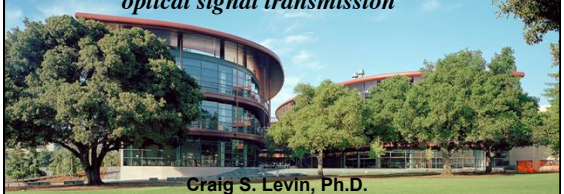
Oxford Summer School "Intelligent Front-End Signal Processing for Frontier Exploitation in Research and Industry" July 9-13, 2013

Molecular Imaging Modalities and Technologies II

A combined dual-modality PET/MR system using optical signal transmission



Craig S. Levin, Ph.D.
Professor of Radiology, Physics, and Electrical Engineering
Molecular Imaging Program at Stanford (MIPS)

MIPS Molecular Imaging Program at Stanford

Stanford University School of Medicine Department of Radiology

PET-MR Hardware 101

Outline of talk

- Motivation for integrating PET with MRI
- Brief review of PET detector technology performance needs
- Potential PET/MR configurations
- MR-compatible PET detector technologies, with details on one called "electro-optical coupling"
- Summary

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Imaging modalities

	Ultrasound	X-ray CT	Optical (fluorescence/ bioluminescence)	Magnetic Resonance	Radionuclide (PET/SPECT)
High resolution anatomy	X	X		X	
Quantitative 3-D data	X	X		X	X
Non-invasive clinical use	X	X		X	X
Clinically approved molecular probes					X
Sensitivity to low concentration signal carriers			X		X
Sensitive molecular imaging?			X		X

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Benefits/applications of combined PET/MR

(Ideal applications will yield enhancements compared to PET or MR alone)

Logistical benefits
- Combine anatomical and molecular information in one study
- Convenience for physician and patient

Technical benefits
- More accurate image registration between PET and MR data sets
- Improving spatial resolution/image reconstruction PET

Adjunct to PET/CT?
- MR has superior soft tissue contrast (e.g head and neck)
- MR does not use ionizing radiation---reduce dose for follow up studies

Applications where both PET and MRI are/could be useful
- Oncology: Detecting/staging head and neck cancer; Post-op tissue characterization; Monitoring MRI-guided therapy; Detecting, guiding biopsy, and/or staging recurrent breast cancer
- Cardiology: Detecting hibernating myocardium; correlating perfusion
- Neurology: Neuro-receptor binding; Parkinson's; Alzheimer's; Characterization of lesions; Neuro-psychiatric-corr. with fMRI

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Benefits/Applications of simultaneous PET/MR

Logistical benefit
- Reduced study time compared to scanning sequentially

Technical benefit
- Use MRI to correct for motion in PET data

Potential clinical applications or studies that can only be performed with the two modalities operating simultaneously??
- To be determined
- Likely an approach we are not currently taking?
- DCE MR and dynamic PET?
- Whole body oncology? (monitoring novel treatments)
- Cardiology? (gated perfusion/viability studies)

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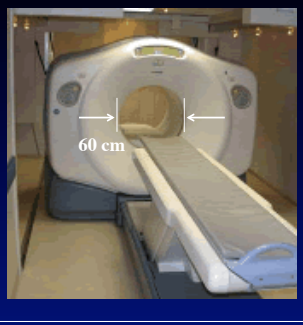
What does a PET System Look Like?



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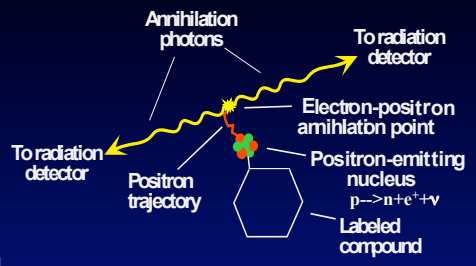
Positron Emission Tomography (PET)



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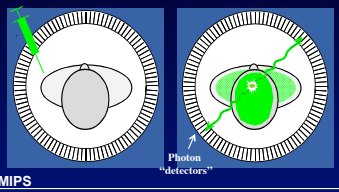
What is Positron Emission Tomography?

- PET is a Nuclear Medicine tomographic imaging technique that uses a tracer compound labeled with a radionuclide that is a positron emitter to study disease and efficacy of treatments.
- A PET study yields cross-sectional image slices representing regional uptake/biodistribution of the radio-labeled chemical
- Quantitative information of rates of biological processes



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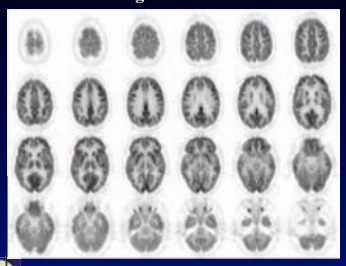
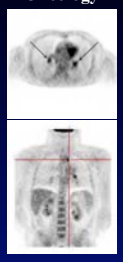
^{18}F-Fluorodeoxyglucose(FDG)-PET

Neurological disorders



Oncology



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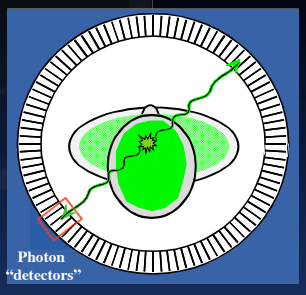
PET System Detector Technology



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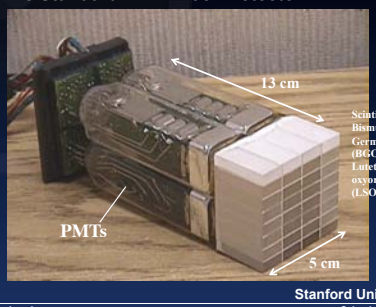
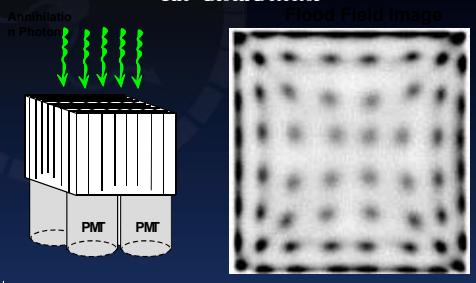
Standard PET detector technology

The Standard PET Block Detector



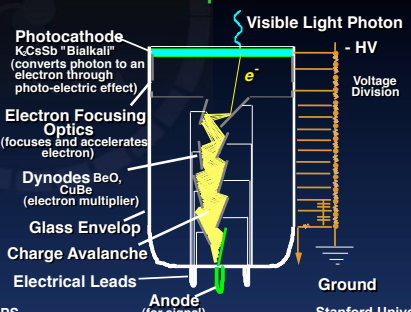
Resolving crystals in PET Detectors

The "Block Detector"



What are the technical challenges?

Photomultiplier Tube



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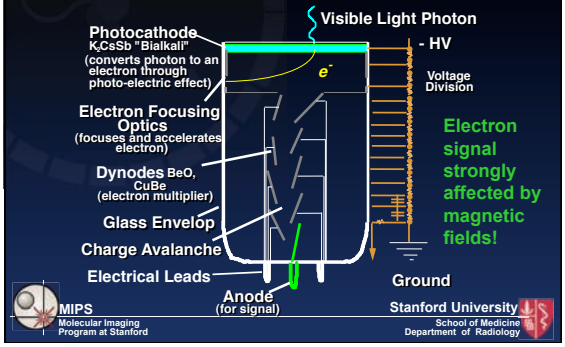

Electron signal strongly affected by magnetic fields!

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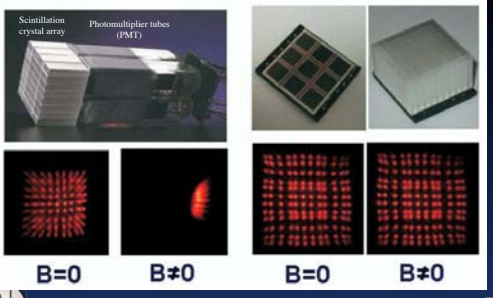
Conventional PET detectors | APD-based PET detectors



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Pichler, Seminars in Nuc Med, 2008

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Besides good crystal identification (spatial information), what other PET detector parameters are important?

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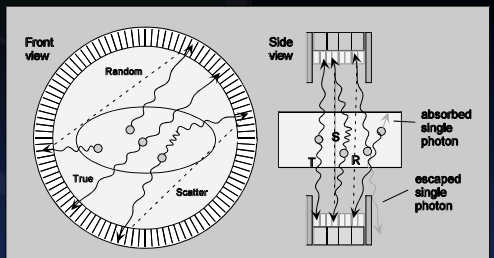
Types of "Coincident" Photon Events



-Tissue scatter coincidence background events mitigated by having excellent energy resolution
-Random coincidence background events are reduced by having excellent coincidence time resol.

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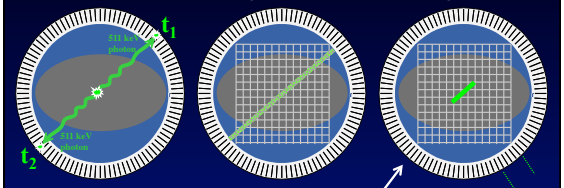
With excellent time resolution, use time-of-flight measurements to constrain the reconstruction volume and improve SNR

Acquire photon data (position, energy, time)

Image reconstruction without time-of-flight capabilities

Image reconstruction with time-of-flight capabilities



Improve signal-to-noise ratio in reconstructed images!

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Besides good crystal identification (spatial information), what other PET detector parameters important?

- 511 keV photon energy resolution
- Photon pair coincidence time resolution

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Options for PET/MR system configuration

Sequential (*a la* PET/CT) | In gap (*a la* XMR) | Inter-twined

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Philips "Ingenuity TF PET/MR"

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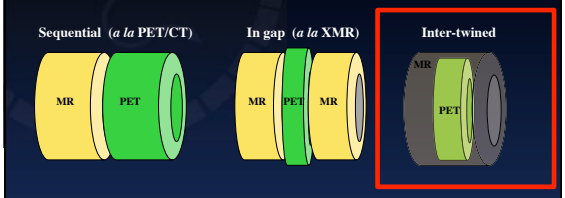
Options for PET/MR system configuration



The focus of this lecture

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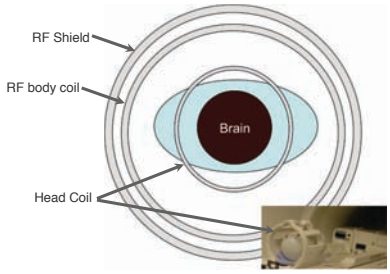
Typical MRI cross-section



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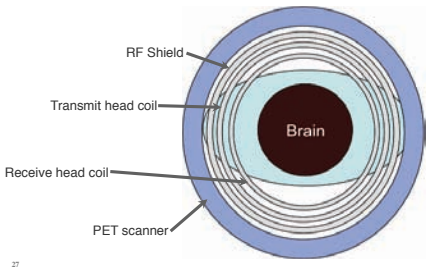
Siemens PET-MRI approach:
Transmit and receive coil inside the PET ring



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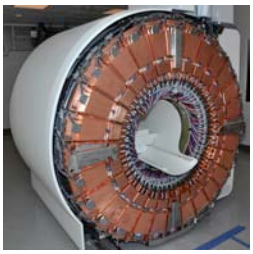
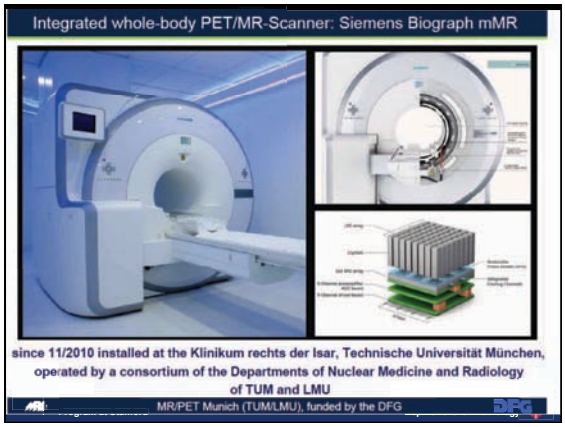
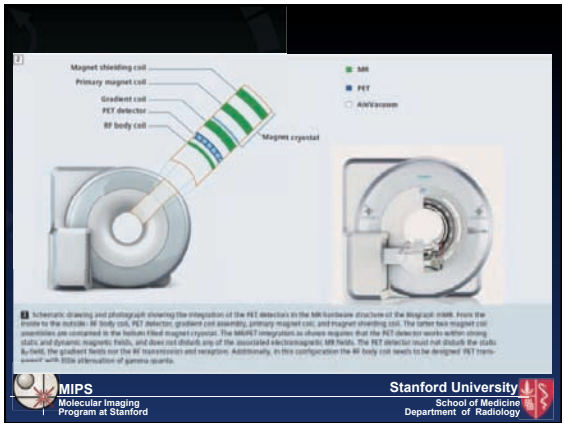
Biograph mMR
Installed at the Martinos Center, MGH

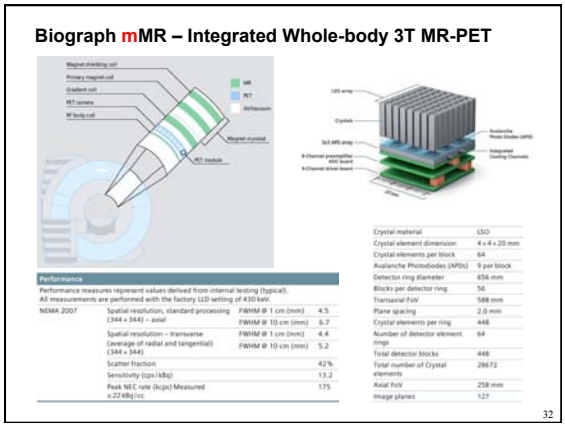
Front view

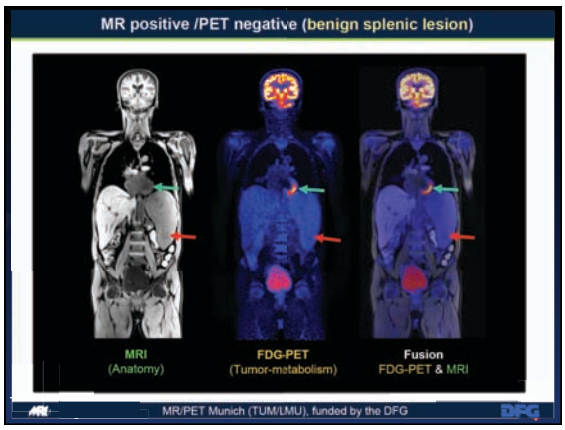


Back view
(without the covers)

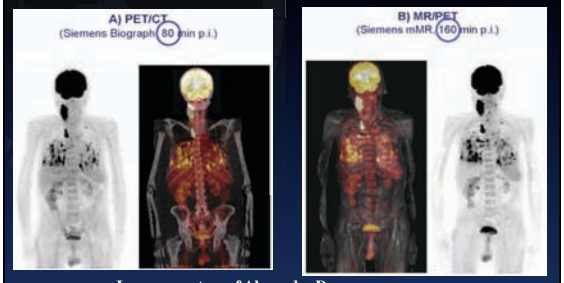



Magnet shielding coil
Primary magnet coil
Gradient coil
PET detector
RF body coil
Magnet cryostat
MR
PET
Air/Vacuum
MIPS
Molecular Imaging
Program at Stanford
Stanford University
School of Medicine
Department of Radiology


Biograph mMR – Integrated Whole-body 3T MR-PET
Performance
Performance measures represent values derived from internal testing (typical).
All measurements are performed with the factory LLD setting of 430 keV.
NEMA 2007
Spatial resolution, standard processing (344 × 344) – axial
FWHM @ 1 cm (mm) 4.5
FWHM @ 10 cm (mm) 6.7
Spatial resolution – transverse (average of radial and tangential) (344 × 344)
FWHM @ 1 cm (mm) 4.4
FWHM @ 10 cm (mm) 5.2
Scatter fraction 42 %
Sensitivity (cps/kBq) 13.2
Peak NEC rate (kcps) Measured 175
@ 22 kBq/cc
Crystal material LSO
Crystal element dimension 4 × 4 × 20 mm
Crystal elements per block 64
Avalanche Photodiodes (APDs) 9 per block
Detector ring diameter 656 mm
Blocks per detector ring 56
Transaxial FoV 588 mm
Plane spacing 2.0 mm
Crystal elements per ring 448
Number of detector element rings 64
Total detector blocks 448
Total number of Crystal elements 28672
Axial FoV 258 mm
Image planes 127
32


MR positive /PET negative (benign splenic lesion)
MRI
(Anatomy)
FDG-PET
(Tumor-metabolism)
Fusion
FDG-PET & MRI
MR/PET Munich (TUM/LMU), funded by the DFG

PET/CT vs. PET/MRI



Images courtesy of Alexander Drzezga, Technische Universität München

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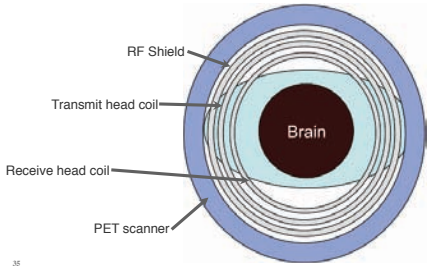
Siemens PET-MRI approach:
Transmit and receive coil inside the PET ring



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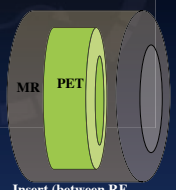
Options for PET/MR system configuration (Continued)

Removable Insert



Insert (between RF-coil and gradient set of the MR system)

- No modifications to the MR
- Must be RF-transparent

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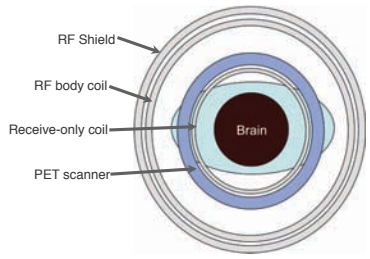
An RF-transparent PET ring that can be inserted into an MR system?



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Prototype RF-Transparent PET Insert

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PET-MR Hardware 101

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- **Summary**

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Different schemes for collecting PET signals from within an MR system

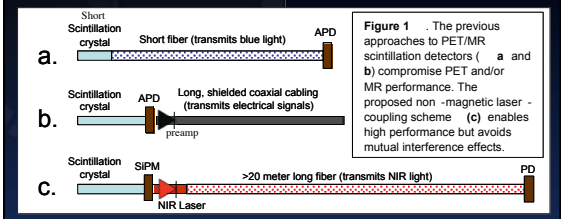

Figure 1 . The previous approaches to PET/MR scintillation detectors (**a** and **b**) compromise PET and/or MR performance. The proposed non -magnetic laser - coupling scheme **(c)** enables high performance but avoids mutual interference effects.

Method "C" is our approach:

Replace bulky coax cable bunch with arrays of VCSELs and densely packed fiber cables

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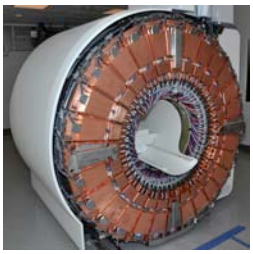
Biograph mMR Installed at the Martinos Center, MGH

Front view

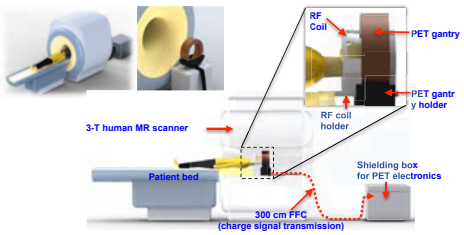


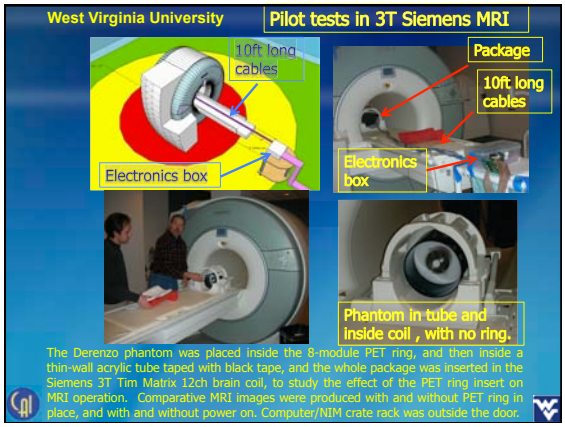
Back view (without the covers)

Insertable Brain PET-MRI (Sogang University, Korea)

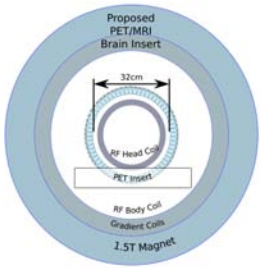
❑ **New design concept**

- Use Geiger-mode avalanche photodiode (GAPD) arrays as a PET photo-sensor
- Use charge signal transmission method that transmit the charge signal of the photo-sensor to the preamplifier through charge transmission cables 3 m in length





PET Brain insert for MRI



For RF-transparency:

Float the PET detector insert relative to the RF ground

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Some PET Tracers for brain imaging

1. Amyvid ([18F]Florbetapir) - the only PET agent that has been approved by FDA for imaging amyloid plaques (approved in March 2012)
2. [11C]PIB (Pittsburg Compound B)- For imaging amyloid plaques.
3. [18F]FDG for imaging Alzheimer's (especially concerning therapy monitoring)
4. [18F]DOPA - Parkinson's disease
5. [11C]Raclopride – schizophrenia
6. PBR radioligands - For imaging microglial activation

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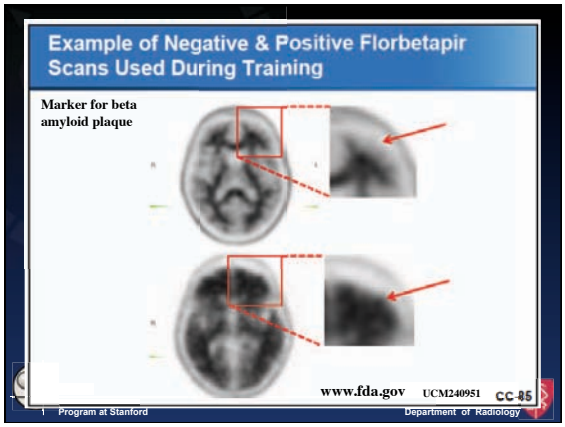
Example of Negative & Positive Florbetapir Scans Used During Training



Technology goal at Stanford:

Come up with a PET detector technology that:

1. Is compatible with and can be inserted into and run concurrently with any MR system;
2. Will not affect the MRI performance at all;
3. Will enable improved performance as compared to the standard clinical PET detector technology, including better time resolution for ToF capability.

Different schemes for collecting PET signals from within an MR system

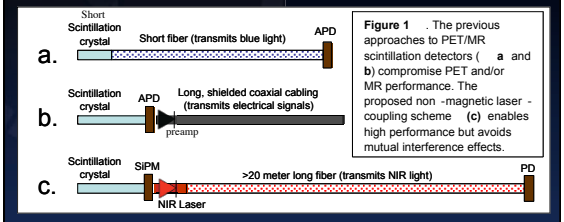


Figure 1 . The previous approaches to PET/MR scintillation detectors (**a** and **b**) compromise PET and/or MR performance. The proposed non -magnetic laser - coupling scheme **(c)** enables high performance but avoids mutual interference effects.

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Replace bulky coax cable bunch with arrays of VCSELs and densely packed fiber cables

What are some of the appealing features of this electro-optical coupling approach?

- Eliminates all electrical cables--->substantially reducing the volume of conductor inside of MR system...and is more compact.
- Transparent to RF transmit signals from MR system.
- Lower power requirements---> not driving long (~5 meters) 50-100 ohm coax cables, or shielded differential ribbon cables.
- Less signal attenuation compared to long electrical cables, and data acquisition electronics can be located in the next room or further.
- Only passive components present inside MR system--> less RF shielding requirements.
- Time-of-flight PET/MR is much easier (electrical cables > 1-2 meters have bandwidth limits, and fast timing electronics in the MR system is challenging).

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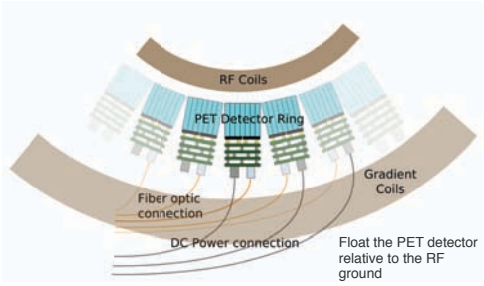
Electro-optical approach to PET detector signal transmission



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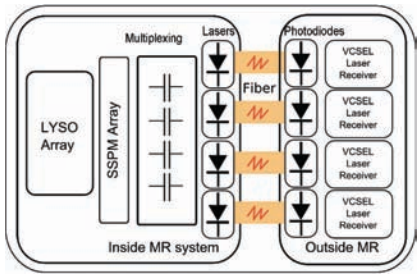
Electro-optical approach to PET detector signal transmission



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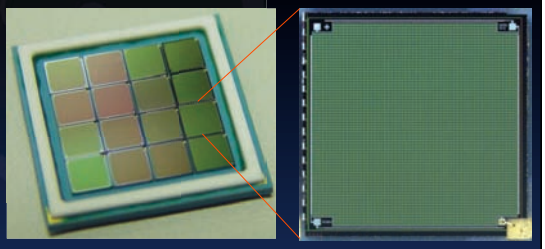
Olcott et al. *Molecular Imaging*, 2009

Silicon photomultipler (SiPM) array



4x4 pixels each with 3×3 mm^2 area and comprising 3,640 Geiger-mode avalanche photodiode cells (right) with a 35 micron active area and 42 micron pitch

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Non-magnetic SiPM array

4x4 pixels each with 3×3 mm^2 area and comprising 3,640 Geiger-mode avalanche photodiode cells (right) with a 35 micron active area and 42 micron pitch

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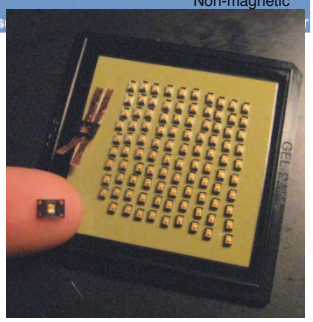
SINGLEMODE / MULTIMODE VCSEL - SILICON PACKAGE

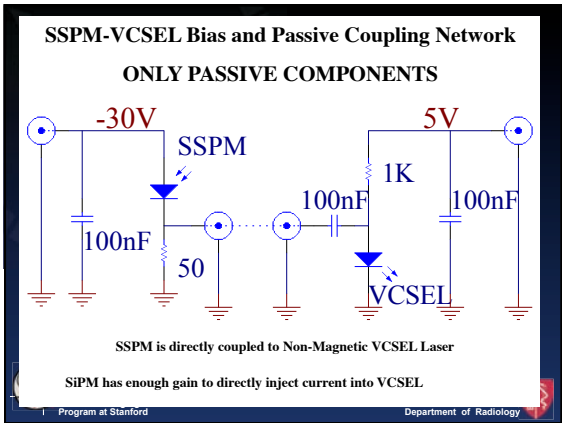
Non-magnetic

VCSEL = vertical cavity surface emitting laser

850 nm VCSEL, >2 Ghz of analog bandwidth



Telecommunication VCSELs: Small, inexpensive, low power



Does electro-optical approach to PET detector signal transmission degrade performance?

No, measurements indicate the "electro-optical link" contributes <12 ps FWHM jitter to time resolution. As always, intrinsic performance is determined by the scintillation crystal and the SiPM used.

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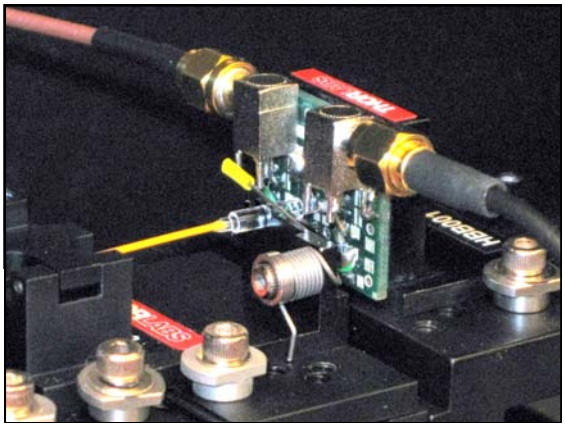
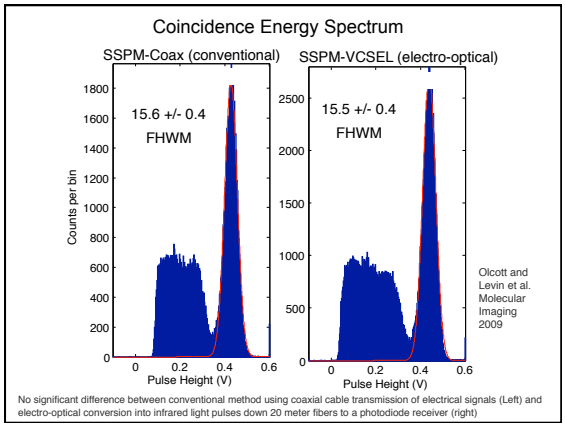
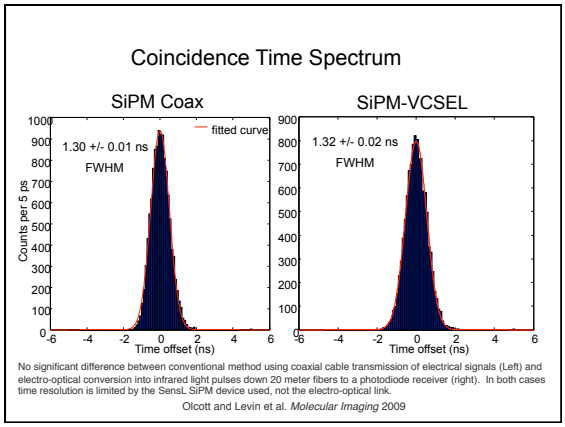




No significant difference between conventional method using coaxial cable transmission of electrical signals (Left) and electro-optical conversion into infrared light pulses down 20 meter fibers to a photodiode receiver (right)



No significant difference between conventional method using coaxial cable transmission of electrical signals (Left) and electro-optical conversion into infrared light pulses down 20 meter fibers to a photodiode receiver (right). In both cases time resolution is limited by the SensL SiPM device used, not the electro-optical link.

Olcott and Levin et al. *Molecular Imaging* 2009

Electro-optical PET detector modules: Alpha version

One 4x4 SiPM array (16 pixels) read out with 4 optical channels (4:1 compression). Uses "capacitive" charge multiplexing.

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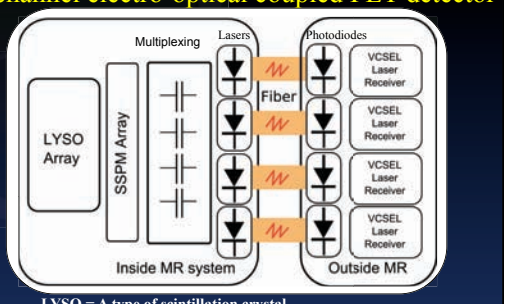
4-channel electro-optical coupled PET detector



LYSO = A type of scintillation crystal
SSPM = A type of scintillation light detector (a.k.a .photodetector)
VCSEL = A type of laser

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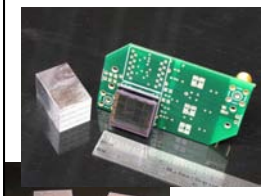
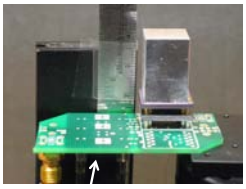
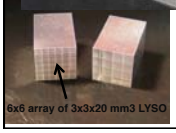
MR-compatible PET detector: LYSO scintillator array coupled to SSPM array electro-optically coupled to fiber optics



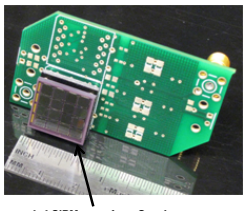




4 VCSEL lasers and fiber launch for each of 4 readout channels are coupled underneath

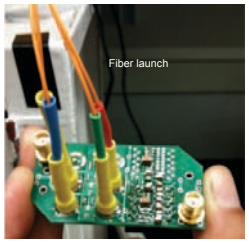
4-channel electro-optical coupled PET detector

Front side



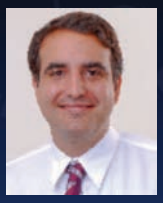
4x4 SiPM array from SensL

Back side



Does the MR interfere with this PET detector's performance and vice versa?

Peter Olcott



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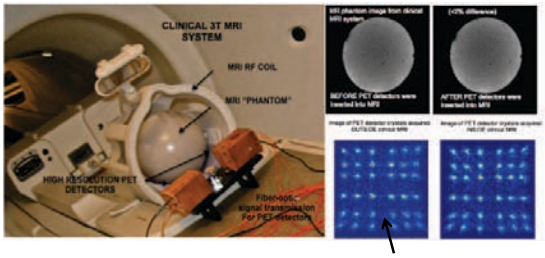
Initial measured data with electro-optical detector modules inside and operating simultaneously with MR system are very promising



6x6 array of 3x3x20 mm3 LYSO

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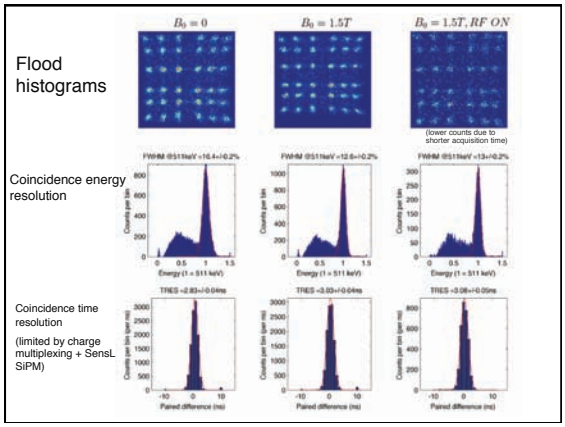

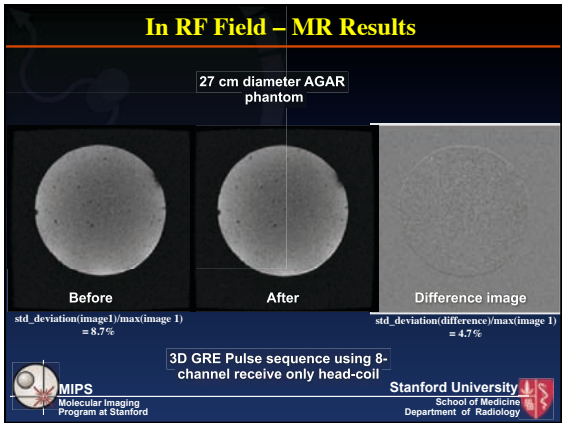

Electro-optical PET detector module: Beta version

Eight 4x4 SiPM arrays (128 pixels) read out with 16 optical channels (8:1 compression ratio).
Uses "Compressed sensing" multiplexing.

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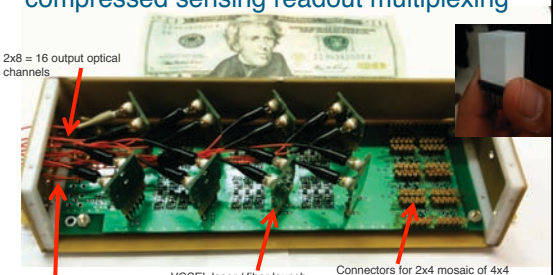
Electro-optical PET detector module with compressed sensing readout multiplexing



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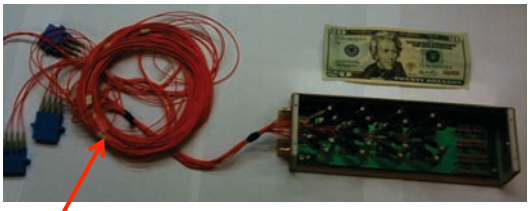
Electro-optical PET detector module



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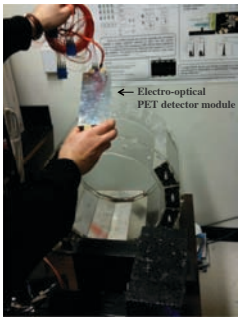
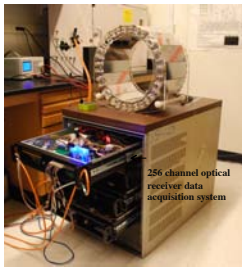
Electro-optical PET insert for PET/MRI





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RF-Transparency of shielded PET insert

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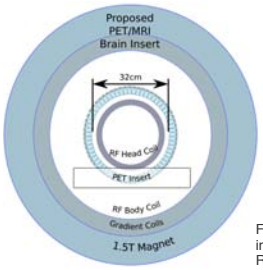
Electro-optical approach to PET detector signal transmission



Float the PET detector insert relative to the RF ground

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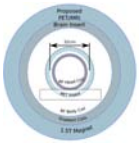
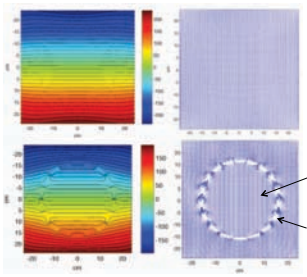
Maxwell equations: Simulations of RF field



No PET ring

With PET ring



With PET detector insert floating relative to the RF ground

MR compatibility:

RF field stays uniform inside PET ring (PET ring is transparent to RF)

RF field drops to zero Inside PET detector

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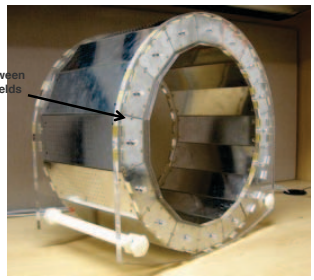
Prototype "RF-transparent" floating PET gantry/RF shielding



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Measurement: Prototype "RF-transparent" floating PET gantry with RF shielding placed inside magnet

MR phantom images

Conclusion:
RF field stays uniform inside PET gantry + RF shielding
(PET gantry + shielding is transparent to RF)

Time-of-Flight for PET/MRI

- Current integrated PET/MRI systems do not have time-of-flight (ToF)
- Coaxial cables require an external ground, are more bulky, and are more vulnerable to electromagnetic interference than optical connections.
- Aim is to pick off timing information with a comparator and replace the coaxial cables with fiber optic cables to enable ToF-PET/MRI. All synchronous electronics will be removed from the MRI bore.

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Time-of-flight PET: Improves signal-noise ratio

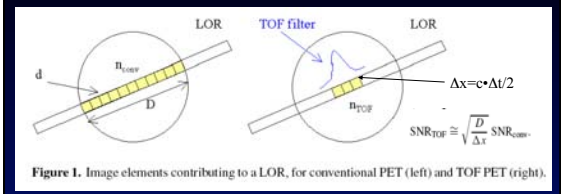

Figure 1. Image elements contributing to a LOR, for conventional PET (left) and TOF PET (right).

Example: If Δt=300 ps --> Δx=4.5 cm
-->SNR improvement is 3.0 for a 40 cm diameter cylinder

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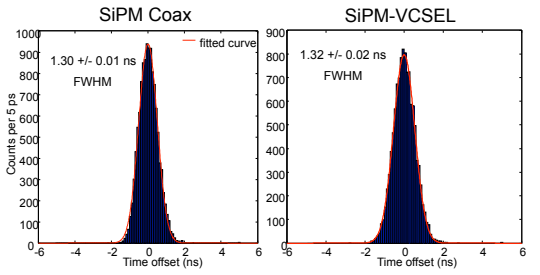
Coincidence Time Spectrum



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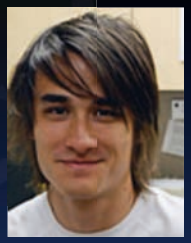
Matt Bieniosek



Time Resolution Performance of an Electro-Optical-Coupled PET Detector for Time-of-Flight PET/MRI. Conference Record of the 2011 IEEE NSS-MIC, October 23-29, Valencia, Spain

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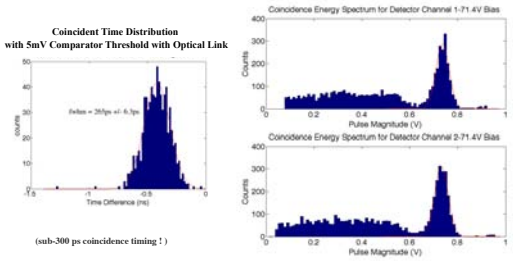
With fast-timing SiPMs and digital pulses…

Improved Time and Energy Resolution Results Achieved for 3x3x20mm LSO Crystals Coupled to 3x3 mm Hamamatu MPPC silicon photomultipliers with electro-optical signal transmission



(sub-300 ps coincidence timing !)

→ Electro-optical coupling may be used for time-of-flight PET/MRI

PET-MR Hardware 101

Outline of talk

- Motivation for integrating PET with MRI
- Brief review of PET detector technology performance needs
- Potential PET/MR configurations
- MR-compatible PET detector technologies, with details on one called "electro-optical coupling"
- Summary

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Summary

- There are logistic and technical reasons for combining PET and MRI, including the ability to simultaneously acquire data.
- Clinical applications are developing but TBD.
- Combining PET and MRI is challenging technically
- Much research has been devoted to developing MR-compatible PET detectors
- It is important not to make choices that do not compromise the PET or MR performance.
- Most approaches to date require significant modifications to the MR system configuration.
- "Electro-optical coupling" shows promise as a technology that enables an RF transparent PET insert that does not require MR system modifications

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Gary Glover

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SensL
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NIH-NCI SMIS Training Grant
California Breast Cancer Research Program
Stanford Interdisciplinary Graduate Fellowship
Stanford Bio-X Graduate Fellowship
Howard Hughes International Graduate Fellowship
AXA Research Foundation
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