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MULTIMODALITY IMAGING: BEYOND PET/CT AND SPECT/CT

Simon R. Cherry, Ph.D.
Department of Biomedical Engineering, Center for Molecular and Genomic Imaging, University of California – Davis

Abstract

Multimodality imaging with PET/CT and SPECT/CT has become commonplace in clinical practice and in preclinical and basic medical research. Do other combinations of imaging modalities have a similar potential to impact medical science and clinical medicine? The combination of PET or SPECT with MRI is an area of active research at the present time, while other, perhaps less obvious combinations, including CT/MR and PET/optical also are being studied. In addition to the integration of the instrumentation, there are parallel developments in synthesizing imaging agents that can be viewed by multiple imaging modalities. Is the fusion of PET and SPECT with CT the ultimate answer in multimodality imaging, or is it just the first example of a more general trend towards harnessing the complementary nature of the different modalities on integrated imaging platforms?

Introduction

This issue of the Seminars in Nuclear Medicine reflects the spectacular advances in fusion imaging with PET/CT and SPECT/CT over the last decade. Building on the foundation laid by early pioneers, the fusion of these modalities has become so totally engrained in routine clinical practice that many of the more recent trainees in the field find it hard to conceive that there was a time, in the not too distant past, when PET and SPECT studies did not automatically come with a registered CT scan.

In retrospect it of course seems obvious that this combination of modalities, in which CT provided the anatomic context to interpret the functional PET or SPECT study (plus the information necessary for a reasonably accurate attenuation correction), would be a successful tool, encompassing not only the clinical applications described in the other articles in this issue, but also important applications in basic medical science and preclinical research that utilize animal models. However, it was far from obvious, when the late Bruce Hasegawa, whose seminal contributions we celebrate in this issue, started working on marrying emission and transmission computed tomography in 1990 and proposed using an x-ray tube rather than a radionuclide source for transmission scanning [1]. With typical prescience, Bruce stated in that article that "…the novel and potentially powerful capabilities of this instrument would derive from its inherent correlation of functional information from SPECT with precise anatomic information from CT…". It was Bruce's early studies in designing, constructing and implementing combined SPECT/CT systems [2–8] that alerted us all to the possible

Address: Department of Biomedical Engineering, University of California – Davis, One Shields Avenue, Davis, CA 95616, Telephone: (530) 754-9419, FAX: (530) 754-5739, srcherry@ucdavis.edu.

opportunities of these hybrid devices, and that directly catalyzed a decade of research in universities, national laboratories and companies around the world.

Even as the first PET/CT scanners were introduced towards the end of the 1990's [9] there was still vigorous debate in the field whether this new "toy" really had a role to play or not [10–12]. After all, an attempt to create multimodality PET/SPECT systems out of dual or triple-headed gamma cameras had been a failure, and as late as 2001 when Jim Sorenson and I rewrote the 3rd edition of our textbook "Physics in Nuclear Medicine" [13], we chose to give little emphasis to PET/CT or SPECT/CT, worrying that is was perhaps a passing fancy that would not stand the test of time. How wrong we were. It is now almost impossible to buy a new clinical PET scanner without an integrated CT scanner and in the preclinical market, just about every manufacturer that offers a PET system offers an accompanying CT scanner as an option. Thus Bruce Hasegawa's vision, articulated in 1990, has become a reality that has changed the face of Nuclear Medicine forever [14,15].

The success of PET/CT and SPECT/CT however raises some interesting questions that are worthy of contemplation as we look to the future. Are there other combinations of imaging modalities that could play an equally important role in clinical medicine or in basic medical research? If so, is it true that the most successful combinations will always be hybrids of anatomical and functional imaging techniques, or is there a role for the combination of two anatomical (e.g. CT and MR) or two functional (e.g. PET and optical) modalities? Is there a set of guiding principles to be considered in developing multimodality or hybrid imaging systems? Finally, it is interesting to look beyond the imaging instruments themselves and also consider the opportunities for multimodality molecular imaging agents. It is these questions and topics that form the subject matter for this perspective on the future of multimodality molecular imaging – beyond PET/CT and SPECT/CT.

Multimodality Imaging: Approaches and Principles

To frame the discussion on multimodality imaging, past, present and future, it is useful to consider the different levels of integration that can be involved [16]. Loosely speaking, multimodality imaging is defined as imaging a subject with two or more modalities with the images being registered in space and in time. Prior to the advent of multimodality PET/CT and SPECT/CT scanners this was accomplished, almost exclusively, through retrospective software registration of the volumetric datasets [17,18]. For tissues with constrained geometry and limited motion, such as the brain, these approaches worked very well. However in many other parts of the body, image registration was challenging due to changes in patient pose on the two separate imaging devices, temporal changes between the two scans, that may have been acquired days or even weeks apart, and limited information in the image datasets (especially the PET or SPECT datasets) to "drive' the algorithms to accurate registration. Nonetheless, these techniques were important in demonstrating the value of multimodality imaging, and are still widely employed for registering modalities for which multimodality instrumentation does not commonly exist.

Current hybrid PET/CT and SPECT/CT systems represent an important, but only partial step towards full multimodality integration. They enable sequential functional and anatomic imaging, without moving the patient off the couch and there is a fixed and known coordinate transformation between the images produced from the two systems, eliminating the need for image registration algorithms. However to all intents and purposes the hardware of the two imaging systems remain separate and the patient is moving sequentially through two independent devices that are bolted together in a tandem configuration. The integration, or hybrid imaging all occurs at the software level – software to control the acquisition of the two datasets, and software to control the reconstruction of the two datasets, the attenuation and

scatter corrections utilizing the CT information, and the display of the fused images. Nonetheless, this is extremely effective, leading to much improved spatial registration over software registration for many parts of the body, and improved temporal registration with only a few minutes separating the PET or SPECT scan and the CT scan.

However, there are two further levels of integration that can be contemplated and that offer tantalizing possibilities for the future. The first is a design such that two separate imaging modalities are able to acquire data from the same tissue volume at the same time. This is an approach actively being pursued in some PET/MRI systems (discussed below) and would allow true simultaneous multimodality imaging. This is of particular interest for following fast dynamic events with more than one modality, for example changes following an intervention. Another approach to more complete multimodality integration would be to develop detector systems and electronics capable of detecting the signals from two modalities at once. For example, a detector that could be used for detecting x-rays and the gamma rays or annihilation photons arising from the decay of radionuclides. In theory, with such a detector, it might be possible to conduct SPECT and CT scans of the same volume simultaneously, or near simultaneously. This would represent the ultimate multimodality device – one detector technology capable of providing images for two distinct modalities. While for many combinations of modalities, this is likely impossible, there are a subset of hybrid imaging combinations, where there is active research to develop such detectors. Such solutions could ultimately reduce cost and increase patient throughput.

In considering hybrid imaging combinations beyond PET/CT and SPECT/CT, the guiding principle has to be that the multimodality system provides some kind of added value. The types of added value that might serve as motivating factors include: i) the ability to address scientific or clinical questions that would be impossible on separate scanners (studies that require simultaneous imaging, or very good spatial registration that cannot be achieved using registration algorithms); ii) improved quantitative accuracy of functional/molecular imaging studies; iii) improved throughput for clinical or preclinical studies; iv) lower cost if components can be shared among modalities. However, multimodality systems typically come with trade-offs that have to be balanced against the perceived added value. Possible negatives and other considerations include: i) any reduction in imaging performance compared with stand-alone system, ii) system cost if greater than the individual components, iii) space requirements, iv) additional operational complexity (increased downtime?) and the need for expertise across quite diverse modalities.

PET/CT and SPECT/CT have demonstrated that there are circumstances where the balance of these factors clearly favors the use of hybrid imaging systems. Yet the history of this example also serves to illustrate that it is not easy to predict the impact of a hybrid system until it has been developed sufficiently to be applied to biomedical or clinical problems. When there is reasonable evidence of value to be gained, there is some truth to the saying “build it and they will come”. Therefore, it is important that research into the development and optimization of new hybrid imaging systems continue to be supported, as it offers one of the best opportunities for major technical innovation and impact in contemporary medical imaging science.

The Next Frontier: PET/MRI and SPECT/MRI

One of the most active areas of endeavor in multimodality imaging at the present time is the integration of MRI with PET or SPECT. Although development started back in the 1990’s [19–21], progress, until recently, was relatively slow. In part, this was due to the substantial difficulties posed by operating these systems in close proximity, and in part due to initial lack of industry interest and concerns over the cost of such a combined device. However, building on the success of PET/CT and SPECT/CT, the last few years have seen an explosion of activity

and the introduction of a number of working prototype PET/MRI systems, both for studies in animal models [22,23] and for applications in the human brain [24]. Critically, the major medical imaging corporations have recognized that there may be a clinical role for PET/MRI or SPECT/MRI and have programs at various stages of development to investigate hybrid products. Two reviews discuss the recent progress and technical developments in PET/MRI [25,26].

One motivating factor for combining PET and SPECT with MRI is to address clinical applications where MRI is the preferred anatomic imaging modality to CT (for example, many neuroimaging applications and cancers in the pelvic area). But perhaps more interestingly, this combination would allow correlation of radiotracer assays with other types of more functional MR measurements, for example dynamic contrast-enhanced MRI, diffusion-weighted MRI, functional MRI, pharmacologic MRI and MR spectroscopy [25]. This opens up a wealth of interesting research opportunities, and with these advanced MR techniques finding increased clinical utility, there likely will be range of clinical applications that combine anatomic MR, some form of functional MR measurement and molecular imaging with PET or SPECT. A third consideration, that is not trivial, is that the radiation dose for PET/MRI will be significantly less than for PET/CT. This is of particular importance for studies that are monitoring disease progression and response to therapy with multiple scans. While these are all good reasons for developing hybrid systems with MR rather than CT, there is one significant drawback of MR that must be acknowledged. MR does not directly provide the information required for attenuation correction of the nuclear medicine study. In particular, it is challenging to separate air and bone, and to measure the density variations in the lung with MRI. MRI-based attenuation correction has therefore become an active area of research [27,28] and its success or otherwise will likely have an important bearing on the ultimate range of clinical applications for PET/MRI.

Interestingly, the majority of PET/MRI or SPECT/MRI systems developed to date have involved placing nuclear medicine detectors inside the MR magnet, often with the goal of being able to perform some kind of functional MRI measurement simultaneously with PET or SPECT. This is a radical departure from the approach used for fusion with CT, where the scanners were arranged in a tandem rather than concentric configuration, and where scans were acquired sequentially. This more integrated approach also significantly increases the technical complexity in building a successful PET/MRI or SPECT/MRI system.

The technical challenges in integrating PET and SPECT with MRI relate primarily to the multiple ways in which the systems can interfere with each other. The PET or SPECT system must operate in a high magnetic field environment, which suggests the use of scintillators coupled to magnetic field insensitive solid state light detectors such as avalanche photodiodes [29,30] or silicon photomultipliers [31]. Alternatively, if traditional photomultiplier tubes are to be used, they need to be placed outside of the magnet in an area where the fringe field is low enough that they can be effectively shielded against the field [20,32,33]. The MRI system requires very good uniformity of its magnetic field (typically 1 part in 10^6 or better) and foreign objects placed in or around the magnet have the potential to perturb that field. The third and generally most challenging issue relates to electromagnetic interference between the two systems. An MRI system generates high power radiofrequency pulses, as well as rapidly switching gradient magnetic fields. It is very easy for these signals to be picked up by the PET or SPECT system, swamping the low amplitude signals produced by the scintillation detectors. It also is very possible that components of the PET and SPECT electronics (such as the power supplies or preamplifier electronics) radiate electromagnetic waves that can interfere with the MR signals. SPECT has two additional challenges, which is perhaps one reason why SPECT/MRI development has somewhat lagged behind PET/MRI development. Firstly, any moving parts are very likely to create artifacts in the MR images, and therefore traditional rotating

gamma camera systems are problematic. Stationary SPECT scanner designs are therefore a better starting point. Secondly, the collimator material and design is an issue, especially if the SPECT system is to be placed inside the MR magnet. The bulk of this material (in the very limited space inside the magnet) and the potential for the generation of eddy currents are further obstacles to the successful realization of SPECT/MRI

Despite these not inconsiderable difficulties, the field has advanced quite impressively in the last 2–3 years. Two MR-compatible PET scanners based on avalanche photodiode detector technology have been developed for small animal imaging and have been successfully applied for a range of *in vivo* applications [22,23]. A variety of other designs also are at various stages of development [32,34,35] including some approaches that involve modifications to the MR system such as split magnet designs [36] and field-cycled systems [37]. Recently the first PET insert for human studies was developed and is now deployed at a number of sites for PET/MR imaging of the brain [24]. Although technical developments continue at a fast pace, the emphasis is clearly shifting to addressing the attenuation correction issue, and to exploring the preclinical and clinical applications for PET/MRI. PET/MRI has now reached the stage that PET/CT was at approximately ten years ago. The first successful systems have been built, but there is much debate (and little consensus) what the ultimate role for this powerful hybrid imaging technology will be [38–40]. Time will tell.

On the Horizon Other Multimodality Approaches to Biomedical Imaging

Given the tremendous opportunities presented by integrating *in vivo* imaging modalities with different strengths, it is not surprising that several other hybrid combinations are being explored. Some of these are primarily directed at small animal research (for example many of those involving optical imaging techniques), but may nonetheless ultimately find some application in the clinic. Here we briefly summarize a small selection of other hybrid imaging systems under development, focusing on the motivation for their development and possible applications.

Hybrid nuclear medicine and optical imaging systems

This merger of two molecular imaging technologies is motivated by the desire to measure multiple molecular targets simultaneously, and by the need for imaging technologies that can serve as a translational platform between the very widely used optical techniques that employ bioluminescent or fluorescent reporter genes, or injected fluorescent probes, in small animal models [41], and nuclear medicine radiotracer assays that can be moved from mouse to human [42]. Prototype tomographic instruments for optical/PET and optical/SPECT in small animals are under development in research laboratories [43–45]. Simple projection/surface imaging systems capable of producing 2-D fluorescence and radiotracer studies, and correlating these with an x-ray radiogram, are already commercially available [46]. One possible path to clinical translation of these hybrid technologies is to use the sensitive whole-body imaging capabilities of PET/SPECT to guide an optical “biopsy” using an endoscope or catheter-based optical imaging probe to provide high resolution and high sensitivity local mapping of fluorescent signals at locations of suspicious “hotspots” seen on a PET or SPECT scan.

Hybrid X-Ray/MR systems

There also is interest in merging two structural imaging techniques for interventional applications. X-ray fluoroscopy has very high spatial and temporal resolution, but provides only two-dimensional images, whereas MRI, although slower, provides 3-D images that can significantly aid in accurate localization. A prototype x-ray fluoroscopy system has been constructed in the bore of a vertical gap interventional MR scanner and successfully deployed for patient studies, with applications including placement of vascular shunts in the liver,

arthrograms, prostate seed implantation, arteriovenous malformations and cystography [47]. A system integrated with a short closed-bore system is being developed consistent with the trend towards the use of these higher field MR systems for interventional applications [47].

Photoacoustic tomography

Uniquely, this hybrid technology relies on the interaction of two imaging modalities, optical imaging and ultrasonic imaging, to take advantage of the high spatial localization capabilities of ultrasound at depth in tissues, and the high sensitivity provided by optical contrast [48,49]. Tissue is excited with a short-pulsed laser beam and absorbed locally by endogenous chromophores such as hemoglobin, or by administered optical contrast agents. Absorption of the light by the chromophore results in small amount of local heating, which is converted to a rise in pressure due to thermoelastic expansion of the tissue. This pressure rise propagates as an ultrasonic wave through tissue and can be detected by an ultrasound transducer. In animal models, this technique allows very high spatial resolution functional and molecular imaging to be obtained at depths of several mm beneath the surface [50]. This technique can provide images of the vasculature, hemoglobin concentration, hemoglobin oxygen saturation, metabolic rate of oxygen and melanin concentration by measuring the absorption of light by native chromophores. Using optically-absorbing targeted contrast agents, it may also be possible to image the distribution of molecular targets and gene expression. The photoacoustic images can be fused with conventional ultrasound images to provide hybrid images of function/structure. Photoacoustic tomography is being explored for a range of clinical applications, including breast imaging, melanoma detection, sentinel lymph node analysis, endoscopic applications, and even brain imaging [48–50].

Hybrid optical and MRI

In vivo optical imaging at any significant depth in tissue typically carries little in the way of structural information and thus, similar to the rationale behind integrating PET or SPECT with CT or MRI, there are good reasons to develop optical imaging in conjunction with high resolution 3-D structural imaging. There have been significant efforts in developing hybrid optical/MRI systems, as reviewed in [51]. Applications range from small animal imaging to human breast and brain imaging. Given the ill-posed nature of the data available to reconstruct 3-D diffuse optical tomography or fluorescence tomography images, the spatially registered MR images can be employed to delineate the boundaries of tissues with different optical properties, and thus potentially improve the accuracy of the 3-D optical reconstructions.

Multimodality Imaging Agents

If we consider the first era of multimodality imaging to have been the development of software tools for image registration, and the second era to be the current emphasis on developing multimodality instrumentation, the third era, which we are just entering, is surely the era of multimodality imaging/contrast agents. A number of large biomolecules (e.g. peptides and proteins) and particles (e.g. microbubbles, liposomes, nanoparticles) offer appropriate platforms for building imaging agents that can provide contrast for more than one imaging modality.

One motivation for developing these hybrid agents is that they enable one to study the same target, with the same imaging agent, on different imaging platforms and at different scales. For example one could take a multimodality agent and do fluorescence imaging in cell culture and small animal models, and then using the same agent perform MRI, PET or SPECT in larger animals or patients. A second possibility is that these agents could be used with multimodality instrumentation. For example, in a PET/MRI system, the high sensitivity of PET could be used to determine areas of focal uptake of a targeted PET/MRI agent in the body, followed by very

high resolution MR imaging of that same agent, but with the MR images only being acquired in the localized regions where a PET signal was seen.

There already is a significant body of work on hybrid optical/MR contrast agents [51]. Examples include fluorescent quantum dots with a paramagnetic coating [52], quantum dots with high native relaxivity [53], lipoproteins incorporating iron oxide nanoparticles and quantum dots [54], liposomes containing Gd and fluorescent agents [55] and antibodies conjugated with both nanoparticles and fluorescent agents [56]. In some cases, these particles and proteins are additionally being designed to incorporate radionuclide tags for PET or SPECT imaging [25,42,57,58]. Ultrasound contrast agents also are being used as a basis for multimodality agents. Microbubbles provide high contrast for ultrasound imaging, and their lipid shells can be labeled with radionuclides or fluorescent agents for multimodality ultrasound-optical-PET detection [59].

Final Reflections

Clearly, multimodality imaging is thriving and still evolving rapidly. Although software approaches to image fusion will continue to be widely used in many applications, the role of hybrid imaging systems is growing, both in research and clinical practice, and new combinations of modalities are being developed, inspired by the success of PET/CT and SPECT/CT. Multimodality imaging agents offer a powerful way to interrogate biological targets *in vivo* using a range of imaging modalities and are highly complementary to the hybrid imaging systems that are being developed. Finally, another important area of integration, not discussed here, is the interface between imaging and disease treatment. There has been huge progress in instrumentation designed for imaging concurrently with radiation therapy and interventional procedures, and in new imaging agents designed to help monitor chemical, biologic and genetic therapies. The integration of structural, functional and molecular imaging with therapeutic intervention represents the ultimate multimodality platform for biomedical research and eventual clinical application.

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