PET Imaging for Clinical and Preclinical Imaging

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Disclosures

1) Research contract with Philips Healthcare
2) NIH Academic industrial partnership: Philips Healthcare (PI)
3) NIH Academic industrial partnership: GE Healthcare (co-inv)
4) NIH STTR: PETX LLC (sub contract: PI)

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Advanced PET Instrumentation Developments

1) Digital photon counting PET detectors
2) Time-of-flight PET/MRI scanners
3) Time-of-flight with depth of interaction PET detectors
4) Advance motion correction methods
5) Advance image reconstructions
6) Organ specific imaging systems (e.g., breast)
7) Operator friendly, desktop pre-clinical PET imaging systems
Advanced PET Instrumentation

Developments

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2) Time-of-flight PET/MRI scanners
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Output: > no. of photons > time stamp(s)
No analog post-processing necessary!

dSiPM – With Digital Photon Counting (DPC)
photons are counted directly

“Therefore, while the APD is a linear amplifier for the input optical signal with limited gain, the SPAD is a trigger device so the gain concept is meaningless.” (source: Wikipedia)

dSiPM - DPC uses intrinsic binary nature of SPADs
(SPAD – Single Photon Avalanche Diode)
Digital Photon Counter is an integrated, scalable solution

- fully integrated
- fully digital signals
- no ASIC needed
- fully scalable

Analog SiPM
- discrete, limited integration
- analog signals to be digitized
- dedicated ASIC needed
- difficult to scale

DPC: dark count management by digitization

- Silicon based light sensors have background noise (dark counts), varying with temperature.
- In digital SiPMs every cell can be addressed individually.
- Cells with high dark counts can be switched off.
- A few cells switched off (1-5%) reduces dark count levels by orders of magnitude.

Performance comparison: Analog versus Digital PET

<table>
<thead>
<tr>
<th></th>
<th>Analog*</th>
<th>Digital**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coincidence timing (ps/eq)</td>
<td>591</td>
<td>307</td>
</tr>
<tr>
<td>Image resolution (FWHM, mm)</td>
<td>4.7</td>
<td>4.0</td>
</tr>
<tr>
<td>Energy resolution (@511 keV)</td>
<td>13.0%</td>
<td>11.2%</td>
</tr>
</tbody>
</table>

* Philips Gemini Time-of-flight PET; ** Philips Vereos digital PET/CT
Motivation PET: clinically useful sens. gain

ToF-PET rel. sensitivity gain as f(CRT)

Variance reduction = Sensitivity Gain \cdot \Delta x \cdot \Delta t


Images courtesy of University Hospital Cleveland
Why add depth of interaction?

1) Depth of interaction reduces positioning parallax errors
2) PET/MRI smaller detector ring diameters
3) Smaller detector ring diameters to reduce cost of systems
4) Future generation, long axial field of view systems

Parallax Error
- Depth-of-interaction (DOI)

Smaller detector ring diameter and longer axial FOV accentuate spatial resolution blurring from parallax errors.
• Combining time-of-flight (TOF) and depth-of-interaction (DOI) especially important for long axial field-of-view PET scanners.
• Long LORs have axial DOI blurring
• High attenuation introduces need for TOF

Typical PET scanner

Long axial FOV PET

Axial dir.

UCDAVIS
Explorer (depth of interaction)

Phosphor (YAG:Ce) coated

Decay time of collected light varies with depth

Explorer (DOI, TOF)

<table>
<thead>
<tr>
<th>DOI Resolution (mm)</th>
<th>PMT</th>
<th>SiPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top coated</td>
<td>12.3</td>
<td>14.5</td>
</tr>
<tr>
<td>One side third coated</td>
<td>7.5</td>
<td>9.1</td>
</tr>
<tr>
<td>All sides third coated</td>
<td>6.6</td>
<td>8.2</td>
</tr>
</tbody>
</table>

Head-on Coincidence Timing Resolution (ps)

<table>
<thead>
<tr>
<th></th>
<th>Before correction</th>
<th>After correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncoated</td>
<td>573 ± 24</td>
<td>375 ± 24</td>
</tr>
<tr>
<td>Top coated</td>
<td>391 ± 15</td>
<td>306 ± 11</td>
</tr>
<tr>
<td>One side third coated</td>
<td>433 ± 25</td>
<td>304 ± 20</td>
</tr>
<tr>
<td>All sides third coated</td>
<td>352 ± 26</td>
<td>445 ± 29</td>
</tr>
</tbody>
</table>

TOF, DOI PET Detector

\[ r_3 = \frac{r_2}{r_1} \]
TOF, DOI PET Detector

Effective FWHM: ~6 mm
Coincidence timing resolution: ~370 psec

PET Imaging of Breast Cancer

Avril, et al., JCO 2000

Partial volume effects and varying metabolic activity (dependent on tumor type) seem to represent the most significant limitations for the routine diagnostic application of PET. The number of invasive procedures is therefore unlikely to be significantly reduced by PET imaging in patients presenting with abnormal mammography. However, the high positive predictive value, resulting from the increased metabolic activity of malignant tissue, may be used with carefully selected subsets of patients as well as to determine the extent of disease or to assess therapy response.

Eubank & Mankoff, Sem Nucl Med 2003

18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been used for detection, staging, and response monitoring in breast cancer patients. Although studies have proven its accuracy in detection of the primary tumor and axillary staging, its most important current clinical application is in detection and defining the extent of recurrent or metastatic breast cancer and for monitoring response to therapy. PET is complementary to conventional methods of staging in that it provides better sensitivity in detecting nodal and lytic bone metastases; however, it should not be considered a substitute for conventional staging studies, including computed tomography and bone scintigraphy. FDG uptake in the primary tumor carries prognostic information, but the underlying biochemical mechanisms responsible for enhanced glucose metabolism have not been completely elucidated. Future work using other PET tracers besides FDG will undoubtedly help our understanding of tumor biology and help tailor therapy to individual patient by improving our ability to quantify the therapeutic target, identify drug resistance factors, and measure and predict early response.

PET Imaging of Breast Cancer

Whole-body PET
- spatial resolution is not sufficient for imaging early-stage breast cancer
- potential for detection of recurrence
- potential for selection/monitoring therapy

restricted to relatively advanced disease

The Problem: Variable Responses

- Despite several biomarker targets (e.g., tumor phenotype, receptor status) used to characterize the cancer and help determine treatment, cancer therapy efficacy is highly variable
- As of 2007, there were 35 approved breast cancer therapies, the most of any cancer
- There are limited means for early evaluation of the success of therapy typically takes months after surgery to measure response with imaging

Consequences in cases of ineffective therapies:
- delays effective treatment; earlier treatment is known to improve outcomes
- patients suffer side-effects associated with the ineffective therapy without benefits
- treatments are very costly

Over 200,000 women in the United States are diagnosed each year with breast cancer (~40,000 mortalities/yr)
**PET/X Proposed Clinical Paradigm**

After diagnosis, use PET tracer uptake as therapy assessment biomarker.

Duration of "window of opportunity" will be case/patient dependent

(e.g. see Gebhart et al., JNM 2013)

**Related ongoing research at UW**

- "Early Assessment of Response to Aromatase Inhibitor (A) Therapy", Linden, et al., ASCO 2009

**Prototype PET/X Mounting Stage**

Prototype PET detector mounting system; GE Essential Senographe

**Design Optimization via Simulations**

Reconstructed Images: analytical and iterative (PWLS)

**Related ongoing research at UW**


**Prototype PET/X Mounting Stage**

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**Design Optimization via Simulations**

Reconstructed Images: analytical and iterative (PWLS)
PET/X Performance Goals

Target: measure 20% change (95% CI) in SUV, for 5 mm lesion with SUV = 5

PET/X preliminary RC estimate from simulations (error bars not yet estimated)

PEM Flex Solo II

Improved spatial resolution ('in plane')

Limited - angle tomosynthesis

Quantitative data corrections not applied

 attenuated photons
scattered photons
random coincidences
dead time count loss

Full quantitative data corrections are applied

RC limited by spatial resolution (partial volume effect)

Using SUV_max

PET/X Under development - target FWHM resolution < 2 mm - quantitative accuracy goals given above

MacDonald et al., Med Phys 2012

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Summary: PET/X

Quantitative Breast PET as a Cancer Biomarker

- Many targeted breast cancer therapies exist
  - efficacy is variable
  - cost is high
- Primary tumor is resected; recurrence or lack thereof determines therapy efficacy
  - failure of first-line therapy means
    - effective treatment is delayed, degrading outcomes
    - suffer side effects with no benefit
    - high cost to healthcare system and patients
- Quantitative PET is showing promise for predicting therapy response earlier than existing methods in several cancers
  - WB-PET spatial resolution deemed insufficient for tumors < 2-3 cm
  - majority of new BC cases present with tumors < 2 cm
- PET/X detector design photon sensitivity vs. spatial resolution trade-off will favor quantitative accuracy and precision
- Most dedicated breast PET systems have focused on detection/diagnosis task
  - this is changing as developers now implement quantitative corrections
- Not discussed: integration with mammography and x-ray tomosynthesis
  - x-ray image may play important role in PET attenuation correction

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Clinical to Pre-clinical Imaging Systems

SIEMENS
Siemens Inveon PET

- 20x20 LSO Array
- 1.59x1.59x10mm pixel
- Short, Tapered Light Guide
- Hamamatsu C-12 P5-PMT
- Highest packing fraction detector ring
- 25,600 Detector elements

The same ring diameter as the Focus 120, but with 50% greater axial FOV.

Siemens Inveon PET

The highest resolution PET system: <1.4mm
The highest sensitivity PET system: >10.5%
The highest countrate PET system: >2.0Mcps peak NEC
The largest FOV: 12.7cm axial x 10cm dia.
Best timing resolution: 1.3 nsec (in the system)
Best energy resolution: 15% ER (in the system)
The only source based attenuation correction in preclinical imaging

Image Courtesy of Dr. J. Weissert
U. Wisconsin, Madison

Innovation is in our genes.

Glypican-3–Targeted 89Zr PET Imaging of Hepatocellular Carcinoma

In Vivo $^{89}$Zr-Antibody Targeting

- **HepG2 (small)**
- **HepG2 (large)**
- **HepG2 (blocked)**
- **HepG2 (donated)**

**Tumor Dimensions:**
- 1.4 x 1.0 mm
- Tumor volume: $\sim$0.71 mm$^3$

**Tumor Dimensions:**
- 3.2 x 1.6 mm
- Tumor volume: $\sim$6.43 mm$^3$

Absolute Tumor Size

- Tumor Dimensions: 1.4 x 1.0 mm
- Tumor volume: $\sim$0.71 mm$^3$

- Tumor Dimensions: 3.2 x 1.6 mm
- Tumor volume: $\sim$6.43 mm$^3$

**Day 0**

**Day 1**

**Day 5**

**Day 7**

**Graph C**

**Graph D**
Small Animal PET

SOFIEBIOSCIENCES
G4 PET/X-ray

SOFIEBIOSCIENCES
G8 PET/CT

IMAGING PAIN POINT
High cost and complexity of current PET scanners limit use, access, throughput and require significant support resources

New users see PET as too complicated, too expensive, lacks diversity and requires one deal with radiation
• Economic challenges effect everyone
• $700k - $1M PET scanners represents only a fraction of cost, including service contracts of $70 - $100k/yr
• Further automation of imaging process to allow experts to focus on more important things
• Provide routine, more affordable access to non-FDG probes
• Technology to remove fears of radioactivity
1995 – UCLA invented microPET
2009 – UCLA invented benchtop PET

G4 PET/XRAY + G8 PET/CT

• 1/3 the cost
• 1/20th to 1/40th the weight
• Increased sensitivity from 2 to 4 times
• equal or higher performance
• simple to use by anyone

• Bench top – minimal facility or staff requirements
• Integrated anesthesia and animal handling, monitoring respiration with control of anesthesia & temp., visual monitoring of animal

SPACE IS PRECIOUS

BREAKING AWAY FROM CONVENTIONAL RING BASED GEOMETRY

14% Sensitivity
1.4 mm Spatial Resolution

Composed of four detector heads closely placed together, which results in very high sensitivity from the large coverage (3D solid angle) on the animal.

Surround the animal with panel detectors
AUTOMATION & LIVE LINK TO THE ANIMAL
• Automatic hook-up for anesthesia and heating
• No more cables
• System takes care of the animal for you

BENCHTOP vs. FLOOR SYSTEMS

PET/MRI

MR Solutions

Mediso Medical

In Vivo Imaging
Future Systems/Applications

• PET combined with fluorescence imaging
• Dual radioisotope PET imaging
• PET for proton and hadron therapy
• PET for neutron therapy
• PET combined with micro-irradiators
• Dedicated organ specific imaging systems
  • brain
  • breast
  • prostate

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