Recent developments and future trends in nuclear medicine instrumentation

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Abstract

Molecular imaging using high-resolution single-photon emission computed tomography (SPECT) and positron emission tomography (PET) has advanced elegantly and has steadily gained importance in the clinical and research arenas. Continuous efforts to integrate recent research findings for the design of different geometries and various detector technologies of SPECT and PET cameras have become the goal of both the academic community and nuclear medicine industry. As PET has recently become of more interest for clinical practice, several different design trends seem to have developed. Systems are being designed for "low cost" clinical applications, very high-resolution research applications (including small-animal imaging), and just about everywhere in-between. The development of dual-modality imaging systems has revolutionized the practice of nuclear medicine. The major advantage being that SPECT/PET data are intrinsically aligned to anatomical information from the X-ray computed tomography (CT), without the use of external markers or internal landmarks. On the other hand, combining PET with Magnetic Resonance Imaging (MRI) technology is scientifically more challenging owing to the strong magnetic fields. Nevertheless, significant progress has been made resulting in the design of a prototype small animal PET scanner coupled to three multichannel photomultipliers via optical fibers, so that the PET detector can be operated within a conventional MR system. Thus, many different design paths are being pursued – which ones are likely to be the main stream of future commercial systems? It will be interesting, indeed, to see which technologies become the most popular in the future. This paper briefly summarizes state-of-the art developments in nuclear medicine instrumentation. Future prospects will also be discussed.

Keywords: SPECT, PET, instrumentation, dual-modality imaging, image reconstruction

Neueste Entwicklungen und zukünftige Trends in der nuklearmedizinischen Bildgebung

Zusammenfassung

Aufgrund ihrer eleganten Ansätze bekommt die molekulare Bildgebung unter Verwendung von Einzelphotonenemissionscomputertomographie (SPECT) und Positronenemissionstomographie (PET) einen immer höheren Stellenwert sowohl in der Forschung als auch in der Klinik. Hierbei ist die Integration von aktuellen Forschungsergebnissen bezüglich des Designs anwendungsspezifischer Geometrien und alternativer Detektortechnologien in SPECT- und PET-Kameras ein primäres Ziel nicht nur der nuklearmedizinischen Industrie sondern auch der akademischen Forschung. Gerade für PET, welche ein stetig wachsendes Interesse in der klinischen Praxis findet, lassen sich verschiedene Trends in der apparativen Entwicklung erkennen. Die Bandbreite der aktuell entwickelten Systeme reicht von „low cost" klinischen Anwendungen bis hin zu sehr hochauflösenden wissenschaftlichen Anwendungen im Kleintierbereich. Die Entwicklung von mehrfachbildgebenden Systemen hat die Praxis der Nuklearmedizin revolutioniert. Ihr Hauptvorteil besteht darin, dass SPECT/PET-Daten bereits intrinsisch mit der anatomischen Information der Computertomographie (CT) ausgerichtet sind, ohne dass externe Markierungen oder interne anatomische Charakteristika angewandt werden müssen. Andererseits ist die Kombination von PET mit Magnetresonanztomographie (MRI) aufgrund der magnetischen Felder eine technologische Herausforderung. Nichtsdestoweniger gibt es signifikante Fortschritte. So wurde ein Prototyp eines faseroptisch gekoppelten PET Detektors vorgestellt, womit eine PET-Kamera in ein konventionelles MRI-System integriert werden konnte. Bleibt die Frage, welche von den verschiedenen Designausführungen die zukünftige Ausrichtung kommerzieller Systeme bestimmen wird und welche Technologien sich in Zukunft durchsetzen werden. Inhalt dieses Artikels ist eine kurze Zusammenfassung moderner Entwicklungen in der nuklearmedizinischen Instrumentierung. Auch zukünftige Erwartungen werden diskutiert.

Schlüsselwörter: SPECT, PET, Instrumentierung, Dualmodalitätenbildgebung, Bildrekonstruktion

1. Introduction

Nuclear medicine imaging including conventional planar scintigraphy, single-photon emission computed tomography (SPECT) and positron emission tomography (PET), relies on the tracer principle, in which a minute quantity of a radiopharmaceutical is introduced into the body to monitor the patient's physiological function [1]. In a clinical environment, radionuclide images are interpreted visually to assess the physiological function of tissues, organs, and organ systems. Alternatively, these images can be evaluated quantitatively to measure biochemical and physiological processes of importance in both research and clinical applications. Nuclear medicine relies on non-invasive measurements performed with external detectors and radiation sources in a way that does not allow the radiotracer measurement to be isolated from surrounding body tissues or cross-talk from radiotracer uptake in non-target regions.

Within the spectrum of macroscopic medical imaging, sensitivity ranges from the detection of millimolar to submillimolar concentrations of contrast media with CT and MRI, respectively, to picomolar concentrations in PET: a 10^8–10^9 difference [2]. With CT and MRI, contrast is produced by detecting differences in tissue density and water content; however, with radiotracer imaging, contrast is conferred by detection of a clearly identified molecule labelled with a radioactive isotope of one of its natural constituent elements. Signal sensitivity is a prerequisite for studies of biological pathways and binding sites which function at less than the micromolar level. It is also important to avoid the pharmacological effects of administering a labelled molecule to study its inherent biodistribution. The sensitivity of *in vivo* tracer studies is achieved *par excellence* with PET, which uses electronic collimation and thereby operates with a wide acceptance angle for detecting emitted annihilation photons. Consequently, the sensitivity of PET per disintegration, with comparable axial fields of view, is two orders of magnitude greater than that of SPECT. PET also benefits by detecting radiopharmaceuticals that have short physical half-lives and high specific activities, which enable clinical and research studies to be performed in most cases at low radiation doses and with low molecular concentrations of the tracer.

Both the academic community and the nuclear medicine industry maintain a continuous learning cycle and assessment of products quality to advance the technology and the operational capabilities of both SPECT and PET cameras [3]. As PET has become integrated into clinical practice, several design trends have developed; with systems now available with a spectrum of features, from those designed for "low cost" clinical applications to others designed specifically for very high-resolution research applications. There is also a continual upward revision and refinement in both hardware and software components for all of these systems. The development of dual-modality imaging systems is an emerging research field and now offers unique capabilities for the medical imaging community and biomedical researchers [4]. Likewise, the progress in image reconstruction has been enormous in the past ten years, the main opportunities arising from the availability of both improved processing speed and faster algorithms. It has long been recognised that the limitations of analytical reconstruction algorithms (including filtered back projection – FBP) is closely related to the assumption of a relatively simple model of the emission and detection processes and would become quite complex if rigorous models were applied. FBP has further limitations due to the presence of streak artefacts that are particularly prominent near hot structures and the noise enhancement that is inherent in the reconstruction. An alternative to analytical reconstruction is the use of iterative reconstruction techniques, which can more readily incorporate more complex models of the underlying physics and also can better accommodate assumptions regarding the statistical variability of acquired data [5]. Unlike analytical reconstruction where FBP dominates, there are many approaches to iterative reconstruction, the most popular being the maximum likelihood – expectation maximization (ML-EM) algorithm and its accelerated version, the ordered subsets EM (OS-EM). The demands placed on reconstruction algorithms continue to expand. There is a strong evolution towards ultra high resolution designs and complex acquisition geometries where the huge size of the data sets compensates for the growing computer speed and, since acceleration of 3D reconstruction has probably reached its limits, the computational demand continues to push technology to its limit. In this paper, recent developments in nuclear medicine instrumentation are outlined, and some of the practical issues involved in optimizing the design aspects discussed.

2. Developments in SPECT instrumentation

SPECT has become one of the major tools for the *in vivo* localisation of radiopharmaceuticals in nuclear medicine and now is performed routinely with commercially available radiopharmaceuticals to answer important clinical questions including those in cardiology, neurology, psychiatry, and oncology. The major challenges to quantitative SPECT can be categorized in 4 classes [6]: (i) factors related to imaging system performance and data acquisition protocols (instrumentation and measurement factors), (ii) those related to the physics of photon interaction with biologic tissues (physical factors), (iii) image reconstruction (reconstruction factors), and (iv) factors related to patient motion and other physiological issues (physiological factors). It is worth to emphasize that despite the worthwhile research that has been performed in this area, there is no clear evidence that current commercial products allow applicability of these techniques in a clinical environment. Moreover, none of the methods published so far was user-independent and accurate enough for wide acceptance by the nuclear imaging community. Further research and development efforts are therefore still required to come up with a unified framework for optimal data collec-

tion, reconstruction and quantification in SPECT. In conjunction with new and existing radiopharmaceuticals, quantitative SPECT may be used non-invasively to measure blood-flow, metabolic function, receptor density, and drug delivery. In oncology, quantitative SPECT is important in radiation dosimetry and treatment planning for internal radionuclide therapy and more specifically for radioimmunotherapy.

Virtually all commercial scintillation cameras used for imaging gamma-ray emitting radiopharmaceuticals are based on the original design proposed by Anger about 60 years ago, which is considered the working horse of contemporary nuclear medicine [7]. Figure 1 illustrates the principle and basic components of the Anger scintillation camera which incorporates a large scintillation sodium iodide crystal doped with thallium (NaI(Tl)), equipped with a parallel-hole collimator that limits the acceptance angle and defines the spatial distribution of gamma radiation viewed by the scintillator. Behind the crystal, a light guide is optically coupled to an array of light sensitive photomultiplier tubes (PMT's) that proportionately convert the distribution of scintillation light into electronic signals. The PMT's outputs then are processed using "Anger logic" electronics that generate output signals representing the spatial position and energy of the individually detected gamma-rays on an event-by-event basis. Images displayed on the console represent the accumulation of the individual events recorded during an imaging study. Depending on the size of the scintillation camera, whole organs such as brain, heart and liver can be imaged. In many cases, large scintillation cameras are capable of imaging the entire body and are used, for example, in whole-body skeletal imaging. Advances in dedicated SPECT instrumentation may stimulate the use of clinical high resolution imaging of the brain. One example of such unconventional systems is the recently marketed NeuroFocus™ multi-conebeam imager (Neurophysics Corporation, Shirley, MA), which produces radionuclide images with an intrinsic spatial resolution of ~3 mm. The operation of the NeuroFocus™ scanner follows the same principles as scanning optical microscopes to obtain high-resolution, three-dimensional images of biological tissue. A highly focused point of light is scanned mechanically in three dimensions to uniformly sample the volume under observation. Since the energetic gamma rays emitted by single-photon tracers cannot be focused by conventional optics, NeuroFocus™ uses proprietary "gamma-lenses™" known as scanning focal-point technology. Further advances in electronics are permitting new counting strategies and advances in electronic component capability are allowing for enhanced sensitivity [8].

The development of dedicated small field-of-view pixelated gamma cameras has received considerable attention during the last decade. The pixelated crystal limits the degree to which the scintillation light spreads laterally and thereby can improve spatial resolution in comparison to cameras that use continuous crystals [9]. A typical design used 4 mm thick CsI(Tl) crystal with a 1.13 mm pixel pitch readout by position sensitive PMT's (PSPMT's) [10]. It should be emphasized that such a design improves spatial resolution at the expense of deteriorating the energy resolution resulting from light losses in the pixelated crystal compared to that of a single crystal. However, cameras with pixelated scintillators also can have the scintillator segments coupled to individual photomultiplier tubes, allowing them to be operated somewhat independently of one another to increase count-rate capabilities for first-pass and other high count-rate imaging applications [3].

The development of strip solid-state detectors for medical imaging is motivated by their excellent energy resolution and direct gamma radiation conversion, thus removing the need for using PMT's, and thereby allowing the system to be more compact, lighter in weight, and more rugged. The better energy resolution of semiconductor detectors is the consequence of the lower energy needed to create an electron-hole pair (3–6 eV) compared to the energy required to create a scintillation photon (~30 eV) in a conventional NaI(Tl) scintillation crystal. In addition, solid-state detectors obviously do not suffer the light losses that occur between a scintillation crystal and the PMT's [11] which also improves the signal generation process in the camera. Among available semicon-

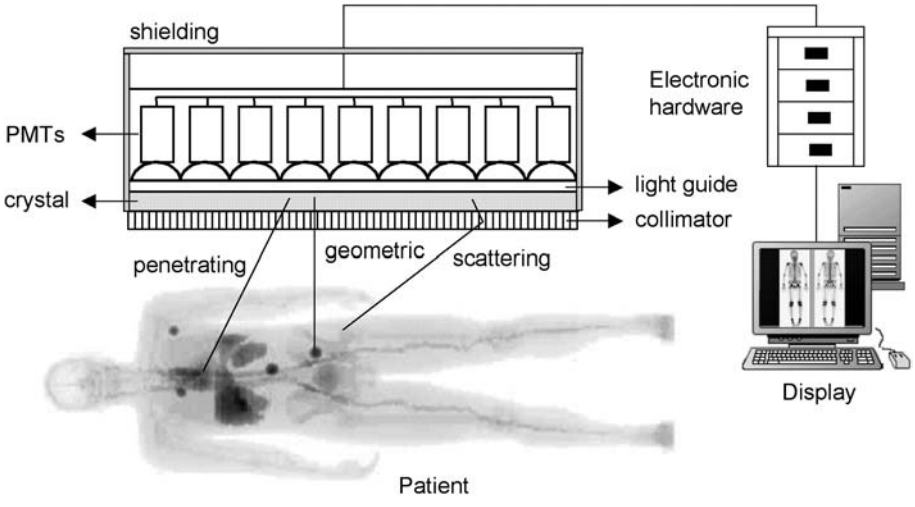

Figure 1 Schematic description of the principles and basic components of an Anger scintillation camera.

ductor detectors, high-purity germanium (HPGe) offers the best energy resolution and thereby allows efficient rejection of Compton scattering in the patient [12]. One such a system designed for clinical applications had 154 (250 mm long, 1.62 mm wide, 12 mm thick) detector strips collimated by parallel tungsten sheets perpendicular to the detector face [13]. However, due to its narrow energy band-gap, HPGe detectors must be operated at cryogenic temperatures. As a consequence, the need for cooling prevented their widespread applicability and encouraged the investigation of the potential of semiconductor detectors operating at room temperature including mercuric iodide (HgI_2), cadmium telluride (CdTe) and cadmium zinc telluride (CdZnTe or CZT) either in the form of single detectors or as segmented monolithic detectors [14]. Both CdTe and CZT currently are regarded as especially promising candidates for nuclear medicine imaging applications with the aim of replacing the conventional NaI(Tl) scintillator for clinical practice, especially for small-field applications such as sentinel node detection and radiopharmaceutical-guided surgery [15].

Another interesting design is the SOLid STate Imager with Compact Electronics (SOLSTICE), which if successful, seems to have the potential of producing a quantum advance in the performance of nuclear medicine instrumentation [16]. This system uses a room-temperature semiconductor detector (CdZnTe) to offer the excellent signal characteristics obtained with direct gamma ray conversion. The system also uses a novel rotating slat collimator which improves both spatial resolution and detection efficiency in a way that relaxes the performance limitations imposed on scintillation cameras by conventional parallel-hole collimators [17]. While the instrument is in a development phase, some promising results have been achieved during the last few years, including studies confirming the significant potential of this design for high resolution small animal imaging [11]. The practicality, clinical utility, and cost-effectiveness of the system still need to be demonstrated.

Except for those that use coded apertures, all collimated imaging systems exhibit a limiting detection sensitivity that is inversely proportional to the system's spatial resolution. This fundamental trade-off has motivated the development of Compton cameras, which provide information about the incoming photon direction electronically without any restriction with respect to the solid detection angle [18]. The mechanical collimation of the Anger camera is thus replaced by "electronic collimation" hereby removing the coupling between sensitivity and spatial resolution. This is achieved by having two detector modules where the gamma rays are first scattered in a solid-state detector and then absorbed in a second scintillation detector. After Compton scattering in the first detector, the scattered photon emerges from the interaction point with less energy and in a different direction than the incident photon. The tandem detectors in the Compton imager record the energies and interaction coordinates of the incident and scattered photons, respectively. This information can be used to calculate the scattering angle θ and the direction of the incident gamma ray. Figure 2 shows the concept and basic principles of the Compton camera approach. The precision in the measurement of the scattering angle θ depends mainly on the energy resolution of the first detector. The classical Compton equation expresses the energy of the scattered-photon as a function of the initial photon energy and the scattering angle θ, and assumes that the incident photon interacts with a free electron at rest. There are corrections to that equation which take into account the fact that the electron actually is not at rest and is bound to an atom. The result is that the photons that scattered through a given angle actually have a distribution of energies sharply peaked about the value calculated by the classical Compton equation [19]. This effect, called Doppler broadening, constitutes an inherent limitation for Compton cameras. In Compton camera imaging, the measured scattering angle therefore is associated with an uncertainty which degrades the spatial resolution of reconstructed images. This uncertainty becomes bigger as the incident gamma ray energy decreases, thereby motivating the development of appropriate compensation methods for this effect [20].

The first application of Compton imaging to nuclear medicine was proposed in 1974 [21]. This was followed by series of seminal papers by Singh and co-workers describing analytical and experimental results of a Compton camera using pixelated germanium as the first detector and a standard Anger camera as second detector [22]. This work was continued at the University of Michigan in collaboration with CERN [23] leading to the development of the C-SPRINT: a prototype Compton camera system for low energy gamma ray imaging [24] and the design of a Compton camera for high energies with CZT detectors [25]. More recently, the potential of the Compton camera approach for scintimammography has also been reported [26]. It is also expected that working Compton cameras based on silicon microstrips and segmented germanium detectors will be demonstrated in the near future [24, 27]. In parallel, appropriate analytic [28] and iterative [29] image reconstruction algorithms were devel-

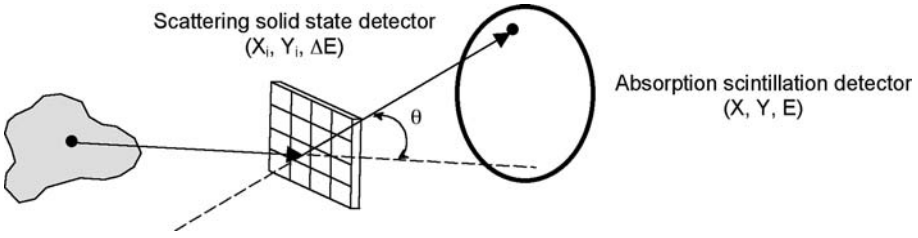

Figure 2 General principle of the Compton camera concept showing the scattering and absorption detectors.

oped specifically for single-photon images acquired with electronic collimation. Significant development is still required before this technology can be considered to be practical and cost-effective in a clinical arena owing to the complexity of the detector technologies, data acquisition system, and image reconstruction techniques needed for Compton imaging. Nevertheless, significant progress has been made during the last decade in demonstrating the feasibility of medical imaging with a Compton camera.

3. Trends in PET instrumentation

When imaging positron-emitting radiopharmaceuticals, pairs of antiparallel 511 keV photons arising from electron-positron annihilations are recorded by block detectors surrounding the patient. A PET tomograph consists of a set of detectors usually arranged in adjacent rings that surround the field-of-view in order to image the spatial distribution of a positron-emitting radiopharmaceutical (Fig. 3). In this case, the annihilation photons traverse a total tissue thickness that is equal to the body thickness intersected by the line between the two detector cells, also called the *line of response* (LOR).

Significant progress in commercial PET instrumentation design was made during the last two decades resulting in a spatial resolution of about 4–6 mm for whole-body imaging, ~2.4 mm for PET cameras dedicated for brain imaging (e.g. HRRT [30]), and submillimeter resolution for female breast and small-animal imaging [31]. Dedicated full-ring PET tomographs are still considered to provide state-of-the-art performance for whole-body imaging whereas different geometries were proposed for dedicated high resolution brain imaging [32]. New detection technologies that emerged include the use of new cerium (Ce) doped crystals (e.g. LSO, GSO, LYSO, $LaBr_3$) as alternatives to conventional bismuth germanate (BGO) crystals [33], and the use of layered crystals (phoswich detectors) and other schemes for depth-of-interaction (DOI) determination, and a renewed interest in old technologies such as time-of-flight (TOF) PET taking advantage of new developments in scintillator technology. In the phoswich approach [34], two detectors are assembled in a sandwich-like design, the difference in decay time of the light is used to estimate depth in the crystal where the interaction occurred. In TOF-PET, the measure of difference of the arrival times of the 511 keV annihilation photons allows restricting the position of positron emission to a subsection of the coincidence line connecting the two scintillation crystals. This technique was suggested and developed with limited success in the 1980s owing to the lack of scintillators combining excellent timing resolution and stopping power [35]. With the introduction of new scintillator crystals, TOF is now a feasible option which allows to improve the signal-to-noise ratio through incorporation of TOF information into the PET reconstruction process [36, 37].

The capabilities of PET instrumentation have undergone continual, and sometimes abrupt, improvements in performance and in their sophistication and complexity. A baseline of performance can be assessed through objective measures of spatial resolution, energy resolution, count-rate response, and other parameters to assess the technical capabilities of both commercial and research systems. The process of objective comparison has been facilitated by the wide acceptance and adoption of the NEMA standards, which provide an objective measure of performance parameters for nuclear imaging systems. Considering the wide variety of tasks encountered in clinical environments, the assessment of image quality is not obvious in PET. For example, the noise equivalent count rate (NEC) metric of count rate performance can be measured to assess the physical performance of a PET scanner but does not give a comprehensive indication of image quality. The 3D mode (septa retracted) increases coincidence efficiency by about a factor of around five in comparison to a 2D acquisition (septa extended) at the expense of increasing randoms and scattered coincidences and system dead-time [38]. It has been shown that the maximum is reached by the NEC in 3D at a lower activity concentration than in 2D as expected from

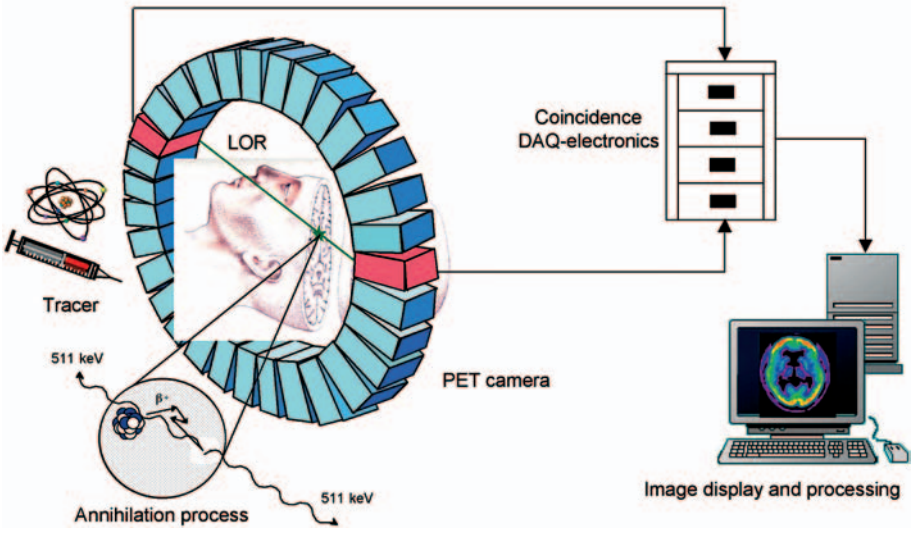

Figure 3 Schematic description of the principles and basic components of a PET tomograph. Following iv. injection of a radiotracer, a positron travels a few millimetres (depending on its energy and electronic density of the medium) before it annihilates with a nearby atomic electron, producing two 511 keV photons emitted in nearly opposite directions. A PET tomograph consists of a set of detectors usually arranged in adjacent rings surrounding the field-of-view. Pairs of annihilation photons are detected using a coincidence data acquisition electronics system and processed on computer to reconstruct tomographic PET images.

the behaviour of the true coincidence rate [39]. The quest for the ideal scintillation crystal to optimize design features of future fully 3D, large axial field-of-view fifth generation PET scanners technology led to comparative assessment studies evaluating the relative performance of different scintillators currently in use or under development for PET applications for the same geometric design. Among the many performance parameters that can be assessed, Figure 4 shows the NEC measured using Monte Carlo simulations of the standard NEMA NU-2 cylindrical phantom (20 cm diameter, 70 cm length), clearly demonstrating the advantage of LSO as the detector material for PET [40]. Even though the NEMA standards attempt to standardise the assessment of image quality using carefully designed phantoms, the measurement of physical parameters cannot account for special requirements of the clinical task being performed, and therefore requires additional assessments of clinical applicability and performance [41]. Inter-laboratory comparison studies of image quality and quantitative accuracy of commercially available PET scanners have proven to be useful to establish guidelines for end-users [42, 43]. The advantages of 3D vs. 2D acquisitions in terms of image quality and lesion detection performance in whole-body imaging still requires further research and development efforts [44, 45].

More recently, the design of whole-body PET imaging systems with larger axial field-of-view is also receiving considerable attention. In particular, the use of rotating flat panel LSO-based detector arrays is a promising design that, if successful, will enable a new generation of high-performance whole-body PET scanners [46]. The proposed design envisions 5 panels mounted in a hexagonal configuration that can be rotated to acquire a full 3D dataset for tomographic reconstruction. Each panel contains 10,080 LSO crystals ($4 \times 4 \times 20$ mm^3) coupled to an array of 88 PMT's which can identify individual crystal elements via a light sharing

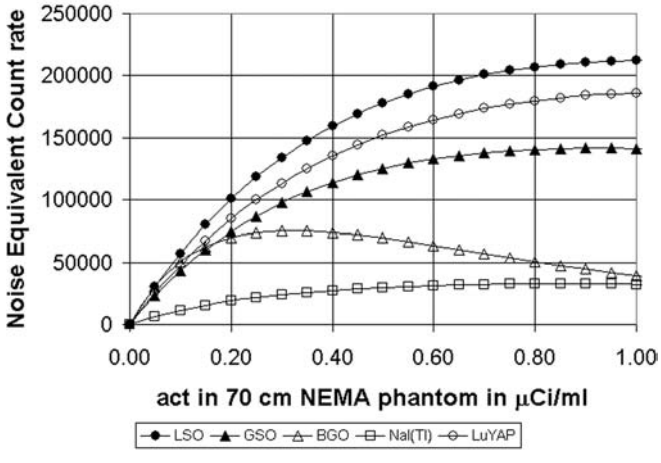

Figure 4 Monte Carlo simulation-based NEC comparison for the ECAT EXACT PET scanner for different scintillation crystals with a 450 keV lower energy discrimination threshold setting. Only detector dead time has been modelled. Reprinted with permission from ref. [40].

scheme. The detector panels are coupled to electronics with fast detector readout and temporal resolution, and configured in a system capable of imaging the whole body significantly faster than is possible with current PET scanner designs [47]. The performance assessment of the system showed that the 5-panel design has the highest peak NEC and largest axial field-of-view compared to other designs thus allowing to acquire whole-body scans in only 2–3 bed positions [48].

The intrinsic physical performance of conventional PET tomograph designs is approaching its fundamental limits, given the performance of existing instrumentation and components. This has encouraged the development of innovative approaches capable of providing improved performance at a reduced or comparable cost to current technologies. For example, Braem et al. [49] have proposed a novel detector design which provides full 3D reconstruction free of parallax errors with excellent spatial resolution over the total detector volume. The key components are a matrix of long scintillator crystals coupled on both ends to hybrid photodetectors (HPDs) with matched segmentation and integrated readout electronics [50]. Computer simulations and Monte Carlo modelling predict that the detector will achieve excellent spatial (~2.2 mm) and energy (~9% for LSO and 3.2% for $LaBr_3$ crystals) resolutions [51]. The design also increases detection efficiency by reconstructing a significant fraction of events that undergo Compton scattering in the crystals. The 3D axial detector geometry is configured from a matrix of 208 (13×16) long crystals each with a cross section of 3.2×3.2 mm^2 and with an intercrystal spacing of 0.8 mm. Scintillation light produced after an interaction of an annihilation photon will propagate by total internal reflection to the ends of the crystal, where it will be detected by the HPDs. The transaxial resolution depends only on the crystal segmentation and not on its chemical composition whereas the axial resolution is closely related to the scintillator properties. The scintillator's optical bulk absorption length should be approximately equal to the crystal length to obtain both a high light yield and a significant light asymmetry required to decode the axial coordinate z of the photon interaction in the crystal matrix.

To take full advantage of the quantitative capabilities of PET imaging, patient-specific correction of background and physical degrading factors must be performed. While most of these corrections (e.g. scatter [52]) are performed using sophisticated computational models, compensation for attenuation relies on reliable assessment of the attenuation map through an external apparatus which is integrated to the PET system design. This can be accomplished using appropriately designed radionuclide-based transmission scanning devices on stand-alone PET scanners or alternatively using X-ray CT on dual-modality imaging units [53]. When radionuclide sources are used to acquire the transmission data, photon statistical noise from the transmission scan can propagate through the reconstruction process, affecting the quality of the reconstructed PET images. To minimize this effect, long transmission scans are normally acquired to

ensure good statistics at the expense of patient throughput especially in the case of whole-body scanning with low-sensitivity tomographic systems. Alternatively, image segmentation can be applied to delineate different anatomical regions (e.g., lung vs. soft tissue) in the attenuation map. The known attenuation coefficients of these tissues then can be applied to the segmented regions to minimize noise in the resulting attenuation map, with the goal of reducing noise in the associated attenuation-corrected emission tomogram. During the last decade, techniques using transmission image segmentation and tissue classification have been proposed to minimize the acquisition time and increase the accuracy of the attenuation correction process, while preserving or even reducing the noise level. The reconstructed transmission image pixels are segmented into populations of uniform attenuation. The classified transmission images are then forward projected to generate new transmission sinograms to be used for attenuation correction of the corresponding emission data. This reduces the noise on the correction maps while still correcting for specific areas of differing attenuation such as the lungs, soft tissue and bone. Care must however be taken with respect to the choice of the transmission image segmentation algorithm [54]. Figure 5 shows typical pitfalls of transmission image segmentation showing a ^{137}Cs-based attenuation map of a clinical whole-body study before and after segmentation using an adaptive local thresholding algorithm [55]. The arrows delineate artefacts resulting from misclassification of the left lung as air. Figure 6 shows the propagation to

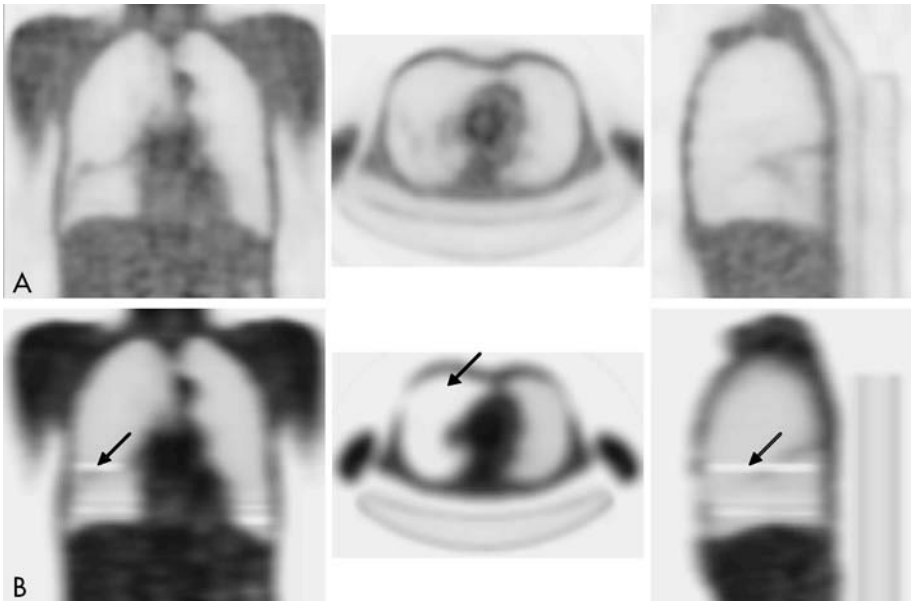

Figure 5 Illustration of transmission images segmentation pitfalls showing ^{137}Cs-based attenuation map of a clinical whole-body study before (A) and after segmentation using an adaptive local thresholding algorithm (B). The arrows delineate artefacts resulting from misclassification of the left lung as air.

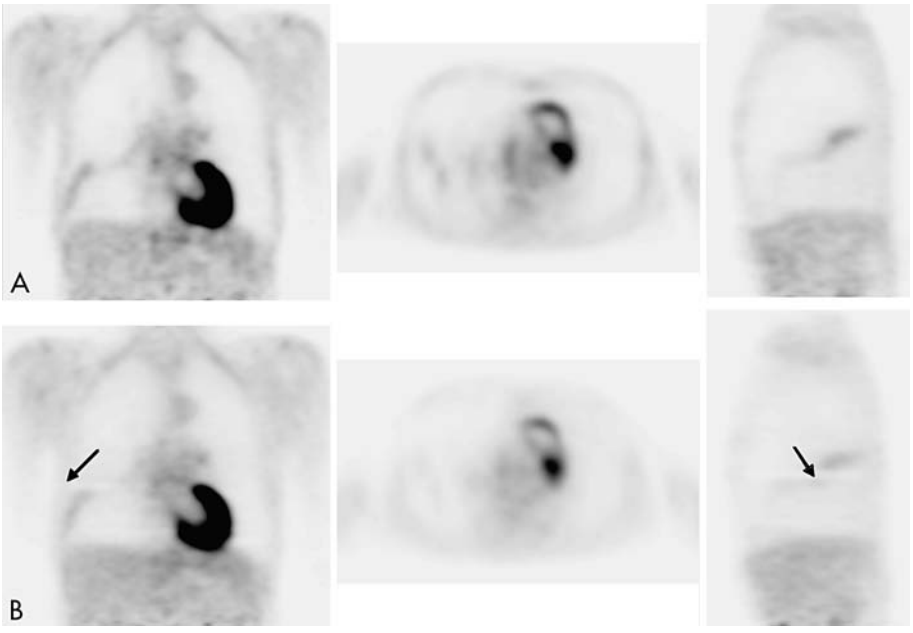

Figure 6 Illustration of PET images reconstructed after attenuation compensation using the attenuation maps shown in Figure 5, respectively.

emission data of misclassification errors illustrated in Figure 5 during the attenuation compensation process.

4. Innovations in small-animal imaging

With the recent developments in radiochemistry and tracer production technology combined with progress made in molecular/cell biology, it has become possible to design specific tracers to image events non-invasively in small animals and humans to investigate disease processes *in vivo* [56]. The role of transgenic and knockout mice in biomedical research now has become profound and widespread, and transgenic animals (mice and rats) at this time can be designed and created in a way that offers almost interesting possibilities for addressing questions concerning the genetic, molecular, and cellular basis of biology and disease [56, 57].

To achieve these goals, several investigators have developed several methods to image single-photon radionuclides in small animals. High spatial resolution projection data suitable for imaging small animals can be obtained using pinhole collimation. The most direct approach simply adds a pinhole collimator to a conventional scintillation camera and can provide excellent spatial resolution and with reasonable detection efficiency [58]. The recent growth of pinhole SPECT-based cameras spurred the development of appropriate modelling strategies to enable the characterization and optimize the design of pinhole collimators [59]. Pinhole imaging is also performed with special-purpose compact scintillation cameras, such as the commercially available system from Gamma Medica, Inc. (Northridge, CA) [60, 61] along with many other designs [62–64]. These compact systems have a small footprint and offer improved rotational stability for microSPECT which can be difficult to obtain with bulky clinical cameras. However, it has been shown that these microSPECT systems require that the animal is administered with significant levels of radioactivity that contribute radiation doses that can change gene expression, and in some cases are near lethality for the animal [65]. For these reasons, other investigators have developed small animal SPECT systems that offer both excellent spatial resolution and high detection efficiency with multiple pinhole detectors [66–69]. Multipinhole configurations include those with multiple compact detectors each with an individual pinhole collimator, or those with a clinical scintillation camera or other large radionuclide imager with a multipinhole collimator. Several investigators have argued that the best approach for small animal imaging would combine multipinhole techniques with multiple compact detectors having a high level of intrinsic spatial resolution including the use of very small scintillator elements (YAP, CsI(Tl), or LSO) read out by position sensitive or multi-channel PMT's to achieve high spatial resolution [67,69]. While these advances in technology have improved performance and reduced cost, the size and low quantum efficiency of PMT's are often limiting factors in these designs. In view of this, solid-state detectors such as silicon p-i-n photodiodes (with unity gain) and silicon avalanche photodiodes (APD's) are being actively considered as replacements for PMT's in nuclear medicine systems.

Likewise, the demand for functional, metabolic, and molecular imaging of small animals also has stimulated the development of dedicated small-bore high-resolution PET systems for imaging mice, rats, small primates, and other mammalian species [70–82]. As in human imaging, both high detection sensitivity and excellent spatial resolution are priorities for PET imaging system design and are needed to achieve suitable levels of image quality and quantitative accuracy. Thus, different PET designs have been suggested encompassing conventional small ring radius cylindrical block-detector based design with DOI capability and APD's readout, a renewed interest in the 3D HIDAC camera that achieves millimetre-scale spatial resolution along with many other designs. Several high-resolution small animal scanner designs have been or are being developed in both academic and corporate settings, with more than seven such devices being offered commercially. More recently, advanced versions of these technologies have begun to be used across the breadth of modern biomedical research to study non-invasively small laboratory animals in a myriad of experimental settings. The first commercially available microPET system [73, 83], developed originally at UCLA, consists of a cylindrical arrangement of $2 \times 2 \times 10$ mm^3 LSO crystals read out by short optical fibres to multi-channel PMT's. The microPET Focus is the latest generation microPET system, which incorporates several changes to enhance its performance compared to the Primate (P4) and Rodent (R4) models [79, 82]. This latest design uses ~1.5 mm square crystals and achieves a spatial resolution of around 1 mm in the center of the field-of-view using a statistical reconstruction algorithm incorporating accurate system modelling. With the introduction of commercial PET systems, small-animal imaging is becoming readily accessible and increasingly popular. The choice of a particular system being dictated in most cases by technical specifications, special attention has to be paid to methodologies followed when characterising system performance. Standardisation of the assessment of performance characteristics is thus highly desired [84].

Similar approaches are being undertaken for positron emission mammography (PEM) devices where both high spatial resolution and sensitivity are required to meet the needs of early detection of breast tumours, hence avoiding biopsy intervention [85–91]. Many conceptual designs developed specifically for small-animal and non-human primates imaging could be applied equally well to high resolution PEM by adapting the design to meet the sampling and resolution requirements specific to breast cancer imaging.

5. Advances in multimodality imaging

Despite the fact that the introduction of dedicated dual-modality imaging systems designed specifically for clinical

practice is relatively recent, the potential advantages of combining anatomical and functional imaging has been recognized for several decades by radiological scientists and physicians [4]. Many of the pioneers of nuclear medicine recognized that a radionuclide imaging system could be augmented by adding an external radioisotope source to acquire transmission data for anatomical correlation of the emission image. However, the conceptual designs were never reduced to practice or implemented in either an experimental or a clinical setting until Hasegawa and colleagues (University of California, San Francisco) pioneered in the 1990s the development of dedicated SPECT/CT [92, 93] and later Townsend and co-workers (University of Pittsburgh) pioneered in 1998 the development of combined PET/CT imaging systems, which have the capability to record both radionuclide and X-ray data for correlated functional/structural imaging [94, 95]. Thereafter, SPECT/CT and PET/CT dual-modality imaging systems were introduced by the major scanner manufacturers for routine clinical use where approximately more than 80% of PET systems sold annually are combined PET/CT units.

Dual-modality SPECT/CT and PET/CT scanners now are available from all of the major medical imaging equipment manufacturers (GE Healthcare Technologies, Siemens Medical Solutions, and Philips Medical Systems) offering the performance available on state-of-the-art diagnostic CT systems. Most SPECT/CT systems incorporate a dual-headed SPECT camera coupled to a single-slice, 2-slice, 6-slice or a 16-slice diagnostic CT scanner whereas current PET/CT systems have up to 64 slice CT capability and have dedicated detectors with either 2D/3D or only 3D PET imaging capability. By providing high-resolution anatomical information from CT, dual-modality imaging correlates functional and anatomical data to improve disease localization [96–100] and facilitates treatment planning for radiation oncology or surgery. Moreover, both SPECT/CT and PET/CT have demonstrated their ability to facilitate attenuation correction using a patient-specific attenuation map derived from CT that can be produced faster and more accurately than attenuation maps generated with external radionuclide sources [53]. Some caution is, however, essential when using contrast agents and in presence of metallic implants which may lead to visible artefacts on CT and consequently on CT-based attenuation-corrected PET images. Figure 7 presents a flowchart of the major steps involved from data acquisition to fused image display. Firstly, the CT processor corrects and reconstructs the CT data. This is followed by downsampling (voxel match) of the resulting CT images to PET image resolution and energy scaling from CT to PET energies using one of the available techniques (bilinear calibration curve or hybrid methods) [53]. The derived attenuation map is then forward projected to generate the attenuation correction factors (ACFs) required to correct the PET data for photon attenuation. The PET processor reconstructs the attenuation corrected emission sinograms, which are finally overlaid on the CT images and displayed on a shared console.

The addition of advanced CT capability allows anatomical images to be acquired after the patient is administered with contrast media to improve lesion detection in oncologic imaging or to visualize the cardiac chambers as well as the coronary and peripheral vasculature. With these capabilities, the next-generation PET/CT and SPECT/CT systems could produce high-resolution structural images of the cardiac chambers and of coronary and peripheral vasculature that can be correlated with myocardial perfusion and other functional assessments with radionuclide imaging. In addition, the use of contrast media could enable advanced radionuclide quantification techniques in clinical studies. These capabilities would have the potential of improving the quantitative assessment of cancer and cardiovascular disease in comparison to studies acquired with SPECT/PET or CT alone.

Traditionally, CT data were acquired following a breath-hold, whereas PET data were acquired over several minutes with the patient breathing quietly. However, these breathing protocols can lead to misregistration artefacts due to anatomical displacements of the diaphragm and chest wall during a PET/CT or SPECT/CT scan [4]. For example, if the position of the diaphragm is displaced in the CT scan, which then is used as an attenuation map for the radionuclide data, this dis-

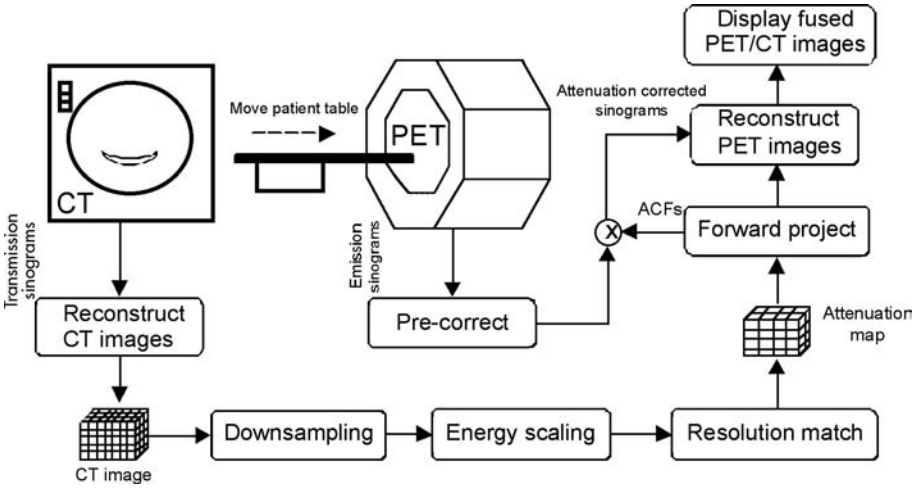

Figure 7 Flowchart of a typical PET/CT data acquisition protocol illustrating the major steps involved for generating attenuation correction factors required for CT-based attenuation correction in PET.

placement can lead to an underestimate or overestimate of radionuclide uptake in the reconstructed emission data. The discrepancy in diaphragmatic position between PET and CT can result in the appearance of the so-called "cold" artefact at the lung base. A recent study [101] noted that in 300 patients with proven liver lesions, approximately 2% appeared to have the lesion localized in the lung due to respiratory motion. Care therefore must be taken when interpreting results from patients with disease in periphery of the lung where noticeable radiopharmaceutical uptake may be contributed by respiratory-induced motion artefacts rather than disease [4].

Modern dual-modality scanners now use CT technology that can acquire the anatomical data within a few seconds after the patient is positioned on the bed. For this reason, the CT acquisition rarely is the factor that limits the speed of the dual-modality image acquisition in comparison to SPECT or PET that can consume several minutes to complete. If additional increases in scan speed are needed, these must be implemented using faster radionuclide scans using newer detector technologies, faster scintillators, increased computing power, and more efficient scanner architectures or detector designs than are currently being used. In PET, this includes the possibility of replacing conventional PET block detectors with LSO panel detectors [47, 48] which would cover a larger axial extent of the patient with the goal of achieving 5 min scan times and thereby would allow even faster scan times than are achievable with current systems. Regardless, faster scan speeds both improve patient comfort and limit the time during which patient motion can occur during the study. In addition, faster scan speeds can promote faster patient throughput and thereby increase system utilization and cost-effectiveness of the study.

Similarly, it is expected that the technology of small animal SPECT/CT [102] and PET/CT [103] will continue to advance. Current small animal radionuclide SPECT systems obtain submillimeter spatial resolution at the cost of reduced detection efficiency. Newer multi-pinhole SPECT systems are under development and offer both improved geometric efficiency and spatial resolution in comparison to current radionuclide imaging approaches in a way that would improve image quality and reduce scan times for dynamic or electrocardiography (ECG)-gated cardiovascular imaging in small animals [66, 69]. Excellent microCT images of live animals are being obtained using cone-beam X-ray CT imaging and reconstruction [104]. The development of microCT systems that allow cardiac gating and *in vivo* coronary imaging would be very useful for functional/structural imaging and quantitative radionuclide assessments of small animals, similar to those that are expected to be developed for clinical dual-modality imaging. Finally, advances in computing power will enable the development and implementation of new anatomically-guided statistical reconstruction algorithms and data processing techniques that will offer advantages for both clinical and small animal imaging with dual-modality imaging.

While all clinical and commercial dual-modality systems have been configured in the form of SPECT/CT or PET/CT scanners, several investigators proposed and in some cases have implemented and tested prototype dual-modality systems that combine MRI with small-animal PET [105–108]. There are, however, several important challenges that must be overcome in implementing and operating a combined PET/MRI or SPECT/MRI imaging system. In comparison to X-ray CT, MRI typically is more expensive, involves longer scan times, and produces anatomical images from which it is more difficult to derive attenuation maps for photon correction of the radionuclide data [109]. Furthermore, virtually all clinical radionuclide imaging detectors use PMT's whose performance can be seriously affected in the presence of magnetic fields which are significantly smaller than those produced by modern MRI scanners. This is especially problematic in an MRI scanner which relies on rapidly switching gradient magnetic fields and radiofrequency (RF) signals to produce the magnetic resonance image. The presence of the magnetic field gradients and RF signals certainly could disrupt the performance of a PMT and PET detector if they were located within or adjacent to the magnet of the MRI system. Similarly, the operation of the MRI system relies on a very uniform and stable magnetic field to produce the MR image. The introduction of radiation detectors, electronics, and other bulk materials can perturb the magnetic field in a way that introduces artefacts in the MR image.

In spite of these challenges, several research groups are investigating methods to integrate a PET system directly in an MRI scanner by designing detectors made from nonmagnetic materials that can be placed within the magnetic field of an MRI/MRS system [110]. For example, the UCLA group developed a 3.8-cm ring of small scintillator crystals that was placed in the MR system for PET imaging [111, 112]. The crystals were optically coupled through 3 m long fibre optics to an external array of position-sensitive PMT's, and which could be read-out through external processing electronics. By keeping the radiation-sensitive elements of the detector within the MR system, while operating the electronics away from the magnetic field, the combined system could perform simultaneous PET/MR imaging. The same group also performed simultaneous PET/MR imaging with a larger (5.6 cm-diameter) detector ring using the same design [113, 114]. Their collaborators at Kings College London placed the system inside of a 9.4-T NMR spectrometer to study metabolism in an isolated, perfused rat heart model. ^{32}P-NMR spectra were acquired simultaneously with PET images of ^{18}F-FDG uptake in the myocardium [115, 116]. This design concept is being extended to develop an MR-compatible PET scanner with one ring of 480 LSO crystals arranged in 3 layers (160 crystals per layer) with a diameter of 11.2 cm corresponding to a 5 cm diameter field of view, large enough to accommodate an animal within a stereotactic frame [114]. The system is designed to offer adequate energy resolution and sensitivity for simultaneous PET/MRI imaging of small animals.

Other investigators have proposed PET/MRI systems configured with suitable solid-state detectors that can be operat-

ed within a magnetic field for radionuclide imaging. Some groups have tested APD's within a high-field (9.7 T) NMR spectrometer and have produced radionuclide data that appear to be free of distortion [117]. However, it is still unknown whether the introduction of the APD's cause distortions in the magnetic field to an extent that would cause severe artefacts in the MR image [110].

6. Summary

In this paper, we have provided a brief overview of current state-of-the art developments in nuclear medicine instrumentation. We emphasize that many different design paths have been and continue to be pursued in both academic and corporate settings, that offer different trade-offs in terms of their performance. It is still uncertain which designs will be incorporated into future clinical systems, but it is certain that technological advances will continue and will enable new quantitative capabilities in nuclear medicine imaging. Reliable molecular imaging plays a valuable role in the assessment of cellular targets, evaluation of response to therapy, differential diagnosis, prediction or selection of patients who will benefit from treatment, and in dosimetry for targeted therapy. Nuclear medicine is poised to advance the application of molecular diagnosis in oncology, neurology, cardiology, infectious diseases, and other types of disease. Nevertheless, nuclear medicine is obviously not the only major non-invasive tool for the assessment of human disease. Major new technologies, such as spiral CT, high-field MRI, bioluminescent and fluorescent imaging, and many other technologies, have now blurred the artificial distinction that once set nuclear medicine apart as a "functional" rather than "anatomic" imaging modality [118]. Nonetheless, nuclear medicine maintains an exclusive standing in the delivery of targeted therapies, but its superior picomolar sensitivity is being challenged by competing technologies such as those using ultra small superparamagnetic contrast agents [119].

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