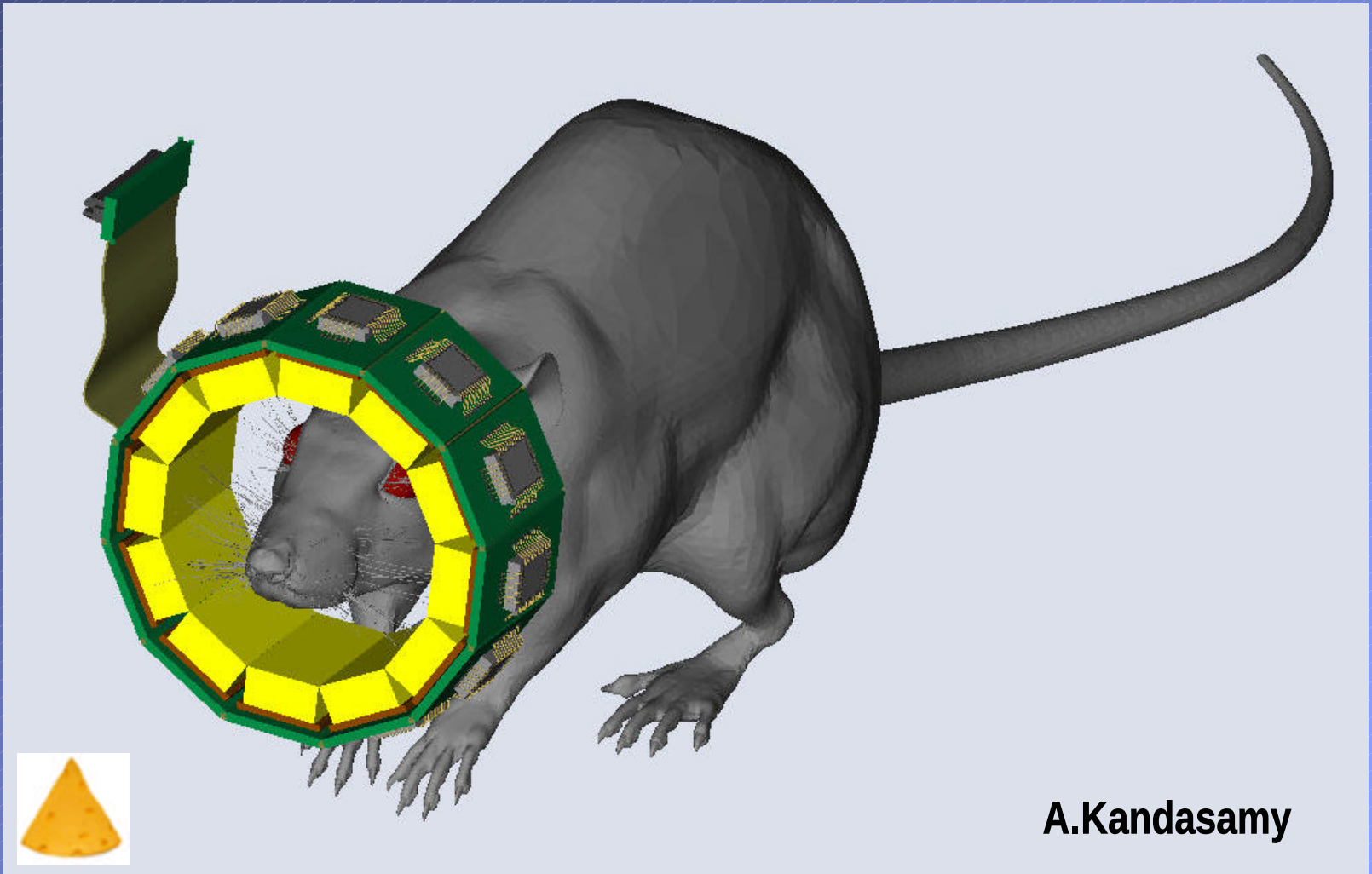
Tomograph Ring with Readout Electronics

LSO blocks, APDs and front end readout electronics will be mounted on a PCB / Multi Chip Module with interconnecting flexstrip cable



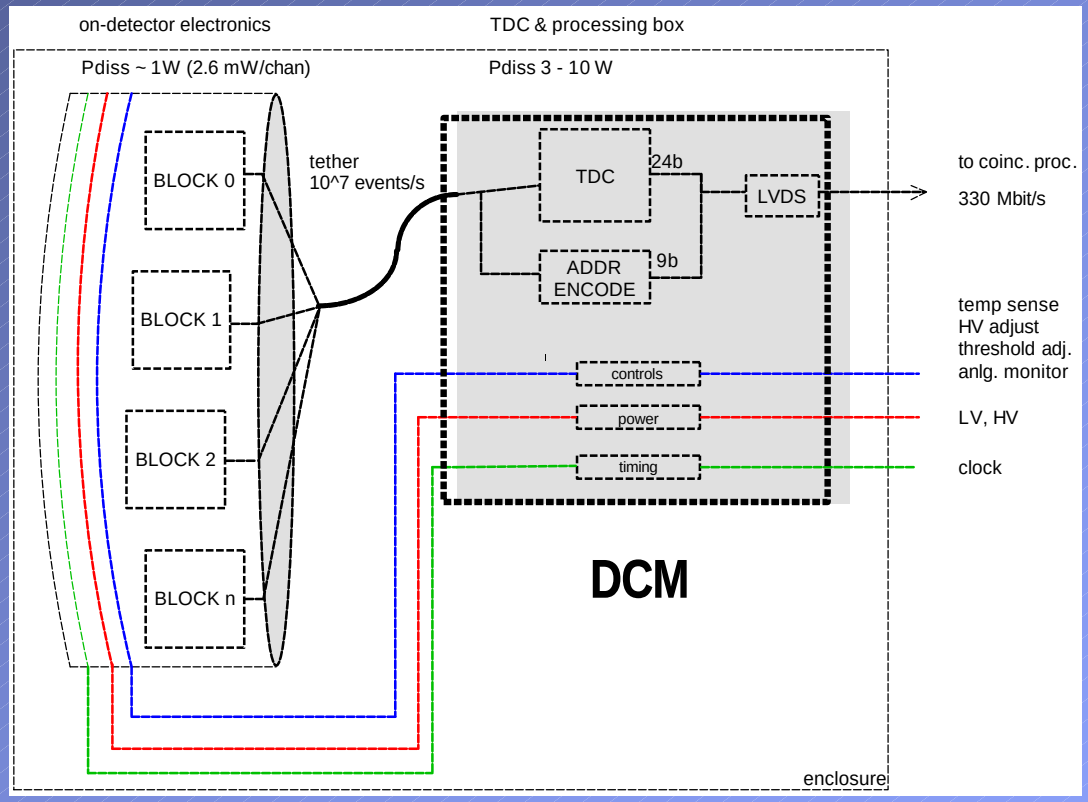
A.Kandasamy

So you want me to put my head in here ?....



Electronics + Readout System

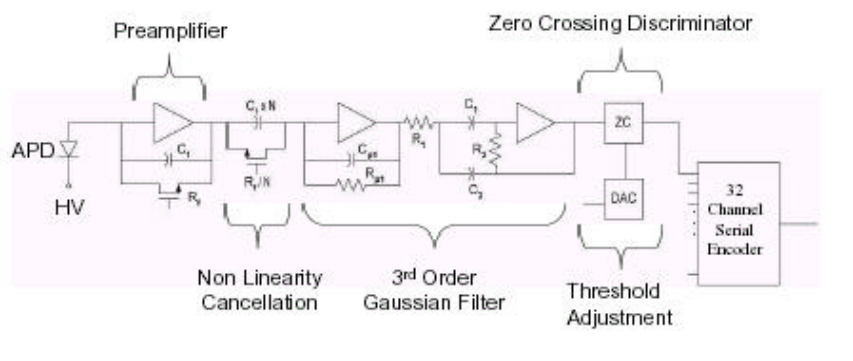
- No analog information
- Single ZCD per channel
- Serial transmission from on-block electronics to a Data Collection Module (DCM) at the top of the tether
- DCM adds time stamp to each event and sends address and time information to a remote coincidence processor
- Individual links from each block to DCM



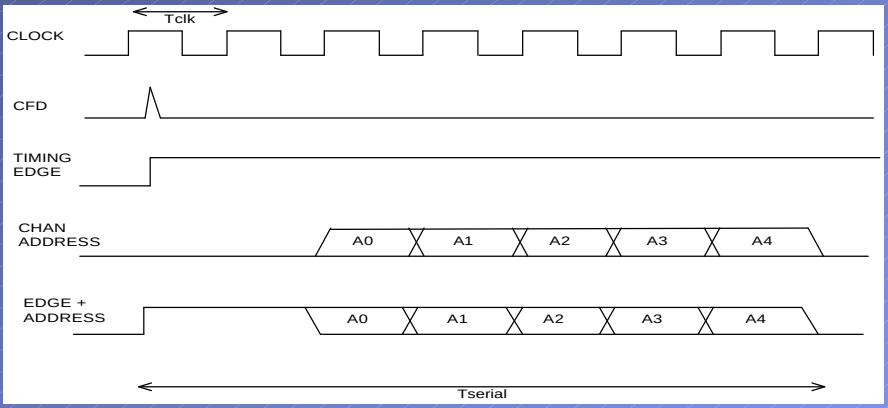
P.O'Connor

~1.5 watts total power on ring

Custom Front End Readout Chip



J-F. Pratte



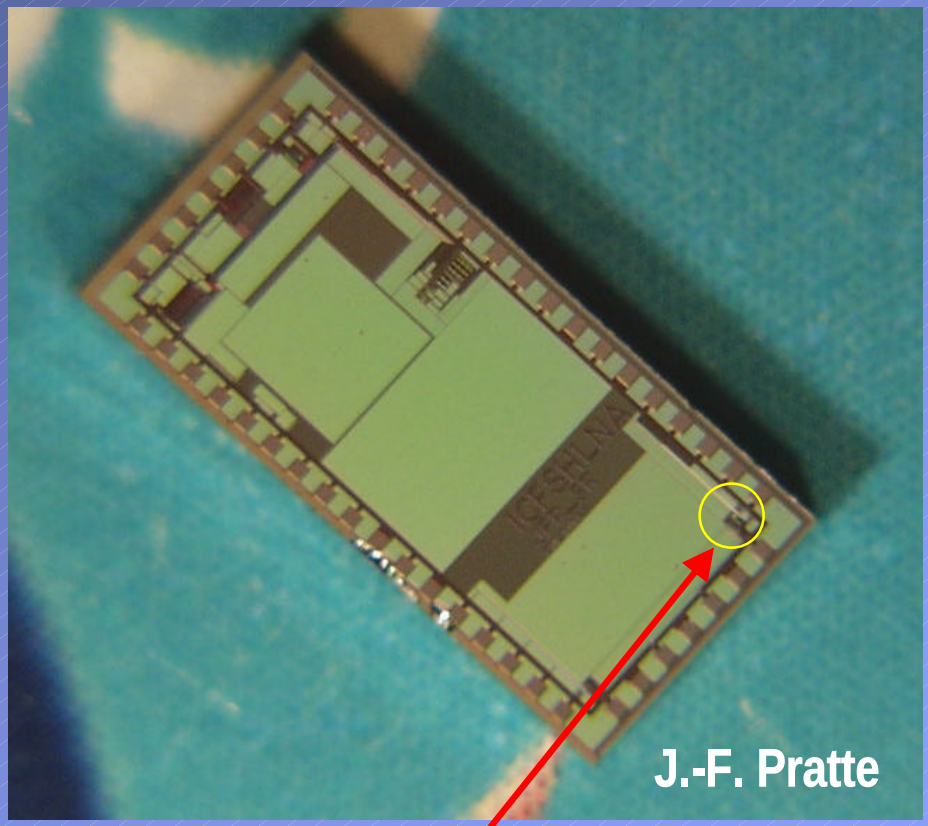
P.O'Connor

Custom ASIC in 0.18 μm CMOS gives ~ 4 mW per channel (~125 mW per chip)

- Discriminator pulse is encoded to give 5 bit address
- Leading edge of encoded serial pulse train gives time information

ASIC Production

- First test chip delivered Feb ‘03 and ready for testing
- 2nd version submitted Nov ‘02
- 3rd version to be submitted March ‘03
- Final version to be submitted fall ‘03



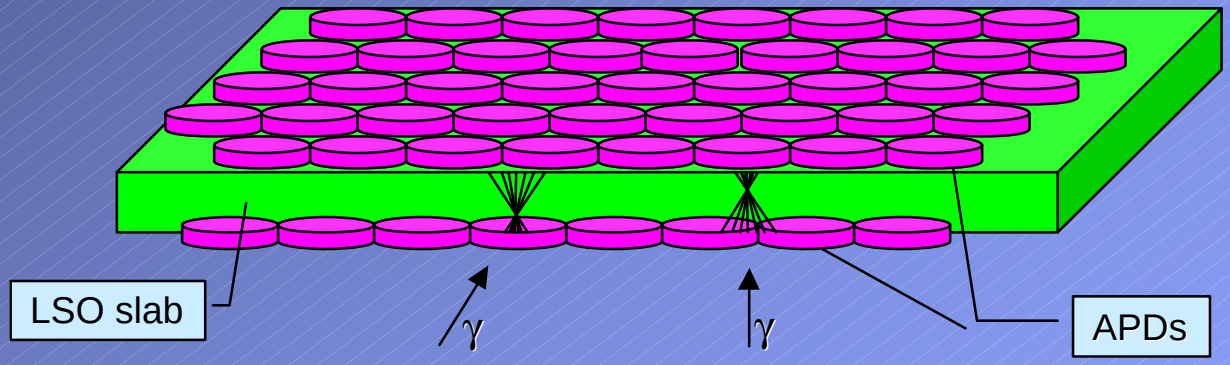
Preamp circuit is contained within the yellow circle

Final size will be ~ 4.3 x 1.6 mm

Alternative Approach: Light-sharing LSO/APD

P.Vaska

- LSO slab ~ 6 cm Ø, 10mm thick obtained from CTI
- Large Area APDs
  Requires low-noise
- Suppliers
  - Adv Phot, P-E, RMD
  - 3 RMD 8x8mm now in hand
- Currently: setting up to measure energy & transverse spatial resolution



The depth of interaction is determined directly without pixelating the crystals

Non-Invasive Wrist Monitor

- A wide range of quantitative PET studies using tracer kinetic modeling demand accurately measured radiotracer concentration in arterial blood as a function of time after injection, known as the Arterial Input Function.

- The common method of measuring the input function is the invasive withdrawal of blood from a wrist artery. However, because of its health risks for both patients and hospital personnel, it is not compatible with clinical studies.

- A small ring tomograph similar to the RatCAP can be used to image the artery and measure the input function

Wrist Anatomy

For human studies, the input function will be taken from the radial artery in the wrist.

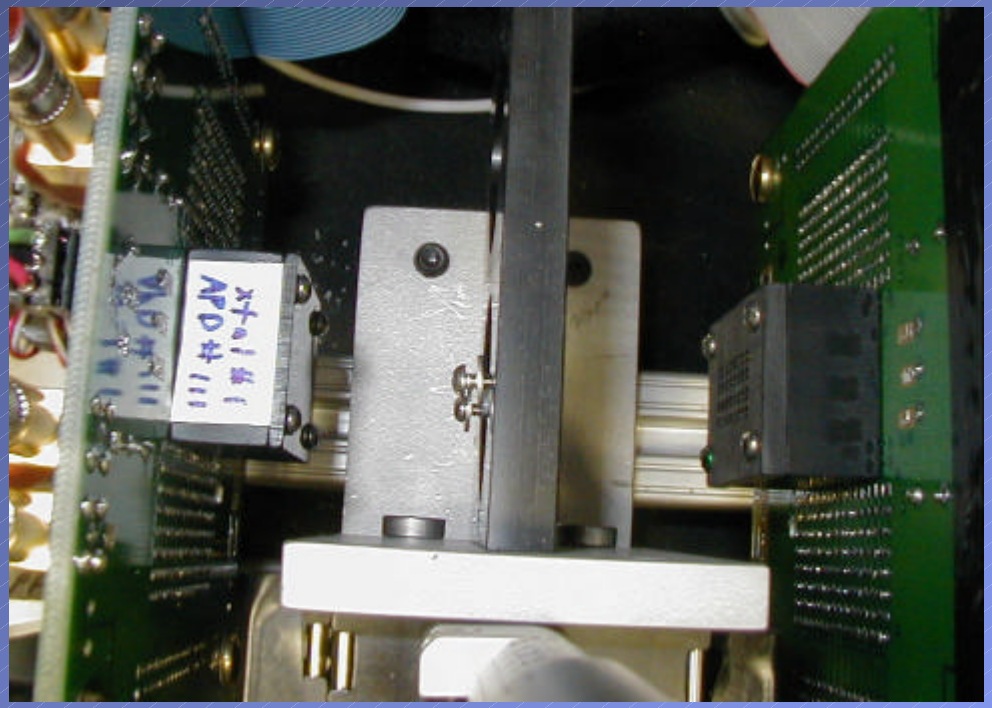
Activity in the surrounding veins produce a significant background which can be rejected using the good spatial resolution of the wrist monitor.

Phantom based on MRI images of the wrist with anatomically correct placement of the vessels

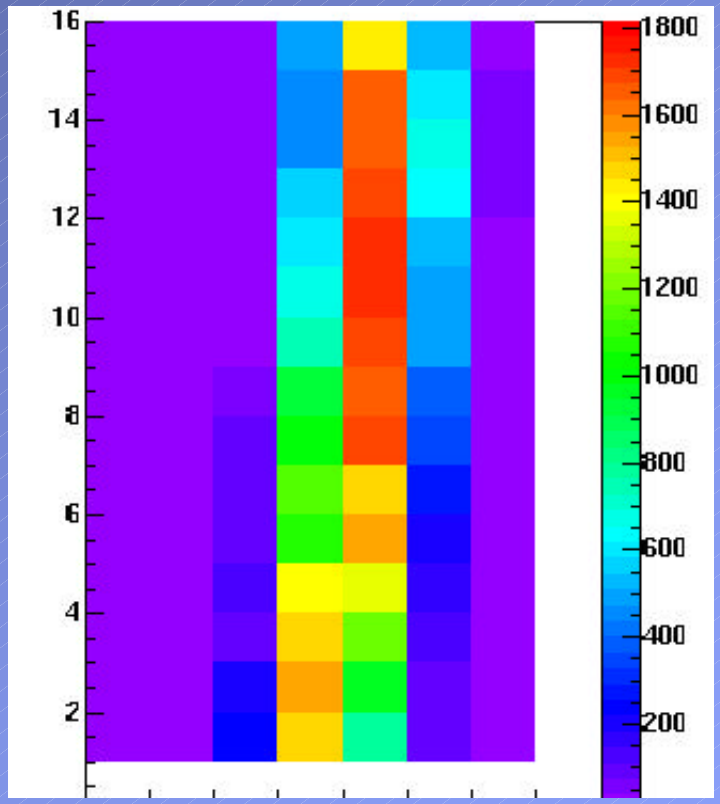
A.Villanueva

Planar Images

Measured with a 1 mm diameter ^{68}Ge line source and two gamma coincidence

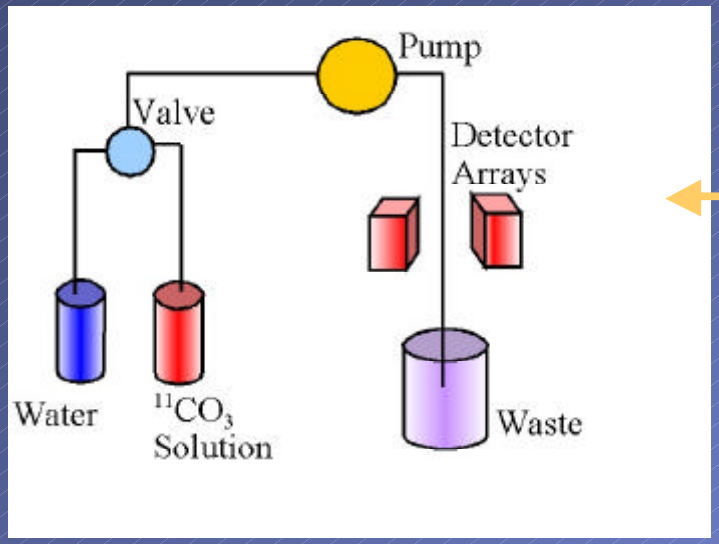


S.Shokouhi, 2002 MIC, submitted to IEEE TNS

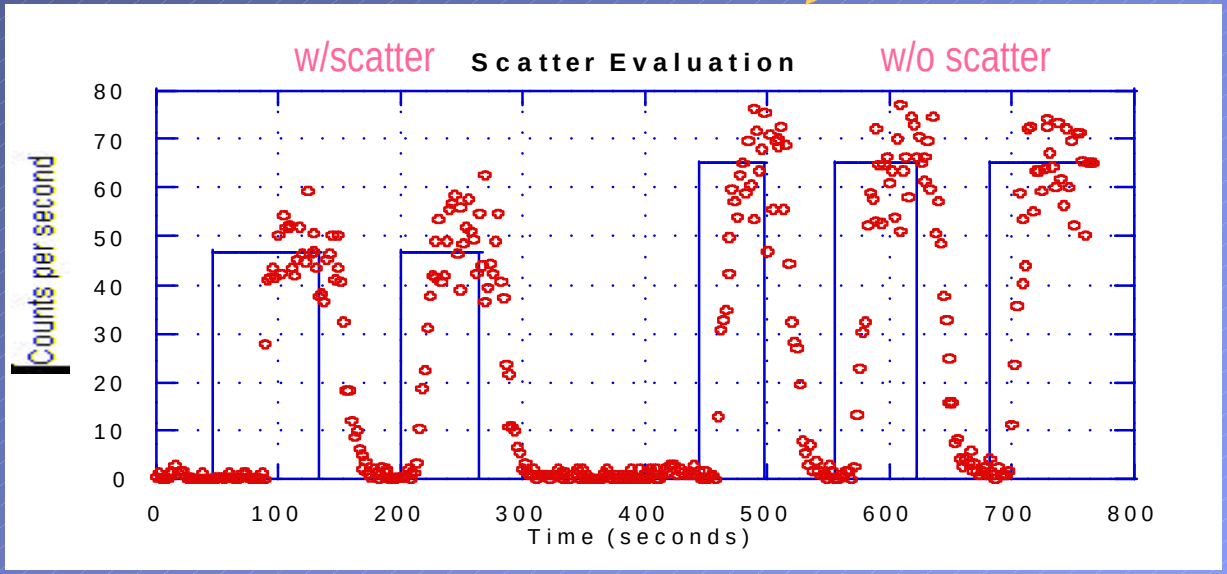


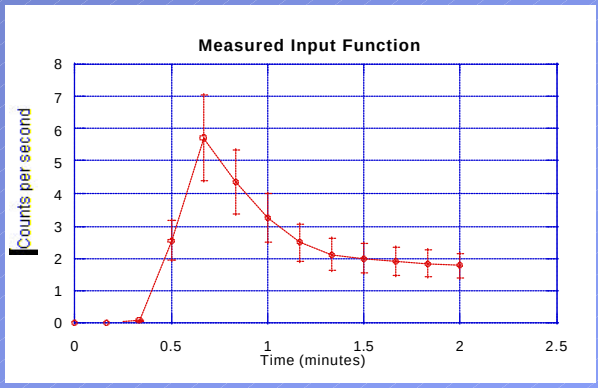
1 x 1 mm^2 pixels

Simulated Input Function Measurement



Measure activity as an aqueous solution of a ^{11}C - labeled radioisotope passes between the two block detectors





Expected Input Function resolution for Wrist Monitor

A.Villanueva

Beta Scintillation Microprobe

- Radioisotopes used in PET emit positrons with energies of a few hundred keV which have a range of several mm in blood or tissue. This range is comparable to the spatial resolution obtained in most PET cameras.

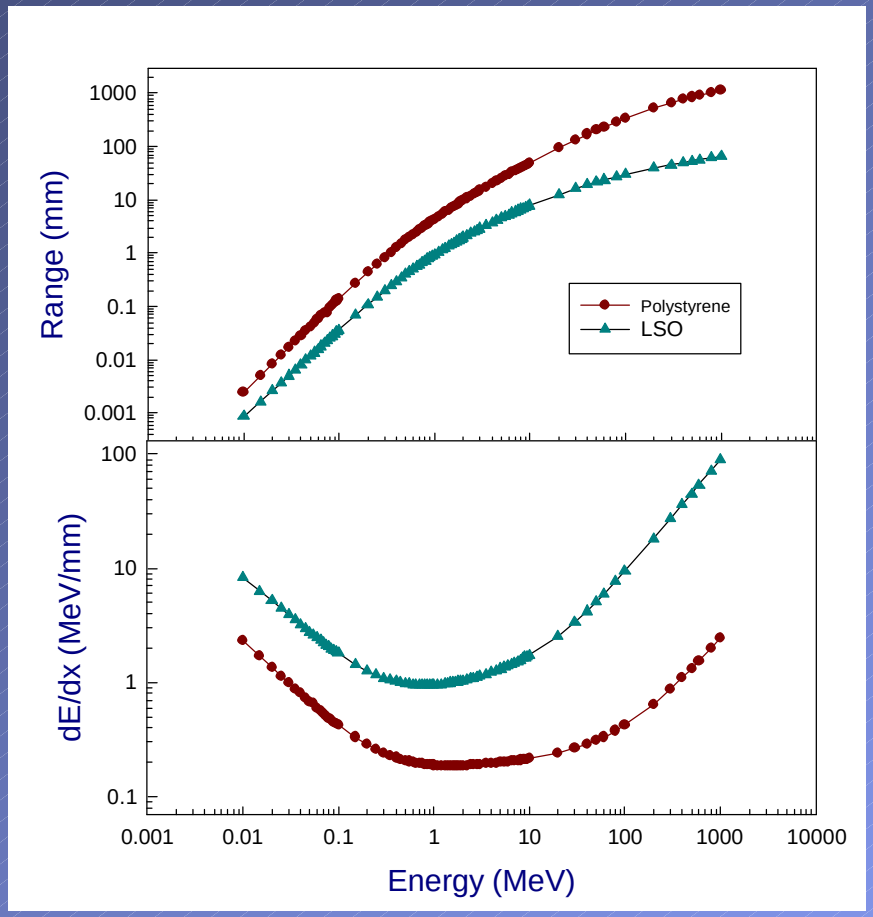
- These positrons can be detected directly using plastic or crystal scintillators. With crystal scintillators which have high density, the positrons will range out, depositing all of their energy in the crystal and producing a large signal.

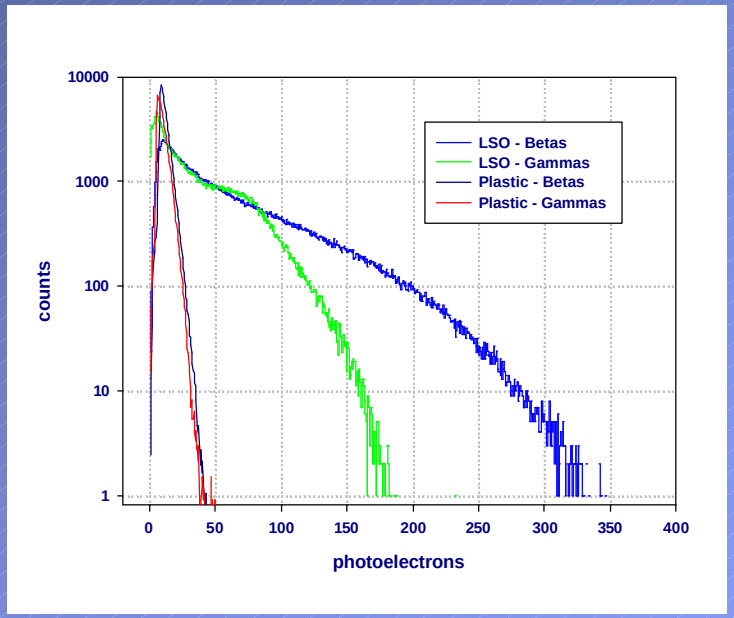
- Small scintillation probes can be used to directly measure the radiotracer concentration in the blood or tissue.

C.L.Woody et.al., IEEE Trans. Nucl. Sci NS-49 (2002) 2208-2212.

Comparison of LSO vs Plastic Scintillator

Range and energy loss of positrons in LSO and plastic scintillator

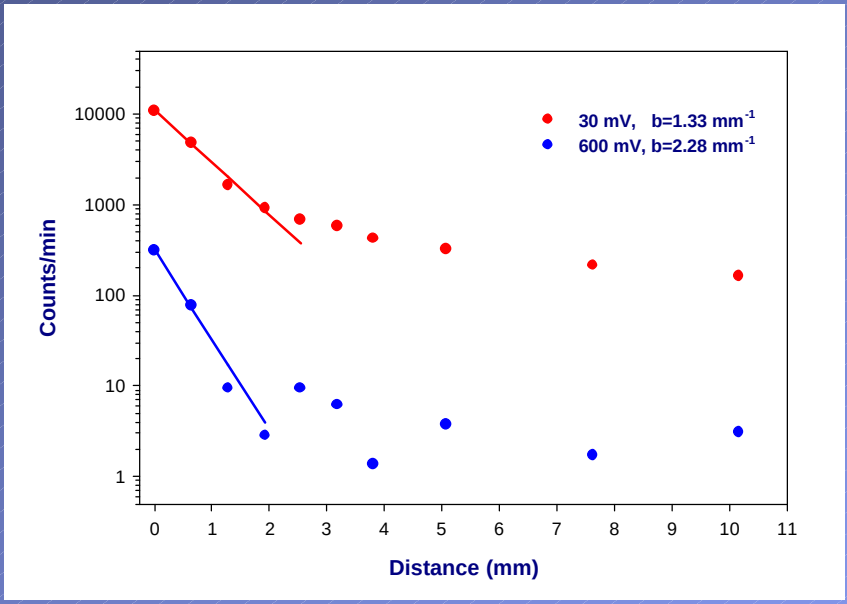




Response of LSO and plastic scintillation probes to betas (^{32}P) and gamma rays (^{137}Cs).

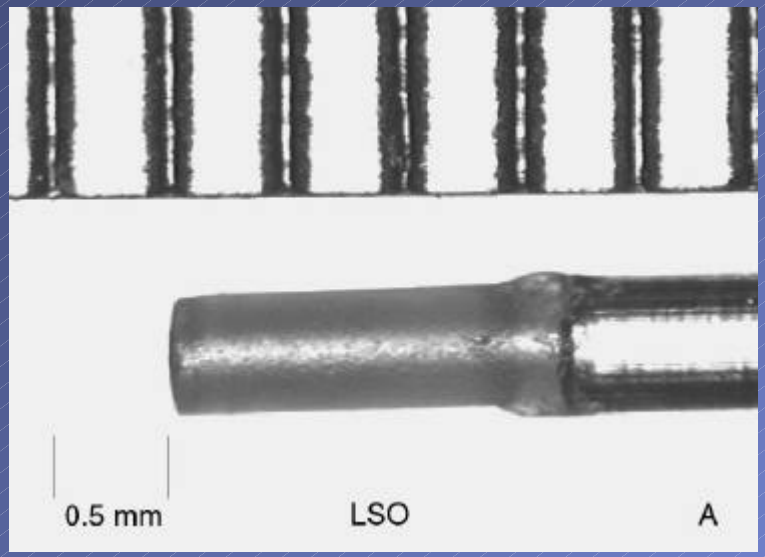
Sensitivity and Position Resolution

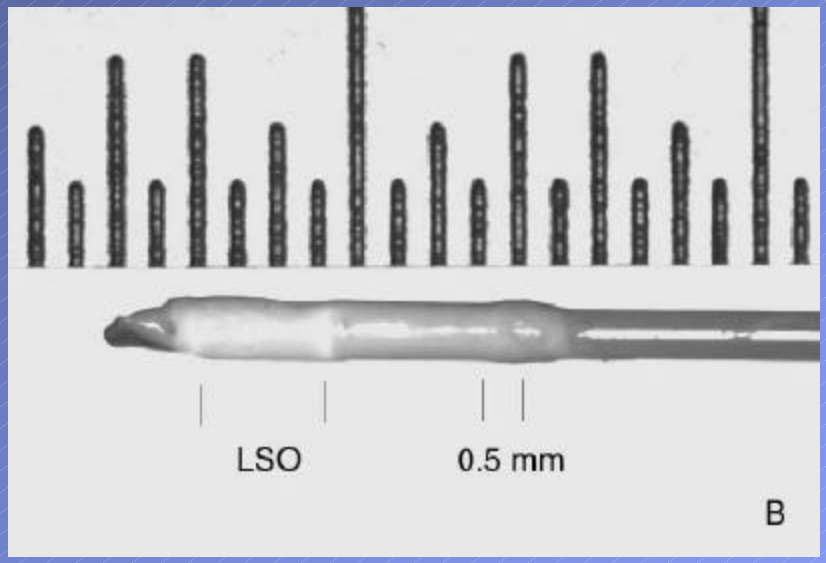
Material	LSO	LSO	Plastic
Size	0.3 x 0.5 mm	0.5 x 1.5 mm	1.0x1.0 mm
Volume	0.035 mm^3	0.295 mm^3	0.795 mm^3
Sensitivity (Hz/mCi/cc)	10.1	20.7	51.2



Region of sensitivity around the probe can be selected by adjusting the readout threshold to improve spatial resolution

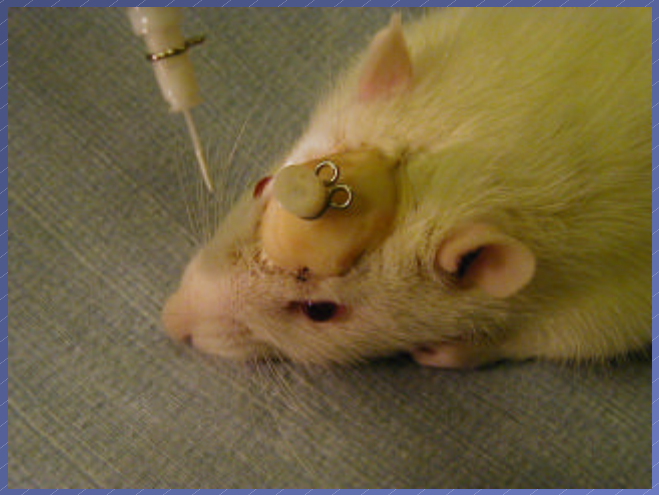
Probe Construction

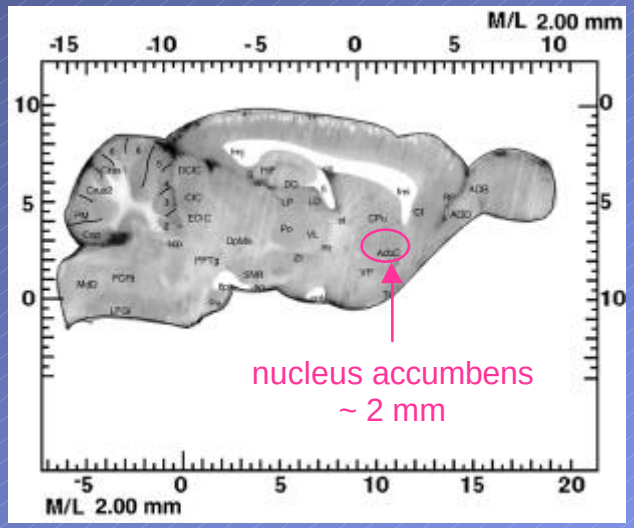


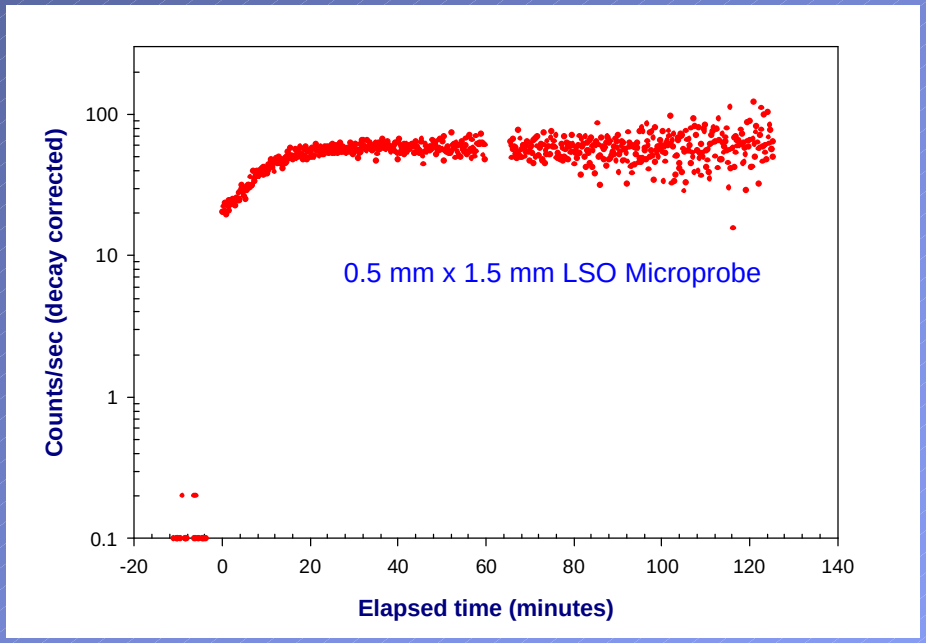


LSO microprobe consisting of 0.5 mm diameter x 1.5 mm long LSO crystal wrapped with several layers of white reflecting teflon and covered with polyester shrink tubing.

Rat Brain Studies with Microprobe

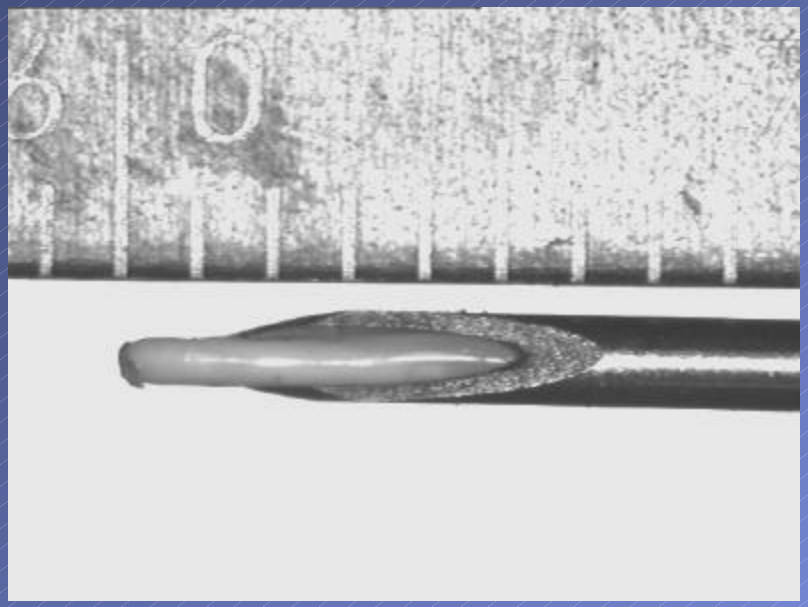


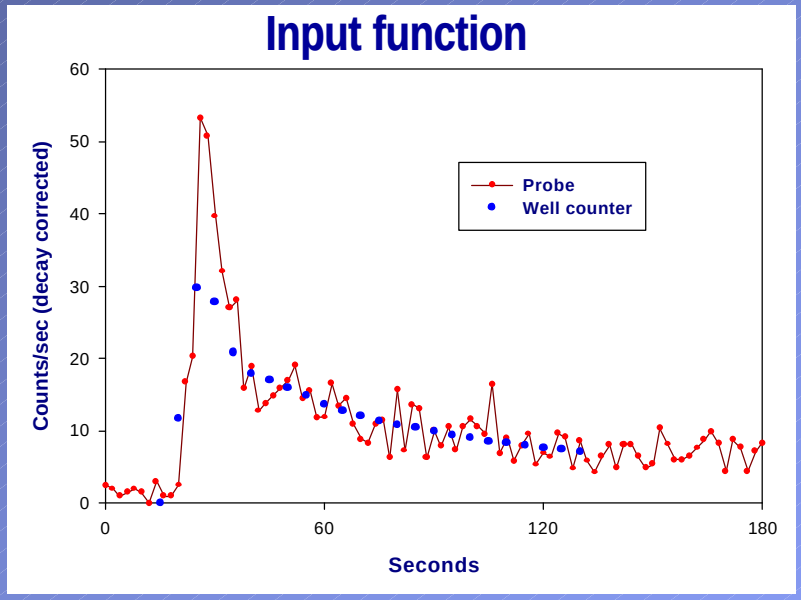




Uptake of ^{11}C-methylphenidate in the nucleus accumbens region of a rat brain with LSO probe

Input Function Measured with Microprobe





LSO microprobe (0.3 mm dia. x 0.5 mm) inserted inside an 18 gauge syringe needle for blood flow study.

Activity of ^{11}C-tyrosine measured in baboon blood flow during a PET scan using a syringe mounted LSO microprobe.

Summary

- New detectors are needed for PET studies of the neurological behavior in live, awake animals
- The RatCap will provide a new tool for carrying out these studies in laboratory rats.
- Similar small ring tomographs can be used to measure the arterial input function in larger animals and humans
- Small scintillation microprobes can be used to directly measure the positron activity in blood and tissue in live, awake animals with a spatial resolution comparable to or better than current PET tomographs

Backup slides

Energy Resolution

	Ei	Si	Wi	Ei*Wi	Si*Wi	Si/Ei	Wi*(Si/Ei)
1	0.656	0.0844	0.1629	0.1069	0.0138	0.1287	0.0210
2	0.552	0.1612	0.1468	0.0810	0.0237	0.2919	0.0429
3	0.602	0.0576	0.1314	0.0791	0.0076	0.0957	0.0126
4	0.530	0.1037	0.1123	0.0595	0.0116	0.1956	0.0220
5	0.566	0.0963	0.0990	0.0560	0.0095	0.1702	0.0168
6	0.452	0.1279	0.0865	0.0391	0.0111	0.2831	0.0245
7	0.556	0.0764	0.0786	0.0437	0.0060	0.1373	0.0108
8	0.520	0.0529	0.0676	0.0352	0.0036	0.1018	0.0069
9	0.600	0.2026	0.0607	0.0364	0.0123	0.3377	0.0205
10	0.650	0.0995	0.0541	0.0352	0.0054	0.1531	0.0083
SUM	5.684	1.063	1.000	0.572	0.104	1.895	0.1862
AVG	0.568	0.1063	0.1000	0.0572	0.0104	0.1895	0.0186

Weighted <Ei> =		0.572	
Weighted <Si> =		0.105	
Weighted <Si>/<Ei> =		0.183	
Avg weighted <Si/Ei> =		0.186	

Npe + ENF of APD			
	Npe/MeV	2400	
	Npe	1200	
	D(Npe)/Npe	0.029	
	F(=2)*D(Npe)/Npe	0.041	
Noise			
	Ne(noise) RMS	3000	
	Ne(signal), G=50	60000	
	Noise/signal	0.050	
Npe+Noise		0.065	
Measured (662 keV)		0.075	
Remainder (Intrinsic + Light Collection)		0.038	

Neurochemistry 101

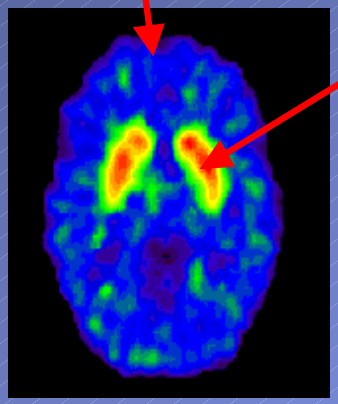
MonoAmineOxydase-B (outside neuron)
Deprenyl given to increase MOA-B

MonoAmineOxydase-A (inside neuron)

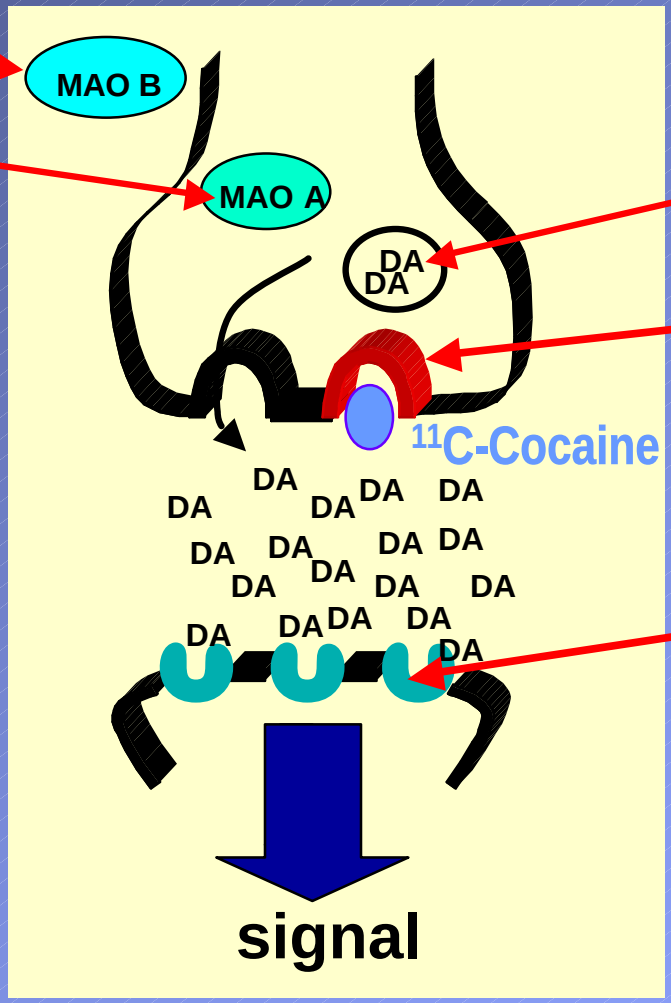
Both MOA- A,B consume dopamine

Methylphenadate (MP) = Ritalin

Ceretonin (neurrotransmitter)
Present in frontal corrtex (Cerebellum)



Striata
High Dopamine concentration
Raclopride concentrates at D2 receptor sites



Vesicules containing dopamine

Dopamine transporters (re-uptake sites) (Cocaine, MP)

Dopamine receptors (raclopride) Only few % receptor sites occupied

The Human Brain