Fundamentals of Positron Emission Tomography (PET)
Content

• Fundamentals of PET
• Camera & Detector Design
• Real World Considerations
• Performance Evaluation
• Clinical Uses
A positron is the anti-particle of electrons, which carries the same mass as an electron but is positively charged.

Positrons are normally generated by those nuclides having a relatively low neutron-to-proton ratio.

An typical example of positron emitter is

\[
\begin{align*}
^{22}_{11}Na & \rightarrow \frac{22}{10}Ne + ^0_1\beta + \nu \\
\end{align*}
\]

FIGURE 3.11. Decay scheme of \(^{22}_{11}Na\).
Annihilation Radiation following Positron Emission

Beta - plus decay or positron decay:

\[ {}^Z \!_A X \rightarrow {}^{Z-1} \!_A Y + {}^0 \!_1 \beta + \nu \]
## Commonly Used PET Isotopes

<table>
<thead>
<tr>
<th>Isotope</th>
<th>half-life (min)</th>
<th>Maximum positron energy (MeV)</th>
<th>Positron range in water (FWHM in mm)</th>
<th>Production method</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{11}$C</td>
<td>20.3</td>
<td>0.96</td>
<td>1.1</td>
<td>cyclotron</td>
</tr>
<tr>
<td>$^{13}$N</td>
<td>9.97</td>
<td>1.19</td>
<td>1.4</td>
<td>cyclotron</td>
</tr>
<tr>
<td>$^{15}$O</td>
<td>2.03</td>
<td>1.70</td>
<td>1.5</td>
<td>cyclotron</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>109.8</td>
<td>0.64</td>
<td>1.0</td>
<td>cyclotron</td>
</tr>
<tr>
<td>$^{68}$Ga</td>
<td>67.8</td>
<td>1.89</td>
<td>1.7</td>
<td>generator</td>
</tr>
<tr>
<td>$^{82}$Rb</td>
<td>1.26</td>
<td>3.15</td>
<td>1.7</td>
<td>generator</td>
</tr>
</tbody>
</table>

*Table 2. Properties of commonly used positron emitting radio-isotopes*
The Tracer Principle Again

- Drug is labeled with positron ($\beta^+$, anti-particle of an electron) emitting radionuclide.
- Drug localizes in patient according to metabolic properties of that drug.
- Trace (pico-molar) quantities of drug are sufficient.
- Radiation dose fairly small (<1 rem).
Why PET

• Interesting Chemistry
  Easily incorporated into biologically active drugs.

• 1 Hour Half-Life
  Maximum study duration is 2 hours.
  Gives enough time to do the chemistry.

• Easily produced
  Short half life $\Rightarrow$ local production.

| $^{18}$F | 2 hour half-life |
| $^{15}$O, $^{11}$C, $^{13}$N | 2–20 minute half-life |
Ideal Tracer Isotope

• Tracers contain elements of life – perfect for providing the functional information such as metabolism rate.

• Electronic collimation – high sensitivity.

• Easier attenuation correction.

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}\text{F}$</td>
<td>2 hour</td>
</tr>
<tr>
<td>$^{15}\text{O}$, $^{11}\text{C}$, $^{13}\text{N}$</td>
<td>2–20 minute</td>
</tr>
</tbody>
</table>
Event detection probability is product of individual photon detection probabilities.

\[ P_1 = e^{-\mu \cdot d_1} \quad P_2 = e^{-\mu \cdot d_2} \]

\[ P = e^{-\mu \cdot (d_1 + d_2)} \]
Ring of Photon Detectors

Detect Radioactive Decays

- Radionuclide decays, emitting $\beta^+$.  
- $\beta^+$ annihilates with $e^-$ from tissue, forming back-to-back 511 keV photon pair.  
- 511 keV photon pairs detected via time coincidence.  
- Positron lies on line defined by detector pair (known as a chord or a line of response or a LOR).

Detect Pair of Back-to-Back 511 keV Photons
Multi-Layer PET Cameras

- Can image several slices simultaneously.
- Can image cross-plane slices.
- Can remove septa to increase efficiency ("3-D PET")

Planar Images “Stacked” to Form 3-D Image
By measuring all 1-dimensional projections of a 2-dimensional object, you can reconstruct the object.
PET data acquisition

- Organization of data
  - True counts in LORs are accumulated
  - In some cases, groups of nearby LORs are grouped into one average LOR (“mashing”)
  - LORs are organized into projections

![Diagram of PET data acquisition](image)
PET data acquisition

2D and 3D acquisition modes

- **2D mode** (= with septa)
- **3D mode** (= no septa)

In the 3D mode there are no septa: photons from a larger number of incident angles are accepted, increasing the sensitivity.

Note that despite the name, the 2D mode provides three-dimensional reconstructed images (a collection of transaxial, sagittal and transaxial slices), just like the 3D mode!
PET image reconstruction

- 2D Reconstruction
  - Each parallel slice is reconstructed independently (a 2D sinogram originates a 2D slice)
  - Slices are stacked to form a 3D volume $f(x,y,z)$
PET data acquisition

- 2D mode vs. 3D mode

**2D mode**

(= with septa)

**3D mode**

(= no septa)

- True detected
- True not detected (septa block photons)
- True detected
PET data acquisition

- Organization of data
  - In 3D, there are extra LORs relative to 2D

3D mode  ➔  same planes as 2D  ➔  +  oblique planes
PET evolution: spatial resolution

Human brain

<table>
<thead>
<tr>
<th>PET III</th>
<th>1975</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECAT II</td>
<td>1977</td>
</tr>
<tr>
<td>NeuroECAT</td>
<td>1978</td>
</tr>
<tr>
<td>ECAT 931</td>
<td>1985</td>
</tr>
<tr>
<td>ECAT EXACT HR(^+)</td>
<td>1995</td>
</tr>
</tbody>
</table>

Monkey brain

Animal PET

~1998

EXACT HR\(^+\)

microPET

Image credits:
Crump Institute, UCLA

Image credits:
CTI PET Systems
PET Camera & Detector Design

• Typical Parameters
• Detector Module Design
PET Cameras

- Patient port ~60 cm diameter.
- 24 to 48 layers, covering 15 cm axially.
- 4–5 mm fwhm spatial resolution.
- ~2% solid angle coverage.
- $1 – $2 million dollars.

Images courtesy of GE Medical Systems and Siemens / CTI PET Systems
What Do We Need for PET Detector?

- Efficient – 511keV gamma rays are not easily stopped in detector.
- Excellent timing accuracy (typically a few ns) – for coincidence measurements.
- Capability of a very high counting rate (e.g. 0.5MC/s per cm²)
- High detector spatial resolution – for high imaging resolution.
- Cost-effective – very large detector volume is needed for practical PET systems.
Scintillator Crystal
(Converts $\gamma$ into Light)

Photomultiplier Tube
(Converts Light to Electricity)

- 3 — 10 mm wide
  (determines in-plane spatial resolution)

- 10 — 30 mm high
  (determines axial spatial resolution)

- 30 mm deep
  (3 attenuation lengths)

+ BGO Scintillator
  ($\text{Bi}_4\text{Ge}_3\text{O}_{12}$).
+ “Parallel” Operation.
- Expensive.
- Difficult to Pack.
BGO Scintillator Crystal Block
(sawed into 8x8 array, each crystal 6 mm square)

4 PMTs
(25 mm square)

Depth of cut determines light spread at PMTs.

Crystal of interaction found with Anger logic (i.e. PMT light ratio).

Saw cuts direct light toward PMTs.

Good Performance, Less Expensive, Easy to Pack
Crystal Identification with Anger Logic

- Uniformly illuminate block.
- For each event, compute X-Ratio and Y-Ratio, then plot 2-D position.
- Individual crystals show up as dark regions.
- Profile shows overlap (i.e. identification not perfect).

Can Decode Up To 64 Crystals with BGO
Event Rates

Singles Events:

~3 ns timing accuracy

$10^6$ events / sec / module (25 cm$^2$)

200 modules $\Rightarrow 2\times10^8$ events / sec / camera

Coincidence Events:

Time window $\sim$10 ns

Lots of chords

$($~280,000,000 in 48 layer camera with septa removed$)$.\n
$5\times10^6$ coincidence events / sec

Parallel Electronics is Necessary
Detect 511 keV Photons With (in order of importance):

- >85% efficiency
- <5 mm spatial resolution
- “low” cost (<$100 / cm²)
- “low” dead time (<1 μs cm²)
- <5 ns fwhm timing resolution
- <100 keV energy resolution

Based on Current PET Detector Modules
Variations (Present & Future)

- Quadrant Sharing
- Other Scintillators
- Partial Ring
- Animal PET
- Time of Flight
- PET / CT
- PET / SPECT
Quadrant Sharing

Each PMT Services 4 Crystal Blocks (Not 1)  
(Number of PMTs = Number of Blocks)

+ Cost of PMTs Reduced 4x
- Dead Time Increased 9x
# Scintillation Crystal Properties

<table>
<thead>
<tr>
<th>Scintillator</th>
<th>Effective Z</th>
<th>Density (g/cc)</th>
<th>Radiation Length (mm)(^a)</th>
<th>Relative Light Yield</th>
<th>Refractive Index</th>
<th>Decay Time (ns)</th>
<th>Peak Emission Wavelength (nm)</th>
<th>Hygroscopic?</th>
<th>Rugged?</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaI(Tl)</td>
<td>51</td>
<td>3.67</td>
<td>3.4</td>
<td>100</td>
<td>1.85</td>
<td>230</td>
<td>410</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CsI(Tl)</td>
<td>54</td>
<td>4.51</td>
<td>2.2</td>
<td>135</td>
<td>1.79</td>
<td>1000</td>
<td>530</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>CsI(Na)</td>
<td>54</td>
<td>4.51</td>
<td>2.2</td>
<td>75</td>
<td>1.79</td>
<td>650</td>
<td>420</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>BGO</td>
<td>74.2</td>
<td>7.13</td>
<td>10.5</td>
<td>15</td>
<td>2.15</td>
<td>300</td>
<td>480</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>LSO(Ce)</td>
<td>65.5</td>
<td>7.4</td>
<td>11.6</td>
<td>75</td>
<td>1.82</td>
<td>40</td>
<td>420</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>CaF(_2)(Eu)(^b)</td>
<td>16.9</td>
<td>3.17</td>
<td>N/A</td>
<td>50</td>
<td>1.43</td>
<td>940</td>
<td>435</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

\(^a\)Radiation lengths for NaI(Tl), CsI(Tl) and CsI(Na) are for 140-keV photons; Values for BGO and LSO are at 511 keV.

\(^b\)CaF\(_2\)(Eu) is used in beta imaging.
Lutetium Orthosilicate (LSO) Scintillator

Compared to BGO, LSO has:

**Same Attenuation Length:**
- Good Spatial Resolution

**Higher Light Output:**
- Decode More Crystals per Block
- Better SNR for “Enhanced” Readout (e.g. Depth of Interaction)

**Shorter Decay Time:**
- Less Dead Time (Allows Larger Block Areas)
- Better Timing Resolution

Reduce Cost OR Increase Performance
Improvements In Scintillators Needed

Combine Best Properties of:

- $\text{LaBr}_3$:30% Ce
  - Timing resolution <100 ps
  - Energy resolution <4%
- LuI$_3$:Ce
  - Light output >100,000 ph/MeV
- PbWO$_4$
  - Density >8 g/cc
  - High atomic number
  - Inexpensive

PET Performance Determined by Scintillator

Image courtesy of Paul Lecoq, CERN
Animal PET Camera

Position Sensitive Photomultiplier Tube
Fiber Optic Bundle

LSO Scintillator Crystals (2x2x10 mm)

17 cm Detector Ring Diameter

Miniature Version of “Standard” PET Camera

*Image courtesy of Simon Cherry, UC Davis
Dual Modality: PET / SPECT
Use SPECT Camera for PET

- SPECT cameras optimized to image 140 keV (not 511 keV) photons.
- Detectors are “thin” (0.8 attenuation lengths) NaI:Tl.
  - lower efficiency
  - higher scatter fraction
- Large gaps in angular coverage
  - rotate for complete sampling
  - lower solid angle coverage.
- Detector area
  - large dead time effects

Less Expensive, But Not Optimized for PET
Dual Modality (PET / X-Ray CT)

*Data courtesy of David Townsend, U. Tenn.*
PET & CT Scanners Must Be Separated Axially

⇒ Cannot Image Same Slice Simultaneously!

*Data courtesy of David Townsend, U. Tenn.
“Standard” Performance Evaluation


- Spatial Resolution
- Scatter Fraction
- Sensitivity
- Count Losses & Randoms
- Uniformity
- Correction (Scatter, Count Rate, Attenuation)

http://www.nema.org/
Real World Effects Limiting the Performance of PET

• Photon Attenuation
• Random Coincidences
• Scatter
• Radial Elongation
Photon Attenuation

• Attenuation length of 511 keV photons in water (i.e. tissue) is 10 cm.

• Brain is 20 cm diameter.

⇒ up to $e^{-2} = 86\%$ of the events are lost.

• Loss fraction depends on position in patient.

⇒ Need to correct for attenuation.
PET: Impaired Image Quality in Larger Patients

- For an equivalent data signal to noise ratio, a 120 kg person would have to be scanned 2.3 times longer than a 60 kg person

1) Optimizing Injected Dose in Clinical PET by Accurately Modeling the Counting-Rate Response Functions Specific to Individual Patient Scans. Charles C. Watson, PhD et al Siemens Medical Solutions Molecular Imaging, Knoxville, Tennessee, JNM Vol. 46 No. 11, 1825-1834, 2005
Attenuation Correction ⇒ Quantitation

*Data courtesy of Duffy Cutler, Washington University

- Accurate Quantitation (μCi/cc) Possible
  - Doubles Image Acquisition Time
Attenuation of Internal Source

Event detection probability is product of individual photon detection probabilities.

\[ P_1 = e^{-\mu \cdot d_1} \quad P_2 = e^{-\mu \cdot d_2} \]

\[ P = e^{-\mu \cdot (d_1+d_2)} \]
Transmission Scan Using an Isotopic Source

- Can reconstruct an image of the attenuation.
- Essentially a 511 keV x-ray CT image.
Can use x-ray CT data to obtain attenuation data

- Attenuation coefficients $\mu$ are energy dependent

$\Rightarrow \mu$ at 70 keV (x-ray CT energy) not equal to $\mu$ at 511 keV

- “Scale” data — use CT to classify voxels as either air, tissue, or bone, then multiply by known ratio of $\mu_{511}/\mu_{70}$ to do correction

*Data courtesy of David Townsend, U. Tenn.*
Random Coincidences

- Simultaneous decays can cause erroneous coincident events called Randoms.
- For 3-D PET, randoms can be as high as 50% of image.
- Random Rate is $\text{Rate}_1 \times \text{Rate}_2 \times 2 \Delta t$
- Randoms reduced by narrow coincidence window $\Delta t$.
- Time of flight across tomograph ring requires $\Delta t > 4$ ns.

$\text{Random Rate} \propto (\text{Activity Density})^2$
What Is Actually Reconstructed?

3 Scans Taken:
- Hoop (external source with nothing in ring).
- Transmission (external source with patient in ring).
- Emission (patient after isotope injected).

\[
\text{Recon.} = \frac{(\text{Emission} - \text{Randoms})}{\text{Attenuation}} / \text{Efficiency}
\]

\[
\text{Attenuation} = \frac{\text{Transmission}}{\text{Hoop}}
\]

\[
\text{Efficiency} = \frac{\text{Hoop}}{\text{Hoop\_Average}}
\]
Scattered Events

- Compton scatter in patient produces erroneous coincidence events.
- ~15% of events are scattered in 2-D PET (i.e. if tungsten septa used).
- ~50% of events are scattered in 3-D Whole Body PET.
- ~30% of events are scattered in 3-D Brain PET.
Penetration of 511 keV photons into crystal ring blurs measured position.

Blurring worsens as attenuation length increases.

Effect variously known as Radial Elongation, Parallax Error, or Radial Astigmatism.

Can be removed (in theory) by measuring depth of interaction.
**Spatial Resolution**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Shape</th>
<th>FWHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detector Crystal Width</td>
<td><img src="image" alt="Detector Crystal Width" /></td>
<td>$d/2$</td>
</tr>
<tr>
<td>Photon Noncollinearity</td>
<td><img src="image" alt="Photon Noncollinearity" /></td>
<td></td>
</tr>
<tr>
<td>Positron Range</td>
<td><img src="image" alt="Positron Range" /></td>
<td>$0$ (individual coupling)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$2.2$ mm (Anger logic)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*empirically determined from published data</td>
</tr>
<tr>
<td>Anger Logic</td>
<td><img src="image" alt="Anger Logic" /></td>
<td></td>
</tr>
<tr>
<td>Reconstruction Algorithm</td>
<td><img src="image" alt="Reconstruction Algorithm" /></td>
<td>$1.3$ mm (head)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$2.1$ mm (heart)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$0.5$ mm ($^{18}$F)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$4.5$ mm ($^{82}$Rb)</td>
</tr>
</tbody>
</table>

- **Dominant Factor is Crystal Width**
- **Limit for 80 cm Ring w/ Block Detectors is 3.6 mm**
Spatial Resolution Away From Center

Point Source Images in 60 cm Ring Diameter Camera

Near Tomograph Center 14 cm from Tomograph Center

Resolution Degrades Significantly...
Loss in Spatial Resolution

Underlying Distribution

Gray / White Ratio = 4:1

Measured Distribution

Gray / White Ratio = 2.5:1
Controlled Charge Collection

In semiconductor, electron and holes are driven by electric field. Spatial spreading of the charge carriers can be better controlled, so that a better spatial resolution can be achieved.
A Typical Measured Energy Spectrum

Measured energy spectrum from HgI₂ semiconductor, 1mm thick, 1x1mm² pixels

Typical energy spectrum from a 3 inch NaI(Tl) scintillation counter
Accurate Quantitation \Rightarrow \text{Large Regions}

Hot Spot Fraction = \frac{\text{Activity Measured}}{\text{True Activity}}

Cold Spot Fraction = \frac{\text{Activity Measured}}{\text{Background Activity}}

Object Must Be 2x–4x Larger Than Scanner FWHM
Sensitivity Measures Efficiency for Detecting Signal

• Increased Axial Extent Increases Sensitivity

Place 20 cm diameter phantom in camera.

Measure True Event Rate.

Sensitivity = True Event Rate / μCi / cc.

Low Image Noise ⇒ High Sensitivity
Increase Sensitivity by Removing Septa

2-D (w/ Septa)
- Septa Reduce Scatter
- Smaller Solid Angle for Trues

3-D (w/o Septa)
- No Scatter Suppression
+ Larger Solid Angle for Trues
Even when you do background subtraction, statistical noise from the background remains.

**Image Noise Not Determined by Sensitivity Alone!**
Signals from Different Voxels are Coupled

⇒ Statistical Noise Does Not Obey Counting Statistics

If there are $N$ counts in the image,

$$SNR = \frac{N}{\sqrt{N}}$$
Noise Equivalent Count Rate (NECR)

\[
\text{NECR} = \frac{T^2}{T + S + R}
\]

T: true count-rate, S: scattered count-rate, R: random count rate

NECR Properties:

- Like a Signal / Noise Ratio (Sensitivity only Includes Signal).
- Includes Noise from Backgrounds.
- Statistical Noise Variance \( \propto \) NECR.

Maximize NECR to Minimize Image Noise
At Small Activities, 3-D has Higher NECR
- Peak NECR in 2-D > Peak NECR in 3-D
- Very Sensitive to Scanner, Definitions, & Phantom Size!
Sensitivity Includes Noise from Background

Even when you do background subtraction, statistical noise from the background remains.

Image Noise Not Determined by Sensitivity Alone!
• Can localize source along line of flight.
• Time of flight information reduces noise in images.
• Time of flight tomographs have been built with BaF$_2$ and CsF.
• Difficult to keep all detectors in accurate time coincidence.

$\frac{500 \text{ ps timing resolution}}{c} \Rightarrow 8 \text{ cm localization}$

$500 \text{ ps timing resolution} \Rightarrow 5 \times \text{Reduction in Variance}$!
Axial Position Determined Accurately w/ TOF

- Can Assign Chord to Correct Axial Plane
- Reduces Axial Blur in Reconstructed Image
- Turns 3-D Reconstruction into 2-D — *Much* Faster!

500 ps Time-of-Flight Localizes Source Position to ~7.5 cm fwhm *Along Direction of Travel*

Because Chord is Nearly Vertical, Source Position Localization is 6x – 200x Finer in Axial Direction
Whole-Body TOF Simulations

2x10^6 Trues, 1x10^6 Randoms, Attenuation Included
OP-OSEM w/ TOF Extensions, 2 Iterations, 14 Subsets

Phantom
(1:2:3 body:liver:tumor)

Conventional

1.2 ns

700 ps

500 ps

300 ps

Clear Improvement Visually

*Data courtesy of Mike Casey, CPS Innovations
**TruFlight™**: Enhanced Diagnostic Confidence

Lymphoma within right iliopsoas muscle with central area of necrosis

116 kg; BMI = 31.2
14 mCi; 2 hr post-inj

*improved delineation of lymphoma activity*

Data courtesy of J. Karp, University of Pennsylvania
Clinical Uses

• Brain Dysfunction
  Tumor vs. Necrosis
  Alzheimer’s Disease
  Epilepsy
• Heart Tissue Viability
• Cancer / Oncology
Tumor vs. Necrosis

- Brain tumor patient given radiation therapy.
- Symptoms recur.
- Too much or too little radiation?
- Check with PET.

Too much radiation ⇒ dead area.

Too little radiation ⇒ rapid metabolism.
Alzheimer’s Disease

- Decreased uptake in temporal and parietal regions.
- No known cure, but can tell if a curable disease is mis-diagnosed as Alzheimer’s disease.
• PET used to identify “focal centers” causing epilepsy.
• Focal centers surgically removed.
Heart Tissue Viability

- Patient has heart attack but lives.
- Heart always sustains some damage.
- How badly is the heart damaged?
  - Badly $\Rightarrow$ Coronary bypass.
  - Not Badly $\Rightarrow$ No surgery.
- PET measures degree of damage.
• Many tumors have higher than normal uptake.
• Image the whole body to find metastases.