PET

PET

PHYSICS, INSTRUMENTATION, AND SCANNERS

Michael E. Phelps, PhD

Norton Simon Professor
Chair, Department of Molecular and Medical Pharmacology
Director, Institute for Molecular Medicine
Director, Crump Institute for Molecular Imaging
University of California School of Medicine
Los Angeles, California

Springer

Michael E. Phelps, PhD
Norton Simon Professor
Chair, Department of Molecular and Medical Pharmacology
Director, Institute for Molecular Medicine
Director, Crump Institute for Molecular Imaging
University of California School of Medicine
Los Angeles, CA 90095, USA

Simon R. Cherry, PhD
Professor, Biomedical Engineering,
University of California, Davis,
Davis, CA 95616, USA

Magnus Dahlbom, PhD
Associate Professor, Department of
Molecular and Medical
Pharmacology/Nuclear Medicine,
David Geffen School of Medicine,
University of California,
Los Angeles, CA 90095-1735, USA

Library of Congress Control Number: 2006920199

ISBN-10: 0-387-32302-3

ISBN-13: 978-0387-32302-2

Printed on acid-free paper.

Printed in the United States of America. (EB)

9 8 7 6 5 4 3 2 1

www.springer.com

CONTENTS

PET: Physics, Instrumentation, and Scanners

Simon R. Cherry and Magnus Dahlbom

Positron emission tomography (PET) is a nuclear imaging technique that uses the unique decay characteristics of radionuclides that decay by positron emission. These radionuclides are produced in a cyclotron and are then used to label compounds of biological interest. The labeled compound (typically 10^{13}–10^{15} labeled molecules) is introduced into the body, usually by intravenous injection, and is distributed in tissues in a manner determined by its biochemical properties. When the radioactive atom on a particular molecule decays, a positron is ejected from the nucleus, ultimately leading to the emission of high-energy photons that have a good probability of escaping from the body. A PET scanner consists of a set of detectors that surround the object to be imaged and are designed to convert these high-energy photons into an electrical signal that can be fed to subsequent electronics. In a typical PET scan, 10^6 to 10^9 events (decays) will be detected. These events are corrected for a number of factors and then reconstructed into a tomographic image using mathematical algorithms. The output of the reconstruction process is a three-dimensional (3-D) image volume, where the signal intensity in any particular image voxel* is proportional to the amount of the radionuclide (and, hence, the amount of the labeled molecule to which it is attached) in that voxel. Thus, PET images allow the spatial distribution of radiolabeled tracers to be mapped quantitatively in a living human. By taking a time sequence of images, the tissue concentration of the radiolabeled molecules as a function of time is measured, and with appropriate mathematical modeling, the rate of specific biological processes can be determined.

This book is designed to give the reader a solid understanding of the physics and instrumentation aspects of PET, including how PET data are collected and formed into an image. We begin with a review of the basic physics underlying PET and discuss in detail the detector technology used in modern PET scanners. The manner in which PET data are acquired is described, and the many correction factors that must be applied to ensure that the data are quantitative are

*A voxel is a volume element in a three-dimensional image array. It is analogous to a pixel in a two-dimensional image array.

introduced. The methods by which PET data are reconstructed into a three-dimensional image volume are explained, along with some of the approaches that are used to analyze and quantify the resultant images. Finally, a variety of modern PET imaging systems are discussed, including those designed for clinical service and research and small-animal imaging, along with methods for evaluating the performance of these systems.

PHYSICS OF POSITRON EMISSION AND ANNIHILATION

Basic nuclear physics and positron emission

The nucleus of an atom is composed of two different types of *nucleons*, known as *protons* and *neutrons*. These particles have similar masses but differ in that a proton has positive charge, whereas a neutron is uncharged. A cloud of negatively charged *electrons* surrounds the nucleus. In an uncharged atom, the number of electrons equals the number of protons. The basic properties of protons, electrons, and neutrons are listed in Table 1. The number of protons in an atom is known as the *atomic number* (often denoted as Z) and defines the element to which the atom belongs. The total number of nucleons is known as the *mass number*, often denoted by A. Atoms with the same Z, but different values of A, are *isotopes* of the element corresponding to atomic number Z. Nuclei usually are defined by the following notation:

$$ {}^{A}_{Z}X \text{ or } {}^{A}X \tag{1} $$

where X is the one- or two-letter symbol for the element with atomic number Z (e.g., Fe for iron and C for carbon), and A is the mass number. For example, ^{18}F is an isotope of fluorine and consists of 9 protons (because it is fluorine) and 9 neutrons. Sometimes, this isotope will also be written as F-18 or fluorine-18.

EXAMPLE 1
How many neutrons and protons are in the nucleus of ^{13}N?

ANSWER
Consulting a periodic table of the elements reveals that nitrogen has an atomic number of 7 and therefore, 7 protons. The mass number of this isotope is 13, so the number of neutrons must be $(13 - 7) = 6$.

EXAMPLE 2
How would an atom with 29 protons and 35 neutrons be written in the notation of Equation 1.

ANSWER
Referring to a periodic table of the elements shows that the element corresponding to $Z = 29$ is copper (symbol Cu). The total number of nucleons is $(29 + 35) = 64$. Therefore, this nucleus is ^{64}Cu.

The nucleus is held together by two opposing forces. The strong force is an attractive force between nucleons and is balanced by the repulsive coulomb (elec-

TABLE 1. Mass and Charge Properties of Nucleons, Electrons, and Positrons

	Proton (p)	*Neutron (n)*	*Electron (e^-)*	*Positron (e^+)*
Mass	1.67×10^{-27} kg	1.67×10^{-27} kg	9.1×10^{-31} kg	9.1×10^{-31} kg
Charge	$+1.6 \times 10^{-19}$ C	0	-1.6×10^{-19} C	$+1.6 \times 10^{-19}$ C

Based on data from Handbook of Physics and Chemistry, 71st Edition, Ed: D.R. Lide, CRC Press, Boca Raton, FL, 1991.

trical) force between the positively charged protons. If a nucleus has either an excess number of protons or neutrons, it is unstable and prone to radioactive decay, leading to a change in the number of protons or neutrons in the nucleus and a more stable configuration. Nuclei that decay in this manner are known as *radionuclides*. For a specific element with atomic number Z, isotopes that are unstable and which undergo radioactive decay are known as *radioisotopes* of that element.

One common method by which nuclei with an excess of protons may decay is through *positron emission* (also known as β^+ or *beta-plus decay*). Essentially, a proton in the nucleus of the atom is converted into a neutron (n) and a positron (e^+). The positron is the antiparticle to the electron with the same mass but opposite electric charge (see Table 1). The positron is ejected from the nucleus, along with a neutrino (ν) that is not detected. An example of a radionuclide that decays by positron emission is ^{11}C:

$$^{11}C \rightarrow {}^{11}B + e^+ + \nu \tag{2}$$

The net energy released during positron emission is shared between the daughter nucleus, the positron, and the neutrino. Positrons are therefore emitted with a range of energies, from zero up to a maximum *endpoint energy* E_{max}. This endpoint energy is determined by the difference in atomic masses between the parent atom and the daughter atom, taking into account gamma-ray emission from excited states that may occur if the transition is not between the ground states of the two nuclei. The mean kinetic energy of the emitted positrons is approximately $0.33 \times E_{max}$. Decay by positron emission is the basis for PET imaging.

Proton-rich radionuclides also can decay by a process known as *electron capture*. Here, the nucleus captures an orbital electron and converts a proton into a neutron, thus decreasing the atomic number Z by one. Once again, a neutrino is released. An example of electron capture would be the decay of ^{125}I:

$$^{125}I \rightarrow {}^{125}Te + \nu \tag{3}$$

Electron capture decay can lead to emission of x-rays (filling of the orbital vacancy created by the captured electron) or gamma-rays (electron capture leaves the nucleus in an excited state with further decay to the ground state by emission of one or more gamma-rays). These emissions may also be used for in vivo imaging but do not share the unique properties of decay by positron emission which are explained in the section on Annihilation (p. 5). Decay by electron capture and positron emission compete with one another, with positron emission usually being the dominant process in low Z nuclei, and electron capture being more likely in higher Z nuclei. Radionuclides that decay predominantly by positron emission are preferred for PET imaging.

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

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

Based on data from Table of Nuclides: www2.bnl.gov/ton (accessed October 17th, 2002)

Many radionuclides decay by positron emission. Table 2 presents a selection of these radionuclides that are commonly encountered in relation to PET imaging. Included in the table are the maximum kinetic energy of the emitted positrons, $E_{\max}$, and the fraction of decays that occur by positron emission. The energy of the emissions from radioactive decay are normally given in units of electron volts (eV), which is a more convenient unit than standard Système International (SI) energy units for handling the relatively small energies involved. One electron volt is defined as being equal to the energy acquired by an electron when it is accelerated through a potential difference of one volt. The conversion to joules, the SI unit for energy is:

$$1 \text{ eV} = 1.6 \times 10^{-19} \text{ J} \tag{4}$$

For PET imaging, units of kiloelectron volts (1 keV = 10^3 eV) and megaelectron volts (1 MeV = 10^6 eV) are commonly used.

Table 2 also lists the half-life of the radionuclides. A sample of identical radioactive atoms will decay in an exponential fashion, and the half-life is the time required for half the atoms in the sample to decay. The relationship between the activity A of a sample at time t, and the half-life, $T_{1/2}$, is given by:

$$A(t) = A(0)\exp(-\ln 2 \times t/T_{1/2}) \tag{5}$$

where A(0) is the activity of the sample at time 0. Activity is measured in units of the number of disintegrations per second:

$$1 \text{ bequerel (Bq)} = 1 \text{ disintegration per second} \tag{6}$$

In the United States, traditional units of the curie (Ci) and millicurie (1 mCi = 10^{-3} Ci) are still frequently used. The conversion is:

$$1 \text{ mCi} = 37 \times 10^6 \text{ Bq} = 37 \text{ MBq} \tag{7a}$$

or

$$1 \text{ MBq} = 27 \times 10^{-6} \text{ Ci} = 27 \ \mu\text{Ci} \tag{7b}$$

For more information on the physics of positron emission, see the textbook by Evans.[1]

EXAMPLE 3
A sample of ^{18}F is measured at 10:40 AM and has an activity of 30 MBq. It is injected into a patient at 11:30 AM. How much activity was injected?

ANSWER
From Table 2, the half-life of ^{18}F is 109.8 minutes. The time elapsed between measurement of the sample and injection is 50 minutes. Using Equation 5, the activity at the time of injection is:

$$A(t) = 30 \text{ MBq} \times \exp(-0.693 \times 50/109.8) = 21.9 \text{ MBq}$$

Annihilation

The positron that is ejected following β^+ decay has a very short lifetime in electron-rich material such as tissue. It rapidly loses its kinetic energy in inelastic interactions with atomic electrons in the tissue, and once most of its energy is dissipated (typically within 10^{-1} to 10^{-2} cm, depending on its energy), it will combine with an electron and form a hydrogen-like state known as *positronium*. In the analogy to hydrogen, the proton that forms the nucleus in a hydrogen atom is substituted by a positron. This state lasts only about 10^{-10} seconds before a process known as *annihilation* occurs, where the mass of the electron and the positron is converted into electromagnetic energy. Because the positron and electron are almost at rest when this occurs, the energy released comes largely from the mass of the particles and can be computed from Einstein's mass-energy equivalence as:

$$E = mc^2 = m_e c^2 + m_p c^2 \tag{8}$$

where m_e is the mass of the electron, m_p is the mass of the positron, and c is the speed of light (3×10^8 m/s). Inserting the values from Table 1, and using Equation 8 and the conversion in Equation 4, the energy released can be shown to be 1.022 MeV.

The energy is released in the form of high-energy photons. As the positron and electron are almost at rest when the annihilation occurs, the net momentum is close to zero. Because momentum as well as energy must be conserved, it is not in general possible for annihilation to result in the emission of a single photon; otherwise, a net momentum would occur in the direction of that photon. Instead, two photons are emitted simultaneously in opposite directions (180° apart), carrying an energy equal to 1.022 MeV/2, or 511 keV, ensuring that both energy and momentum are conserved. This process is shown schematically in Figure 1. Higher order annihilation, in which more than 2 photons are emitted, is also possible, but only occurs in about 0.003% of the annihilations.

The annihilation process has a number of very important properties that are advantageous for imaging and lead directly to the concept of PET. First, the annihilation photons are very energetic (they fall in the gamma-ray region of the electromagnetic spectrum and are roughly a factor of ten higher in energy than diagnostic x-rays), which means they have a good chance of escaping the body for external detection. It is, therefore, the annihilation photons that are detected in PET imaging, not the positrons (which are absorbed locally). Second, two photons are emitted with a precise geometric relationship. If both photons can

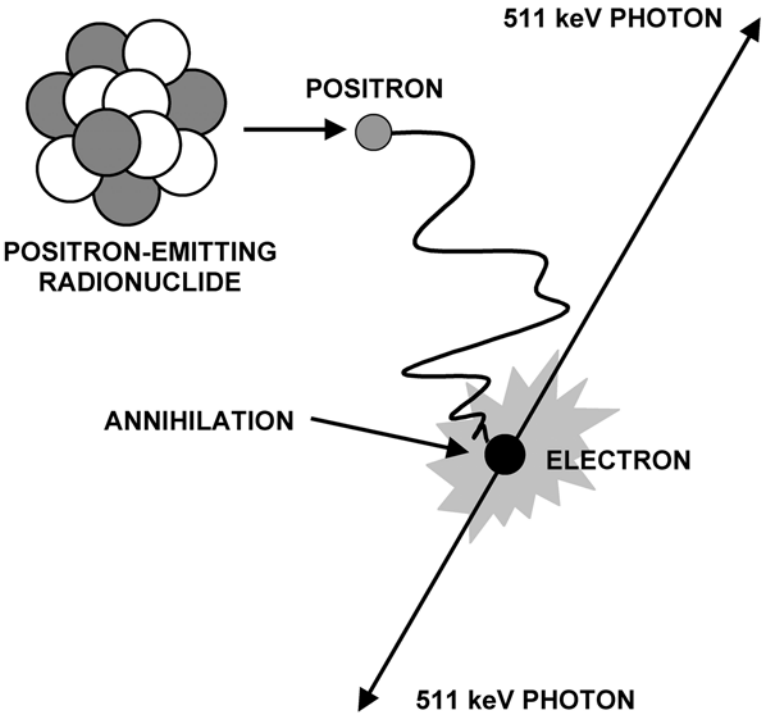

FIGURE 1. The process of positron emission and subsequent positron-electron annihilation results in two 511 keV annihilation photons emitted 180° apart. The site of annihilation is usually very close to the point of positron emission because the emitted positrons rapidly lose their energy in tissue (see Figure 5).

be detected and localized externally, the line joining the detected locations passes directly through the point of annihilation (Figure 2A). This was originally referred to as *electronic collimation*.[2] Because the point of annihilation is very close to the point of positron emission, this also gives a good indication (again to within a line) of where the radioactive atom was in the body. Contrast this with radioactive decay schemes that result in emission of a single photon. Although a single detector can be used, the detection and localization of a single photon tells nothing about where it came from in the body (Figure 2B). The direction of the photon can only be determined by the using a form of absorptive collimation, which only allows photons emitted in a certain direction to impinge on the detector (Figure 2C). This reduces the number of events that are detected for a given amount of radioactivity in the body by at least 1 to 2 orders of magnitude compared with electronic collimation. Electronic collimation also allows events to be collected from many different directions simultaneously leading to the capability of rapid tomographic imaging (see Image Reconstruction, p. 70). Third, all positron-emitting radionuclides, independent of the element involved, or the energy of the emitted positrons, ultimately lead to the emission of two back-to-back 511 keV photons; that is, a PET scanner can be designed and optimized for imaging all positron-emitting radionuclides at this single energy. One drawback to this, however, is that it is not possible to perform dual-radionuclide studies with PET and distinguish between the radionuclides based on the energy of the emissions. Because the annihilation photons fall in the gamma-ray region of the electromagnetic spectrum, the terms photons and gamma-rays are often used interchangeably when referring to the annihilation photons. Annihilation photons is technically the correct term because the radiation does not

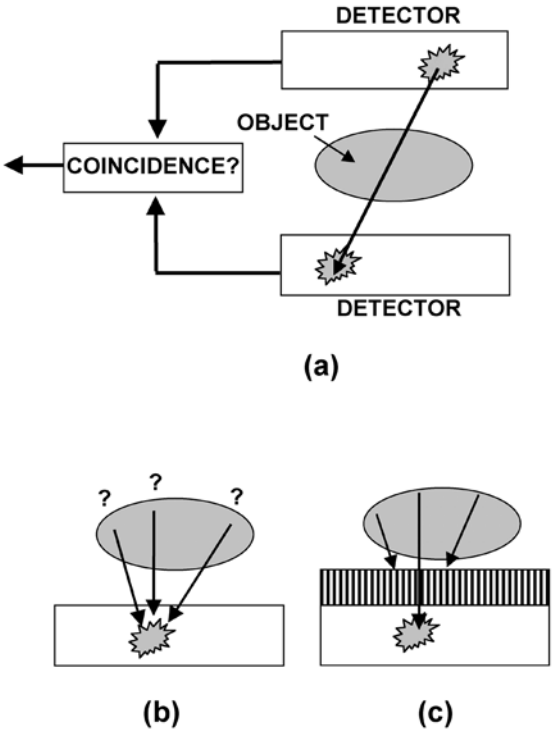

FIGURE 2. (A) Radionuclides that decay by positron emission result in two annihilation photons emitted 180° apart. If both photons are detected, the detection locations define (to within the distance traveled by the positron prior to annihilation) a line along which the decaying atom was located. (B) 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).

arise directly from the nucleus. However, the properties of annihilation photons are absolutely identical to a 511-keV gamma-ray—the difference in terminology reflects their different origins.

The annihilation process forms the basis for PET imaging. A PET scanner is designed to detect and localize the simultaneous back-to-back annihilation photons that are emitted following decay of a radionuclide by positron emission (Figure 3). In a typical PET scan, many millions of these photon pairs will be detected from a compound that is tagged with a positron-emitting radionuclide and which has been injected into the body.

As described above, the detection of the annihilation photons only localizes the location of the radioactive atom to within a line joining the detecting positions. Two approaches can then be used to form an image that reflects the actual locations of the radioactive atoms and, therefore, the compound to which it is attached. The first approach is conceptually the most simple, but is rarely used. It involves measuring the difference in arrival time of the two photons at the detectors. Obviously, if an annihilation occurs closer to detector 1 than detector 2, then the annihilation photon directed towards detector 1 will arrive at that detector earlier than the annihilation photon directed towards detector 2. The relationship between the difference in arrival time of the two annihilation photons, Δt, and the location d of the annihilation with respect to a point exactly half-way between the two detectors, is given by:

$$d = \frac{\Delta t \times c}{2} \tag{9}$$

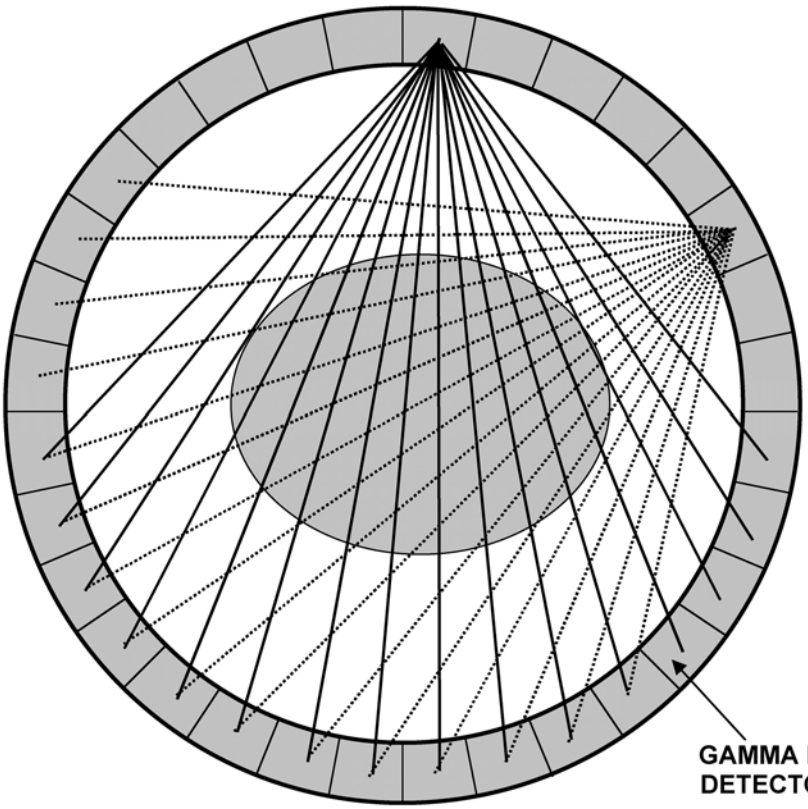

FIGURE 3. Schematic drawing of a PET scanner consisting of a ring of high-energy photon (gamma-ray) detectors. A ring geometry is shown, but other possibilities include polygonal assemblies of panels and opposing rotating planar detectors. The detectors are designed to record as many of the annihilation photons as possible and to locate the line along which the decay occurred by determining the two interaction vertices. Each detector is in electronic coincidence with a fan of detectors on the opposite side of the ring, so the object is simultaneously sampled from many different angles. For clarity, the measured lines of response for just two detectors are shown in this figure. Typically, 10^6 to 10^9 events (detections of annihilation photon pairs) are needed in a PET scan to reconstruct a statistically meaningful image of the distribution of radioactivity in the body.

where c is the speed of light (30 cm/ns). In practice, this method, known as *time of flight*, is very difficult and costly to implement because of the very small time differences involved. Even a timing resolution as fine as 100 ps would only yield a positional resolution of ~1.5 cm. With currently available detector technology, the best timing resolution that can be achieved is on the order of a few hundred picoseconds. Therefore, time-of-flight approaches do not yield the desired accuracy of a few millimeters, and no PET scanners are currently manufactured using this technique. The approach that is used almost universally involves the concept of *computed tomography*. By measuring the total radioactivity along lines that pass at many different angles through the object, mathematical algorithms can be used to compute cross-sectional images that reflect the concentration of the positron-emitting radionuclide in tissues throughout the body. This is discussed in Image Reconstruction (p. 70).

Positron range and noncolinearity

There are two effects in PET imaging systems that lead to errors in determining the line along which a positron-emitting radionuclide is to be found. These effects place some finite limits on the spatial resolution attainable with PET and manifest themselves as a blurring of the reconstructed images.

The first of these effects is positron range. As shown in Figure 4 (top), this is the distance from the site of positron emission to the site of annihilation. A PET scanner detects the annihilation photons which define the line along which the annihilation takes place, not the line along which the decaying atom is located. Because the positrons follow a tortuous path in tissue, undergoing multiple direction-changing interactions with electrons prior to annihilation, the total path length the positron travels is considerably longer than the positron range. From the perspective of PET imaging, it is the perpendicular distance from the emission site to the line defined by the annihilation photons that matters and which causes mispositioning.

As described earlier, radionuclides differ in the energy of emitted positrons. Some radionuclides emit, on average, higher energy positrons than others, making the positron range effect radionuclide-dependent. Figure 5 shows the annihilation locations for positron emission from a point source emitter located at the center of a block of tissue-equivalent material. Notice the broader distribution for oxygen-15 (a high energy positron emitter with $E_{max} = 1.72$ MeV) compared to fluorine-18 ($E_{max} = 0.64$ MeV). Profiles through these distributions reveal that they are nonGaussian in nature and are best fitted by exponential functions. Several groups have either measured,[3] computed,[4] or simulated[5] these distributions. Although the trends are similar, some disagreement between these studies is noted on the exact width and shape of the distribution. The blurring effect on the final PET image, however, clearly ranges from a few tenths of a millimeter up to several millimeters, depending on the radionuclide and its E_{max}.

Positron range limits the ultimate resolution attainable by PET. Studies have shown the ability to reduce positron range, particularly in radionuclides with large E_{max}, by using strong magnetic fields.[6–8] However, this is not currently practical to implement in the complex setting of a PET system. The positron range distribution may also in theory be deconvolved from the PET image.[9,10] In practice, the data rarely, if ever, have the statistical quality (sufficient number of events) to make this advantageous, as deconvolution leads to noise amplification. A better approach may be to incorporate positron range distribution information into iterative reconstruction algorithms (Iterative Reconstruction Methods, p. 86), which should lead to improvements in image resolution that are consistent with the statistical quality of the data when using positron-emitters with a high E_{max}. To put this discussion in perspective, it should also be pointed out that positron range is not a major limiting factor in PET imaging at the present time, except perhaps in animal studies of the very highest resolution using positron emitters with relatively high values (> 1.5 MeV) of E_{max}.

The second effect comes from the fact that the positron and electron are not completely at rest when they annihilate. The small net momentum of these particles means that the annihilation photons will not be at exactly 180° and will, in fact, be emitted with a distribution of angles around 180°. This is known as