Fundamentals of Medical Imaging: PET

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Outline:
- Fundamentals of PET
- Camera & Detector Design
- Real World Considerations
- Performance Evaluation
- Clinical Uses
**Step 1: Inject Patient with Radioactive Drug**

- 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).

**Drug Distributes in Body**

PET stands for positron emission tomography. In PET, the patient is injected with a biologically active, radioactively labeled drug. The drug then localizes somewhere in the patient, depending on the metabolic properties of the drug. Because PET is very efficient at imaging the injected drug, the amount of injected drug is quite small (a “trace” amount), which both prevents the drug from perturbing the patient’s biology and minimizes the radiation dose to the patient.
There are a limited number of radioactive isotopes that can be used for PET. If you could design the ideal isotope, the characteristics that it would have (in addition to positron emission) would be: interesting chemistry (in order to be incorporated into useful drugs), a half-life of about an hour (to give enough time to synthesize the drug, but not so long that the images take forever to acquire), and be easily produced (as the short half-life implies that the isotope must be produce nearby).

There are two main isotope production devices, a cyclotron and a generator. Cyclotrons, which you probably all know about, are expensive to both buy and maintain. A generator is a device in which a parent isotope with a relatively long half-life decays to form a positron emitting isotope with a short half life, which is then chemically separated from the parent isotope. The generator must be periodically re-charged with the cyclotron (or reactor) produced parent isotope, but generators are much less expensive and more portable than cyclotrons.

The isotopes that are most commonly used are $^{18}\text{F}$, $^{15}\text{O}$, $^{11}\text{C}$, $^{13}\text{N}$. Oxygen, carbon, and nitrogen can be substituted into biomolecules for non-radioactive isotopes of the same element, and fluorine can often be substituted for the hydroxyl group (OH). All of these are produced by cyclotrons — the main generator-produced isotope is $^{82}\text{Rb}$, which sees some use in cardiac studies. The number of compounds onto which these isotopes are commonly labeled is actually rather limited, but the task of creating and labeling new tracer compounds is a very active (and promising) area of research.
After the drug localizes in the patient, the radioisotope decays by emitting a positron (hence the name) which is stopped in the tissue and annihilates with an electron to form two back-to-back photons. These photons pass through the patient and are detected.

A typical PET camera consists of a planar ring of small photon detectors, with each photon detector placed in time coincidence with each of the individual photon detectors on the other side of the ring. When a pair of photon detectors simultaneously detect 511 keV photons, then you know that a positron decayed somewhere on the line connecting the two detectors. This line is known as a line of response (LOR) or a chord, and the method of using time coincidence between two detectors (rather than a collimator and one detector) to restrict events to a line is known as electronic collimation.
Most modern PET cameras consist of several of these planar rings stacked on top of each other to form a multi-layer system, as shown above. This allows several parallel images (known as slices) to be acquired simultaneously, and also allows additional images to be acquired with cross-plane slices. The lead shields prevent activity from the patient from causing spurious counts in the tomograph ring, while the tungsten septa provide partial collimation to reject some of the events in which one (or both) of the 511 keV photons suffer a Compton scatter in the patient. These septa are often removable to acquire “fully 3-D” data – removing the septa significantly increases the efficiency for detecting both “true” coincidences and Compton scattered events.

It is possible to move the patient through the scanner a section at a time, stopping to acquire an image at each section. These sections can be reconstructed and displayed next to each other to for a whole body image of a patient.
The final step is to produce an image of the drug concentration using computed tomography. The benefit of computed tomography is that it separates the object into planes, eliminating contributions from objects in other planes. Thus, computed tomography allows us to produce clearer images of the drug distribution in the patient.

This is evident in the two x-ray images of an automobile transmission. The image on the left is a conventional planar (shadow) image—while the resolution is good, it is difficult to see detail clearly as objects from above and below are superimposed on the image of the desired plane. The image on the right is of the same transmission using computed tomography. The image is much clearer as the superposition from other planes is eliminated.
It is impossible to briefly but accurately describe how computed tomography works, so I will merely give a plausibility argument. If you take a one-dimensional projection of a two-dimensional object, you can see the main features of the object (e.g., the larger white circle corresponds to a dip while the smaller black circle corresponds to a bump). If you take a projection from another angle, you see the same features, but their position within the projection image changes. I assert without proof that if you take one-dimensional projections from many angles, you have enough information to reconstruct the two-dimensional image.
I will now describe a typical PET camera.
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

Here are pictures of typical commercial PET cameras. The patient usually lies down on the bed, and the imaging planes are oriented perpendicular to the floor.

I would like to give you an order of magnitude estimate of the typical ring parameters in a modern PET camera, realizing that there are many variations. Most cameras are designed to image either the brain or the thorax, with the main difference being the size of the patient port. Brain machines usually have a 30 cm diameter patient port, while thorax machines (also known as whole body machines) usually have a 50–60 cm diameter patient port. Modern PET cameras usually have between 500 and 700 detector elements per layer. The axial coverage is usually about 15 cm, and the cost for a PET camera is several million dollars.
The most obvious way to make a 511 keV photon detector is to individually couple photomultiplier tubes to a dense, inorganic scintillator crystal, usually BGO. The width of the crystal is usually between 3 and 10 mm, and this size determines the in-plane spatial resolution of the camera (more on this later). The height of the crystal is usually between 10 and 30 mm, and this height determines the thickness of the plane that you image, and hence the axial resolution. Notice that if the size of the object that you wish to image is thinner than this imaging plane (or is not uniform through the thickness of the plane), you will get an inaccurate measurement of the activity in that object. This is known as the partial volume effect. Finally, almost all cameras have 30 mm deep scintillation crystals – this is determined by the attenuation length of 511 keV photons in BGO.

This “individually coupled” design is capable of very high resolution. Since the design is very parallel (all the photomultiplier tubes and scintillator crystals operate independently), it is capable of very high throughput. The disadvantages of this type of design are that it requires a lot of photomultiplier tubes (thus is expensive), and that connecting round photomultiplier tubes to rectangular scintillation crystals leads to problems packing the crystals to form a solid ring.
Modern PET detectors instead use an “analog” coding scheme, where the ratio of light output (i.e. Anger logic) is used to determine the crystal of interaction. In the example above, 4 photomultiplier tubes are coupled to a block of BGO that has been partially sawed through to form 64 “individual” crystals. The depth of the cuts are critical – deep cuts tend to focus the scintillation light onto the face of a single photomultiplier tube while shallow cuts tend to spread the light over all four photomultiplier tubes.

This type of coding scheme places stringent requirements on photomultiplier tube linearity and uniformity, as well as scintillator crystal uniformity. However, most commercial PET cameras use an analog coding scheme since it is much less expensive due to the fewer number of photomultiplier tubes required.
This figure shows the decoding pattern in a 7 x 8 crystal block detector. The entire block is uniformly illuminated with 511 keV photons, and whenever an interaction is detected, the X and Y position estimators are computed and plotted on this 2-D scatter plot. The dark regions in the plot show the positions of the individual crystals in this ratio space, and show that the ability to decode crystals is generally quite good.

However, the decoding is not perfect! Due to the limited light output of BGO, less than 200 photoelectrons are produced with each 511 keV interaction. As the profile shows, statistical fluctuations broaden the individual peaks so that the tails of the distributions for adjacent crystals overlap. The amount of overlap is almost exactly what is predicted based on fluctuations due to counting statistics.
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
  (~280,000,000 in 48 layer camera with septa removed).
- $5 \times 10^6$ coincidence events / sec

Parallel Electronics is Necessary

Current PET detector modules have ~1 µs dead time and cover 25 cm$^2$. This is adequate for most studies, but higher rate capability is desired in some circumstances, particularly when using short-lived isotopes or when collecting data for attenuation correction (more on this later).

The coincidence circuitry must be able to determine coincident events with ~10 ns resolution for each chord. The timing requirement is set jointly by the time-of-flight across the detector ring (4 ns) and the BGO-BGO resolving time (~3 ns). The most stringent requirement, however, is the vast number of possible chords — 6 million in a 48 layer camera with septa in place and 280 million with the septa removed!

It is impractical to have individual coincidence circuits for each chord, so tomograph builders use parallel organization to solve the combinatorial problem. A typical method is to use a high speed clock (typically 500 MHz) to mark the arrival time of each 511 keV photon and a digital coincidence processor to search for coincident pairs based on this time marker. This search can be done extremely quickly by having multiple sorters working in parallel. Custom integrated circuits and programmable logic arrays are frequently used for this task.

Data acquisition is either done in “histogramming mode” (where there is a memory location for each chord, and that location contains the number of events observed in the chord) or “list mode” (in which the identity of each chord is sequentially written to disk/memory on an event by event basis, resulting in a long list of events). In either case, it must store events that occur in 280 million chord locations at rates of 5 MHz.
There are a number of requirements that a PET detector module must satisfy. The most important is that it detects 511 keV photons with high efficiency, as PET is essentially starved for statistics. It must localize the position of interaction to better than 5 mm in order to provide acceptable spatial resolution. The cost must be less than $100 per cm² of front surface area in order to be cost competitive. It must have a low dead time figure of merit (the product of the detector module dead time and the front surface area), provide a sufficiently accurate timing signal, and acceptable energy resolution.
Variations (Present & Future)

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

There are quite a number of “normal variations” that a PET camera can have. I now describe these variations and the motivation for them.
Quadrant sharing is a way to reduce the cost for PET cameras. With a conventional block detector, there are four PMTs per block of scintillator crystal, and the area of each PMT is one quarter the area of the block of scintillator crystal. In a quadrant sharing scheme, larger PMTs are used, with the area of each PMT equal to the area of the block of scintillator crystal. A single scintillator block is still read out by four PMTs, but each PMT now services four (instead of just one) block of scintillator crystal. The advantage is that the number of PMTs is reduced by a factor of four, but the dead time is increased by a factor of nine.
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

The performance of a PET detector module is mainly determined by the scintillator. The recently discovered scintillator LSO (cerium doped lutetium orthosilicate) has properties that are nearly ideal for PET. It has similar stopping power to BGO, but with significantly higher light output and shorter decay time. This alters the tradeoffs imposed on detectors, and has lead to many new LSO based design proposals, most of which have significantly higher performance than BGO based designs. LSO has largely replaced BGO in the PET cameras manufactured by CTI, Inc.
As the detector modules account for about half of the parts cost of a conventional PET camera, a low-cost alternative is to eliminate half of the detector modules, leaving two opposing banks of detectors. These banks are rotated around the patient to provide complete angular coverage. The main drawbacks of this scheme are reduced detection efficiency and increased mechanical complexity.
There has been a lot of interest recently in animal PET systems, usually for imaging mice. This activity is driven by the pharmaceutical, genetic, and physiology communities, for which the mouse is the “animal model” of choice. The design of these cameras is conceptually identical to a “miniaturized” conventional PET camera. The patient port and axial extent are smaller due to the reduced size of the “patient,” and the scintillator crystals are smaller in order to obtain higher spatial resolution.
One normal variation in PET cameras is the “time-of-flight” or TOF design. By measuring the difference in arrival time at the two detectors, the positron source can be localized along the line of flight. Doing this does not improve the spatial resolution, but improves the signal to noise ratio (the mechanism will be described in more detail in the next slide) — the variance improves by a factor of $2D/c\Delta t$, where $D$ is the diameter of the radionuclide distribution, $c$ is the speed of light, and $\Delta t$ is the TOF resolution. Several TOF PET systems were built in the 1980’s with barium fluoride or cesium fluoride scintillators. They achieved ~500 ps timing resolution, which results in 8 cm localization. For objects the size of the human head (which was what most PET cameras imaged in the 1980’s) the net result is a tomograph with a factor of ~2 lower variance than a non-TOF BGO tomograph.

Problems arose from the use of barium fluoride as a scintillator. It is less dense than BGO, and so the spatial resolution is degraded. In addition, the wavelength of its fast emission is in the hard UV, which made it difficult to work with (i.e. expensive) because it does not penetrate glass-windowed photomultiplier tubes or any known glue (to couple the crystal to the photomultiplier tube). Finally, it was difficult to keep these cameras in tune. Thus, TOF PET largely died at the end of the 80’s. However, the advent of LSO and other new PET scintillators (that can provide excellent timing resolution without the material drawbacks of barium fluoride) makes TOF a promising direction for modern PET.
Why does TOF information affect the noise? The reason is due to the nature of statistical noise in PET images. If there were a single point source in the field of view, then the noise in the image of that source would obey counting statistics. However, the fundamental measurement made in PET is the number of counts observed in a single chord. If activity is placed in another voxel, then counts due to the second source also contribute to the measured activity along the chord containing the two sources, increasing the statistical noise in that chord. Thus, the noise from activity in different voxels is correlated and greater than that from a single source.

Using time of flight information, activity from different voxels can effectively be ignored during reconstruction, provided that the voxels are well-enough separated in space that the timing resolution can distinguish between them. In this case, noise correlations only exist between nearby voxels (rather than all of the voxels), reducing the correlation and making the noise closer to the limit imposed by counting statistics.
Dual modality imaging, especially PET/CT, has become extremely popular recently. PET provides relative low resolution images of function while x-ray CT provides high resolution images of structure. The combination of the two modalities yields more information than either can by themselves. It has been especially useful in cancer studies in the thorax, as PET often cannot determine exactly which organ a tumor is in, while CT often cannot identify tumors. Although this development was first proposed fairly recently, the majority of PET cameras sold today include a CT scanner.
The original hope for PET/CT systems was that both the PET and the x-ray CT portions would image the same “slice” of the patient simultaneously. This turns out to be impractical — even though detectors for both the PET and CT system might each cover less than half of the angle around the patient, the necessary support structures and readout electronics prevent them from easily sharing the same slice. Instead, a complete-ring PET camera and an x-ray CT scanner are offset axially, but share a common patient bed.
Another form of dual modality imaging that has seen a lot of interest recently has been PET/SPECT. The most common configuration is to equip a dual-head gamma camera with coincidence circuitry and to then run in PET mode (i.e., using electronic collimation rather than mechanical collimators to image the 511 keV gamma rays). The performance of these cameras is usually inferior to dedicated PET cameras — the SPECT detector system is not optimized for the higher energy and higher event rates usually found in PET. Manufacturers have worked to improve the PET performance by using thicker scintillator crystal or by using denser scintillator materials than NaI:Tl, but this usually degrades the SPECT performance.
PET / SPECT: PET / SPECT Performance Inferior to PET, But Still Clinically Valuable

*Data courtesy of Tom Lewellen, University of Washington

The success of this concept is likely to hinge on whether the PET performance of these systems, although not as good dedicated PET systems, can still be clinically useful.
Thus far I have described the operation of a PET camera in the ideal world. There are several real world effects that limit the performance of these cameras or require that corrections be made.
A significant problem is the attenuation of the 511 keV photons inside the patient, which can cause a large fraction of the events to be lost. This attenuation is position dependent, and so cannot be accurately modeled or estimated.
Fortunately, it is possible to measure and correct, chord by chord, for attenuation effects in PET. A result is that activity concentration can be measured quantitatively, where the absolute activity concentration in tissue (in units of µCi/cc) is determined. The main drawback is time — the additional time necessary to collect the data needed for the attenuation correction nearly doubles the scanning time.
The attenuation correction is traditionally performed as follows. Consider a positron source inside a uniform attenuator. The probability that the first photon escapes to be detected is given by the expression for $P_1$, while the probability that the second photon escapes to be detected is given by the expression for $P_2$. The event detection probability is the product of these two probabilities (as the two photon detections are independent), and is given by the expression for $P$.

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

\[ P = e^{-\mu \cdot (d_1 + d_2)} \]
Now consider a positron source outside the uniform attenuator, but one that would excite the same chord as in the previous example. The probability that the first photon penetrates the absorber and is detected is given by the expression for $P$, while the probability that the second photon is detected is unity (there is no absorber between it and the detector). Therefore, the event detection probability is just $P$, which is the same as for the internal source. In reality, our absorbers are not uniform, (this merely means that the simple exponential expression turns into a line integral), but the result remains the same: the event detection probability is independent of the position of the positron emitter on the line.

This attenuation measurement is done for all chords using either a hoop containing uniform activity or an orbiting positron source, and is called a transmission scan. This same hoop or orbiting source can also be used, after removing the absorber (i.e. the patient), to correct for individual crystal / chord efficiencies — this is frequently referred to as a hoop or blank scan.

The detector dead time places severe limits on the transmission scan. The transmission source produces very high singles rates (~1 Mhz) in the detector modules closest to it. Significantly higher source strengths (10x – 100x) are greatly desired in order to reduce the time taken for the scan, but detector dead time will not allow any increase in activity.
Transmission Scan

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

This chord by chord attenuation measurement that we have just done represents the same information that is collected in an x-ray CT scan, except the “x-ray” energy is 511 keV. This information can be reconstructed, forming images such as the ones above. The physiological features shown in these images can even be used to help position the patient.
Attenuation Correction w/ X-Ray CT

• 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.

Speaking of CT scans, why not just use the x-ray CT data (if you have a dual mode PET/CT scanner) to obtain the attenuation correction factors? The short answer is that people are, and that this is an active area of research.

X-ray CT gives a high spatial resolution map of the exponential attenuation coefficient $\mu(x)$. Unfortunately, this data cannot be used directly for the PET attenuation correction, as the attenuation coefficients depend on the energy. The x-ray energy is ~70 keV, and the $\mu$ values are significantly different at 511 keV. The most common solution to this problem is to “scale” the attenuation factors. First the image is “segmented”— each voxel is classified as air, tissue, or bone, depending on its $\mu$ value as measured with x-ray CT. Each voxel in the attenuation map is then multiplied by the ratio of $\mu$ values (at 511 keV versus 70 keV). The ratio depends on the tissue type, hence the segmentation. The PET attenuation correction is then based on these computed values. This works quite well, but has some difficulty with misalignment artifacts, inhomogeneous voxels (e.g., one containing half tissue and half bone), and “other” materials in the patient (e.g., CT contrast agent or metallic implants).
Simultaneous decays can cause random coincident “events” that must be corrected for. They can be reduced by using the narrowest coincident timing window possible, but cannot be reduced below 4 ns due to time of flight considerations. Randoms can be corrected for (on a chord by chord basis) by measuring the random event rate. This measurement is usually done by measuring the singles rates for all crystals. Since these random events are uncorrelated in time, the random coincident rate for a give chord is just the product of the singles rates for its two crystals times twice the coincidence window width.
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).

Recon. = (Emission – Randoms) / Attenuation / Efficiency

Attenuation = Transmission / Hoop

Efficiency = Hoop / Hoop_Average

These two effects, attenuation and random coincidences, as well as the individual chord efficiency, can be corrected for on a chord by chord basis. These corrections are usually the only corrections applied in a routine clinical study.

The data that is actually reconstructed is collected as follows. A hoop scan is acquired, and from it the efficiency for each chord is computed by dividing the observed count rate for that chord by the average count rate for chords with a similar geometry (i.e. length). This is typically done once a day, usually before the first patient arrives. Once the patient is in position in the camera, a transmission scan is taken, and the attenuation factor for each chord is computed by dividing its transmission count rate by its hoop count rate. The patient is then injected with the isotope, and an emission scan taken, during which time the random count rate is also measured. For each chord the random event rate is subtracted from the emission rate, and the difference divided by the attenuation factor and the chord efficiency. The resulting value is reconstructed, usually with the filtered backprojection algorithm (although iterative algorithms are seeing an increasing amount of use).
A serious problem that cannot be corrected for on a chord by chord basis is due to events in which one of the 511 keV photons Compton scatter in the patient, then interacts in the detector ring. This results in a coincident event, but it is assigned to the wrong chord. This effect can be reduced by rejecting events with photon energies less than 511 keV, but the energy resolution of BGO is poor enough that this is not very effective (a tight energy threshold rejects too many good events, while a loose energy threshold doesn’t reject much scatter). Scatter between layers in a multi-layer machine can also be reduced using tungsten septa. A current research topic is using the emission and attenuation data to predict, and therefore subtract, the scatter contribution to an image.
Radial Elongation

- 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.

A final problem that affects high resolution tomographs is called radial elongation, and is caused by 511 keV photons penetrating into the detector ring before they interact and are detected. Photons impinging on the face of a crystal at an oblique angle will frequently penetrate and interact in adjacent crystals, which causes the event to be assigned to the wrong chord. The blurring is insignificant near the center of the tomograph ring, but becomes more pronounced the farther the source is from the center. This problem is worse with less dense scintillators such as barium fluoride or sodium iodide. The effect can be removed by measuring the depth of interaction in the scintillator crystal, but few tomographs have yet been built that have this capability.

The combination of the need for high detection efficiency (3 attenuation lengths deep) and this penetration artifact are directly responsible for BGO and LSO being the present scintillators of choice for PET. They have the shortest attenuation length of the commonly available scintillators, and so have the smallest penetration artifacts.
These images give an idea of the magnitude of the radial elongation. The reconstructed image of a point source near the tomograph center is circular and small, but it becomes non-circular and degrades significantly for a point source 14 cm away from the center of a 60 cm diameter camera ring.
I will now define some commonly used measures of PET camera performance.
Spatial Resolution

• Dominant Factor is Crystal Width
• Limit for 80 cm Ring w/ Block Detectors is 3.6 mm

The intrinsic in-plane spatial resolution is mostly determined by the thickness of the scintillator crystal. However, infinitely fine spatial resolution cannot be achieved with infinitely thin crystals – other physical effects such as the photon acollinearity, event mis-positioning in the block detector, positron range, and blurring due to the reconstruction algorithm conspire to worsen the resolution.

The same effects determine the axial resolution, except that it is the crystal height (not thickness) that is the main factor and that the reconstruction algorithm factor is not present.

The spatial resolution in patients is further degraded by patient motion, low statistics, and the partial volume effect (*i.e.* the dimensions of the object vary in the imaged slice).
The major consequence of finite spatial resolution (other than “fuzziness”) is that it limits the ability to obtain quantitative data. If the voxels are relatively large, then they may contain a non-uniform tracer concentration. In this case, the average concentration in the voxel is imaged. This is known as the partial volume effect, and it generally reduces the contrast in the image.
In order to obtain accurate quantitation (i.e., average tracer concentration in a region of interest or ROI), the size of the region that you average over must be two to four times larger in diameter than the reconstructed spatial resolution of the camera.
The sensitivity is a measure of how efficiently the tomograph detects coincident events, and has units of count rate per unit activity concentration. It is measured by placing a water filled 20 cm diameter phantom in the field of view, mixing a known amount of activity into the water, and measuring the resulting coincident event rate. High sensitivity is desired, as it implies more efficient use of the isotope. Most tomographs have high individual detection efficiency for 511 keV photons impinging on the detector (>80%), so the sensitivity is mostly determined by geometrical factors, that is, the solid angle subtended by the tomograph. As more slices are added, the solid angle coverage increases and you obtain higher system sensitivity. Note that sensitivity is proportional to the square of the slice thickness – not only is the solid angle proportional to thickness, but the amount of activity in the field of view is also proportional to the thickness.
If the septa are removed, the solid angle increases and thus the sensitivity increases. However, the scatter and randoms also increase greatly. Imaging with inter-plane septa is known as 2-D PET, while septaless imaging is known as 3-D PET.
Sensitivity Includes Noise from Background

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

Image Noise Not Determined by Sensitivity Alone!

However, sensitivity is not everything, and can even be misleading because it includes background events. Even if you are able to subtract the average values of these backgrounds, you cannot subtract their statistical fluctuations.
Noise Equivalent Count Rate (NECR)

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

NECR Properties:

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

Maximize NECR to Minimize Image Noise

A measure that attempts to correct for these background events is the “noise equivalent counts.” This measure is the product of “true” events and the contrast, which is defined as the fraction of the total events that are “true.” A nice feature of the noise equivalent count measure is that it includes the statistical uncertainties that background processes add and so it obeys counting statistics, that is, its standard deviation is equal to its square root. The noise equivalent count equation assumes that scatter and randoms are subtracted perfectly (and so the only noise they contribute is from the fluctuations about their mean), but scatter is difficult to measure or model accurately. Therefore, the noise equivalent counts is not always an accurate measure of imaging ability either!
The True and Scatter event rates are proportional to the activity density, but the Random event rate is proportional to the square of the activity density. Therefore, the NECR depends on the activity density. At low activity concentration, the True term dominates and the NECR increases nearly linearly with activity concentration. If the same camera is operated with or without septa, the slope is steeper (at low activity) in 3-D mode than in 2-D mode. At higher activity concentrations the Randoms outnumber the Trues and dead time losses become significant, causing the NECR to decrease with increasing activity concentration! The maximum possible NECR is higher when a camera is operated in 2-D mode than it is when operated in 3-D mode. This is because the septa remove more Scatter and Random background than True events, yielding a higher quality signal. However, this peak NECR signal always occurs at higher activity concentration in 2-D as compared to 3-D, and can occur at activity concentrations that exceed the maximum allowable dose to the patient. Finally, while the general trends are reasonably invariant, the numerical values for the NECR are very sensitive to the phantom size, as well as the exact definitions of True, Random, and Scatter events. Thus, you must be extremely careful when comparing NECR values obtained with different cameras.
There is a written standard from NEMA (http://www.nema.org) for evaluating the performance of a PET camera. Definitions and descriptions on how to perform the various performance measures are explicitly defined. These definitions and standardization are badly needed, as relatively subtle changes in the phantom geometry or measurement definition can significantly change the numerical result.
Finally, we turn to the clinical uses of PET. It is used to image metabolism, so is used mostly to image organs whose size or shape does not tell whether they are functioning (such as the brain or the heart), or with diseases the exhibit a metabolic abnormality (such as cancer). The disease or dysfunction that you are looking for determines which compound and isotope is used.
Brains metabolize sugar, so a commonly used agent for measuring brain metabolism is a fluorine labeled sugar analog called FDG (short for fluorodeoxyglucose). The brain begins to metabolize FDG as if it were sugar, but cannot metabolize it fully, and so it accumulates in the brain tissue rather than being washed out. This property is very helpful, because it means that the tracer becomes concentrated in the tissue rather than being ejected and diffusing throughout the body.

While other modalities (based only on structure) can detect the initial formation of a tumor more easily than PET can, they have difficulty determining if a tumor is responding to treatment. Cancers usually have different metabolic rates than normal brain tissue (higher or lower, depending on the type), so a FDG image can tell you if a tumor is still alive or not. The picture above shows a recurrent tumor, as evidenced by the bright ring of new growth surrounding the dark tumor core.
Alzheimer’s disease is characterized by decreased metabolism in certain parts of the brain. While there is no known cure for Alzheimer’s disease, there are several curable diseases that have similar symptoms, and PET can be used to rule these out. PET can also be used to measure the effect of experimental “cures.” The picture above shows a patient with 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.

The difference between anatomical images and metabolic images is shown by this epileptic patient. The NMR image of an epileptic looks like a normal brain, while the PET image shows an increase in activity in regions that are associated with the epileptic area.

While the actual determination of the “focal centers” that cause the epileptic seizures is somewhat complicated, PET can be used to determine the location of these focal centers, which then can be surgically removed.
Heart Tissue Viability

- Patient has heart attack but lives.
- Heart always sustains some damage.
- How badly is the heart damaged?
  - Badly ⇒ Coronary bypass.
  - Not Badly ⇒ No surgery.
- PET measures degree of damage.

The ability to quantitatively measure metabolism is vital when imaging heart attack patients. There is always some damage after a heart attack; PET tells you how much damage and whether the damaged tissue has any hope of recovering. This knowledge can then be used to determine whether or not to perform bypass surgery, which is one of the important clinical applications for PET.

The image above is of the left ventricle of a human heart (which is the chamber that pumps blood through our body). This chamber’s shape is similar to an African drum — roughly cylindrical, with one open end and the other end tapering down until it closes. The imaging plane shown is perpendicular to the axis of this cylinder, and a healthy heart would show up as a uniformly thick, uniformly bright circle. This patient’s heart has sustained some damage, which shows up as a dark area in the otherwise uniform circle.
Many types of cancer, including breast cancer, have a significantly higher uptake of FDG than either normal tissue or benign tumors do. This property allows PET to screen patients for tumors, search for metastases (which are difficult to see with other modalities, since they are small and can occur anywhere in the body), and evaluate the effect of treatment (since it provides information on metabolism).

The three images above show the response of a breast cancer patient to chemotherapy. Before therapy, metastases are visible in the axillary (armpit) and mediastinal (center of the chest) nodes, as well as in the lung. Two months after chemotherapy was begun, all tumors are in remission except the one in the lung. After four months of chemotherapy, all tumors are in remission. The other visible objects in these images are the brain, the bladder, and the heart.

These images were obtained with a technique known as the whole body scan. A multi-slice (24 plane) PET camera with a large axial field of view (15 cm) is used, and the patient is imaged in several 15 cm thick sections. To save time, transmission data is not collected, so these images are not corrected for attenuation. The “gray scale” is opposite from the previous images — regions of large uptake appear dark and regions of low uptake appear light.
Further Reading


http://laxmi.nuc.ucla.edu:8000/lpp/ “Let’s Play PET”, an outstanding tutorial from UCLA covering many instrumentation and clinical aspects of PET.

http://www.icppet.org/ WEB site for the Institute for Clinical PET, which is concerned with clinical acceptance for PET.

The Sandler book has good sections on PET and SPECT, as well as sections on the clinical aspects. The Derenzo article is hardware oriented, and has remained surprisingly current. The Moses article is also hardware oriented. The other references include some hardware, but tend to focus on the clinical and medical research uses of PET. While not listed above, there was a seven part series of review articles (from 1979 to 1986) in the Journal of Computer Assisted Tomography whose titles began with “Quantitation in Positron Emission Computed Tomography”. All had either E. J. Hoffman or M. E. Phelps as one of the authors. Finally, I hesitate to put down WEB sites as references due to their volatility, but the “Let’s Play PET” WEB site is extremely informative and well worth the visit.
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