Multimodality In Vivo Imaging Systems: Twice the Power or Double the Trouble?

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Abstract

Many different types of radiation have been exploited to provide images of the structure and function of tissues inside a living subject. Each imaging modality is characterized by differing resolutions on the spatial and temporal scales, and by a different sensitivity for measuring properties related to morphology or function. Combinations of imaging modalities that integrate the strengths of two modalities, and at the same time eliminate one or more weaknesses of an individual modality, thus offer the prospect of improved diagnostics, therapeutic monitoring, and preclinical research using imaging approaches. This review discusses the advantages and challenges in developing multimodality imaging systems for in vivo use, highlights some successful combinations that are now routinely used in the clinic and in research, and discusses recent advances in multimodality instrumentation that may offer new opportunities for imaging.
INTRODUCTION

In vivo imaging is one of the primary tools used to evaluate structure and function non-invasively in a living subject. Electromagnetic radiation, including radio waves [magnetic resonance imaging (MRI)], visible and near-infrared light (optical imaging), X-rays [X-ray computed tomography (CT)], gamma rays [single photon emission computed tomography (SPECT)], annihilation photons [positron emission tomography (PET)], and high-frequency sound waves, or ultrasound, are all successfully employed to interrogate the structure and/or function of tissues (1). In some cases, endogenous contrast may be intrinsic to the body tissues (electron density for CT, proton density and tissue relaxation times for MRI, acoustic properties of tissue for ultrasound, intrinsic optical properties of tissue for optical imaging). In many cases, contrast agents, designed to provide or augment the imaging signal, are introduced into the body. Depending on the modality, these may be radiolabeled probes (PET, SPECT), molecules laden with high Z nuclei (CT), paramagnetic agents (MRI), acoustically active microbubbles (ultrasound), or fluorescent molecules (optical imaging). By exploiting different types of radiation and using different contrast agents, an enormous variety of parameters can be imaged in vivo, ranging from basic tissue density with X-rays to specific molecular targets, gene expression, and protein-protein interactions using targeted contrast agents, and in some cases genetically manipulated cells (2–4).

The reason that several different imaging modalities exist is that they operate within a defined parameter space that renders them well suited for some applications, while often very poorly suited for other applications. This parameter space generally is characterized by factors such as spatial resolution, temporal resolution, detection sensitivity, tissue penetration, signal-to-noise, and quantitative accuracy, with important considerations also related to issues such as radiation dosimetry (for modalities employing ionizing radiation), cost and throughput, and contrast agent toxicity. For example, a common wish one hears is to have an imaging instrument with the spatial resolution of MRI, the temporal resolution of ultrasound, and the sensitivity of PET. Looking beyond these basic imaging parameters, it is also clear that each major imaging modality measures fundamentally different information. Thus X-rays can provide exquisite structural detail in bone, but optical imaging with fluorescently labeled molecules in vivo, using the principles of fluorescent resonance energy transfer (FRET), would likely be the way to look at protein-protein interactions in vivo. Another consideration that tips the balance between different modalities is the volume of the tissue under interrogation. For whole-body human imaging, the penetrating power of radiofrequency radiation, X-rays and gamma rays, and ultrasound in the range of 2–4 MHz is indicated. However, for imaging of isolated and accessible tissues, such as skin, breast, and limbs, or preclinical imaging in small-animal models such as mice and rats, higher frequency ultrasound and optical radiation also become important players.

Because no one imaging modality can provide information on all aspects of structure and function, an obvious approach is to interrogate a subject using multiple imaging modalities. This is not a new idea. For many decades, patients have been...
moved from one imaging machine to another to obtain data from different imaging modalities. Initially, information would be analyzed by a simple visual synthesis of the image datasets by the physician or researcher. Quickly, powerful image registration techniques were developed that allowed tomographic data from one imaging modality to be coregistered with data from the same patient obtained on a different imaging system (5). This allowed direct overlay of the images and the ability to move a linked cursor across two 3-D datasets that come from different scanners. These approaches have important practical advantages. Existing equipment is used to capture the image data, and the two scans can be scheduled at different times to maximize the throughput on individual scanners. However, there are also clear limitations. First of all, images are not perfectly registered. In some parts of the body, notably the brain, misalignments can be very small. The fact that the brain is well approximated by a rigid body contained within the skull often allows for accurate registration between modalities using features in the images themselves, fiducial markers mounted on the bed, or multimodality headholders (5). However, in other parts of the body, organ shape and location depends critically on how a subject is positioned in the scanner. Some organs can change shape over time (for example, the bladder filling with urine). Thus, accurate registration becomes far more difficult. Although nonrigid registration approaches have been developed, they are only robust across a certain set of conditions. The other disadvantage of acquiring sequential scans on two different scanners is that it is not possible to simultaneously measure two different parameters and correlate time-dependent changes in those parameters. Finally, if two modalities are required, it would be more efficient from the patients’ perspective to acquire them simultaneously or at least in rapid succession on a single instrument, rather than moving a patient from system to system and all the scheduling challenges that imposes.

For these reasons, there has been considerable interest over the past 10–15 years in examining the possibility of building multimodality imaging systems in which two or more imaging modalities are integrated to a greater or lesser extent into a single imaging unit. At one end of the spectrum is the concept of taking two imaging scanners and placing them side by side, with perhaps the only integration being a common patient bed that moves through the system. At the other extreme would be a fully integrated system with a single set of detectors or sensors that can detect the radiation from two different modalities. In the following sections, the early evolution of multimodality systems is traced, with an emphasis on PET/CT and SPECT/CT as examples of multimodality systems that have become widely adopted. A selection of other multimodality approaches will be reviewed, although this will not be a comprehensive review of all the possible approaches being studied, rather a summary of those that have particularly interesting or promising features. Finally, some of the challenges of multimodality imaging are examined and future opportunities discussed. The review focuses on imaging systems that combine two or more modalities via a hardware approach and does not discuss multimodality imaging that is achieved via image registration from two completely separate imaging systems, nor the integration of an imaging modality with other nonimaging instrumentation, such as depth electrodes, stereotactic biopsies, or delivery of radiotherapy.
STRUCTURAL-FUNCTIONAL IMAGING WITH PET/CT AND SPECT/CT

Imaging modalities can be divided very roughly into two groups: Those that excel primarily at providing structural information (i.e., CT, MRI, and ultrasound) and those that excel primarily at providing functional or molecular information (i.e., PET, SPECT, and optical imaging). Therefore, it is not surprising that much of the effort in multimodality imaging has been devoted toward integrating one technique from each group, thus enabling function and structure to be examined within the same individual and at the same time. There are many examples where having both structural and functional information is critical, for example, in localization of functional abnormalities prior to localized treatment with surgery or radiation, or, in novel gene or cell-based therapies, determining the location within the body of therapeutic cells or gene products.

The most concerted efforts have been in integrating one of the nuclear medicine techniques (PET or SPECT) with CT (6, 7). Both methods use high-energy electromagnetic photons; in the case of CT, these photons are used in transmission mode with an external source, in nuclear medicine a radioactive probe is injected into the patient resulting in internal emission of the photons. PET/CT and SPECT/CT whole-body imaging systems are commercially available and have been widely adopted, and similar approaches are being developed for preclinical imaging in small-animal models and for breast cancer imaging. The development of these systems was based on the motivation of providing anatomical localization of nuclear medicine radiotracer uptake, especially outside the brain, where the elastic transformations required to register datasets from two separate scanners and imaging geometries are of limited accuracy. Nowhere has this been more important than in oncologic applications (8), where the location (determined by CT) of suspicious lesions (determined by high radiotracer uptake) is key to diagnosis and patient staging. In hindsight, it seems such an obvious combination, yet it took roughly 30 years of development before the concept was embraced. Some of the key developments and ideas are introduced below.

Emission/Transmission Imaging with Radionuclide Sources

Some form of transmission scanning has been incorporated into nuclear medicine imaging for well over 35 years (9). Initially, the goal of transmission scanning was to provide information on the body contours to help determine the location of radiotracer accumulation on 2-D projection images. Thus, approaches that utilized the existing nuclear medicine detector system, usually a gamma camera, together with an external radionuclide transmission source, were implemented (10–12). With the development of the tomographic techniques of PET and SPECT in the 1970s, the role of the transmission scan was extended to that of providing the information necessary to correct the nuclear medicine images for the depth-dependent attenuation of the emission photons (13–15). A range of different radionuclide sources and geometries was investigated to optimize the overall quality and accuracy of the transmission scan (9).
Figure 1

Transmission image at level of thorax obtained with an external radionuclide source on a gamma camera (left). Image courtesy of Dr. Freek Beekman, Utrecht University, The Netherlands. X-ray CT scan of thorax (right). Image courtesy of G.E. Healthcare. Note better spatial resolution, signal-to-noise ratio, and soft tissue contrast obtained with dedicated CT system.

The quality of the transmission or structural images that can be obtained with an external radionuclide source is relatively poor for a number of reasons (Figure 1). Nuclear medicine imaging systems operate in pulse mode (i.e., each event is handled individually) because pulse-height information is important in rejecting scatter radiation, and in PET, each photon must be analyzed to see if it meets the time coincidence criterion. Thus the flux of radiation that can be handled by the electronics is relatively low, and hence the counting statistics are limited. Furthermore, the external radionuclide source usually is of an energy comparable to the emission photon energy (so that it can be used for photon attenuation correction), but at these energies, soft tissue contrast is poor. Last, the resolution of most nuclear medicine detector systems is on the order of several millimeters, thus limiting the resolution of the transmission image to similar values. Therefore, despite a huge effort to optimize transmission scanning with an external radionuclide source, the primary role of the transmission data in recent times has been for attenuation correction and improved quantification of nuclear medicine studies, and the transmission scan is rarely, if ever, used as a diagnostic tool on its own merits.

Early Combined X-Ray and Nuclear Medicine Imaging Systems

Hasegawa and his colleagues at the University of California, San Francisco, were the first group to develop a simultaneous emission/transmission system that incorporated an X-ray tube for the transmission component and had the explicit goal of producing high-quality structural information (7). In the early 1990s, they developed a system
based on a linear array of high purity germanium detectors (HPGe) that were used to simultaneously detect both the 100–200 keV emission gamma rays from an injected radiotracer, and the transmitted X-rays from a low-power 120 kVp X-ray tube (16, 17). Because the detector operated in pulse mode, processing the signal from each photon interaction one at a time, only limited X-ray flux could be utilized. Nonetheless, the image quality for anatomic imaging was dramatically improved, and this represents the first true example of dual modality imaging (Figure 2). It is also one of the few examples of a truly integrated (rather than combined) imaging system in which a single detector system is used for both imaging modalities. The system was used primarily to perform highly quantitative studies in cardiovascular and oncology models in large-animal models (18). It was never translated into clinical use, primarily owing to the high cost of the large volume of HPGe or other semiconductor detectors that would be required for human imaging.

Because of the difficulty of designing detector/electronic systems that can handle the huge X-ray flux in pulse mode, the focus rapidly moved away from a single detector system to the idea of integrating two separate detector systems, one optimized for X-ray imaging, the other for nuclear medicine imaging. In its simplest forms, this involved placing a PET or SPECT scanner immediately adjacent to a CT scanner and designing a common patient bed that could move through the two systems. This very practical approach to dual-modality imaging does not permit simultaneous PET/CT or SPECT/CT, but it involves absolutely no compromise in the image quality obtained from either system. Early prototype systems were developed by Hasegawa and colleagues (SPECT/CT) (19) and by Townsend in collaboration with CTI, Inc. (PET/CT) (8), and they quickly demonstrated the combined power of these imaging modalities for clinical cancer imaging (20, 21) and for improved quantification of nuclear medicine research studies (22–24). Commercial implementation rapidly followed (25–27), and at the present time, PET/CT and SPECT/CT are the fastest growing areas in medical imaging instrumentation.

Figure 2
Images of the thorax and myocardium of a pig obtained from a high-purity germanium detector system developed at UCSF and capable of simultaneous SPECT and CT imaging. Reprinted with permission from Reference 18.
Clinical Whole-Body PET/CT and SPECT/CT

All commercial systems today are based on the “tandem” approach described above (28), where two separate imaging systems are combined in a single housing, and where the integration occurs at the level of the patient bed, with sophisticated software that integrates data acquisition, image reconstruction, data correction, image quantification, and image display between the two modalities. For example, one synergistic application of the two modalities is the use of the CT data to correct for photon attenuation in the PET or SPECT study (29). Photons emitted from a radionuclide deep inside the body are more likely to be absorbed or scattered prior to reaching an external detector system than photons emitted at a shallower site, and therefore quantitative nuclear imaging requires correction for this depth-dependent attenuation of photons. The CT scan shows the attenuation properties of the tissue averaged over the spectrum of X-ray energies used; however, the use of this data for attenuation correction of the PET or SPECT dataset is not as trivial as one might think. CT data are inherently polyenergetic, whereas the photons emitted from radionuclides in PET and SPECT are monoenergetic, and often are higher in energy than the maximum X-ray energy generated by the X-ray tube. Thus, the linear attenuation coefficients (μ values) of different tissues at the energies of the radionuclide photons cannot be simply derived from information in the CT scans. Simple segmentation approaches have limitations because of the continuous nature of the μ-value distribution in a patient (29). Approaches to map from CT-derived energy-averaged μ values to values appropriate for attenuation correction of PET or SPECT data arising from monoenergetic photons have therefore been developed (30, 31). These methods have largely been successful; although, as discussed later, in the presence of CT contrast agents and implanted metallic objects, problems may occur (29, 32). Dual-energy X-ray imaging can be used to unambiguously scale μ values across energies for low-Z materials (33); however, this increases the complexity (and possibly the dose) of the CT imaging component. Whichever method is used, one must also take care to match the spatial resolution of the CT-derived attenuation correction data to that of the PET or SPECT emission data, otherwise artifacts may occur at tissue boundaries that relate to differences in the spatial resolution of the two imaging techniques (34).

Once the appropriate μ values are computed, the CT data may also be used as the input for modeling and correcting the distribution of Compton-scattered photons in PET and SPECT.

In addition to providing the anatomic context for radiotracer signals, and CT-based attenuation and scatter correction of PET and SPECT images, there are other, admittedly challenging, opportunities for synergistic use of PET/CT and SPECT/CT datasets. A major problem in the quantification of radiotracer uptake in tissues of interest is the partial volume effect, which comes into play for structures smaller than about three times the spatial resolution of the PET or SPECT images (35). Radiotracer uptake can be severely underestimated in hot spots (for example, accumulation of a radiopharmaceutical in a small tumor) or overestimated in cold spots (for example, a perfusion deficit in heart muscle) owing to this effect. Because the CT images are obtained at considerably higher spatial resolution than the nuclear medicine images (typically 1 mm or better versus >4 mm for PET or SPECT), the
dimensions of organs, lesions, and other structures, assuming there is sufficient contrast, can be accurately determined from the CT images. With knowledge of the size and geometry of structures of interest, it may be possible to improve quantification of radiotracer uptake within that structure (22, 36), especially in cases where the geometry is quite simple and the background radiotracer distribution outside the structure of interest is low, or at least uniform. A second opportunity that remains to be carefully studied and exploited is the integrated reconstruction of the two datasets. Currently, the PET and CT datasets are each reconstructed independently. Thus, no prior information regarding possible correlation and colocation of structural and functional information is taken into account. Because structure and function often are correlated, this association could be used to reconstruct one dataset based on information in the other (e.g., use the CT image as a constraint for the PET or SPECT reconstruction to encourage the reconstruction of the radiotracer distribution to correlate with anatomical boundaries) (37–43). An extension of this approach would be to reconstruct both datasets simultaneously with structure informing function and vice versa. The obvious objection to these approaches is that there are cases where the relationship between structure and function either does not exist or it breaks down owing to some pathological process. Therefore, the correlation between the two forms of data must be achieved in a probabilistic fashion, with deviations permitted if the data do not support the anticipated correlation. Clearly, developing robust and generalizable algorithms that incorporate these ideas is very challenging; nonetheless, there may be very specific applications where robust approaches could be developed and where integrated image reconstruction may improve diagnostic accuracy or quantification of PET or SPECT data.

Whole-body PET/CT and SPECT/CT systems have revolutionized nuclear medicine imaging, especially in oncology, where hot spots with suspiciously enhanced uptake of a tumor-seeking radiotracer can now be accurately localized and correlated with anatomy. An example of a contemporary PET/CT scan is shown in Figure 3.

Despite the clear success of these multimodality systems, plenty of questions and challenges remain. One obvious difficulty is caused by various forms of patient motion. Because of the often lengthy duration of the PET or SPECT studies (typically tens of minutes), it is quite possible that patients may move at some point during the study. There are methods for detecting motion, but correction generally requires the use of elastic software techniques that have their limitations, one of the reasons these multimodality imaging systems were developed in the first place. Internal motion, such as filling of the bladder and bowel motion that occur during the scanning period, is particularly difficult to deal with and can lead to significant misregistration of images in these regions. The best way in which to reduce these problems is to speed up the PET or SPECT study such that the entire study can be acquired in a few minutes. The second form of motion is due to the cardiac and respiratory cycles. With fast CT scanners, the standard imaging protocol when imaging the thorax is to acquire data while the patient holds their breath at maximum inspiration, thus effectively eliminating respiratory motion. However, the PET or SPECT data are acquired over many respiratory cycles, and therefore are blurred by the respiratory motion. Not only does this cause problems in interpreting dual modality data in the region of the
Figure 3
Whole-body PET and CT images from a multimodality PET/CT system. The center image shows the $^{18}$F-fluorodeoxyglucose PET scan in which image intensity is reflective of glucose metabolism. A large, metabolically active tumor is easily visualized. The right-hand image shows a fusion of the PET and CT images allowing accurate localization of the tumor. Images courtesy of Dr. Cameron Foster and Dr. Ramsey Badawi, UC Davis Medical Center, Davis, California.

diaphragm but it also can cause significant artifacts in PET or SPECT images of the heart, lungs, and liver owing to errors in the attenuation correction (32, 44, 45). For example, portions of the heart (especially the apex) in the respiration-averaged PET or SPECT dataset appear to be located in the lung in the breath-hold CT image, and are therefore undercorrected for photon attenuation. This can lead to the appearance of apical defects that could be mistaken for pathology. The best match of the CT and PET/SPECT data appears to occur when the CT is acquired using a breath hold at end expiration (46, 47); however, this may not be possible for all patients because it is considerably more difficult than a deep inspiration breath-hold protocol. One possible solution to respiratory motion is to gate the PET or SPECT studies to the respiratory cycle (48); however, this results in a significant fraction of the data being rejected and a significant increase in imaging time for the same signal-to-noise level. Another approach is to acquire the CT data over the entire respiratory cycle so that it is blurred to match the PET or SPECT data; however, this can obviously impact the diagnostic quality of the CT scan. Clearly, motion correction at all levels remains a critical area of research for multimodality PET/CT and SPECT/CT imaging.
A second challenge relates to imaging when the attenuation values in the CT scan are perturbed by a foreign entity. One class of such studies is in cardiac imaging of patients with implanted devices such as pacemakers and defibrillators (49). Another problematic area is imaging in the presence of high-Z orthopedic and dental prostheses (50, 51). High-Z materials can cause beam hardening artifacts in the CT images that can be propagated, via the attenuation correction, into the PET or SPECT images. They also create problems in the mapping of $\mu$ values from CT energies (where photoelectric interactions are dominant in high-Z materials) to PET or SPECT energies (where Compton scatter is often the dominant mechanism). The magnitude of these effects vary depending on exactly how the attenuation correction is derived from the CT data, but may be reduced by appropriate precorrection of the CT images. A second, more common class of studies are those in which some form of CT contrast agent is employed. The contrast agent changes the attenuation coefficients in the CT scan in a concentration and time-dependent fashion and dramatically complicates the mapping of attenuation values between different energies (52–54). Once again, the magnitude of these effects depends on the exact conditions of the study and the method used to derive the PET/SPECT attenuation coefficients from the CT data (53–55).

One final challenge relates to the relatively small transverse field of view found in the CT components of most dual-modality imaging systems. A field of view diameter is 50 cm, which in large patients, with their arms down (positioning typically used for lengthy dual modality studies) often leads to truncation of the arms, and occasionally in the abdomen. For CT alone, there are methods for minimizing truncation artifacts in reconstructed images (56, 57). But when the CT is used for attenuation correction of PET or SPECT data, it becomes a more difficult problem because the truncated tissue needs to be accounted for. This can only be corrected by estimating the missing tissue based on an extrapolation of the patient boundaries from the available information (58).

**Dual Modality Systems for Breast Cancer Imaging**

Another area that has received considerable attention, but has yet to make a significant clinical impact, is the combination of nuclear and X-ray imaging for the detection and management of breast cancer. A variety of approaches are being investigated, including incorporating gamma ray detectors into a mammography unit (59–61), integrating PET detectors into a biopsy unit (62), and combined emission/transmission mammotomography systems (63). We are also involved in a project to develop a dedicated breast PET/CT scanner building on the platform of existing breast CT scanner (64) and breast PET scanner (65) prototypes.

The general goal of these approaches is to utilize the uptake of tumor-avid or tumor-specific radiotracers to help improve the specificity of X-ray mammography for classifying benign versus malignant lesions, and to base biopsy sites on both functional and structural information. Figure 4 shows an example of a mammogram and a positron emission mammography image taken from a combined system. A further role for such technology might be in monitoring response to neoadjuvant
therapy. Clinical implementation is hampered by the relative paucity of clinical trial data, and in the general diagnostic setting will be challenging due to the very low cost and high throughput of traditional mammographic techniques, despite their poor specificity. Nonetheless, multimodality systems may have specific applications, for example, in patient populations at high genetic risk for breast cancer, where a more intensive screening protocol might be indicated, or those with prior breast surgery or interventions that render mammographic data difficult to interpret on its own. As these multimodality systems are developed, well-designed clinical trials will be critical in evaluating their potential contributions to improving the diagnosis and management of breast cancer patients.

Preclinical PET/CT and SPECT/CT

A major area of development in imaging over the past decade has been small-animal imaging, especially as a testing platform for drug development and molecular imaging strategies. Novel targeted PET and SPECT radiopharmaceuticals, radiotracer-sequestering reporter gene systems (66), and labeling of therapeutic cells (67, 68) have opened up enormous opportunities for studying animal models of human disease and for testing new therapeutic strategies in vivo. Just as in the clinical environment, there is a need to know the location of the molecules and cells once injected so that data can be appropriately and quantitatively interpreted, especially given that the size of many structures of interest in the mouse are at or close to the resolution limits of dedicated animal PET and SPECT systems.

Over the past few years, research and commercial animal SPECT/CT systems have become available, based on small scintillation cameras with pinhole or parallel-hole collimation for SPECT, and small focal-spot, low power X-ray tubes and digital X-ray detectors operated in a 3-D cone-beam configuration for CT (69–71). Like their clinical counterparts, these are effectively two independent systems with integrated software control. Because small-animal X-ray imaging is typically achieved with X-ray tube voltages of 40–80 kVp (rather than the 80–120 kVp typically used for human clinical imaging), there is a marked difference between the energy of the

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**Figure 4**

Example of matched X-ray mammogram and \(^{18}\)F-fluorodeoxyglucose positron emission mammography (PEM) images showing a metabolically active lesion. Images courtesy of Naviscan PET Systems Inc., Rockville, MD.
Simultaneously acquired PET and CT images showing distribution of $^{18}$F-fluoride ion in a mouse. Reprinted with permission from Reference 72.

X-ray photons and the nuclear medicine photons, especially for PET/CT imaging, allowing them to be discriminated quite easily from each other. Furthermore, unlike clinical CT with a rapidly rotating scanner and a high-powered X-ray tube, small-animal CT employs a relatively slow rotation and it often takes minutes to acquire a complete dataset of a mouse. Therefore, acquisition times for PET and CT can be quite similar, and there may be advantages to simultaneously acquiring the PET and CT datasets. This can be achieved relatively easily in a coplanar imaging system with some minor shielding of the PET detectors to prevent X-rays from entering the PET detectors (72). Simultaneously acquired PET and CT images of a mouse taken with such a system are shown in Figure 5.

Another advanced concept under development is a single detector and electronics system that can be used for both X-ray and nuclear medicine imaging. High luminosity scintillators, such as lutetium oxyorthosilicate (LSO), or stacks of different scintillators (73), are combined with fast digitizers and digital electronics that can process up to 1 million X-rays per detector element per second in CT mode. Thus CT and PET or SPECT data could be acquired in rapid succession using just a single detection system (74).

The main reason that in vivo microCT systems predominantly use a low-power X-ray tube and a slowly rotating gantry is one of practicality. It keeps the cost low. But there would be clear scientific advantages to having a high-powered X-ray tube mounted on slip-ring technology for fast dynamic CT imaging. Such a system has been developed (75), but its cost and size (even without dual-modality capability) may limit its installation to large research institutions and companies. One important challenge therefore is to find a way to build a fast, compact, and relatively low-cost PET/CT or SPECT/CT system that is consistent with the broader preclinical research environment.

**INTEGRATION OF PET AND MRI SYSTEMS**

The idea of combining one of the nuclear medicine modalities with magnetic resonance imaging and spectroscopy is tantalizing in that this combination of modalities might find ways to take advantage of the high spatial resolution and excellent...
Photomultiplier tube (PMT): a vacuum tube with a photocathode that converts visible light into electrons and amplifies the number of electrons by a factor of $10^6$ to $10^7$. Widely used in PET and SPECT systems.

The challenges in integrating nuclear and magnetic resonance imaging are far greater than for the integration of nuclear imaging and X-ray imaging discussed previously, as there are several ways in which the two imaging systems can interact and interfere with each other, causing major artifacts and a serious degradation in image quality. Some of the primary issues to be considered are maintaining the homogeneity of the $B_0$ field and the linearity of the gradient fields in the MR system, avoiding radiofrequency interference between the MR transmit/receive coils and the electronics of the nuclear imaging system, susceptibility artifacts and eddy currents related to the placement of materials inside the MR magnet, and the effect of the magnetic field (both the static and switching gradient fields) on the nuclear imaging system. Magnetic field effects are particularly problematic for detector systems based on photomultiplier tubes (PMTs) that are highly sensitive to magnetic fields owing to their impact on electron trajectories inside the vacuum of the PMT.

Despite these challenges, significant progress has been made over the past 15 years. It is interesting to note that nobody has yet explored the simplest approach to this problem, namely placing two separate imaging systems back to back with some moderate shielding of the nuclear system to allow the PMTs to operate satisfactorily, in analogy to the clinical PET-CT approaches. Instead, researchers have generally focused on methods to integrate the nuclear imaging system inside, or as part of, the MR system. Because of the inherent need for a bulky, high-Z collimator and moving parts to obtain SPECT images, the focus has been almost exclusively on the combination of PET and MRI.

The earliest motivation for combining PET with MRI was not driven by a desire to make complementary measurements but rather to use the strong magnet of the MRI system to help restrict the range of the positrons prior to annihilation (76–79). Positrons are positively charged particles and therefore they will spiral around the magnetic field lines, reducing their range (the distance traveled before they annihilate with an electron and produce the two back-to-back 511 keV photons that are imaged) in two of the three spatial dimensions. Because positron range is one factor that can limit the spatial resolution of PET imaging, especially when using morphologic discrimination of MRI and the exquisite sensitivity of nuclear imaging, in both preclinical and clinical imaging (6). Furthermore, one can consider the possibilities of integrating more advanced MR measurements, such as dynamic contrast-enhanced MR, diffusion-tensor imaging, functional MRI, MR spectroscopic imaging, neuronal tract tracing, cell trafficking, and paramagnetic contrast agents, with tracer kinetic experiments utilizing essentially massless radiolabeled probes that are targeted to specific aspects of the biology of interest. Although clinical applications of such technology are not immediately clear, especially when one considers that the cost of a combined instrument is likely to be high, there are surely interesting research questions that could be addressed with a multimodality system, especially if the MR and nuclear data can be acquired in a simultaneous or rapidly interleaved fashion, allowing direct temporal correlation of the MR and nuclear signals during or following some form of therapeutic intervention. Such applications could not be addressed using scans acquired at separate times on separate machines that are subsequently registered by software.
radionuclides that emit relatively high-energy positrons (>1 MeV), this could lead to improvements in spatial resolution. Simulations and measurements clearly demonstrated that field strengths in the range of 4–10 T could significantly reduce positron range effects for several radionuclides of medical interest (76, 79). This would have most impact for very high-resolution small-animal studies using high-energy positron emitters, such as $^{124}$I and $^{15}$O, where positron range starts to become a dominant factor (80). It is unusual in any clinical studies for positron range to be the limiting factor, rather, overall study statistics and photon noncolinearity tend to be the dominant effects.

In the mid 1990s, interest grew in building systems that could acquire both MR and PET images. In collaboration with Marsden and colleagues at King's College London, we developed a series of simple MRI-compatible PET inserts to demonstrate that simultaneous PET and MR measurements were indeed possible (81–83). The most sophisticated of the prototypes (82) consisted of a ring of 72 small LSO scintillator crystals, coupled by 4-m-long optical fibers to multichannel PMTs and electronics that were placed outside the magnet. This system was used for simultaneous FDG PET and spin echo MRI studies in vivo (Figure 6), simultaneous FDG PET and NMR spectroscopy in an isolated, perfused rat heart preparation (84), and to assess artifacts in dual modality imaging at field strengths from 1.0 to 7.4 T (83). Although the system produced images, there were serious compromises in the PET performance owing to the limited number of detectors that restricted the sensitivity to approximately 0.03%. Scaling up the design to reach the sensitivity of state-of-the-art animal imaging systems, or to the size of a human imaging system, was deemed impractical owing to the very large volume of optical fibers and the lack of space within the magnet bore to accommodate those fibers.

There has been a series of recent developments in PET/MRI related to the availability of improved semiconductor light sensors, namely avalanche photodiodes (APDs). These sensors are very thin, and because of the high internal electric field and the short transit distances of the charge carriers, they are quite immune to high magnetic fields. This allows them to be placed inside a magnet and to operate quite normally (85). A number of groups are now exploring the development of PET inserts, both for animal and clinical imaging, that employ APD-based PET detectors. The challenges related to interference of the systems outlined above still exist, and are actually harder given that the photodetector now resides inside the magnet; nonetheless, by careful design of the detectors, electronics, and shielding, high-quality preliminary results have been obtained, as shown in Figure 7. At least three groups (Siemens; University of Tübingen; and University of California, Davis) are currently developing APD-based PET inserts for MRI systems, so within the next 1–2 years, the success or shortcomings of this approach should become clear.

A completely different approach is being taken at the University of Cambridge (86), where a novel split coil magnet has been designed in which a ring of conventional PMT/fiber-optic-based detectors is placed in the gap of the MRI system (Figure 8). This allows a large number of PET detectors to be placed within the imaging field of view, without the need to bring the fiber-optics out through the bore of the magnet. This system is currently under construction.
Clearly, integrated PET/MRI imaging systems are at a very early stage of development, yet there are encouraging signs that the new generation of systems will be undergoing evaluation in the near future. The optimal design for PET/MRI systems ultimately will be dictated by the applications. Whether simultaneous PET and MR imaging are required, whether PET is being performed in conjunction with advanced MR techniques that have particularly stringent pulse-sequence and field homogeneity requirements, and the compromise in performance one is able to accept in the integrated system in comparison with two independent dedicated instruments will drive future designs. For PET/MRI to become more than a scientific curiosity, and to share in the success of PET/CT or SPECT/CT, it will be critical to define scientific and clinical applications that uniquely require the integrated system.
Figure 7

(a) Schematic of detector module with four blocks of scintillator coupled to arrays of APD sensors, mounted on electronics board containing fast preamplifiers. (b) Photograph of two detector modules. (c) Modules and shielding inside MRI system. (d) Simultaneously acquired PET and MRI images of a phantom. Images courtesy of Dr. Matthias Schmand and Dr. Ralf Ladebeck (Siemens Medical Solutions).
SELECTED OTHER MULTIMODALITY IMAGING SYSTEMS

Integrating Optical Imaging with Radiologic Imaging Modalities

Optical imaging is the most widely utilized modality for preclinical molecular imaging, due in large part to easy accessibility of fluorescent probes and bioluminescent and fluorescent reporter proteins (87, 88). Until recently, optical imaging in small animal models was largely confined to qualitative or semiquantitative 2-D imaging of the light distribution reaching the surface of the animal. Several groups have been making excellent progress toward quantitative 3-D optical (89) fluorescence (90, 91) and bioluminescence tomography (92, 93). A related method, diffuse optical tomography, is also being pursued for clinical applications, especially for breast imaging and neonatal brain imaging (94).
Owing to the limited anatomic information obtained from photons emitted at depth inside tissue, there is interest in combining optical systems with other modalities, such as CT, MRI, and ultrasound, that provide high-resolution structural information. An example of this is the work of Ntziachristos et al., in which a fiber-optically coupled near-infrared imager was placed in the bore of a 1.5 T MR system for concurrent MRI and optical imaging. The system was used for contrast-enhanced diffuse optical tomography of the breast (95) and to perform MR-guided optical spectroscopy in breast lesions (96). Anatomic information also is being used as a constraint in algorithms for 3-D optical tomography (97, 98), and these approaches would benefit from dual modality optical/structural imaging systems.

Research is under way to couple optical imaging with PET and SPECT to allow multimodal functional and molecular imaging. Chatziioannou et al. have been investigating detector designs that are capable of detecting the faint bioluminescence signals from luciferase reporter genes and can also efficiently convert the 511 keV annihilation photons emitted from PET radiotracers into light utilizing transparent scintillators (99). The goal is to develop a single detector system that could be utilized for optical and PET imaging. This could allow, for example, the expression of two reporter genes to be monitored at the same time, or other novel approaches to dissecting molecular pathways and interactions.

While not strictly multimodality imaging, laser-induced photoacoustic tomography shows promise as an in vivo imaging tool. It combines optical excitation of tissue using a fast laser, with ultrasound detection of the photoacoustic waves produced by laser-induced thermoelastic expansion of the tissue. Photoacoustic approaches can lead to large improvements in spatial resolution over conventional optical imaging deep inside tissue, and improvements in contrast and a reduction in noise compared with conventional ultrasound imaging. Both structural and functional in vivo imaging have been accomplished with this technique (100).

Brain Mapping with Simultaneous fMRI and High-Density EEG

Functional MRI (fMRI) is widely used to study the hemodynamic consequences of task or event-related neuronal activation, providing high spatial resolution localization of these events, but on a relatively slow timescale (seconds). Monitoring the brain surface with high-density electroencephalography (EEG) or magnetoencephalography provides high temporal resolution (milliseconds); however, the electromagnetic fields mapped at the surface of the brain cannot unambiguously be reconstructed to provide the 3-D location of the sources of these fields within the brain without using constraints or additional information (101). There is clearly value, therefore, in combining these techniques, and it is now possible to simultaneously and continuously record EEG information within a magnet during the acquisition of fMRI data (102). Combining the high temporal but low spatial resolution EEG surface maps, with the high spatial but low temporal resolution volumetric fMRI data, provide highly complementary data that is critical in understanding neural circuitry and pathways. Although many of the technical challenges of combined fMRI/EEG imaging have been solved, there still remain many questions regarding how best to design the study.
protocols and analyze the resulting data to extract the maximum information possible from these studies.

**Combined PET/SPECT Systems**

Although PET and SPECT provide similar functional and molecular imaging capabilities, and would therefore perhaps not seem like good candidates for multimodality imaging systems, they are both to a certain extent limited by the availability of radiotracers, especially at sites that do not have extensive radiochemistry facilities. For example, SPECT does not have the equivalent of fluorodeoxyglucose, a widely applicable metabolic marker, whereas PET does not have a high-quality perfusion agent that can easily be distributed. Another problem for PET is that only one radiotracer can be imaged at a time. Dual tracer studies are not possible because the energy of the photons emitted (511 keV) is independent of the radionuclide used. Thus, to make two measurements simultaneously requires that PET be combined with a second modality.

In small-animal molecular imaging and clinical imaging, one wants to take advantage of the entire complement of available radiotracers, whether they be labeled with a positron-emitting or single gamma-emitting radionuclide, and hence a single instrument capable of PET and SPECT would be of value if the performance of the individual systems is maintained and the cost of the multimodality instrument is less than the cost of the two individual instruments. For clinical imaging, there was a trend in the 1990s of taking multiheaded gamma cameras designed for SPECT and adding coincidence circuitry between the two heads to permit PET imaging (103). However, the quality of the PET datasets was limited by the count-rate performance of the large-area gamma camera detectors, and the relatively low efficiency of the detector heads for the high-energy 511 keV photon emissions of positron-emitting radionuclides (104). More recently, a prototype PET/SPECT imaging system has been developed with the goal of not compromising either PET or SPECT performance. The detectors are based on two layers of scintillator: a layer of NaI(Tl) scintillators, primarily to detect the lower-energy single photons from SPECT radionuclides, such as $^{201}$Tl and $^{99m}$Tc, and a layer of LSO scintillator, primarily to detect the higher-energy 511 keV annihilation photons for PET (105). For small-animal imaging, a multihead PET/SPECT system based on a scintillator known as YAP has been developed and undergone initial evaluation (106). This system can be configured to acquire SPECT only, PET only, or both modalities simultaneously. This system would be unique in allowing a PET radiotracer to be imaged at the same time as a SPECT radiotracer, allowing two aspects of biologic function to be assessed simultaneously.

**CONCLUSIONS AND FUTURE DIRECTIONS**

The goal of multimodality imaging systems, whether consisting of a simple combination of two separate imaging devices or the complete integration of two modalities at the level of the detectors, electronics and software, should be to provide unique

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**Sodium iodide [NaI(Tl)]:** A bright scintillator widely used in gamma cameras and SPECT systems.
or enhanced information that impacts clinical diagnostics or scientific research. One would like to avoid compromising the image quality obtained from either device, but when this is not possible, it becomes necessary that the multimodality system provide some added value that is significant enough to overcome the deficiencies of the combined system.

Naturally, because of this requirement, a lot of the emphasis in multimodality imaging research is on system design and data corrections that minimize any interference or other undesirable consequences of bringing two systems together. From the work cited in this article, it is evident that a great deal has been achieved in this regard, although many challenges remain. As multimodality imaging systems start to mature, the research focus will shift (and in some cases this has already happened) to working out how to make the best use of the two complementary datasets to inform the user of the location, quantitative magnitude, and the time course of the signals of interest.

A development that will likely impact multimodality imaging instrumentation is the rapid development in multimodality contrast agents (107, 108) and reporter genes (109). The ability to label molecules, cells, and targeted microbubbles or nanoparticles in a generic and combinable fashion with radioactive, fluorescent, magnetic, or acoustic tags and the advent of multimodal reporter genes all auger well for the future of multimodality imaging systems. One can imagine powerful approaches to understanding the distribution and kinetics of molecules, drugs, therapeutic cells, and genes in vivo utilizing a combination of imaging modalities that are able to visualize the same labeled entity with differing spatial, temporal, and sensitivity scales.

Finally, there are two areas in which important developments are likely to occur. In the clinical imaging arena, the integration of multimodality functional/structural imaging with therapeutics (whether radiotherapy, cell or gene-based therapies, or conventional drug-based therapies) will continue to grow. If the dream of patient-specific treatment is to become a reality, imaging will play a key role in predicting which therapies to use (for example, by determining which molecular target or pathway is involved in a particular patient), in planning therapies (for example, defining target volumes for radiotherapy based on a functional measure coregistered with anatomy), and in monitoring therapies (for example, determining the location and number of functional therapeutic cells in the days, weeks, and months following treatment). At the other end of the spectrum, in the growing field of imaging animal models of disease and developing molecular imaging strategies, there is a critical need to correlate in vivo imaging with ex vivo imaging from histopathology, autoradiography, and other high-resolution techniques. There is at present a paucity of approaches for registering excised biopsy or postmortem tissue with its exact location in an in vivo imaging study, and such tools will be critical in correlating changes at the cellular level with those observed at the more macroscopic tissue level using in vivo whole-body imaging approaches. An early attempt at bridging the divide between in vivo and ex vivo imaging is the work of Humm et al. (110, 111).

The field of multimodality imaging has clearly flourished over the past 15 years, driven by the realization that different imaging modalities offer uniquely different perspectives on their biological subjects, and by the development and increasing
clinical relevance of physiologic, metabolic, and molecular imaging studies that demand multimodality approaches to correlate function and structure. The field also has been enabled by a growing group of interdisciplinary imaging scientists who have spurned a modality-centric ethos for an application-driven approach to imaging. Significant improvements surely are ahead of us, but it is already clear that 1 + 1 can add up to more than 2 when it comes to multimodality imaging systems.

SUMMARY

1. Multimodality imaging systems should provide important scientific or diagnostic information not readily attainable using two separate imaging systems, and where possible, the performance of each imaging system should be preserved.

2. Multimodality imaging systems are being developed for clinical applications (e.g., diagnostics and for clinical trials of new therapeutics) and for preclinical applications (e.g., drug development, evaluating cell and gene-based therapies, and new molecular imaging assays).

3. The combination of structural and functional/molecular imaging techniques, especially PET/CT and SPECT/CT, is the most successful example of multimodality imaging systems to date. The combination of PET and MRI offers tantalizing opportunities, but also significant challenges.

4. There are relatively few examples of truly integrated multimodality imaging systems in which a single system of detectors and electronics is used for two different modalities. In most cases, two separate instruments are placed in close proximity and integrated primarily through software.

5. Multimodality imaging systems are commercially available, and their range of applications is growing rapidly. Numerous opportunities exist to improve existing multimodality imaging systems, and to develop new combinations of modalities. Opportunities also exist for better use of the data being generated by existing systems, especially in terms of the reconstruction of tomographic images and quantitative evaluation of those images.

DISCLOSURE STATEMENT

S.C. is a paid consultant with CTI Concorde/Siemens.

LITERATURE CITED


58. Important paper describing a method to deal with the truncation artifacts common in PET/CT and SPECT/CT systems.


74. Describes the development of a single detector/electronics system for a truly integrated multimodality PET/CT system.


111. The first example of attempts to spatially register in vivo and ex vivo imaging techniques.
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