Fundamentals of Positron Emission Tomography (PET)
What are the two major attractions of PET as a molecular imaging modality?
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 (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>$^{11}\text{C}$</td>
<td>20.3</td>
<td>0.96</td>
<td>1.1</td>
<td>cyclotron</td>
</tr>
<tr>
<td>$^{13}\text{N}$</td>
<td>9.97</td>
<td>1.19</td>
<td>1.4</td>
<td>cyclotron</td>
</tr>
<tr>
<td>$^{15}\text{O}$</td>
<td>2.03</td>
<td>1.70</td>
<td>1.5</td>
<td>cyclotron</td>
</tr>
<tr>
<td>$^{18}\text{F}$</td>
<td>109.8</td>
<td>0.64</td>
<td>1.0</td>
<td>cyclotron</td>
</tr>
<tr>
<td>$^{68}\text{Ga}$</td>
<td>67.8</td>
<td>1.89</td>
<td>1.7</td>
<td>generator</td>
</tr>
<tr>
<td>$^{82}\text{Rb}$</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
What is $^{[18F]}$FDG?

**GENERAL INFORMATION**

Chemical name of $^{[18F]}$FDG is $^{[18F]}$-2-Fluoro-2-deoxy-β-D-glucopyranose, Chemical Abstract Service registry number 63503-12-8. More commonly it is called $^{[18F]}$Fluorodeoxyglucose or simply FDG.

This compound is a radioactive derivative of 2-deoxy-D-glucose labelled with positron-emitting isotope $^{18}F$ in the position 2 of the glucose core structure.

Relative molecular mass: 181.15 g/mol

**NAMES:**

FDG

$^{[18F]}$FLUORODEOXYGLUCOSE

$^{[18F]}$-2-Fluoro-2-deoxy-β-D-glucopyranose

For more details please refer to the [review article](#) on radiohalogenated sugars.
Annihilation Radiation following Positron Emission

Beta-plus decay or positron decay:

\[ _Z^A X \rightarrow _{Z-1}^A Y + _1^0 \beta + \nu \]
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
FIGURE 2. (A) Radionuclides that decay by positron emission result in two annihilation photons emitted 180° apart. If both photons are detected, the detection locations define (to within the distance traveled by the positron prior to annihilation) a line along which the decaying atom was located. (B) Radionuclides that decay by emitting single photons provide no positional information, as a detected event could originate from anywhere in the sample volume. (C) For single photon imaging, physical collimation can be used to absorb all photons except those that are incident on the detector from one particular direction (in this case perpendicular to the detector face), defining a line of origin just like the coincident 511-keV photons do following positron emission. To achieve this localization, however, the radiation from the majority of decays has been absorbed and does not contribute to image formation, leading to the detection of many fewer events for a given amount of radioactivity in the object. Absorptive collimation of this kind is the approach used in planar nuclear medicine imaging and in single photon emission computed tomography (SPECT).
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).
The mathematical formulation of PET image formation process, in terms of
• Radon Transform,
• Filter back-projection image reconstruction,
• Maximum-likelihood reconstruction.
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-url)
PET data acquisition

- **2D and 3D acquisition modes**

  **2D mode**
  (= with septa)

  ![2D mode](image)

  **3D mode**
  (= no septa)

  ![3D mode](image)

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 $f(x,y,z)$
The value of the projection function \( p_\phi(x') \) at this point is the integral of the function of \( f(x,y) \) along the straight line: 
\[
x' = x \cos \phi + y \sin \phi
\]

The integral of a line impulse function and a given 2-D signal gives the projection data from a given view ...

\[
p(\phi, x') = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} f(x, y) \delta(x \cos \phi + y \sin \phi - x') \, dx \, dy
\]
Filtered Back-projection

The Ram-Lak filter in spatial domain

\[ h_{RL}(x) = \frac{1}{2\pi} \int_{-\infty}^{\infty} H_{RL}(\omega) \exp(i x \omega) \, d\omega \]

\[ = \frac{1}{2\pi} \int_{-2\pi B}^{2\pi B} |\omega| \exp(i x \omega) \, d\omega \]

\[ = 2B^2 \text{sinc}(2\pi Bx) - B^2 \text{sinc}^2(\pi Bx) \]

\[ \hat{f}(x, y) = \frac{1}{\pi} \int_{0}^{\pi} d\phi \int_{-\infty}^{\infty} dx' \, p_\phi(x') h(x \cos \phi + y \sin \phi - x') \]
Statistical Description of the Projection Data

The probability of a given projection data $g=\left(g_1, g_2, g_3, \ldots, g_M\right)$ is

$$p(g) = \prod_{m=1}^{M} p(g_m) = \prod_{m=1}^{M} \frac{g_m^{g_m}}{g_m!} e^{-g_m}$$

where $\bar{g}_m$ is the expected value for the number of counts on detector pixel $\#m$

$$\bar{g}_m = \sum_{n=1}^{N} f_n p_{nm}$$

Remember that

$$\begin{pmatrix} \bar{g}_1 \\ \bar{g}_2 \\ \bar{g}_3 \\ \vdots \\ \bar{g}_M \end{pmatrix} = \begin{pmatrix} p_{11} & p_{12} & p_{13} & \cdots & p_{1N} \\ p_{21} & p_{22} & p_{23} & \cdots & p_{2N} \\ p_{31} & p_{32} & p_{33} & \cdots & p_{3N} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ p_{M1} & p_{M2} & p_{M3} & \cdots & p_{MN} \end{pmatrix} \begin{pmatrix} f_1 \\ f_2 \\ f_3 \\ \vdots \\ f_N \end{pmatrix}$$

Measured no. of counts on detector pixel $m$.

In the context of emission tomography, $p_{nm}$ is the probability of a gamma ray generated at a source pixel $n$ is detected by detector element $m$. 

NPRE 435, Principles of Imaging with Ionizing Radiation, Fall 2022
The Maximum Likelihood Reconstruction

Recall that the likelihood function, \( L(f,g) \), of a possible source function \( f \) is

\[
L(f, g) = p(g \mid f)
\]

So that the maximum likelihood solution (the image that maximizing the likelihood function) can be found as

\[
\hat{f}_{\text{ML}} = \arg\max_{f} L(f, g)
\]

or equivalently

\[
\hat{f}_{\text{ML}} = \arg\max_{f} \log[L(f, g)] = \arg\max_{f} l(f, g)
\]

where \( l(f, g) \) is the log-likelihood function

\[
l(f, g) = \log[L(f, g)]
\]
Methods to Estimate the Underlying Image

The Maximum Likelihood Expectation Maximization (MLEM) Algorithm

\[ f_n^{(new)} = \frac{f_n^{(old)}}{\sum_{m=1}^{M} P_{nm}} \sum_{m=1}^{M} \frac{g_m}{\sum_{n'=1}^{N} P_{n'm} f_n^{(old)}} p_{nm}, \quad n = 1, 2, ..., N \]
Can you name a few physical processes that fundamentally limit the spatial resolution of PET?
Annihilation Radiation following Positron Emission

FIGURE 4. Error in determining the location of the emitting nucleus due to positron range (top) and noncolinearity (bottom). The positron range error is dependent on the energy of the emitted positrons. Noncolinearity is independent of radionuclide, and the error is determined by the separation of the detectors. The deviation from noncolinearity is highly exaggerated in the figure; the average angular deviation from 180° is about ± 0.25°. (Reproduced with permission from Cherry SR, Sorenson JA, Phelps ME. Physics in Nuclear Medicine, W.B. Saunders, New York, 2003.)
## Positron Range

### TABLE 2. Select List of Radionuclides That Decay by Positron Emission and Are Relevant to PET Imaging

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>$E_{max}$ (Mev)</th>
<th>$\beta^+$ Branching Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{11}$C</td>
<td>20.4 min</td>
<td>0.96</td>
<td>1.00</td>
</tr>
<tr>
<td>$^{13}$N</td>
<td>9.97 min</td>
<td>1.20</td>
<td>1.00</td>
</tr>
<tr>
<td>$^{15}$O</td>
<td>122 s</td>
<td>1.73</td>
<td>1.00</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>109.8 min</td>
<td>0.63</td>
<td>0.97</td>
</tr>
<tr>
<td>$^{22}$Na</td>
<td>2.60 y</td>
<td>0.55</td>
<td>0.90</td>
</tr>
<tr>
<td>$^{62}$Cu</td>
<td>9.74 min</td>
<td>2.93</td>
<td>0.97</td>
</tr>
<tr>
<td>$^{64}$Cu</td>
<td>12.7 h</td>
<td>0.65</td>
<td>0.29</td>
</tr>
<tr>
<td>$^{68}$Ga</td>
<td>67.6 min</td>
<td>1.89</td>
<td>0.89</td>
</tr>
<tr>
<td>$^{76}$Br</td>
<td>16.2 h</td>
<td>Various</td>
<td>0.56</td>
</tr>
<tr>
<td>$^{82}$Rb</td>
<td>1.27 min</td>
<td>2.60, 3.38</td>
<td>0.96</td>
</tr>
<tr>
<td>$^{124}$I</td>
<td>4.17 d</td>
<td>1.53, 2.14</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Based on data from Table of Nuclides: www2.bnl.gov/ton (accessed October 17th, 2002)
FIGURE 5. A: Simulations for several PET radionuclides showing the distribution of positron annihilation sites in water for positrons emitted at the center of the image (position 0.0 mm). B: Profiles through the simulated distributions showing measured FWHM and FWTM of the distributions. Abbreviations: FWHM, full width at half maximum; FWTM, full width at tenth maximum. (Reproduced with permission from Levin C, Hoffman EJ. Phys Med Biol 1999, 44: 781–799.)

PET: Physics, Instrumentation, and Scanners
Simon R. Cherry and Magnus Dahlbom
Noncollinearity

Noncollinearity. This effect is independent of radionuclide because the positrons must lose most of their energy before they can annihilate; hence, the initial energy is irrelevant. The distribution of emitted angles is roughly Gaussian in shape, with a full width at half maximum (FWHM)* of $\sim 0.5^\circ$. After detecting the annihilation photons, PET assumes that the emission was exactly back to back, resulting in a small error in locating the line of annihilation (Figure 4 bottom). Assuming a Gaussian distribution and using the fact that the angles are small, the blurring effect due to noncollinearity, $\Delta_{nc}$, can be estimated as:

$$\Delta_{nc} = 0.0022 \times D$$  \hspace{1cm} (10)

where $D$ is the diameter of the PET scanner. The error increases linearly as the diameter of the PET scanner increases. Once again, the effect is relatively small compared with the detector resolution in most clinical PET scanners. In PET scanners used for animals, $D$ generally is small, and as illustrated in Example 4, noncollinearity is not a major limiting factor at the present time.

**EXAMPLE 4**
Calculate the blurring due to photon noncollinearity in an 80-cm diameter PET scanner designed for imaging humans and in a 15-cm diameter PET scanner designed for imaging small animals.

**ANSWER**
From Equation 10, the blurring is calculated as:

For the 80-cm human scanner:

$$\Delta_{nc} = 0.0022 \times D = 0.0022 \times 800 \text{ mm} = 1.76 \text{ mm}$$

For the 15-cm small-animal scanner:

$$\Delta_{nc} = 0.0022 \times D = 0.0022 \times 150 \text{ mm} = 0.33 \text{ mm}$$
Current PET detector technology is dominated by scintillation detectors.

• What are the desired properties of a scintillation crystal used for PET application?

• In the most typical PET detector configuration, in which a scintillation crystal array is coupled to a Silicon-Photomultiplier (SiPM) array, can you explain how a SiPM works?
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
PET Cameras

**FIGURE 15.** Photograph of a large-area NaI(Tl) detector designed for PET applications. The scintillator plate is 50 cm long by 15 cm wide by 2.5 cm thick and is read by thirty, 5-cm diameter PM tubes. Six of these detectors have been used in an hexagonal array to form a PET scanner. (Photograph courtesy of Dr. Joel Karp, University of Pennsylvania.)

**FIGURE 12.** Schematic drawing of a typical PET block detector. A block of scintillator is segmented into an $8 \times 8$ array using a diamond saw. White reflective material is used in the saw cuts to optically isolate elements. Depth of the saw cuts determines the spread of scintillation light onto four single-channel photomultiplier tubes. By looking at the ratio of signals in the four PMTs, the detector element in which an annihilation photon interacted can be determined. (Reproduced with permission from Cherry SR, Sorensen JA, Phelps ME. *Physics in Nuclear Medicine*, W.B. Saunders, New York, 2003.)
Block Design Using Anger Logic

- Saw cuts direct light toward PMTs.
- Depth of cut determines light spread at PMTs.
- Crystal of interaction found with Anger logic (i.e. PMT light ratio).

BGO Scintillator Crystal Block (sawed into 8x8 array, each crystal 6 mm square)

Good Performance, Less Expensive, Easy to Pack
Event Rates

Singles Events:

~3 ns timing accuracy

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

200 modules $\Rightarrow 2 \times 10^8$ events / sec / camera

Coincidence Events:

Time window ~10 ns

Lots of chords

($\sim 280,000,000$ in 48 layer camera with septa removed).

$5 \times 10^6$ coincidence events / sec

Parallel Electronics is Necessary
(Gas) Multiplication Process in Solid-State Photon Sensors??

**Figure 6.3** Basic elements of a proportional counter. The outer cathode must also provide a vacuum-tight enclosure for the fill gas. The output pulse is developed across the load resistance $R_L$.

**Figure 9.3** Curve of pulse height versus voltage across a gas-filled pulse counter, illustrating the ionization chamber, proportional, and Geiger regions.

**Figure 7.1** The mechanism by which additional avalanches are triggered in a Geiger discharge.

Photodiode Detectors

Figure 1-1 Photodiode cross section

Typical reversed-biased photodiode detectors
- No internal gain
- Very high QE for red light (up to 90%)
- Limited timing resolution

Hamamatsu photodiode technical information
Avalanche Photodiode (APD)

Avalanche Photo Diodes (APD), proof to be suitable detectors for PET/MRI

- Could be operated inside strong magnetic field
- Added internal gain
- Fast timing property
- Gain critically depends on bias voltage
- Temperature stability could be an issue


http://learn.hamamatsu.com/articles/avalanche.html

Refresher Short Course RC4, MIC
Next Generation PET/MRI Systems

University of Tuebingen, Germany

- Larger FOV transaxial 7.2 cm/ axial 7cm
- LSO Blocks: 15x15 crystals (1.6x1.6x10mm³)
- 16 cassettes each 3 blocks
- Higher Sensitivity: 4-5% (estimated)

This slide was derived from Martin S. Judenhofer, Seminars in Nuclear Medicine, with permission.

Refresher Short Course RC4, MIC
Next Generation PET/MRI Systems

University of Davis, California, USA

- Located inside 7 Tesla MRI
- Use position sensitive APDs (14x14mm²)
- 4 rings with 24 detector blocks (each),
- based on LSO arrays (1.2x1.2x14mm³) and PSAPDs
- 60 mm axial FOV (whole body mouse)
- ~ 3-4% sensitivity (simulation)
- 1.3mm spatial resolution
Silicon Photo Multipliers (SiPM, Geigermode-APD) a novel MR compatible PET detector

- Each cell is operated above breakdown
- Output signal is sum of all cells
- Each cell provides maximum-gain signal on photon interaction

This slide was derived from Martin S. Judenhofer, Seminars in Nuclear Medicine, with permission.
Silicon Multiplier (SiPM) Detectors

FIGURE 1. (a) Simplified structure of a SiPM composed of G-APD cells. The G-APDs are joined together on a common substrate and are electrically decoupled. The outputs of the cells are connected to an Al grid used for the readout of the output signals. Each cell has a quenching resistor in series. (b) Each cell (G-APD) is a p–n junction with a very thin depletion layer between p+ and n+ layers.15 Drawings courtesy of Julien Bec, UC Davis.

FIGURE 2. (a) Simplified electric structure of a SiPM composed of several G-APDs in series with a quenching resistor. (b) Equivalent circuit of a single cell when the device is on (a bias voltage Vbias is applied) and is detecting photons. The capacitor Ccell initially charged at Vbias discharges through Rcell dropping the bias voltage to Vbreakdown. The avalanche process is quenched via the quenching resistor and then the device is recharged.


Refresher Short Course RC4, MIC
Silicon Multiplier (SiPM) Detectors

FIGURE. (a) Resistive network for a 4 x 4 SiPM array, (b) Crystal map acquired with a $^{22}$Na source irradiating a 4x4 array of 1.5 x 1.5 x 20 mm$^3$ LSO scintillator crystals coupled to the SiPM array.

FIGURE 3. Pulse height spectra from a 131 mm$^2$ Ham- amatsu MPPC S10362-11-025C acquired for three different light intensities (the red and blue curves correspond to the lowest and strongest intensities, respectively) showing peaks corresponding to different numbers of photoelectrons generated.

Silicon Multiplier (SiPM) Detectors
Sogang University, Korea – GAPD based PET insert

- based on 4x4 GAPD arrays
- 3x3x10 mm^3 LYSO scintillators
- 16 block detectors
- 70 mm inner diameter / 13 mm axial
- 2.8 mm spatial resolution
- charge signal transmission readout

Kang J, et al., A small animal PET based on GAPDs and charge signal transmission approach for hybrid PET-MR
JInst. 6-P08012, Aug 2011
Coincidence detection in PET:

• How does the so-called Time-of-Flight (TOF) PET work?

• Why TOP-PET would offer an improved image quality over non-TOP PET?
Fig. 1 Compared to conventional PET, the estimated time-of-flight difference ($\Delta t$) between the arrival times of photons on both detectors in TOF-PET allows localization (with a certain probability) of the point of annihilation on the line of response. In TOF-PET, the distance to the origin of scanner ($\Delta x$) is proportional to the TOF difference via the relation: $\Delta t: \Delta x = \frac{c \Delta t}{2}$, where $c$ is the speed of light. $t_1$ is the arrival time on the first detector, and $t_2$ is the arrival time on the second detector.
Clinical Benefit of Time-of-Flight PET

Fig. 1 Coronal images reconstructed from a non-TOF scan (left) and a TOF scan (right) in a patient with lung cancer. The acquisition time was 3 min per bed position for both images. At the same number of counts, the image quality is better with the TOF reconstruction.
Clinical Benefit of Time-of-Flight PET

Fig. 3  Transaxial, coronal and sagittal images in a patient with nodules in the pelvic region showing FDG uptake (top non-TOF image, bottom TOF image). Arrows uptake focus not visible in the non-TOF images