Small Animal PET and Monte Carlo simulation

What is PET?

Positron Emission Tomography (PET) is a non invasive imaging technique that provides three-dimensional (3D) tomographic images of radiotracer distribution within a living subject (1). Molecular probes can be labeled with positron-emitting nuclides (^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{64}C, etc) and administered into subjects via different routes. These proton-rich radionuclides spontaneously convert a proton to a neutron, resulting in the emission of a positron and a neutrino. The emitted positron equal in mass and opposite in charge to an electron, slows down through a series of collisions with the surrounding matter, then combines with an electron before it annihilates. The mass of positron and electron is converted to two high energy photons of 511 keV each that travel in approximately opposite directions (2). Coincidence detection of these gamma rays, which are highly penetrating and can escape from the subject, and reconstruction of the location of the annihilation events using analytical or statistical methods form the basis of PET.

With its dynamic capability, PET provides both spatial and temporal measurements of the distribution of the biomolecules within a living subject. Combined with kinetic modeling, PET provides quantitative measurements of biological processes in vivo. This unique factor and the wide variety of biomolecules that can be labeled with positron-emitting nuclides of different half-lives make PET an extremely powerful tool to study normal development and diseases in humans, the pharmacokinetics of new drugs, and animal models of human diseases.

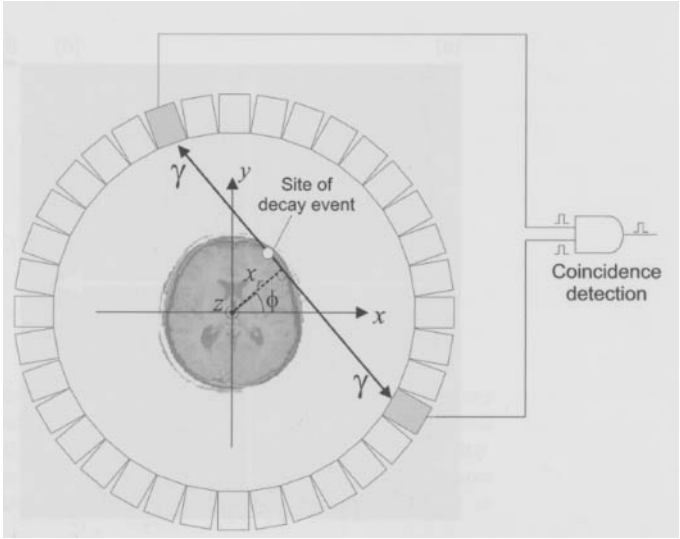

Figure 1.- Coincidence detection in PET

Instrumentation

Detector Technology

The highly penetrating nature of 511 keV gamma rays requires PET detectors to have sufficient stopping power to effectively detect the signal. At this energy, gamma rays interact with detectors primarily through Compton scatter and photoelectric

interaction. The photoelectric interaction is the preferred mechanism for detection because the energy of the incoming gamma ray is completely absorbed, which allows energy discrimination to reject gamma rays that have undergone Compton scatter in the subject. We are interested in detectors made of high atomic number (Z) and high-density material to maximize the photoelectric cross-section and detector efficiency for PET applications.

Coincidence detection of the annihilation gamma rays further requires the detectors to have quick timing response to minimize the effects of random coincidences. Random coincidences occur when two gamma rays from different annihilation events are detected by two detectors within a predetermined timing window (3). Random coincidences introduce statistical noise in the data and may become the primary limiting factor of system performance at high counting rate applications (4). The amount of random coincidences is directly proportional to the width of the predetermined timing window. An improvement in detector timing response can extend the operation of a PET system to high-activity experiments, resulting in a wider dynamic range and better counting rate performance.

Another factor is scatter, which occurs when one of the annihilation gamma rays undergoes a Compton scattering inside the subject or the detectors. Intrasubject scatter reduces the contrast of the image and can be significant for a large subject, such as a human, in a 3D PET system. Intra or inter detector scatter, however, may or may not cause mispositioning of the event depending on the detector design. The preferred correction is to design the detector so that the location of the initial Compton interaction can be identified and the coincidence event can be preserved. Detectors with good energy resolution have the potencial to implement these more sophisticated scatter corrections.

Inorganic scintillator with high density, high Z, and quick decay time have been the dominant detector technology for PET. The scintillation mechanism depends on the energy states of the crystal lattice of the material. The 511 keV gamma rays interact with the scintillation crystal and produce photoelectrons or Compton electrons. These energetic electrons produce a large number of electron-hole pairs that can drop into the impurity sites within the crystal lattice. Electrons at the excited states release energy through fluorescence to produce light photons, which are then detected by secondary photon detectors.

Scintillation material	**Density (g/cm^3)**	**Effectiv Atomic Number (Z)**	**Primary decay constant (ns)**	**Emission Intensity (% relative to NaI)**	**Emission wave-length (nm)**	**Attenuation coefficient at 511 keV (cm^{-1})**
NaI(Tl)	3.67	51	230	100	410	0.35
LSO	7.40	65	40	75	420	0.86
GSO	6.71	59	60	30	430	0.70
BGO	7.13	75	300	15	480	0.95
YAP	5.55	32	27	40	350	0.37
BaF_2	4.88	53	2	12	220, 310	0.45
YSO	4.45	36	70	45	550	0.36
LGSO	7.23	65	60	40	420	0.84
LuAP	8.34	64	17	30	365	0.87

Table 1.- Physical and optical properties of commonly used scintillation materials in PET

Scintillators detectors require a secondary detector to convert the scintillation light to

an electric signal. For PET applications, this secondary detector needs to be sensitive to the emission spectrum of the scintillator and provide adequate signal amplification and quick timing response. The most common light detector is the photomultiplier tube (PMT). PMT provides several stages of charge amplification to achieve a typical gain of more than 10^6. It also provides excellent timing response, which is ideal for PET applications. The primary disadvantage of PMT is the relatively low quantum efficiency of the photocathode and the high manufacturing cost. Nevertheless, it is still the most widely used light detector in PET to date and provides the highest performance in terms of spatial and timing resolutions for all scintillation-based detector.

Detector Design

Coincidence detection of the annihilation gamma rays is an indirect measurement of the positron origin. The spatial resolution of a PET system is known to be limited by three factors: (a) positron range, (b) acolinearity of positron annihilation, and (c) detector intrinsic resolution. A positron travels a short distance from its origin before it annihilates. Depending on the radionuclide, the average positron range varies from a few hundred micrometers to a few milimeters (table 2). The average positron range should not be confused with the resolution loss due to the range effect, which is significantly smaller than the average positron range.

Radionuclide	**^{11}C**	**^{13}N**	**^{15}O**	**^{18}F**	**^{45}Ti**	**^{60}Cu**	**^{61}Cu**
$Energy_{avg}$(MeV)	0.386	0.492	0.735	0.250	0.349	0.977	0.499
$Range_{avg}$(mm)	1.52	2.05	3.28	0.83	1.78	4.50	2.09

Radionuclide	**^{62}Cu**	**^{64}Cu**	**^{66}Ga**	**^{76}Br**	**^{82}Rb**	**^{86}Y**	**^{94m}Tc**	**^{124}I**
$Energy_{avg}$(MeV)	1.315	0.278	1.744	1.184	1.475	0.666	1.072	0.818
$Range_{avg}$(mm)	6.21	0.97	8.37	5.55	7.02	2.93	4.98	3.70

Table 2.- Average energy and positron range in soft tissue for commonly used positron emitters

The positron also does not come to a complete stop at the instant of annihilation. To conserve the momentum and energy, the two emitted gamma rays travel at directions that are slightly deviated from 180°. The angular distribution of the deviation was reported to have a mean of 0.5° FWHM (5). The uncertainy in identifying the source of origin is also proportional to the distance between a pair of detectors in coincidence. This can be expressed as FWHM(acolinearity)= 0.0022·D, where D is the distance between a pair of detectors (6).

The sensitivity of a PET system is determined by the geometric efficiency of the system and the intrinsic detection efficiency of the detectors. The geometric efficiency of a system is the probability of the annihilating gamma rays intercepting the detectors, which corresponds to the solid angle coverage of the detectors. The closer a detector is positioned to the source, the larger the solid angle it can cover.

The intrinsic efficiency of a detector is the probability of detection when a gamma ray intercepts the detector, a factor related to the composition and thickness of the detector material. The probability of interaction grows as the thickness increases. When a gamma ray enters a detector, the depth of interaction may result in uncertainty in the identification of the origin of the gamma rays (7). This effect is ilustrated in figure 2. If the source is located near the center of the FOV, gamma rays enter the two detectors at near-normal angle. The depth of interaction does not affect the positioning accuracy of the coincidence line-of-response (LOR) defined by the two detectors. When the source is off-center, the gamma rays enter the detectors at an oblique angle that increases with the radial offset of the source. Depending on the depth of interaction (DOI), the detector in which the interaction occurs may not be the

same detector that initially intercepts the gamma ray. If the design of the detector can identify the depth of interaction, the coincidence LOR can be accurately defined. However, if the detector is not capable of providing DOI information and only assumes a predetermined depth as the interaction point, there is a finite probability that the coincidence LOR is mispositioned. The loss of radial resolution can be seen in figure 2 as the source is moved away from the center of the FOV. This parallax error caused by the DOI effect depends on four factors: (a) the radius of the system, (b) the total depth of the detector, (c) the radial offset of the source, and (d) the detector material.

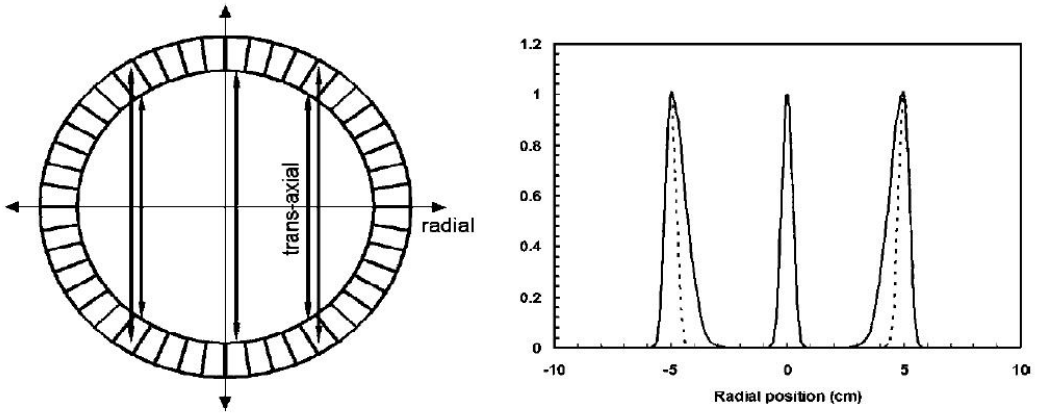

Figure 2.- A PET camera with cylindrical geometry has detectors arranged in single or multiple rings (left). A gamma ray originating near the center enters the detector at near-normal angle. The depth of interaction of the gamma ray in the detector does not affect the positioning of the coincidence LOR. If the source is off-center, each gamma ray travels along the path that may intercept multiple detectors. The depth of interaction determines which detector along the path will receive the signal. If this DOI is unknown, an uncertainty in the accurate positioning of the event arises. The radial resolution of the system is reduced as the detection profile widens at large radial offset (right).

Combining these factors, one would see that a small system radius leads to higher geometric efficiency at the cost of loss of radial resolution. Reducing the depth of the detector can reduce the DOI effect and preserve the image resolution, but at the cost of lower intrinsic detection efficiency. If one restricts the radial offset of the source to preserve both sensitivity and resolution, the system will have a very limited imaging FOV that may be acceptable.

Scintillation crystal-based PET detectors can be divided into three categories: continuous crystal, block detector, and discrete crystal, as ilustrated in figure 3. In the three cases, the detectors can be configured as full rings that completely surround the patient of as partial rings with rotational motion to obtain the needed angular sampling.

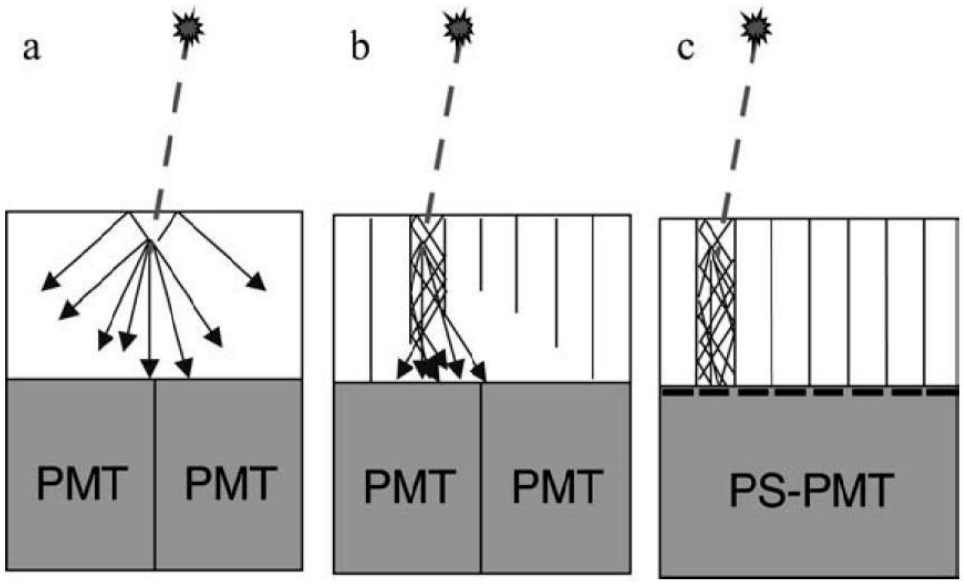

Figure 3.- Three common designs for scintillation-crystal-based PET detectors: (a) continuous crystal detector, (b) block detector, and (c) discrete crystal detector. The location of gamma-ray interaction in the detector can be calculated from the weighted PMT signals for the continuous crystal detector and block detector. For the discrete crystal detector, individual crystals can be decoded by position-sensitive light detectors, such as position sensitive PMT (PS-PMT) or multichannel PMT.

Image Reconstruction

After the gamma-ray data have been acquired, the next step is to compute, or reconstruct, images from these data.

Conventional approaches to image reconstruction from PET data are based on the method of Filtered Back Projection (FBP). FBP is a mathematical technique based on an idealized model of PET data that ignores many significant features of real data. Specifically, FBP assumes that the number of detected gamma-rays events traveling along a particular direction approximates an integral of the radiotracer distribution along that line, that is, the parallel projection $p(x_r,\phi)$ defined in the figure 4. In spite of its approximate nature, FBP has enjoyed widespread use and great longevity, largely because of its computational simplicity.

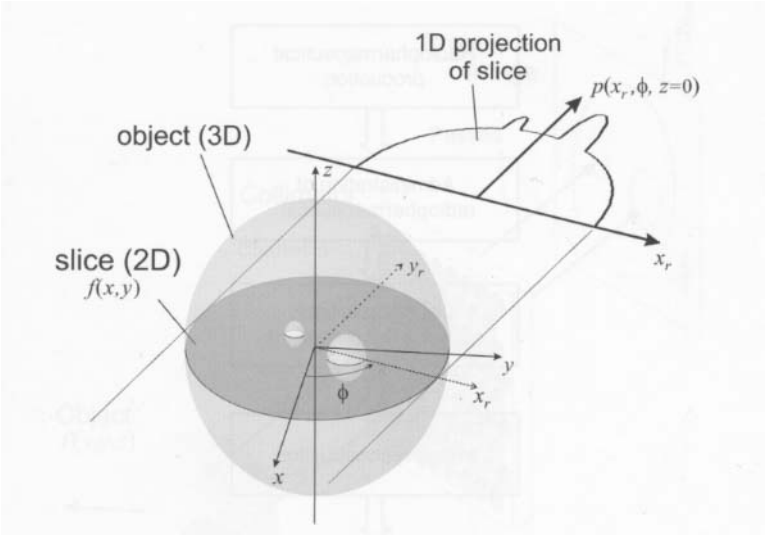

Figure 4.- One-dimensional parallel projection of a two-dimensional slice through an object.

We should bear in mind that introducing FBP, we neglect all the important effects that FBP fails to consider, such as noise, attenuation, scatter, and blur. Suboptimal, but reasonable, results can be obtained in practice using FBP, even if attenuation, scatter, and blur are not accounted for. However, noise must always be accounted for in some way, and this is usually achieved in FBP by smoothing the projections prior to reconstruction or by smoothing the image afterward.
To illustrate the workings of the FBP, let us suppose we wish to image the 2D slice of the simple object shown in figure 4. The figure illustrates the parallel projection of this slice at angle ϕ. To form a complete PET data set, PET systems measure projections from many points of view about the object (i.e., projections for many values of angle ϕ). Our particular slice, which is shown as an image in figure 5a, yields a set of projections $p(x_r,\phi)$ that can itself be viewed as 2D image (Fig. 5b) with dimensions x_r and ϕ. This image is often referred to as a sinogram because a point source traces out a sinusoidal path through this diagram.

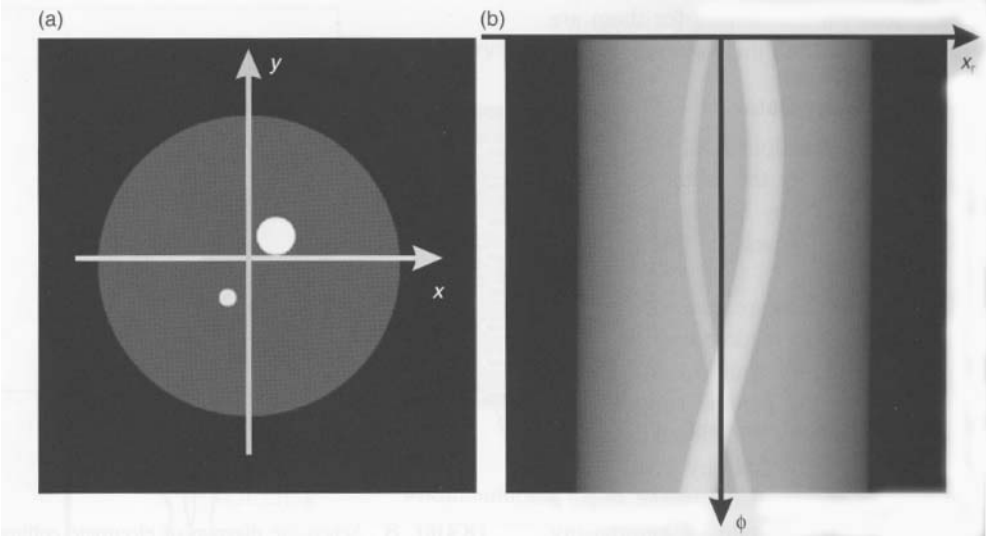

Figure 5.- (a) Image of object slice f(x,y) and (b) sinogram $p(x_r,\phi)$ of this slice

To turn the sinogram into the image, the FBP algorithm uses a procedure called backprojection, which consists of smearing each projection back into the object region along the direction ϕ in which was measured. Figure 6a shows the process of idealized forward projection, and figure 6b shows the process of backprojection for a single angle ϕ. By backprojecting the projection for every angle into the image region and adding together the results of all these smearing operations, one can obtain a reasonably good representation of the original object, but the result will be somewhat blurry. It turns out that backprojection is nearly the correct way to produce the image from the sinogram; however, backprojection alone produces an image that is blurred. Thus, the FBP algorithm involves the application of a sharpening operation to the projections that exactly cancels the blurring effect.

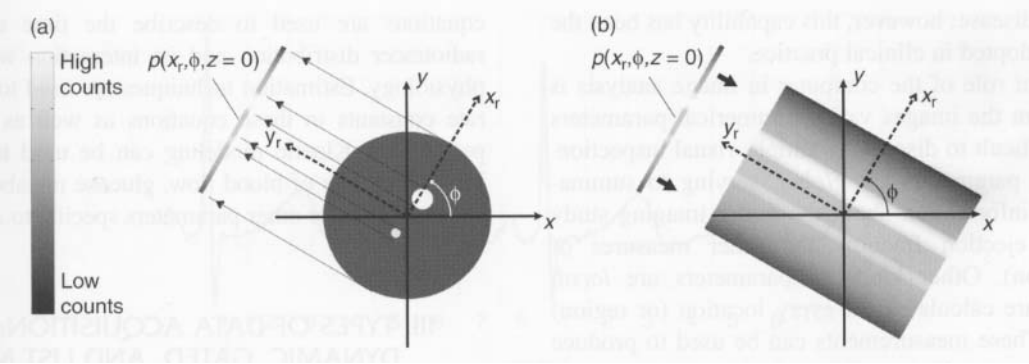

Figure 6.- (a) Idealized forward projection of image slice for a particular angle and (b) backprojection for the same angle. Bright areas of the image and projection denote high count rates, as indicated by the color bar a far left. Actual PET data are not well described by this simplified projection model because of attenuation, blur, scatter, and noise; however, the model does capture the essential process of forming an image from projection data. With proper corrections, the filtered backprojection method produces reasonably good images in spite of its adherence to an idealized model of the imaging process.

The method of FBP is an example of category of image reconstruction approaches referred to as analytic methods to distinguish them from iterative methods. Analytic methods typically neglect noise and complicating physical factors in an effort to obtain frameworks that yield explicit inversion formulas for the reconstruction problem. Analitic methods usually produce solutions that are relativily practical to compute and provide insight about data-acquisition issues such as sampling.

Iterative algorithms are based on the attempt to maximize or minimize a target function determined by the particular algorithm used. The target is reached through several analytic processes called iterations. A major advantage of this type of algorithm is the possibility of incorporating different a priori information, such as noise component, attenuation, or characteristics of detector nonuniformity, for more accurate image reconstruction; however, it must be pointed out that inclusion of additional parameters means increase in processing times.

Depending on the method, different numbers of iterations are required to reach the target function, keeping in mind that too many iterations can easily lead to noise amplification with image quality deterioration. For this reason, it is important to perform an accurate evaluation of the number of iterations needed to obtain the best image quality. Different iterative algorithms are present in literature, some base on methodologies of numeric linear algebra and other based on statistical approaches. To the latter class belongs the maximum-likelihood expectation maximization (MLEM), which is able to estimate more accurate radiotracer distribution. The MLEM is based on the maximization of the logarithm of a Poisson-likelihood target function (8). The attempt is to obtain a reconstructed slice whose forward projection generates a projection dataset almost equal to the original one. The main feature of its reconstruction algorithm is to update the image during each iteration by using a multiplicative factor assessed as the ratio between the original acquired projections and the newly estimated ones. Advantages of this iterative method are very low noise amplification without loss of spatial resolution and the fact that all reconstructed values will be positive because a nonnegativity condition is imposed on the original data. The main disadvantage is the large number of iterations required to converge to an optimal solution and then the long processing times, hampering its aplicability in clinical routine.

To overcome the problem of slow convergence rate, the ordered-subsets expectation maximization (OSEM) algorithm was proposed in 1994, which is now the most widely used iterative reconstruction method in whole-body PET imaging (9).

The OSEM is a modified version of MLEM (the target is still the maximization of the log-likelihood function) with the main difference being that projections are grouped into subsets having projections uniformly distributed around the volume to be imaged. Within each iteration the target function is update as many times as the number of subsets, proportionally accelerating convergence. An optimization of subsets and iterations number is required when the method is applied to real, noisy data, because the algorithm can cycle without converging to the MLEM function.

Why use PET in Laboratory Animal Research?

Many of the traditional medical imaging technologies, including positron emission tomography (PET), are being adapted for use in small laboratory animal imaging. PET can be viewed as an in vivo counterpart to autoradiography, tissue detection and other techniques that involve imaging or counting excised tissue samples taken from animals into which a radioactively labeled tracer has been introduced prior to sacrifice. The advantage of a non invasive imaging technique such as PET is that the entire time course of the biodistribution or a radiolabeled tracer can be determined in a single living animal. Furthermore, that animal can be studied again at a later time, permitting longitudinal, within-subject study designs to follow desease models and interventions over periods of days, weeks, and even months. Because the same animal is used at every time point, each animal serves as its own control and variability due to interanimal differences is effectively removed. Therefore, a single animal studied multiple times by PET may in some instances provide the same data that would have required tens of animals using traditional invasive techniques that requires sacrifice of the animal. This clearly is in keeping with the desire to reduce the number of laboratory animals used in experiments, but equally important, it has the potential to dramatically reduce the cost of experiments and to speed up the availability of results. It may also improve the quality of the data (because of the within-subject design), although this has yet to be unequivocally demonstrated.

A large number of positron-labeled compounds have been syntheized (10) thus enabling a wide range of biological processes to be measured quantitatively, non-invasively and repeatedly using PET (11). Combined with the very high sensitivity of radiotracer methods, this flexibility to interrogate living biological systems at the level of specific enzymes, proteins, receptors, and genes makes PET extremely attractive for studies in laboratory animals.

A final important advantage of using medical imaging techniques such as PET in small animal models of desease is that imaging provides a bridge between the animal model and human studies. A valid concern in the use of animal models relates to how well that model predicts what will happen in the human. Techniques such as PET provide the opportunity to perform exactly the same experiments in mouse and human, facilitating direct comparison and appropriate interpretation of the animal model data.

Challenges of the small animal PET?

Challenges common to all imaging techniques include (a) the design of probes or probing techniques that are highly specific to the biological processes of interest, (b) optimization of imaging systems to provide the highest sensitivity and image resolution, and (c) minimization of perturbation to the biological processes under observation so that the experimental outcomes correlate to the biology and not the probing process.

There are a number of issues that must be carefully considered in animal PET studies. Some of these have much in common with designing and optimizing PET scanners for human imaging; others are problems specific to small animal imaging. The

underlying challenge, as always, is to obtain as many counts as possible and to localize these counts as accurately as possible. Accurate localization of counts depends primarily on the spatial resolution of the detectors and the ability to remove or correct events such as scatter, accidental coincidences, and pile-up that are incorrectly positioned. Maximizing the detected counts requires injection of the maximum radioactivity possible based on mass and specific activity considerations, and using an imaging system with high-efficiency detectors and large solid-angle coverage. The system must also be able to run at high counting ratees so that no counts are lost to dead time and have a narrow timing window to minimize accidental coincidences.

The first challenge to PET imaging technology clearly comes from the vast difference in physical size between the subject for which clinical PET systems have been developed, the human (weight ~70 kg), and the laboratory rat (weight ~300 g). This represents more than 200 fold decrease in volume. Laboratory mice, at ~30 g, account for another order of magnitude decrease in volume. Therefore to achive similar image quality and to address the same biological questions in mice that can currently be studied in humans, PET system must be developed with similar improvements in spatial resolution. This suggest a reconstructed spatial resolution <1 mm in all directions (<1 μl in volume) as opposed to the ~10 mm (~1 ml in volume) reconstructed image resolution typical in human whole body studies. This stringent requirement calls for new approaches in both detector materials and design.

The absolute detection sensitivity of the imaging instrument (the fraction of radiactive decays that result in a detected event) must be at least as good, and preferably much better than, the typical PET scanner. Whole-body human PET scanners detect on the order of 0.3-0.6\% of the coincident annihilation photons in two-dimensional (2D) mode and 2-4\% in 3D acquisition mode (12, 13). For sensitivity is clearly not possible to use the previous argument. Even with perfectly efficient detectors and complete solid angle coverage around the animal, the best we can hope to achieve is about 200-fold increase in 2D mode and 30-fold increase in 3D mode. An approach to compensate for the sensitivity problem is to use more sophisticated reconstruction algorithms that make better use of the available counts. Iterative algorithms that accurately model the physics of the scanner and the statistics of the raw data will probably play an important role in very-high-resolution PET studies because they can produce improvements in either resolution or signal-to-noise relative to analytic reconstruction algorithms. Another approach can be to inject larger amounts of radiactivity, but there are some fundamental issues that limit how far the dose can be raised and we will discuss them below.

One might be tempted to think that because laboratory animals are not subject to the same radiation exposure rules and procedures applicable to humans, the injected dose per gram of tissue could be adjusted upward, thereby increasing the detected counts per resolution element and overcoming some of the sensitivity challenges outlined above. However, the whole idea of a tracer kinetic experiment is that the mass levels are sufficiently low so as not to perturb the biological system under study. For a given specific activity of radiotracer (the fraction of the molecules in the tracer solution which are radiolabeled at a given time and it is expressed in units Bq/g becquerels per gram or, more commonly, in concentration units of Bq/mol becquerels per mole), the injected mass is lineraly proportional to the injected activity. There are many circumstancies in which the tracer mass will limit the amount of radioactivity that can be injected into a mouse in the range of 0.037 to 3.7 MBq (14). The amount of mass that can be injected without violating tracer principles must be carefully determined on a case by case basis.

There are cases in which relatively large amounts of radioactivity can be injected into

an animal, in these cases dead time and count rate performance may become the limiting factor.
Other factors, such as energy resolution, dead time characteristics, the ability to perform attenuation correction, and imaging field-of-view (FOV), pose different constraints to the design of detector and system and need to be taken into consideration. The accuracy of the biological models derived from animal PET experiments depends on the quantitative accuracy of imaging. PET data needs to be corrected, notably for normalization, attenuation, scatter, and dead time, to achieve quantitative images. The implementation of these correction techniques can be affected by the choices of the system design. Compromises in performance characteristics are often necessary, and should consider the targeted applications of the system, the availability and cost of technologies, and the ease and cost operation.

Monte Carlo Simulation

Monte Carlo methods are numerical calculation methods based on random variable sampling. The technique of random sampling to solve mathematical problems has been known since 1770. Only with the advent of quantum mechanics in which matter-radiation interactions were interpreted using cross sections as probabilities, the random sampling technique (name "Monte Carlo method" because the Monte Carlo casino was the most famous centre for playing games involving random drawing) was applied to nuclear physics. In the early 1960s, the Monte Carlo method was used by H.O. Anger to simulate the physical response of his new scintilliator camera. Since then, thanks to the possibility of modelling different physical processes independently, the method has been applied in medical radiation physics to a wide range of problems that could not be easily addressed using experimental of analytical approaches. As proofs, an increasing number of scientific papers concerning Monte Carlo studies in nuclear medicine, radiation therapy, diagnostic X-rays as well as radiation protection have come in the scientific literature (figure 7).

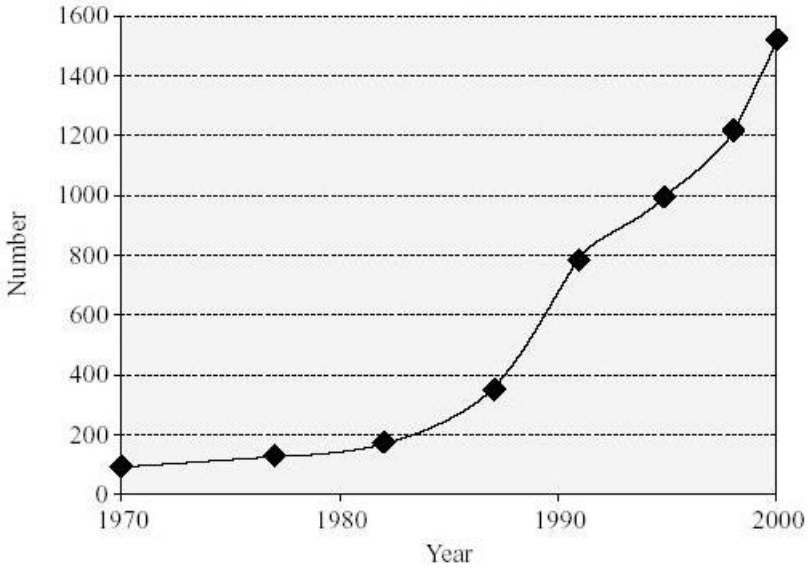

Figure 7.- Number of published papers on Monte Carlo applications in medical radiation physics from 1970 to 2000.

In Nuclear Medicine, and particularly in SPECT (Single Photon Emission Computed Tomography) and PET, the use of Monte Carlo methods was advantage by the possibility of using general purpose codes developed for high energy physics or dosimetry. High-energy (>1 MeV) processes, secondary and low-energy radiations

could be neglected as they were not involved in SPECT and PET. On the other hand, the similarity of physical and geometrical characteristics of most emission tomographs suggested specific models to be developed thus favouring the creation of codes dedicated to simulations of emission tomography configurations.
Several SPECT/PET dedicated Monte Carlo software packages were developed for simulating a variety of emission tomography studies. Among them, public domain codes have been made available in last years, allowing the use of the Monte Carlo method by the whole scientific community and even in the clinical environment.
Several topics were addressed by Monte Carlo simulations in both PET and SPECT, among which optimisation of imaging system design (including detector, collimator, and shield design), development of correction methods for improved image quantitation, evaluation of correction techniques (scatter/randoms/attenuation correction, partial volume effect), development and assessment of image reconstruction algorithms, ROC studies, pharmaco-kinectic modelling.
Two types of Monte Carlo codes can be used for simulating SPECT and PET: 1)general purpose code, which simulate particle transportation and were developed for high energy physics or for dosimetry, 2)dedicated codes, designed specifically for SPECT or PET simulations. Table 3 summarises the main codes currently available. General-purpose packages include well-validated physics models, geometry modelling tools and efficient visualization utilities. However, it is quite difficult to taylor these packages to PET and SPECT. On the other hand, the dedicated Monte Carlo codes developed for PET and SPECT suffer from a variety of drawbacks and limitations in terms of validation, accuracy and support (15)
All Monte Carlo codes share some common components, such as random number generator, rules to sample probability distributions, and sets of probability density functions. The features that make the codes different are related to the accuracy, flexibility, efficiency and ease to use of the codes.

Generic codes	
Dedicated codes	**EGS4 (radiation dosimetry) [16]** **MCNP (radiation dosimetry)[17]** **ITS (high energy physics)[18]** **GEANT 3 (high energy physics)[19]** **GEANT 4 (high energy physics)[20]**
SPECT only:	**SIMIND[21]** **SimSPECT (derived from MCNP) [22][23]** **MCMATV[24][25]**
PET only:	**PETSIM[26][27]** **EIDOLON[28]** **Reilhac[29]** **PET-EGS[30]**
SPECT and PET:	**SIMSET[31][32]**
Dedicated based on Generic codes:	
SPECT and PET:	**GATE (based on GEANT 4)[33]**

Table 3.- Main Monte Carlo codes currently available for SPECT and PET simulations

The accuracy of the code depends on: 1) the particle interactions which are simulated and how they are simulated; 2) the components of the detector that are simulated and how interactions in these components are modelled; 3)whether the code has been extensively tested for bugs and validated.
The flexibility of the code depends on: 1) the types of source distributions that can be simulated; 2) the types of detectors that can be modelled; 3) the types of acquisition configurations that can be set up; 4) the types of output data can be generated.
The efficiency of the code mostly depends on the type of optimisation strategies adopted to increase the speed of simulations. Indeed, the major drawback of Monte Carlo methods is the high computation burden required to perform simulations with numbers of events representative of those involved in SPECT and PET.
Apart from programming virtuosity, the most common optimisation strategies concern: 1)analytical models of physical effects, allowing Monte Carlo simulation of some processes to be avoided while taking into account the resultant effects a posteriori, on the final response of the system; 2) approximations, based on geometrical considerations, in configuring tomographs and radioactive sources; 3)variance reduction techniques; 4) parallelisation techniques.
Finally, the ease of use of a code is a function of: 1) the programming language and the supported platforms; 2) whether the code is in the public domain; 3) the availability of documentation and support.
One of the most important issues related to the use of a Monte Carlo code is how the code has been validated. Obviously, the problem of validation is strictly connected with the problem of accuracy: only the results of thorough validation studies can warrant the accuracy of a code. The problem lies in defining "thorough".
For both general purpose and dedicated Monte Carlo codes, validation deals at least with two aspects: 1)validation of the models for radiation emission, transport and interactions from the radioactive source to the measurement system; 2) debugging. In the case of dedicated codes or when a general purpose code is used for simulating PET and SPECT configurations, there is a third important aspect: validation of the code with respect to the actual response of the measurement system, in our case, the tomograph.

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