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

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

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-Life</th>
<th>Decay Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbon-11</td>
<td>20.4 min</td>
<td>boron-11</td>
</tr>
<tr>
<td>fluorine-18</td>
<td>110 min</td>
<td>oxygen-18</td>
</tr>
<tr>
<td>nitrogen-13</td>
<td>10 min</td>
<td>carbon-13</td>
</tr>
<tr>
<td>oxygen-15</td>
<td>2 min</td>
<td>nitrogen-15</td>
</tr>
</tbody>
</table>

Tracers can be used to study 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

The effect of anesthesia on the uptake of $\beta$-CFT on dopamine transporters in the monkey brain.

Reduction in glucose metabolism with isoflurane in humans

Similar effects are seen in the rat

H. Hideo et al., Synapse 42 (2001) 273-280
RatCAP: Rat Conscious 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

Part of a larger project for Imaging The Awake Animal also involving motion tracking in both PET and MRI
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
  ⇒ 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
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 mm² LSO crystals read out with APD arrays
Comparison of sensitivity with other small animal PET scanners

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

Calculated Image Spatial Resolution of BNL nanoPET

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

P.Vaska
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

CTI white powder reflector

Proteus bonded 3M reflector

Proteus glued 3M reflector
Contributions to Energy Resolution

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

\(\Delta E\) = \text{Energy resolution}

\(N_{sc}\) = Number of scintillation photons produced

\(N_{col}\) = Number of photons collected

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

\(\delta_{noise}\) = Dark current noise

137Cs 662 keV g

S/lm ~ 7.5%
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

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Length</th>
<th>Type</th>
<th># Meas.</th>
<th>pe/MeV</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTI</td>
<td>8mm</td>
<td>slotted block</td>
<td>3</td>
<td>2512</td>
<td>0.23</td>
</tr>
<tr>
<td>Proteus</td>
<td>5mm</td>
<td>glued</td>
<td>2</td>
<td>1402</td>
<td>0.18</td>
</tr>
<tr>
<td>Proteus</td>
<td>5mm</td>
<td>not glued</td>
<td>1</td>
<td>2265</td>
<td>0.12</td>
</tr>
<tr>
<td>3M Reflector</td>
<td>10mm</td>
<td>glued</td>
<td>2</td>
<td>2272</td>
<td>0.17</td>
</tr>
<tr>
<td>3M Reflector</td>
<td>10mm</td>
<td>not glued</td>
<td>1</td>
<td>2660</td>
<td>0.13</td>
</tr>
</tbody>
</table>

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

S. Stoll
Avalanche Photodiodes

Hamamatsu S8550

4x8 array
1.6 x 1.6 mm²
active pixel area
$C_T \sim 10$ pF

Typical $G \sim 50$
$N_{pe} \sim 1200$
$\Rightarrow \sim 60K$ signal electrons
Expected noise in final ASIC
$\sim 500-600$ e’s

Improvements in Gain and Dark Current
Jan ‘01
Jan ‘02
Gain and Quantum Efficiency Variation

Measured with N\textsubscript{2} laser + optical fiber

Channel to channel differences dominated by quantum efficiency variation

Gain + QE variation

Quantum efficiency variation

Channel to channel gain variation

S.Stoll
Timing Resolution

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

DT ~ 5 ns fwhm
Presently dominated by noise in electronics setup

Expect time resolution to improve considerably with new ASIC

S. Stoll

B. Yu
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)

Spatial resolution is 2.1 mm FWHM

S. Shokouhi
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

S. Shokouhi

Image reconstructed using incomplete data set

Image reconstructed using incomplete data set with interpolation
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.
LSO blocks, APDs and front end readout electronics will be mounted on a PCB / Multi Chip Module with interconnecting flexstrip cable
So you want me to put my head in here?....

A. Kandasamy
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

~1.5 watts total power on ring
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

- 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
Simulated Input Function Measurement

Measure activity as an aqueous solution of a $^{11}\text{C}$-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.

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

<table>
<thead>
<tr>
<th>Material</th>
<th>Size</th>
<th>Volume</th>
<th>Sensitivity (Hz/mCi/cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSO</td>
<td>0.3 x 0.5 mm</td>
<td>0.035 mm³</td>
<td>10.1</td>
</tr>
<tr>
<td>LSO</td>
<td>0.5 x 1.5 mm</td>
<td>0.295 mm³</td>
<td>20.7</td>
</tr>
<tr>
<td>Plastic</td>
<td>1.0 x 1.0 mm</td>
<td>0.795 mm³</td>
<td>51.2</td>
</tr>
</tbody>
</table>

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

![Graph showing counts per minute vs. distance](chart.png)
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
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

<table>
<thead>
<tr>
<th></th>
<th>Ei</th>
<th>Si</th>
<th>Wi</th>
<th>Ei*Wi</th>
<th>Si*Wi</th>
<th>Si/Ei</th>
<th>Wi*(Si/Ei)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.656</td>
<td>0.0844</td>
<td>0.1629</td>
<td>0.1069</td>
<td>0.0138</td>
<td>0.1287</td>
<td>0.0210</td>
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<tr>
<td>2</td>
<td>0.552</td>
<td>0.1612</td>
<td>0.1468</td>
<td>0.0810</td>
<td>0.0237</td>
<td>0.2919</td>
<td>0.0429</td>
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<tr>
<td>3</td>
<td>0.602</td>
<td>0.0576</td>
<td>0.1314</td>
<td>0.0791</td>
<td>0.0076</td>
<td>0.0957</td>
<td>0.0126</td>
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<tr>
<td>4</td>
<td>0.530</td>
<td>0.1037</td>
<td>0.1123</td>
<td>0.0595</td>
<td>0.0116</td>
<td>0.1956</td>
<td>0.0220</td>
</tr>
<tr>
<td>5</td>
<td>0.566</td>
<td>0.0963</td>
<td>0.0990</td>
<td>0.0560</td>
<td>0.0095</td>
<td>0.1702</td>
<td>0.0168</td>
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<tr>
<td>6</td>
<td>0.452</td>
<td>0.1279</td>
<td>0.0865</td>
<td>0.0391</td>
<td>0.0111</td>
<td>0.2831</td>
<td>0.0245</td>
</tr>
<tr>
<td>7</td>
<td>0.556</td>
<td>0.0764</td>
<td>0.0786</td>
<td>0.0437</td>
<td>0.0060</td>
<td>0.1373</td>
<td>0.0108</td>
</tr>
<tr>
<td>8</td>
<td>0.520</td>
<td>0.0529</td>
<td>0.0676</td>
<td>0.0352</td>
<td>0.0036</td>
<td>0.1018</td>
<td>0.0069</td>
</tr>
<tr>
<td>9</td>
<td>0.600</td>
<td>0.2026</td>
<td>0.0607</td>
<td>0.0364</td>
<td>0.0123</td>
<td>0.3377</td>
<td>0.0205</td>
</tr>
<tr>
<td>10</td>
<td>0.650</td>
<td>0.0959</td>
<td>0.0541</td>
<td>0.0352</td>
<td>0.0054</td>
<td>0.1531</td>
<td>0.0083</td>
</tr>
<tr>
<td>SUM</td>
<td>5.684</td>
<td>1.063</td>
<td>1.000</td>
<td>0.572</td>
<td>0.104</td>
<td>1.895</td>
<td>0.1862</td>
</tr>
<tr>
<td>AVG</td>
<td>0.568</td>
<td>0.1063</td>
<td>0.1000</td>
<td>0.0572</td>
<td>0.0104</td>
<td>0.1895</td>
<td>0.0186</td>
</tr>
</tbody>
</table>

- Weighted $<E_i> = 0.572$
- Weighted $<S_i> = 0.105$
- Weighted $<S_i>/<E_i> = 0.183$
- Avg weighted $<S_i/E_i> = 0.186$

- 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
Cerotonin (neurotransmitter)
Present in frontal cortex (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