TOPICAL REVIEW

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TOPICAL REVIEW

Multimodality imaging of structure and function

D W Townsend

Departments of Medicine and Radiology, University of Tennessee Medical Center, 1924 Alcoa Highway, Knoxville, TN 37920, USA

E-mail: dtownsend@mc.utmck.edu

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Abstract

Historically, medical devices to image either anatomical structure or functional processes have developed along somewhat independent paths. The recognition that combining images from different modalities can nevertheless offer significant diagnostic advantages gave rise to sophisticated software techniques to coregister structure and function. Recently, alternatives to retrospective software-based fusion have become available through instrumentation that combines two imaging modalities within a single device, an approach that has since been termed hardware fusion. As a result, following their recent introduction into the clinic, combined PET/CT and SPECT/CT devices are now playing an increasingly important role in the diagnosis and staging of human disease. Recently, although limited to the brain, the first clinical MR scanner with a PET insert, a technically-challenging design, has been undergoing evaluation. This review will follow the development of multimodality instrumentation for clinical use from conception to present-day technology and assess the status and future potential for such devices.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

The early 1970s saw the introduction of the first x-ray computed tomography (CT) scanner, initially for brain imaging and then later for whole body. Following CT, the 1980s witnessed the appearance of clinical magnetic resonance (MR), a technique of particular importance for imaging patients because it does not require the use of ionizing radiation. These two techniques, CT and MR, located within radiology departments came to dominate the imaging of human anatomy. However, in diagnosing and staging disease or monitoring response to therapy, anatomical imaging does not always provide the complete picture. Functional or metabolic changes can and do occur even in the absence of a corresponding anatomical correlate. Nuclear medicine techniques, initiated in the late 1940s, image functional processes
by using radioactive tracers and photon detectors (gamma camera). Tomographic imaging with radionuclides actually predates CT with early attempts dating from 1963. The first human tomographic images with positron-emitting isotopes were presented in 1972 (Chesler 1973) thus establishing positron emission tomography (PET) on the map of medical imaging technologies, to be joined by single photon emission tomography (SPECT) a year or so later following on from the pioneering work of the early 1960s.

Historically, instrumentation for tomographic imaging of function (SPECT, PET) evolved along a path distinct from that of anatomical imaging devices (CT and MR), and the corresponding clinical studies were performed and interpreted separately in the different medical departments of nuclear medicine and radiology, respectively. Despite this segregation, the usefulness of combining anatomical and functional planar images was evident to physicians even in the 1960s (Wagner 2006), preceding the invention of computed tomography. The alignment of tomographic images is a complex procedure owing to the large number of degrees of freedom and without some common features coregistration may be problematic. In addition to simple visual alignment, or the use of stereotactic frames that are undesirable or inconvenient for diagnostic imaging, sophisticated image fusion software was developed from the late 1980s onwards (Levin et al. 1988). For (relatively) rigid objects such as the brain, software can successfully align images from MR, CT and PET whereas in more flexible environments, such as the rest of the body, accurate alignment is difficult owing to the large number of possible degrees of freedom.

An early attempt to localize a radionuclide distribution by acquiring anatomical images in a single device was the use of transmission sources in SPECT imaging (Butler et al. 1988). Arterial perfusion images acquired with the SPECT tracer $^{99m}$Tc-MAA could thus be localized with the transmission images for the evaluation of patients undergoing regional chemotherapy. Obviously, the transmission images were not of CT quality but it represents an attempt to overcome the problems of software fusion by combining devices (emission and transmission) rather than fusing the images post hoc, an approach that has now coined the term hardware fusion. A combined, or multimodality, scanner such as SPECT/CT or PET/CT can acquire coregistered structure and function in a single study. The data are complementary allowing CT to accurately localize functional abnormalities and SPECT or PET to highlight areas of abnormal metabolism. Although technically more challenging, the simultaneous acquisition of MR and PET has also been demonstrated, initially for pre-clinical imaging of small animals, but more recently for the human brain. An added advantage of combined instrumentation is that the CT images can be used to correct the functional images for attenuation (Kinahan et al. 1998, LaCroix et al. 1994) and scatter (Beyer et al. 2000), thus replacing the traditional PET or SPECT transmission scan. The CT can also be used to correct for partial volume effect, particularly in tumors (Soret et al. 2007). Such corrections are important in order to achieve accurate and objective assessment of functional parameters such as myocardial perfusion, tumor uptake values (SUV) and dosimetry for treatment planning and monitoring response.

Since the commercial introduction of PET/CT in 2001 and SPECT/CT in 2004, adoption of the technology has been rapid, particularly for oncology. Advances in CT and PET instrumentation have been incorporated into the very latest PET/CT designs, and SPECT/CT has also benefited from the advances in CT technology. A recent paper (Muehllehner and Karp 2006) offers an excellent overview of PET imaging and summarizes major advances in instrumentation. This review will follow the early pioneering work that culminated in the commercial exploitation of multimodality imaging and led to the current designs. The impact of recent advances in CT and PET performance on these designs will be discussed. The review will include a description of CT-based attenuation correction (CT-AC) and the challenges that must be addressed since this has become an important aspect of multimodality
imaging. Finally, the clinical impact of PET/CT and SPECT/CT and the potential influence of MR/PET on the future of multimodality imaging will be assessed.

2. Historical concepts

The origins of tomographic imaging in medicine date from the 1960s or even earlier, whereas fusion of tomographic images was not explored systematically until the late 1980s (Levin et al 1988). Following on from the earlier superposition of planar images (Wagner 2006), the 1990s have seen two principal approaches to image fusion: software and hardware. The software approach attempts to align two image sets post hoc after they had been acquired on different scanners at different times. In contrast, the hardware approach combines the instrumentation for two imaging modalities and thus acquires both modalities within the same reference frame thereby ensuring accurate alignment.

2.1. Image fusion with software

A thorough discussion of the topic is beyond the scope of this paper. However, it is instructive to review some of the principles of software fusion and the level of success that has been achieved; a thorough review of software fusion methods can be found in Hawkes et al (2003) and in Slomka (2004) specific aspects are presented of merging anatomic and molecular information and of how they relate to combined PET/CT and SPECT/CT. Fusion of two image sets is achieved either by identifying common landmarks or fiducials that can then be aligned or by optimizing a metric based on image intensity values. Whatever the method, the number of possible degrees of freedom between the two image volumes defines the complexity of the subsequent transformation. For distributions that do not involve a change in shape or size, rigid body transformations are adequate. When shears (or a non-isotropic dilation without shear) are involved, an affine transformation comprising a linear transformation and translation is indicated. When there are no constraints on the deformation, a nonlinear (warping) transformation is used. Although methods involving the alignment of extracted features or fiducials (Mountz et al 1994, Pelizzari et al 1989, Pietrzyk et al 1990) have shown some success, at least for the brain, most currently-used methods are intensity based and images are coregistered by assessing the intrinsic information content. Metrics include intensity ratios (Woods et al 1993) and mutual information (Maes et al 1997, Studholme et al 1997). While such techniques have shown great success in aligning images of the brain acquired with CT, PET, SPECT and MR, they have been less successful in other parts of the body. Earlier clinical assessment in the lung (Wahl et al 1993) and pelvis (Hamilton et al 1999) were disappointing demonstrating a local registration accuracy of 5–8 mm, compared with an accuracy of about 2 mm that can be achieved for the brain (West et al 1997). A recent review (Hutton and Braun 2003) suggests that software fusion can achieve an accuracy of about half a pixel, or 2–3 mm, for some studies even though clinical results from more recent generations of fusion software have not been particularly encouraging in applications such as recurrent colorectal cancer (Kim et al 2005). Software development has nevertheless continued, as illustrated by the recent publication of an automated warping algorithm to align CT and PET images of the thorax (Slomka et al 2003).

Commercial software has considerably improved over the past few years both in the accuracy of the registration algorithms and in the sophistication of the user interface and display. As an example, Hermes Medical Solutions (Stockholm, Sweden) offers advanced fusion software for many clinical applications, including correction of misalignment errors for PET/CT scans, registration of PET/CT scans with MR, registration of longitudinal PET/CT scans.
or SPECT/CT studies, alignment of PET and MR scans in Alzheimer’s disease and other forms of dementia, and registration of SPECT or PET myocardial perfusion studies with CT or MR of the heart. Fusion software can also play an important role in radiation therapy planning where PET or SPECT images are used to define the treatment plan (Dizendorf et al 2002, Gregoire et al 2007). Fusion of the PET/CT study with the simulation CT can result in modification of the standard CT-only treatment plan in a significant percentage of cases, particularly for lung disease. Traditionally, software fusion has played a significant role in registering SPECT studies to CT or MR. As combined SPECT/CT scanners become more widely available the demand for software fusion may decline. Finally, despite considerable progress, fusion software will probably never compete with the simplicity and convenience of coregistered studies acquired on a combined PET/CT or SPECT/CT scanner.

2.2. Multimodality prototypes

The pioneering work of Hasegawa and colleagues in the late 1980s (Hasegawa et al 1990, 1991) really set the stage for the hardware solution to image fusion. The aim of this work was to design a device that could perform emission (radionuclide) and transmission (x-ray) tomography with the same detector that, in this case, was segmented high purity germanium operated in fast counting mode (Hasegawa et al 1991). Although this approach is attractive, the difficulty is to design a detector that does not compromise performance for at least one of the two modalities. The work was significant, however, in that it highlighted the potential of having a single device that could perform both anatomical (CT) and functional (SPECT) imaging (Lang et al 1992). Of comparable significance was the use of the CT images to generate attenuation correction factors for the emission data (Hasegawa et al 1993). The device was used for studies in phantoms and animals, in particular a study of myocardial perfusion in a porcine model (Kalki et al 1997). However, recognizing the difficulty of building a detector that would operate optimally for both CT and SPECT, Hasegawa turned to a different design.

2.2.1. The first SPECT/CT

In 1996, Hasegawa and co-workers presented a combined SPECT/CT design comprising a clinical SPECT gamma camera in tandem with a clinical single-slice CT scanner (Blankespoor et al 1996). The CT scanner (9800 Quick; GE Healthcare) was positioned in front of, and aligned with, a scintillation camera (600 XR/T; GE Healthcare), as shown in figure 1(a). The same bed was used to acquire both studies and the images were registered by taking into account the axial displacement between the CT and SPECT imaging fields. After injection of the radiotracer and an uptake period, the patient was scanned first in the CT and subsequently in the SPECT scanner. The CT data were used to generate the SPECT attenuation correction factors. The combined device performed a small number of clinical studies, such as for quantitative estimation of radiation dosimetry in brain tumor patients (Tang et al 2001).

2.2.2. The first PET/CT

The proposal to combine PET with CT was made independently in the early 1990s by Townsend, Nutt and co-workers. The suggestion was also made to use the CT images to generate the PET attenuation correction factors (Beyer et al 1994). The first prototype PET/CT scanner became operational in 1998 (Beyer et al 2000), designed and built by CTI PET Systems in Knoxville, TN (now Siemens Molecular Imaging) and clinically evaluated at the University of Pittsburgh. The design incorporated a single-slice spiral CT scanner (Somatom AR.SP; Siemens Medical Solutions, Forchheim, Germany) and a rotating ECAT ART scanner (CTI PET Systems, Knoxville, TN). The PET detectors were mounted on
Figure 1. The first multimodality prototypes developed in the mid 1990s: (a) a SPECT/CT scanner (photos courtesy of Bruce Hasegawa, PhD, UCSF), (b) a PET/CT scanner evaluated clinically at the University of Pittsburgh and (c) an MR/PET scanner for small animals (photos courtesy of Simon Cherry, PhD, UC Davis).

the rear of the CT support and the entire assembly rotated as a single unit (figure 1(b)). The data processing included an algorithm (Kinahan et al 1998) to scale the CT images from x-ray energy to PET annihilation photon energy (511 keV) and generate the appropriate attenuation correction factors (see section 5). Over 300 cancer patients were scanned on the prototype and the findings presented in a series of publications (Charron et al 2000, Kluetz et al 2000, Meltzer et al 2000). The results from the prototype demonstrated the importance of high resolution anatomy accurately registered with functional data. The coregistered anatomy localized functional abnormalities and clarified equivocal situations, thus improving the accuracy and confidence of the scan interpretation. The use of a rapidly-acquired, low-noise CT scan in place of a lengthy conventional PET transmission scan reduced the overall scan duration.

2.2.3. The first MR/PET. Given the design of PET (and SPECT) detectors based on photomultiplier tubes (PMTs), an MR/PET configuration is obviously technically more challenging than the combination of functional imaging and CT because phototubes are sensitive even to low magnetic fields. MR is a more complex imaging modality than CT in that it measures different characteristics of human tissue such as relaxation times and spectroscopy and there is therefore considerable interest in combining such a versatile modality with PET (or SPECT). MR demands very high field homogeneity and the presence of PET detectors within the field could interfere with MR imaging. In contrast, the PET detectors have to withstand not only a high static field level (up to 3T for clinical scanners) but also the rapidly changing field gradients required by the imaging process.

Hammer and co-workers were one of the first groups to address some of these issues in the mid 1990s (Christensen et al 1995, Hammer et al 1994). Their design was based on
placing PET detectors inside a clinical MR scanner and extracting the information from the scintillator over light guides that transported the signals to phototubes positioned outside the magnetic field. One aspect the group studied was the ability of a high magnetic field to ‘focus’ the positrons and reduce the effect of positron range (Iida et al 1986, Raylman et al 1996) and improve spatial resolution. The focusing effects are unfortunately not significant at current clinical magnetic field levels (up to 3 T). The first simultaneous acquisition of FDG uptake data and NMR spectra in an isolated, perfused rat heart model was published in 1996 (Buchanan et al 1996). The device used was a novel gamma photon detector operated inside a 9.4 T MR spectrometer. At around the same time as this work, Shao, Cherry and co-workers developed a small ring of PET detectors for pre-clinical, small animal imaging. The detector ring was 3.8 cm in diameter and was placed inside an MR scanner with the light signals extracted from the PMTs over 3 m long optical fibers (Shao et al 1997a) (figure 1(c)). A second, larger prototype was built with a ring diameter of 5.6 cm (Shao et al 1997b) and simultaneously acquired MR and PET data in small animals using a number of different pulse sequences (Slates et al 1999). The PET detector ring was also evaluated in a 9.4 T MR spectrometer and demonstrated good results (Garlick et al 1997). However, in contrast to the SPECT/CT and PET/CT developments, MR/PET was destined to remain in the pre-clinical arena for another decade until, in 2006, the first simultaneous MR and PET images of the human brain were acquired.

3. Multimodality instrumentation

As the end of the 1990s approached it was unclear where the pioneering work in multimodality imaging devices described in the previous section would lead. For a physician wishing to review fused images, the only option was software fusion as described in section 2.1. Apart from the drawbacks of fusion software already discussed above, access to image data from different modalities was far from routine, even with picture archiving and communication systems (PACS) available. Thus, fusion imaging was performed at most for only a small number of patients. Software fusion packages were, nevertheless, available on many imaging systems, particularly those used for radiation oncology (Caldwell et al 2001). This situation then changed forever in 1999 when GE Healthcare launched a dual-head scintillation camera combined with a low-power x-ray tube and detectors, called the Hawkeye (GE Healthcare) (Bocher et al 2000, Patton et al 2000). The design features two rectangular sodium iodide camera heads with a 350 W x-ray tube. The scintillation camera includes coincidence circuitry that allows it to perform either SPECT or to image positron-emitting nuclides (Delbeke et al 2000). The anatomical imaging capability is limited by the performance of the x-ray components and transmission scans are acquired at a speed of 23 s per rotation for a 40 cm diameter transaxial field-of-view (FOV), resulting in 15 min scan durations. In contrast with the reduced scan duration achieved with PET/CT compared to PET-only scanners, the low-performance anatomical imaging of the initial Hawkeye design actually reduces the throughput on the scintillation camera. This device was the first commercial scanner to offer combined anatomical and functional imaging in a single unit.

Less than 2 years after the first Hawkeye installation, PET/CT scanners incorporating clinical CT and clinical PET performance became commercially available, and 3 years after that the combination of a SPECT camera with clinical CT. The most recent addition to the range of multimodality instrumentation is a PET detector insert that functions in a clinical MR scanner. The following sections review the current status of SPECT/CT, PET/CT and MR/PET devices and some other interesting multimodality combinations that may one day become clinical.
3.1. SPECT/CT

The Infinia Hawkeye (GE Healthcare) has remained a viable option for SPECT imaging combined with low resolution anatomy (Bocher et al 2000, Patton et al 2000). The latest design, the Infinia Hawkeye 4, features a 4-row detector unit with a rotation speed of 23 s (figure 2(a)). An axial field of 40 cm is now scanned in about 3–4 min. Apart from their obvious role in localization, the anatomical images can be used to generate attenuation correction factors. This is even more advantageous for SPECT than for PET because the SPECT attenuation correction factors depend on the (unknown) depths in tissue of the detected photons. The energy scaling algorithm required to convert the CT values at x-ray energy to SPECT energy is based on the original work of LaCroix et al (1994) and Blankespoor et al (1996), as presented in Hasegawa et al (2002). A similar algorithm will be described in section 5 for PET/CT.

In 2004 the first combined clinical SPECT/CT system, the Symbia T2 (Siemens Medical Solutions), was launched comprising a dual slice Emotion CT scanner and a dual-head Symbia S scintillation camera (figure 2(b)). This is the first commercial design that incorporated a fully-clinical CT scanner with a 40 kW power generator and a 0.8 s minimum rotation time. The maximum spiral scan time is 100 s and the patient bed has a maximum scan length in whole-body mode of 200 cm. The Symbia T2 has a 70 cm patient port and the axial FOV of the scintillation camera is 53.3 cm with a maximum rotation speed of 3 rpm. This design, now named the Symbia TruePoint SPECT/CT, is also available with 6-slice and, most recently, with 16-slice Emotion CT scanners. The Symbia T, a limited-functionality version of the Symbia T2, is available at lower cost. All models include CT-based attenuation correction and acquisition, with data processing and display provided by a syngo MI workstation. Philips now offers a high-performance SPECT/CT scanner with their Precedence platform (figure 2(c)). The design is available with a 16-slice CT scanner that has a minimum rotation time of 0.4 s. The CT has a 60 kW power generator, a maximum spiral scan time of 100 s and a scan length of 150 cm. The patient port is 70 cm (73 cm for SPECT). The EPIC-AZ SPECT detectors have a
Figure 3. A novel SPECT/CT design that is based on a combination of a Philips SKYLight SPECT camera and a stand-alone Picker PQ5000 CT scanner (Bailey et al 2007).

38.1 cm axial FOV and a maximum rotation speed of 2 rpm. CT-based attenuation correction is included and data acquisition, processing and display are performed from a JETStream acquisition console.

A recent novel approach to SPECT/CT that combines a CT scanner with existing nuclear medicine equipment has been proposed by Bailey and co-workers (Bailey et al 2007). A single-slice spiral CT scanner (Picker PQ5000) is positioned in proximity to a Philips SKYLight gamma camera (figure 3). The most efficient geometrical configuration chosen by the authors places the SPECT and CT scanners 180° opposed in an in-line configuration. The CT bed is used for both the CT and the SPECT scan. After acquisition of the spiral CT scan, the bed is retracted and the SKYLight scintillation camera moved into position so it can rotate around the bed. CT-based attenuation correction (Brown et al 2006) has been implemented based on a bi-linear scaling function such as will be described in section 5. A threshold of 0 Hounsfield Units (HU) is used to separate the two scaling functions. Data processing and display is performed on a HERMES workstation.

Since the introduction of the Hawkeye in 1999, there are an increasing number of publications highlighting the benefit of combined SPECT and anatomical imaging (O’Connor and Kemp 2006), and since 2004 applications of SPECT with clinical CT are now starting to appear. The clinical status of SPECT/CT will be briefly reviewed in section 7.

3.2. PET/CT

The first commercial PET/CT scanner to be announced was the Discovery LS (GE Healthcare) in early 2001. This was followed a few months after by the Biograph (Siemens Medical Solutions), and then somewhat later by the Gemini (Philips Medical Systems). In the past 6 years, PET/CT designs from all vendors have evolved following the advances in CT and PET instrumentation to be described in section 4.

To summarize the current situation, five vendors worldwide now offer PET/CT designs: GE Healthcare, Hitachi Medical, Philips Medical Systems, Toshiba Medical Corporation and Siemens Medical Solutions. Current PET/CT designs offered by Siemens Medical Solutions, GE Healthcare and Philips Medical Systems are summarized in figure 4. The specifications and performance of the PET components are vendor specific, with the Biograph HI-REZ TruePoint (figure 4(a); Siemens Medical Solutions) offering good spatial resolution in 3D with 4 mm × 4 mm × 20 mm lutetium oxyorthosilicate (LSO) crystals (Brambilla et al 2005);
Current PET/CT scanner designs from three of the major suppliers of medical imaging equipment: (a) the Siemens Biograph TruePoint, (b) the GE Healthcare Discovery range and (c) the Philips Gemini series. Note that the Gemini series (c) includes the Gemini TF, the first commercially-available PET/CT that has time-of-flight capability with a timing resolution of about 600 ps.

Figure 4. Current PET/CT scanner designs from three of the major suppliers of medical imaging equipment: (a) the Siemens Biograph TruePoint, (b) the GE Healthcare Discovery range and (c) the Philips Gemini series. Note that the Gemini series (c) includes the Gemini TF, the first commercially-available PET/CT that has time-of-flight capability with a timing resolution of about 600 ps.

the original Biograph design was based on 6.4 mm × 6.4 mm × 25 mm LSO detectors. The Biograph is currently offered with 6-, 40- and 64-slice CT scanners. The Discovery LS, the original PET/CT design from GE Healthcare, combined the Advance NXi PET scanner with a 4-, 8- or 16-slice CT (Mawlawi et al 2004a). The Discovery ST (figure 4(b); GE Healthcare) has 6.2 mm × 6.2 mm × 30 mm bismuth germanate (BGO) detectors in combination with a 4-, 8- or 16-slice CT scanner; unlike the Discovery LS, the gantry of the PET scanner matches the dimensions of the CT scanner. The higher resolution Discovery STE has 4.7 mm × 6.3 mm × 30 mm BGO detectors in combination with 8- or 16-slice CT scanners; the Discovery VCT is an STE configured with a 64-slice CT scanner. The Gemini GXL (figure 4(c); Philips Medical) comprises 4 mm (in plane) and 6 mm (axial) gadolinium oxyorthosilicate (GSO) detector pixels, 30 mm in depth; the Gemini is also an open design with the capability to physically separate the CT and PET scanners for access to the patient. The Gemini GXL incorporates a 6- or 16-slice CT scanner. A recent addition to PET/CT designs is the Gemini TF, the first commercial time-of-flight (TOF)-PET scanner (Surti et al 2007). The Gemini TF has 4 mm × 4 mm × 22 mm LYSO (LSO with a small percentage of yttrium) detectors and is combined with a 16 or 64-slice CT scanner. All designs other than the Discovery LS offer a 70 cm or greater patient port for both CT and PET. While the Discovery and Gemini also offer standard PET transmission sources as an option, in practice, as mentioned above, most, if not all, institutions use CT-based attenuation correction because of the advantages of low noise and short scan times that facilitate high patient throughput. The Gemini and Biograph acquire PET data in 3D mode only, whereas the Discovery series incorporates retractable septa and can acquire data in both 2D and 3D mode.

Since 2001, numerous publications have documented the benefits of PET/CT compared with PET and CT, with and without software fusion. A good review of the literature prior to September 2006 has been published by Czernin et al (2007). Clinical applications for PET/CT will be discussed further in section 7.
3.3. MR/PET

The latest addition to multimodality clinical imaging is a combined MR/PET device. Following on from the early pioneering work described in subsection 2.2.3, development of MR-compatible PET detectors focused primarily on pre-clinical applications in high magnetic fields, and interesting results were obtained at 4.7 T and 9.4 T with simultaneous MR and PET acquisitions (Garlick 2002, Mackewn et al. 2005, Marsden et al. 2002). A larger PET detector ring, 11.2 cm in diameter, designed to fit inside an MR animal scanner with a 20 cm bore was built (Slates et al. 1999) based on the same principle as the earlier prototypes (Shao et al. 1997). A similar approach using long fiber optic light guides and LSO detector arrays for operation in a 3 T magnetic field has been explored by Raylman and co-workers (Raylman et al. 2006). However, designing a larger system for clinical imaging with the scintillation light transported over long optical fibers to PMTs outside the magnetic field is impractical due to the large number of fibers required. Instead, alternatives to PMTs, such as avalanche photodiodes (APDs) (Lecomte et al. 1996, Ziegler et al. 2001), have been adopted because APDs do not show the performance degradation characteristic of PMTs in high magnetic fields, even up to 9.4 T (Pichler et al. 1997). This work subsequently led to the development of an LSO-APD detector module (Pichler et al. 2004, 2006) that could be operated in a 7 T MRI scanner.

The next phase has been a hybrid approach in which position-sensitive APDs (PSAPDs) are coupled to LSO arrays over very short optical fiber bundles 10 cm in length (Catana et al. 2006, Judenhofer et al. 2007). The diameter of the LSO detector ring is 60 mm and the individual crystals are $1.43 \times 1.43 \times 6$ mm$^3$. The transaxial FOV is 35 mm and the axial FOV is 12 mm. The combined MR/PET has been operated successfully without either degradation of the MR image due to the presence of the PET detectors or any significant effect on the performance of the PET detectors from the static magnetic field or changing gradient fields. The device has successfully acquired simultaneous PET and MR images of a mouse with the PET biomarker $^{18}$F$^-$ injected for skeletal imaging. A review of the rationale for combining MR with nuclear imaging for pre-clinical applications can be found in Wagenaar et al. (2006).

While all the successful MR/PET developments described above relate to pre-clinical systems, a clinical system for brain or whole-body imaging remains a considerable technical challenge. Nevertheless, the first human brain MR/PET device has recently been demonstrated successfully (Bubar et al. 2006, Schlemmer et al. 2007, Schmand et al. 2007). The PET detector ring is designed as an insert that can be placed inside a Siemens 3 T Trio MR scanner (Siemens Medical Solutions). The insert has an internal diameter of 35.5 cm and comprises 192 detector blocks arranged in six rings (figure 5(a)). Each LSO block comprises a $12 \times 12$ matrix of $2.5 \times 2.5 \times 20$ mm$^3$ crystals for an axial FOV of 19.25 cm (Schmand et al. 2007). Each detector block is directly coupled to a compact $3 \times 3$ APD array. The point source sensitivity of the PET scanner measured with a line source in air is 5.6% and the spatial resolution is 2.1 mm at the center of the FOV. No degradation of the MR images was observed due to the presence of the PET detectors and no detrimental effect on the performance of the PET detectors was observed for a number of standard MR pulse sequences. The MR/PET system has been used to image the brain for patients injected with 10 mCi (370 MBq) of FDG and for a 35 lb dog injected with 5 mCi (185 MBq) of FDG. In each study, MR and PET data of the brain were acquired simultaneously, including proton spectroscopy and echo planar gradient-echo sequences (Schlemmer et al. 2007). A limited number of PET inserts will be evaluated at different medical institutions with the goal of a commercial MR/PET for the brain within a year or so, culminating eventually in a whole-body device.

MR-based attenuation correction is not as straightforward as CT-based attenuation correction since the MR image is not a simple map of linear attenuation coefficients. This
difficulty and some possible solutions will be discussed in subsection 5.3. The question as to the clinical utilization of MR/PET and the potential impact on PET/CT applications is of special interest and will be summarized in section 7.

3.4. Other devices

Clinical multimodality imaging is not only limited to PET/CT and SPECT/CT although most other devices are currently in the design or exploratory phase. The focus is generally on application-specific tasks such as imaging of breast and prostate. Examples include a combination of scintigraphy and mammography (Goode et al 1999) to reduce the false positive rates from standard mammography, and a combination of 3D CT breast imaging with SPECT (Crotty et al 2007) and with PET (Tornai et al 2005, Wu et al 2006). Of particular interest is perhaps the combination of ultrasound with other imaging modalities such as conventional mammography (Sinha et al 2007) and PET as in the ClearPEM/Sonic development (Lecoq 2007). The latter device is based on the Clear-PEM system (Abreu et al 2007); a tri-modality device that combines US/PET/SPECT is also under consideration (Lecoq 2007). Since, as seen in section 2, some clinical multimodality instrumentation originates from the pre-clinical domain, it is worth noting that there is at least one commercial development of a SPECT/MR device for small animal imaging (Wagenaar et al 2006, 2007; Gamma Medical-Ideas, Northridge, California). If a demand exists, this may eventually lead to a clinical SPECT/MR design.

4. Recent advances in CT and PET performance

4.1. Multi-detector CT scanners

Following the appearance of single-slice spiral CT scanners in the early 1990s (Kalender et al 1990), CT performance evolved with the advent of multi-detector arrays (MDCT),
accompanied by increases in x-ray power (60 kW or greater) and computer capacity for data processing and image reconstruction. Dual and 4-slice CT scanners first appeared around 1998 with scan times of 500 ms, followed by 16-slice (2002) and more recently 64-slice (2004). The increasing number of detector rows (slices) has been accompanied by faster rotation times so that state-of-the-art scanners can now achieve a full rotation in as little as 330 ms. Spatial resolution has improved from about 10 Lp cm\(^{-1}\) in 1990 to 25 Lp cm\(^{-1}\) or better today, and with a slice thickness of less than 1 mm. A significant innovation that will contribute to increased CT performance is the Straton x-ray tube (Schardt et al 2004). In the Straton tube, the entire vacuum vessel including the anode and cathode rotates resulting in much more effective cooling and heat dissipation, a limitation of the conventional tube (Kalender 2005). Cooling rates 5–10 times higher than for conventional tubes can be achieved with the Straton tube that result in shorter rotation times and faster scans. Since weight is a problem for conventional x-ray sources, the dual-source Definition CT (Siemens Medical Solutions) is made possible because of the Straton tube. After many years of slow but steady progress, the past decade has seen significant advances in both hardware and software for CT. Some of the opportunities and concerns raised by these advanced systems with 64-row detectors are addressed by Boone (2006).

4.2. PET scanners

The publication (Muehllehner and Karp 2006) provides an excellent review of progress in PET instrumentation, including a summary of the physical performance of the new, fast scintillators recently introduced for PET. This section will summarize some of these advances as they relate to current PET/CT scanner performance.

4.2.1. Sensitivity. PET is intrinsically a 3D imaging methodology, replacing physical collimation required for single-photon imaging with the electronic collimation of coincidence detection. The first multi-ring PET scanners incorporated septa, lead or tungsten annular shields mounted between the detectors rings. The purpose of the septa was to shield the detectors from photons that scattered out of the transverse plane, restricting the use of electronic collimation to within the plane, a limitation that, while it makes poor use of the radiation emitted from the patient, limits scatter and allows 2D image reconstruction algorithms to be used. The availability from 1990 onwards of BGO scanners with retractable septa encouraged the use of 3D methodology, at least for the brain where the net increase of a factor 5 in sensitivity could be realized even with accompanying increases in both scatter fraction and randoms (Townsend et al 1998). The situation for whole-body imaging is far less favorable, in part due to the presence of significant activity just outside the imaging FOV in most bed positions. Instead, particularly for large patients, 2D imaging has been recommended even though higher injected levels of FDG are required to obtain adequate count rates. This situation changed in the late 1990s with the appearance of LSO- and GSO-based scanners that could be operated with short coincidence time windows (4.5–6 ns) and higher energy thresholds (400–450 keV) compared with 10–12 ns and 350 keV for a typical BGO scanner. Significantly improved whole-body image quality has been achieved in 3D with a 10 mCi (370 MBq) injection of FDG. A recommended injected dose of 12–15 mCi corresponds to operation at peak Noise Equivalent Count Rate (NECR) for an LSO scanner in 3D (Watson et al 2005).

A recent publication (Lodge et al 2006) compared 2D and 3D operation for an LSO-based PET-only scanner (ECAT ACCEL, Siemens Molecular Imaging). The results demonstrated that under conditions of matched target-to-background ratios, the 3D mode showed significantly less variability than 2D. Since the LSO and GSO PET/CT scanners have
no septa and acquire data in 3D mode only, no similar comparison could be made for PET/CT. However, within the past 2 years, a limited number of LYSO-based PET/CT scanners with retractable septa have been evaluated in 2D and 3D and recent publications confirm the results from the ACCEL (Kemp et al. 2006, Strobel et al. 2007).

The sensitivity of a scanner can also be improved by the addition of more detector material. Planar sensitivity can be increased by extending the thickness of the scintillator (figure 6(a)). In this example, a 50% increase in thickness (20 mm → 30 mm) results in a 40% increase in sensitivity. However, increasing the axial extent by 33% will result in a 78% increase in volume sensitivity (for 3D acquisition with no septa), as shown in figure 6(b). The latter thus makes more efficient use of the increased volume of LSO although there will also be an increase in the number of phototubes required (and hence increased cost). Following an injection of a radioactive tracer such as FDG, the patient receives a radiation dose from all annihilation photons, not just those emitted within the imaging FOV of the scanner. Therefore, the greater the axial coverage, the better use is made of the emitted radiation and the more efficient use is made of a given volume of scintillator. For most PET/CT scanners, axial PET coverage is about 16 cm, with one design having an axial extent of 18 cm (Surti et al. 2007). The most recent design to be announced has an extended FOV covering 21.8 cm axially. The latter comprises over 32 000, 4 mm × 4 mm × 20 mm LSO pixels and images 109, 2 mm thick transaxial planes in a single position. Data acquisition is in fully 3D and the scanner has a peak NECR of around 160 kcps (Jakoby et al. 2006, Townsend et al. 2007).

4.2.2. Signal-to-noise. The availability of fast scintillators with high stopping power such as LSO (and LYSO) has revived interest in PET time-of-flight (TOF) (Budinger 1983), interest that has been further stimulated by the recent announcement of the first commercial PET/CT with TOF—the Philips Gemini TrueFlight (TF) (Surti et al. 2007). The principle of TOF PET is illustrated schematically in figure 7; positron annihilation occurs in the patient at a distance \( d + d_1 \) from one detector and \( d - d_1 \) from the other detector. For photons traveling at the speed of light \( c \), the arrival time difference between the two photons at the detectors is \( 2d_1/c \). Photons originating from the center of the field-of-view \( (d_1 = 0) \) obviously arrive in the

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Figure 6. Two methods of improving the sensitivity of a PET scanner by (a) increasing the thickness of the scintillator from 20 mm to 30 mm and (b) by increasing the axial length of the scanner from 16.2 cm to 21.8 cm. The increase in the axial extent (b) also implies an increase in the number of PMTs. For a scanner operating in 3D, method (b) compared to (a) will result in a factor of 2 increase in sensitivity with 40% less LSO.
Figure 7. A schematic illustrating PET data acquisition with the incorporation of time-of-flight (TOF) reconstruction. (a) Without TOF information and (b) using TOF information so that the annihilation point can be localized with an accuracy depending on the timing resolution.

detectors at the same time. Scanners with fast scintillators and electronics can measure this time difference to within a certain resolution. For example, for a scanner with a coincidence timing resolution of 500 ps, the spatial uncertainty on the position of the annihilation is 7.5 cm. This measurement is not sufficient to place the annihilation within a 2 mm voxel (and thereby eliminate reconstruction) but it is superior to having no timing information at all and assigning equal probability to all voxels along the line-of-response (figure 7(a)). Instead, the most probable location of the annihilation is at the center of the uncertainty distribution in figure 7(b). The TOF information is incorporated directly into the reconstruction algorithm leading to an improvement in signal-to-noise (SNR). The increase in SNR is proportional to $\sqrt{D/\delta d}$, where $D$ is the diameter of the activity distribution and $\delta d$ is the spatial uncertainty. For a 40 cm diameter uniform distribution and a 7.5 cm uncertainty, the increase in SNR is a factor of about 2.3. As the TOF resolution improves, the spatial uncertainty decreases and the SNR increases by a larger factor. TOF PET was first exploited in the early 1980s with scintillators that were fast but did not have good stopping power for 511 keV photons. Interest declined until the recent emergence of scintillators that are both fast and sensitive. The new TOF PET scanners based on LSO or LYSO must demonstrate good timing resolution that is stable over time so as to avoid frequent detector recalibration. While promising, the clinical impact of TOF PET has yet to be established. A more detailed review of the published contributions to TOF development can be found in Muehllehner and Karp (2006).

4.2.3. Reconstruction algorithms. There has been significant progress during the past few years in image reconstruction methods through the introduction of statistically-based algorithms into the clinical setting. Previously, one of the earliest and most widely-used 3D reconstruction methods was the reprojection algorithm (3DRP) based on a 3D extension of
the standard 2D, filtered backprojection algorithm (Kinahan and Rodgers 1989). While this algorithm works well for the lower noise environment of the brain, the quality for whole-body imaging is less than optimal, particularly when rod source attenuation correction factors are applied to low count emission data. Figure 8(a) shows a coronal image of a patient with a body mass index (BMI) of 25 reconstructed using 3DRP. Since CT-based attenuation correction factors have been applied the quality is actually better than would have been obtained with rod source attenuation correction factors. The development of Fourier rebinning (FORE) (Defrise et al 1997) was a breakthrough that enabled 3D data sets to be accurately rebinned into 2D data sets and then reconstructed in 2D with a statistically-based expectation-maximization (EM) algorithm. However, it was not until the accelerated convergence achieved by the ordered-subset EM (OSEM) algorithm (Hudson and Larkin 1994) that iterative methods became of clinical interest. While FORE and OSEM offer improved image quality compared with 3DRP, the incorporation of attenuation-based weights (AWOSEM) as suggested in the original paper by Hudson and Larkin further improves image quality. This is demonstrated in figure 8(b) where the same data set as in figure 8(a) has been reconstructed with FORE and AWOSEM (Comtat et al 1998). Further improvement has been achieved by eliminating the rebinning step and implementing OSEM fully in 3D with corrections for randoms, scatter, attenuation and detector efficiency variations incorporated into the system model (Comtat et al 2004, Liu et al 2001). The result, again for the same data set, is shown in figure 8(c). Finally, in a recent development termed high definition (HD) PET, the detector spatial response function has also been included in the reconstruction model (Panin et al 2006). The point spread...
function (PSF) varies throughout the field-of-view owing to the oblique penetration of the detectors by annihilation photons. By measuring this variability and then modeling the PSF, improved and near-uniform spatial resolution can be achieved throughout the field-of-view; the improvement can be seen by comparing figure 8(c) with the PSF reconstruction in figure 8(d); all reconstructions except 3DRP are unsmoothed.

The images in figure 8 are reconstructed with clinical software from a specific vendor (Siemens Molecular Imaging). Of course, all vendors provide comparable software capable of producing clinical images of high quality. The VUE Point algorithm (GE Healthcare) is an implementation of 3D OSEM that includes corrections for randoms, scatter and attenuation and also a z-axis smoothing. The Gemini TF (Philips Medical Systems) has TOF capability and therefore the TOF information must be incorporated into the reconstruction (Surti et al 2007). For their Gemini scanners, Philips implemented a distributed list-mode TOF algorithm (DLT) that is based on a TOF list-mode maximum likelihood approach developed by Popescu et al (2004). They have also used a row-action maximum-likelihood algorithm or RAMLA (Daube-Witherspoon et al 2001). The scatter correction algorithm requires modification to incorporate TOF information. The greatest outstanding effect on image quality and a challenge to reconstruction algorithms is now the size of the patient, a significant problem given the current levels of obesity among the US population. TOF-PET offers proportionately greater improvement in SNR for larger activity distributions and thus the Gemini TF may show increased benefit for imaging these larger patients, although that has yet to be established clinically.

5. Attenuation correction factors

For PET/CT and SPECT/CT, a recognized strength is the availability of CT images for attenuation correction of the PET (Kinahan et al 1998, 2003) and SPECT (Blankespoor et al 1996) data, eliminating the need for an additional, lengthy transmission scan. The use of the CT to generate attenuation correction factors (ACFs) thus reduces significantly the scan time. The CT images have much lower levels of statistical noise compared with the traditional PET transmission images resulting in more precise ACFs. Improved accuracy will depend on factors other than statistical noise, such as patient movement, the presence of CT contrast media, and respiratory and cardiac motion (see below). Since the attenuation values (µ) are energy dependent, the CT scan at a mean photon energy of ∼70 keV must be scaled to SPECT (e.g., 140 keV) and PET (511 keV) energies. The mean energy of a polychromatic x-ray beam is defined as the energy of a monochromatic beam that would give the same linear attenuation as the polychromatic beam integrated over energy (Watson et al 2004). The polychromatic beam also results in beam hardening, the preferential interaction of lower energy photons as the beam traverses the body causing the mean energy to increase and the corresponding µ values to decrease.

5.1. Energy scaling algorithm for CT

The attenuation of x-rays through tissue depends on the density and the effective atomic number ($Z_{\text{eff}}$) of the material. At these energies, the physical processes by which x-rays are attenuated are the photoelectric effect and Compton scattering. The photoelectric probability varies approximately as $Z_{\text{eff}}^4$ and scales as $1/E^3$ with photon energy ($E$). The Compton scattering probability has little dependence on $Z_{\text{eff}}$ and decreases linearly with $1/E$. The linear attenuation coefficient for a given material is expressed by the sum of the two components:

$$\mu(E) = \rho_e \sigma_e(E) + \sigma_{\text{ph}}(E, Z_{\text{eff}})$$

where $\rho_e$ is the linear attenuation coefficient for electrons and $\sigma_e(E)$ is the photoelectric cross-section. The Compton cross-section $\sigma_{\text{ph}}(E, Z_{\text{eff}})$ depends on both the energy and the atomic number of the material.
Figure 9. The bi-linear scaling function used to convert CT numbers (Hounsfield Units) to linear attenuation values at 511 keV. The attenuation correction factors are generated by reprojecting the $\mu$-map at 511 keV; w, water; cb, cortical bone; $k$ is the concentration of the components of the mixture.

where $\rho_e$ is the electron density and $\sigma_{ph}$ and $\sigma_c$ are the photoelectric and Compton cross sections per electron, respectively. However at photon energies above about 100 keV in tissue, the photoelectric contribution is essentially negligible compared with the Compton contribution and therefore the expressions for the attenuation coefficient at x-ray energy $E_x$ and annihilation photon energy $E_\gamma$ are

$$
\mu(E_x) = \rho_e \{\sigma_c(E_x) + \sigma_{ph}(E_x, Z_{eff})\}
$$

$$
\mu(E_\gamma) = \rho_e \sigma_c(E_\gamma).
$$

As a consequence of the two separate contributions to $\mu(E_x)$, a single measurement of $\mu(E_x)$ will not uniquely determine $\mu(E_\gamma)$, because, for example, an increase in $Z_{eff}$ could offset a decrease in $\rho_e$ resulting in no change in $\mu(E_x)$. In general, therefore, a simple energy scaling of $\mu(E_x)$ is insufficient to yield $\mu(E_\gamma)$. By restricting the problem to biological tissues for which $Z_{eff}$ are all fairly comparable and noting that the contribution from $\sigma_{ph}$ is relatively small even at x-ray energies, changes in $\mu(E_x)$ are primarily due to changes in tissue electron density. Thus, for the limited range of biological tissues, a single scaling factor can be used to convert $\mu(E_x)$ to $\mu(E_\gamma)$ for lung, liver, fat, muscle and other soft tissues. For spongiosa and cortical bone, however, the same scale factor will not apply because of the significant calcium and phosphorous contents of bone tissue that result in $Z_{eff}$ different from other tissues.

This issue has been addressed for SPECT (Blankespoor et al 1996) and PET (Kinahan et al 1998) by segmenting bone from soft tissue at a specific threshold and applying different scale factors to the two different tissue classifications—bone and non-bone corresponding to different values of $Z_{eff}$. For SPECT/CT, Blankespoor and co-workers used a threshold of 0 Hounsfield Units (HU) (Blankespoor et al 1996) whereas for PET/CT Kinahan and co-workers adopted a threshold of 300 HU (Kinahan et al 1998). Subsequently, for PET/CT, Watson et al (2004) propose a mixture model in which all tissues with $\mu < \mu$(water) are treated as a mixture of air and water at various concentrations, while tissues with $\mu > \mu$(water) are treated as a mixture of water and cortical bone. Since this approach limits the composition to a single value for a given $\mu(E_x)$, a bi-linear scaling function can be defined for biological tissues, as shown in figure 9. This function for the conversion to 511 keV is comparable to the
scaling function from x-ray to a typical SPECT energy (Hasegawa 2002, figure 7) of 140 keV. Recent publications on CT-based attenuation correction for PET also propose a break-point at 0 HU (µ value for water) (Burger et al 2002) although the most appropriate choice may be slightly greater than zero because some soft tissues and blood conform to the air–water mix but with densities greater than water. Therefore, a break-point around 60 HU is more appropriate for the bi-linear scaling function for PET.

The calibration function for SPECT is derived from measurements made with a phantom containing inserts of water, saline, fat-equivalent material (ethanol) and bone-equivalent material (K2HPO4) (Blankespoor et al 1996, LaCroix et al 1994). The calibration function for PET has been derived from similar phantom measurements and has also been validated with patient data (Watson et al 2006). For SPECT, a calibration function is required for each radioisotope, whereas for PET the annihilation photons have the same energy whichever positron-emitting radionuclide is used. The calibration of the CT scanner ensures that the soft tissue values (µ < 60 HU) are independent of the kVp setting of the x-ray tube. This independence does not apply to bone-like tissue with µ > 60 HU and therefore different regression lines are required for each kVp setting (Carney et al 2006).

The CT is acquired before the emission data so the ACFs can be generated for the entire volume. The CT images at $E_x \approx 70$ keV are resampled to the spatial resolution of the emission data. The images are then scaled voxel-by-voxel to the energy of the emission data by applying the bi-linear scaling function (figure 9). The resampling should be performed before scaling to avoid statistical fluctuations in CT pixels acquired at low tube currents leading to misclassification of µ values (Fahey et al 2007). The scaled CT images are then forward projected to generate ACFs that match the sampling of the emission data. Since the introduction of the PET/CT scanner, CT-based attenuation correction has been a significant focus of research to address the various possible artifacts. The following sections will review the status of this work and the outstanding challenges that remain for CT-based attenuation correction for PET/CT.

5.2. Artifacts specific to CT-based attenuation correction

While the benefits of CT-based attenuation are now well known and documented, a number of challenges have emerged as the technique has become more widely adopted for PET/CT (Bockisch et al 2004, Cohade and Wahl 2003). There are two main reasons for possible artifacts: (1) the presence of materials in the patient with $Z_{eff}$ values that do not conform to the basic assumptions in the bi-linear model and (2) mismatch between the CT and PET due to patient respiration, cardiac motion and bowel movement (Nakamoto et al 2004). Since the first commercial PET/CT installation in 2001, these issues have received considerable attention. Examples of (1) include metallic objects (Cohade et al 2002, Goerres et al 2003), dental hardware (Kamel et al 2003), calcified lymph nodes, and intravenous (Antoch et al 2004a, Yau et al 2003) and oral contrast (Carney et al 2002, Cohade et al 2003). Materials with high $Z_{eff}$ may even exceed the dynamic range of attenuation values measurable by CT and severe artifacts can be generated in the images. Of particular importance in the assessment of head and neck cancer is the presence of dental fillings (Kamel et al 2003). A number of metal artifact reduction techniques have been explored (Schafers et al 2006), including modified reconstruction methods (Lemmens et al 2006) and segmentation approaches (Mirzaei et al 2005) that can significantly reduce the artifacts.

Some typical artifacts associated with CT-based attenuation correction are illustrated in figure 10. When tidal breathing is adopted for both CT and PET, respiration effects include an apparent displacement of the dome of the liver into the lower lobe of the right lung (Sarikaya
Figure 10. Potential image artifacts generated from CT-based attenuation correction: (a) an artifact due to respiration in which the dome of the liver is displaced into the base of the right lung, (b) curved photopenic areas above the liver and spleen caused by CT and PET mismatch from respiratory movement of the diaphragm, (c) an artifact due to a bolus of intravenous contrast in a major vessel (arrowed) and (d) an artifact due to the presence of an abdominal chemotherapy port. Part (c) courtesy of Todd Blodgett MD, University of Pittsburgh.

et al 2003) creating a corresponding region of apparent activity on the PET scan (arrowed). A curved photopenic region at the top of the liver and spleen in the PET image (figure 10(b)) is also observed in some studies. Although such artifacts may occur for any patient following a tidal breathing protocol (Romer et al 2004), the documented incidence is much reduced for faster, higher performance CT scanners. The clinical significance of respiratory artifacts has been studied for an early PET/CT design in a series of 300 patients (Osman et al 2003a). Figure 10(c) illustrates an artifact caused by a bolus of intravenous contrast in a major vessel that generates focal uptake (arrow) on the PET image and figure 10(d) shows focal uptake (arrow) caused by the presence of a chemotherapy port. In many situations, however, artifacts on the CT do not propagate through to the PET images.

5.2.1. Intravenous contrast. The use of intravenous contrast may be indicated when the CT scan is performed for clinical purposes as opposed to low-dose CT performed for attenuation correction and localization only. Intravenous contrast contains iodine at concentrations high enough to enhance CT values without a corresponding change in density, and it is used in CT to enhance attenuation values in the vasculature by increasing the photoelectric absorption compared to the blood. CT contrast results in a 40% change in attenuation at CT energies whereas, at 511 keV where the photoelectric effect is negligible, the presence of contrast has only a 2% effect or less on attenuation (Carney et al 2006). However, if contrast-enhanced tissue pixels are misidentified as a water–bone mix, the scaling factor will be incorrect and the erroneously scaled pixels may generate artifacts in the PET image (Antoch et al 2002). Tens of thousands of PET/CT scans have now been performed in the presence of intravenous contrast and experience has shown that contrast administration does not generally cause a problem that could potentially interfere with the diagnostic value of PET/CT (Berthelsen et al 2005, Mawlawi et al 2006, Yau et al 2003). This is largely due to the fact that intravenous contrast is fairly rapidly dispersed throughout the vascular system. An exception may be the passage of the contrast bolus through a major vessel (figure 10(c)), although even this does not always
Figure 11. The robustness of CT-based attenuation demonstrated by imaging situations in which artifacts might be anticipated but do not actually occur: (a) a bolus of intravenous contrast, (b) the presence of oral contrast in the colon, (c) the presence of metal artifacts due to dental hardware and (d) bilateral hip replacements. Part (c) courtesy of Claude Nahmias PhD, University of Tennessee, Knoxville, TN.

generate an artifact on the PET image (figure 11(a), arrow). Optimized CT protocols have been developed for the administration of intravenous contrast that avoid most of the issues (Brechtel et al 2006). In some protocols, contrast CT is performed in addition to the low-dose CT for attenuation correction and localization, thereby increasing the radiation dose to the patient. However, a low-dose whole-body CT in addition to a clinical CT with contrast over a limited axial range (single PET bed position) may involve less radiation dose than a whole-body clinical CT with contrast. A recent publication (Gollub et al 2007) has documented a rate of 2 patients in the 100 studied where an incorrect management decision would have been made because of the use of non-contrast, low-dose CT acquired for localization and CT-AC only. However, if accurate SUVs are required such as when assessing response to therapy, the use of intravenous contrast is not generally recommended.

5.2.2. Oral contrast. Oral contrast is administered to enhance the gastrointestinal tract and the distribution of the contrast material is somewhat variable, both in spatial distribution and level of enhancement. Modifications to the basic scaling algorithm have been introduced to distinguish oral-contrast-enhanced pixels from bone pixels (Carney et al 2006). As with intravenous contrast, there is no evidence that the presence of oral contrast results in diagnostic errors of any significance. Figure 11(b) shows a patient imaged with oral contrast; enhancement of the colon on the CT image (left; arrows) shows no corresponding artifactual uptake on the PET image (right). Of course, CT-AC problems caused by oral contrast can be eliminated entirely if negative contrast agents such as mannitol or even water are used in place of the more usual high-Z contrast media (Antoch et al 2004b).

5.2.3. Metal implants. Dental artifacts can be corrected on CT through the use of novel reconstruction techniques (Lemmens et al 2006), as shown in figure 11(c). The uncorrected
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(left) and corrected (right) images for CT (top) and PET (bottom) demonstrate that even though the reconstruction algorithm significantly improves the CT image, it has very little impact on the PET image, verifying that CT-based attenuation correction is actually a robust technique. Metallic implants such as artificial hip prostheses (figure 11(d)) can cause quite severe CT artifacts although it would be somewhat rare for the specific pathology under study to be located in the region affected by the prosthesis. The non-attenuation-corrected image is always available to resolve ambiguities.

5.2.4. Respiratory motion. Within the past 6 years, the most widely-addressed issue related to CT-based attenuation correction has been respiratory motion (Bacharach 2007, Beyer et al 2003, Osman et al 2003b, Papanastassiou et al 2005) and the artifacts created by the mismatch between CT and PET (Beyer et al 2005). Rotating $^{68}$Ge sources used in conventional PET scanners resulted in a transmission scan that averaged patient respiration in a way compatible with the corresponding emission scan. The use of CT-AC suggests that a number of different protocols must be explored in order to resolve the mismatch problem. For example, the advent of fast, spiral CT scanners made breath-hold CT a reality although clinical images are typically acquired with full inspiration to separate lung structures. Such an expansion of the chest does not match a PET scan acquired with shallow breathing and results in serious attenuation correction artifacts in the anterior chest wall. The appearance of artifacts due to respiratory motion and the spatial and temporal mismatch between CT and PET images has led to an intensive research initiative to identify the best respiratory protocol. A number of different protocols have been explored, including the following:

- Continuous shallow breathing for both CT and PET (Beyer et al 2003).
- CT acquired with limited breath-hold over diaphragm (Beyer et al 2003).
- Breath-hold CT acquired with partial inspiration (Beyer et al 2003).
- Motion-averaged CT over many respiration cycles (Pan et al 2005, Chi et al 2007).
- Cine CT acquiring full breathing cycle per slice (Alessio et al 2007).
- Respiratory-gated CT; PET with shallow breathing (Pan et al 2004).
- Breath-hold CT; gated PET (Dawood et al 2007, Martinez-Moller et al 2007).
- Respiratory-gated CT and PET (Nagel et al 2006).

Currently, the simplest and most widely-used protocol is shallow breathing for both CT and PET (Beyer et al 2003). Early single or dual slice PET/CT designs exhibited a high incidence of breathing artifacts (figures 10(a) and (b)) (Romer et al 2004) but with the incorporation of fast, MDCT into PET/CT scanners, the incidence of such artifacts has been greatly reduced. However, the CT images still do not exactly match the motion-averaged PET acquisitions and protocols such as slow CT acquisition have also been explored. The clinical significance of these attenuation correction effects continues to be debated, particularly with respect to lesions in the base of the lung and dome of the liver where curved photopenic areas are observed (figure 10(b)). Displacement of such lesions may result in incorrect localization or, worse, a failure to identify them correctly leading to misdiagnosis. Shallow breathing during PET/CT has been shown to be inadequate for the comprehensive staging of lung cancer (Allen-Auerbach et al 2006).

Finally, two other effects can also influence the accuracy of CT-AC: the truncation of the transverse FOV (Beyer et al 2006) and the presence of scattered radiation. Truncation of the FOV arises because CT scanners typically have a 50 cm diameter FOV whereas PET supports 60 cm. Simple software extrapolation techniques have proved effective in extending
the CT FOV to match that of PET, at least with an accuracy adequate for CT-AC (Carney 2001, Mawlawi 2004b). Scatter is enhanced by imaging with the arms in the FOV. However, the short scan times achievable with state-of-the-art PET/CT allow patients to easily tolerate imaging with arms raised, reducing the effects due to increased scatter. The exception is head and neck cancer where the patient is scanned with arms down.

Despite the issues discussed above and rare opinions to the contrary (Zaidi 2007b), CT-based attenuation correction has become the de facto standard for PET/CT and SPECT/CT even though both modalities are affected by the artifacts described above. The advantages, which include convenience and short acquisition times, largely outweigh the drawbacks. In a small number of studies, quantitative comparisons have been made between ACFs generated from standard PET transmission scans and from CT (Nakamoto et al 2002, Papathanassiou et al 2005, van Dale et al 2007) and even though some differences in SUV values have been noted nothing of diagnostic significance has been documented.

5.3. MR-based attenuation correction

The use of the MR images to generate ACFs is not as straightforward as for CT because the MR images do not represent maps of attenuation coefficients ($\mu$ maps). A number of different approaches are being explored, suggesting that the best method has yet to be determined. The difficulty is that MR anatomical images map proton density whereas photon attenuation as shown above is proportional to electron density. The distinction is clearly demonstrated by the fact that both air and cortical bone give no measurable MR signal whereas there is a 2500 HU difference in their photon attenuation properties. Although not straightforward, the generation of accurate ACFs will be significantly easier for the brain than for the rest of the body. For the brain, approaches are based mainly on MR segmentation (Kops et al 2006, Zaidi et al 2003), and registration to an atlas of MR and CT image pairs (Hofmann et al 2007). In the latter approach, the principle is to align the MR acquired for the MR/PET study with an average MR image from an atlas comprising pairs of registered MR and CT scans. The same transformation determined from the alignment of the MR of the patient with the MR in the atlas can be applied to the CT scan from the atlas. A combination of the registered CT scan and the patient-specific MR can be used to generate a pseudo CT scan of the MR/PET study from which the ACFs can be derived (Hofmann et al 2006, 2007). In view of the absence of an MR bone signal, the skull can be extracted from the registered atlas CT scan and combined with an MR image segmented for air and soft tissue. A similar approach has been suggested for extra-cranial MR/PET (Beyer et al 2006) although this method requires the patient to present with images from a pre-existing CT (or PET/CT) scan from which a pseudo CT, aligned to the MR, can be generated. MR and CT image registration is performed using fusion software based on standard metrics such as mutual information (section 2.1). Finally, an approach under consideration is to incorporate a pulse sequence into the MR/PET scan that generates a signal from bone, although the procedure will increase, maybe significantly, the overall duration of the study. Further investigation will be required to identify the most accurate and reliable methodology for MR-based attenuation correction (Zaidi 2007a).

6. Radiation dosimetry

The exposure to the patient from a PET/CT or SPECT/CT scan is both external from the CT scan and internal from the PET- or SPECT-injected radionuclide (Brix and Beyer 2005).
6.1. External dose

Dose assessment in CT is challenging and depends not only on the body region exposed but also on a variety of scan-specific parameters including tube potential (kVp), tube current and exposure time (mA s), slice collimation and pitch (ICRP 87 2000). In addition, the dose also depends on certain technical features of the scanner such as beam filtration, beam shaping filter, geometry and the acquisition algorithm. Therefore, values for CT patient dose vary considerably between centers and between scanners. The tendency is to oversimplify the situation by not taking all of these factors into account. For whole-body CT scans that extend from the level of the thyroid to the symphysis, the effective CT dose \( E_{ext} \) can be estimated approximately as

\[
E_{ext} = \Gamma_{CT} \cdot \text{CTDI}_{vol}
\]

where \( \Gamma_{CT} = 1.47 \text{ mSv mGy}^{-1} \) is the dose coefficient that relates the volume CT dose index \( \text{CTDI}_{vol} \) to the effective dose. For a typical set of clinical scan parameters, the \( \text{CTDI}_{vol} \) is 13 mGy (Brix et al 2005) resulting in a total effective whole-body dose of 19 mSv. However, many centers acquire the CT scan for attenuation correction and localization only, reducing the whole-body dose to as low as 3 mSv or less. In addition, there are a number of strategies to make better use of the radiation such as tube current modulation and automatic exposure control (Kachelriess et al 2001, Kalender et al 1999).

6.2. Internal dose

The internal radiation dose will depend upon the biodistribution and the physical and biological half-life of the biomarker. The dose is expressed as the radiation exposure to the whole-body and individually to the various organs. The critical organs are those that receive the maximum radiation dose. The effective dose \( E_{int} \) resulting from intravenous administration of a given biomarker with activity \( A \) can be estimated from

\[
E_{int} = \Gamma \cdot A
\]

where \( \Gamma \) is a dose coefficient computed for the adult hermaphrodite MIRD phantom.

6.2.1. Radiation dose for PET. The main clinical biomarker of interest is FDG for which the dose coefficient is 19 \( \mu \text{Sv MBq}^{-1} \) (ICRP 53 1999), although a higher dose coefficient of 29 \( \mu \text{Sv MBq}^{-1} \) has also been published (Deloar et al 1998). The dose coefficient holds for standard patients with a body weight of about 70 kg and is generic rather than patient specific since age, gender of patients and individual pharmacokinetics are not taken into account. In fact, the radiation risk is somewhat higher for females and for younger patients when compared to males and older patients. Age- and gender-specific dose coefficients can be found elsewhere (Hays et al 2002). Based on the published value (ICRP 53 1999) for the dose coefficient, the average whole-body dose for a typical 10 mCi (370 MBq) injection of FDG is 7 mSv. However, most biomarkers do not distribute uniformly in the body, and the critical organ with FDG, for example, is the bladder due to excretion through the urinary system.

6.2.2. Radiation dose for SPECT. Similar considerations apply to SPECT radiopharmaceuticals as to PET biomarkers in that the radiation dosimetry is dependent on the biodistribution of the tracer and the physical and biological half-life. For SPECT studies, nuclides that emit gamma rays of different energies can be used, introducing an additional variable into the dosimetry. \(^{99m}\text{Tc}\) with a half-life of 6 h is the most widely-used radionuclide for SPECT studies. Thus, \(^{99m}\text{Tc}\)-phosphates that are used for imaging bone
Figure 12. Shipments of PET and PET/CT scanners for the US market as recorded by the Nuclear Equipment Manufacturers Association (NEMA) for the period January 2002 to October 2007. Note that the figures (in $M) reflect the total revenue for all shipments from which the selling price and individual unit type cannot be determined. Shipments of PET-only scanners declined during this period to zero from January 2006 onwards. The overall market for PET or PET/CT remained fairly constant throughout this period, although since January 2007, with the reduction in reimbursement due to the introduction of the Deficit Reduction Act, sales declined somewhat.

metastases deliver an effective dose equivalent of $5.7 \mu Sv MBq^{-1}$ injected with maximum dose to the red marrow and kidneys. $^{99m}Tc$-MIBG for tumor imaging has an effective dose of $8.5 \mu Sv MBq^{-1}$ injected with the kidneys as the critical organ. A complete list of radiation doses from SPECT radiopharmaceuticals and the corresponding critical organs can be found in ICRP 53 (1999).

6.3. Total radiation dose

The total effective dose for PET/CT or SPECT/CT is the sum of the internal and external doses. For a fully-clinical CT and FDG-PET scan, the effective dose will be around 25 mSv. However, this can be reduced to 10 mSv or less when a low-dose CT is acquired for localization and attenuation correction only. In practice, the PET/CT dose to a specific organ will depend upon the exact protocol; for example, if the CT scan does not include the bladder, the dose to the bladder wall will be due entirely to FDG. For a smaller patient or a higher sensitivity scanner, a lower FDG dose can be used, potentially limiting the effective dose to 5 mSv or less. Similar considerations apply to dose calculations for SPECT/CT studies. The worldwide average annual dose due to the natural radioactive background is 2.4 mSv.

7. The clinical role for multimodality imaging

Prior to the introduction of PET/CT, essentially all multimodality clinical imaging was based on software fusion techniques (Hutton and Braun 2003), limited mainly to the brain. The appearance of the Hawkeye (GE Healthcare) in 1999 followed less than 2 years later by the first commercial PET/CT scanner has irreversibly transformed the field of multimodality imaging. From 2001, the sales of PET-only scanners decreased to zero by 2006 to be replaced by PET/CT (figure 12). Currently, in 2008, a worldwide installed base of over
2000 units attests to the rapid adoption of the modality by physicians despite the difficulties discussed above. The Hawkeye has experienced increasing popularity for SPECT where even low resolution anatomy can significantly impact image interpretation. The introduction of SPECT/CT in 2004 offers physicians the additional choice of a full clinical CT scan aligned with the SPECT study. Since oncological applications have been the primary focus of these multimodality devices, the clinical role of PET/CT, and to a lesser extent SPECT/CT, will now be assessed for diagnosing and staging disease, defining treatment plans and monitoring response to therapy. Possible applications in cardiology will also be outlined.

7.1. Diagnosis and staging of disease

Given the installed base of PET/CT scanners worldwide, the majority of which are in routine clinical operation, there is, at least for oncology, now a growing body of literature that supports the accuracy of staging and restaging with PET/CT compared to either CT or PET acquired separately (Czernin and Auerbach 2005, Czernin et al 2007). Many of these publications are recent, within the past 2 or 3 years, and they clearly document significant improvements in specificity and to some extent also in sensitivity, and especially in early detection of cancer recurrence (Israel and Kuten2007). These improvements are incremental when compared to PET that alone demonstrates high levels of sensitivity and specificity for a wide range of disease states. Improved accuracy has been documented for a variety of cancers including head and neck (Chen et al 2006, Schafer et al 2006), thyroid (Palmedo et al 2006), lung (Cerfolio et al 2006, Lardinois et al 2003, Osman et al 2002), breast (Fueger et al 2005, Tatsumi et al 2006), esophageal (Bar-Shalom et al 2005, Guo 2007), colorectal (Cohade et al 2003, Kim et al 2005) and melanoma (Reinhardt 2006). There is also evidence that PET/CT improves accuracy in lymphoma (Freudenberg et al 2004) and solitary pulmonary nodules (Kim et al 2007, Yi et al 2006), in spite of the fact that in lymphoma the accuracy of PET alone is very high (Alavi et al 2007).

In summary, therefore, the improvement in accuracy of PET/CT compared with PET or CT for staging and restaging is statistically significant and averages 10–15% over all cancers (Czernin et al 2007). To illustrate a typical state-of-the-art PET/CT scan, figure 13 shows a study acquired on a Biograph 6 TruePoint TrueV PET/CT (Siemens Molecular Imaging) with a 21.8 cm axial FOV. The patient is a 50-year-old female with a diagnosis of pancreatic cancer. The images were acquired 94 min after injection of 10.3 mCi of $^{18}$FDG. The total scan duration was 10 min with acquisition of five bed positions at 2 min per position. The CT was acquired at 130 kVp and 180 mA s (Siemens CAREDose). The images demonstrate intense uptake of $^{18}$FDG in a primary neoplasm $3.4 \times 2.6$ cm in size that can be accurately located in the head of the pancreas as a consequence of having the CT and PET scans aligned. No FDG uptake was identified in any of the proximal nodes although the likelihood of micrometastases would be high. The patient was scheduled for radiation therapy and the plan was developed based on the PET/CT findings.

Clinical SPECT/CT is currently less widely available than PET/CT. However, there is an installed base of Hawkeye systems that is still expanding. Numerous studies performed on Hawkeye systems have confirmed the utility of coregistered anatomical information for the interpretation of SPECT images (Schillaci 2005). SPECT imaging has access to a much wider range of biomarkers and radiopharmaceuticals than clinical PET which is limited to $^{18}$FDG for glucose utilization and $^{82}$Rb for cardiac perfusion studies. Some of the SPECT tracers are highly specific to the disease process and the corresponding images offer little or no anatomical information compared to an FDG whole-body study. Examples of such specific biomarkers include $^{131}$I for metastatic thyroid disease (Ruf et al 2004, Tharp et al 2004) and
A study acquired on a Biograph 6 TruePoint TrueV PET/CT scanner. The patient is a 50-year-old female with pancreatic cancer. The transverse (a), frontal (b) and sagittal (c) images show intense uptake in the head of the pancreas. The images were also used for planning radiation therapy.

$^{131}$I-labeled cholesterol for adrenal studies. SPECT/CT can also play an important role for imaging infection and lymphoma with $^{67}$Ga-citrate (Keidar et al 2003, Palumbo et al 2005), for imaging bone disease with $^{99m}$Tc-MDP to distinguish foci of increased metabolism (Horger et al 2004, Romer et al 2005), and neuro-endocrine tumor imaging (Schillaci 2004) with $^{111}$In-octreotide, $^{111}$In-pentetreotide (Krausz 2003) or $^{131}$I-MIBG (Ozer et al 2004) where uptake can be highly tumor specific and impossible to localize anatomically without the coregistered CT. In bone imaging, for example, combined SPECT/CT may improve diagnostic accuracy compared with SPECT only and help distinguish between osteomyelitis (Horger et al 2003), aseptic necrosis and metastatic disease. As with PET/CT, SPECT/CT has been shown to be beneficial in recurrent head and neck cancer imaged with $^{123}$I-IMT (Plotkin 2006). The accuracy of sentinel node mapping is improved by accurately localizing the affected nodes (Even-Sapir et al 2003). The coregistered CT should also improve the diagnostic accuracy of $^{111}$In-capromab pendetide (ProstaScint) imaging for prostate cancer, a disease for which FDG-PET is of questionable value although other PET biomarkers not yet clinically available show some promise (Husarik and Hany 2007). One study where SPECT/CT is compared with SPECT alone for parathyroid adenomas imaged with $^{99m}$Tc-sestamibi (Gayed et al 2005) demonstrates the benefits of coregistered anatomy. Most of these earlier publications are for studies performed with Hawkeye systems and therefore the addition of clinical CT to SPECT can only enhance the results obtained to date. As the installed base of SPECT/CT scanners grows, publications documenting the benefits will no doubt appear in the literature. For example, in an initial objective assessment of the impact of CT on SPECT reporting in a sample of 50 studies with a variety of biomarkers, Roach et al (2006) identified a significant change in 26% of cases and a minor change in an additional 30% of cases.

As with PET/CT, the addition of CT to SPECT provides attenuation correction and good localization that if anything is even more important for SPECT studies than for FDG-PET. The importance of localization is illustrated by the SPECT/CT studies shown in figure 14. Figure 14(a) shows a scan of a female patient with fever and aortic valve infection. The
Figure 14. SPECT/CT images acquired on combined SPECT/CT scanners: (a) imaging infection with $^{67}$Ga-citrate in a female patient with fever and aortic valve infection (images courtesy of Dale Bailey, PhD) and (b) imaging bone disease on a Symbia T2 SPECT/CT with $^{99m}$Tc-MDP (images courtesy of Wolfgang Romer, MD).

7.2. Treatment planning

An application for which PET/CT is also having an impact is that of radiotherapy treatment planning. As mentioned earlier, the incorporation of FDG-PET images into therapy planning was already taking place prior to the introduction of PET/CT (Caldwell et al 2001) employing software fusion techniques (Mutic et al 2001, Yu et al 1995). In some cases, the availability of the PET images led to a change in treatment plan by redefining the biological target volume based on FDG uptake. This was particularly effective for the lung (Bradley et al 2004), where reactive changes such as atelectasis could be distinguished from malignancy as a result of the differential uptake of FDG. Reasonable registration accuracy at the centimeter level could be achieved locally through the use of fiducials although the software fusion techniques used were cumbersome and labor intensive.

In anticipation of application to radiotherapy treatment planning, the patient port on early PET/CT designs was already increased to 70 cm diameter. From the beginning, PET/CT provided more convenient and routine access to fused CT and PET images and early assessment of the consequences of using PET/CT in planning (Ciernik et al 2003, Esthappan et al 2004, Schmucking 2003) was encouraging. Despite these results, some in radiation oncology felt that initially PET/CT was being oversold (Xing 2005) and that the earlier software approaches were as effective. However, as suggested, the convenience of having fused CT and PET
images for every patient immediately following the PET/CT scan could not be matched by even the most sophisticated software, and recent surveys (Gregoire et al 2007, Yap et al 2004) have confirmed the earlier conclusions for PET/CT in radiation oncology. Increasingly, PET/CT scanners are being acquired by radiation oncology departments and PET images are contributing directly to the definition of treatment volumes on CT-based plans (Ashamalla et al 2005, Daisne et al 2004). This will continue to be an area of growth, particularly in meeting the demands of intensity-modulated radiation therapy (IMRT) and the availability of devices such as the CyberKnife (Accuray Inc., Sunnyvale, CA). Access to other PET biomarkers mapping processes such as hypoxia (Dehdashti et al 2003, Rasey et al 1996) that increase the radio-resistance of tumors could potentially expand the role of PET in radiation oncology. Plans to increase the PET/CT patient port to almost 80 cm will facilitate the imaging of patients in treatment position.

Finally, MR imaging, offering improved soft tissue contrast, could potentially replace CT for simulation purposes (Mah et al 2002) and software may then play a role in fusing the MR simulation with PET/CT for treatment planning. Alternatively, should whole-body MR/PET become a reality, the device could ultimately replace PET/CT entirely for treatment planning.

7.3. Monitoring response to therapy

Molecular imaging is increasingly being used to monitor response to therapy (Weber and Figlin 2007), both for chemotherapy (Nahmias et al 2007, Pottgen 2006, Wieder et al 2005, de Geus-Oei 2007) and for radiation therapy (Erdi 2002), and for combinations of each (Weber and Wieder 2006). It has become increasingly evident that simple response evaluation criteria for solid tumors (RECIST) (Therasse 2000) based on anatomical measures of tumor size are inadequate to accurately assess therapy response. The molecular signal is likely to be a more sensitive indicator as it reflects tumor metabolism rather than just tumor size. A metabolic change may be more suggestive of a response than a size change. Modifying the RECIST criteria to incorporate PET findings has already been suggested (OConnell 2004) although even today the perception is that assessment of therapy response by FDG-PET has still to be validated. As with radiation therapy planning, PET was already finding a role in assessing therapy response before the introduction of PET/CT and a detailed discussion of the use of PET/CT for monitoring therapy response may be found elsewhere (Weber and Figlin 2007).

The combination of having both CT and PET for monitoring response offers a number of unique possibilities in spite of the technical difficulties associated with CT-based attenuation correction. Firstly, the anatomical and functional volume of the tumor can be estimated, the former from CT measurements and the latter by summing all voxels with a standardized uptake value (SUV) above a threshold that defines malignancy. Therapy response can be assessed from changes in both these metrics or from a change in the total lesion glycolysis that is calculated as the product of the average SUV in the tumor and the volume (Larson 1999). The advantage of the CT is that an accurate measurement of tumor volume is available both before and after treatment. It is also helpful and more reliable to define the tumor region-of-interest (ROI) directly on the CT and then to transfer the same ROI onto the PET image. The boundary of the tumor may be difficult to determine from the PET scan, particularly for metabolic responders as the lesion SUV decreases. The CT images may also be used to improve partial volume correction by dividing the SUV from the PET image with a recovery coefficient based on the spherical tumor diameter. Since tumors generally have a complex shape, a more sophisticated partial volume correction method is desirable (Soret et al 2007). Thus, for both technical and practical reasons, PET/CT is continuing to successfully promote the use of PET for monitoring response to different forms of therapy.
7.4. Myocardial viability and perfusion

The role of PET/CT in cardiology still remains somewhat controversial. PET has never been as widely used in clinical cardiology as it is in oncology because cardiac SPECT offers a more cost-effective alternative. Issues such as low count rate, marginal target-to-background ratios and need for localization that are features of whole-body tumor imaging are of less importance for myocardial imaging of perfusion and metabolism. There has, therefore, been little demand for fusion imaging of the heart since the majority of clinical imaging studies have traditionally been performed with SPECT tracers such as $^{201}$TI, $^{99m}$Tc-sestamibi and $^{99m}$Tc-tetrofosmin. However, as discussed above, PET/CT technology has evolved by embracing the advances of each individual modality. Since the development in CT has been driven primarily by cardiology demands for faster scans, the top-of-the-line PET/CT now incorporates a 64-slice MDCT and is in principle ideally suited to cardiac PET/CT. The ability to image both structure and function could, for example, enhance the characterization of atherosclerotic plaques by imaging the inflammatory process associated with the plaque. The combination of CT angiography together with a measurement of myocardial perfusion using a PET tracer such as $^{82}$Rb could, in a single exam, assess both the integrity of the cardiac arteries and the metabolic consequences to the myocardium. This approach has been termed the ‘one-stop shop’ for cardiac evaluation (Wijns 2005, von Schulthess et al 2006), although some still feel that the PET/CT is of almost no value in the evaluation of cardiac disease (Alavi et al 2007). However, in a recent publication (DiCarli 2007) DiCarli states that “The clinical evidence suggests that integrated PET/CT is a powerful, non-invasive modality for diagnosing and managing coronary artery disease (CAD)”.

Cardiac PET/CT applications are in their infancy (Namdar et al 2005) and have recently encountered a number of difficulties. Obviously, the effects of cardiac and respiratory motion are critical for these studies. The problems of mismatch associated with CT-based attenuation correction discussed above are potentially more serious for cardiac studies than they are for oncology in that all cardiac studies will be affected rather than just those whole-body studies with lesions in certain sensitive regions such as lung. This misregistration results in what appears to be perfusion deficits in segments of the heart associated with the misalignment. A recent publication (Gould et al 2007) finds that up to 40% of cardiac PET/CT studies could be affected by misregistration. A number of different strategies are being developed to address this issue, including (1) manual realignment of CT and PET, (2) acquiring a cine CT of the breathing motion and generating an average CT for attenuation correction and (3) acquiring multiple CT scans to ensure at least one matches the PET scan as closely as possible. Obviously, the role of PET/CT in cardiology has yet to be determined but if a strong clinical demand exists it is to be expected that transient technical challenges such as the misalignment issue will ultimately be solved. A complete review of the status of PET/CT in cardiology can be found in DiCarli et al (2007).

The fusion of CT and SPECT images from stand-alone systems has already demonstrated clinical utility (Gaemperli et al 2007). Thus, the combination of SPECT with a 16-slice CT offers interesting further possibilities for cardiac SPECT. Misalignment issues between CT and SPECT images are similar to those with PET/CT and therefore suitable protocols must be developed that may involve manual realignment of the images. Nevertheless, the combination of calcium scoring from CT and a cardiac SPECT study with $^{201}$TI for tissue viability and $^{99m}$Tc-sesamibi for perfusion is an attractive possibility. The future development of a combined whole-body MR/PET system may present further interesting possibilities for multimodality imaging in cardiology.
8. Summary

This review has followed the historical development of multimodality imaging devices from their inception in the early 1990s to the present day. There is little doubt that such devices, and in particular PET/CT, have had a significant impact on clinical imaging. Ironically, while the pre-clinical designs and early clinical prototypes were received with enthusiasm, the introduction of commercial PET/CT scanners into the clinic encountered a certain amount of resistance. The technology was accused of being disruptive (Wiley 2005), expensive (Alavi et al. 2007), wasteful of resources, clinically unproven (Zaidi 2006), oversold (for treatment planning) (Xing 2005) and successful only as a consequence of the marketing strategy of the major equipment vendors (Zaidi 2006). It has also been argued that software fusion offers an equally effective and less costly approach to hybrid imaging and that very few clinical settings justify the use of PET/CT over PET alone, even in oncology (Alavi et al. 2007). As always, initially, there was an element of truth in some of these concerns. The technology has certainly been disruptive in the sense that it has brought together medical specialties that have not traditionally worked together. A demand has arisen for cross-training of both the technologists who operate the devices and the physicians who interpret the studies. Guidelines have been published (Coleman 2005) and new standards established leading to a very different situation today from the way radiology and nuclear medicine have traditionally functioned.

SPECT/CT currently has a smaller installed base than PET/CT, but the modality is also growing. In 2006, there were about 21 million SPECT studies performed in the US compared with 1.5 million PET and PET/CT studies. The likelihood is that SPECT/CT will continue to grow with expanding applications in cardiology, oncology, infectious disease imaging and others. Similar guidelines on SPECT/CT operation have been published recently (Delbeke et al. 2006). A feature common to both the PET/CT and SPECT/CT designs is the low level of integration of the imaging components. The CT and PET or SPECT are arranged in line with the CT in front of the PET and behind the SPECT. Simultaneous imaging of the anatomy and the molecular biomarker distribution covering the same region of the patient is not possible. This approach has some drawbacks although as has been seen it leads to a simpler and more flexible hardware design. In contrast, MR/PET for brain allows simultaneous acquisition of both modalities, potentially creating new research applications for neuro imaging. In the future, new devices such as whole-body MR/PET and PET/US for breast imaging are highly likely to appear, further expanding the range of clinical multimodality technology. While there have been some suggestions that MR/PET could replace PET/CT (Zaidi et al. 2007), the issue is more whether the addition of a PET insert to an MR scanner will attract clinical applications away from PET/CT. This does not seem to be very likely, since both CT and MR have strengths in certain medical areas, a situation that is unlikely to change because of the addition of PET. Whatever the outcome of this and other debates, multimodality imaging of structure and function is going to play a major role in the management of human disease for the foreseeable future.

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