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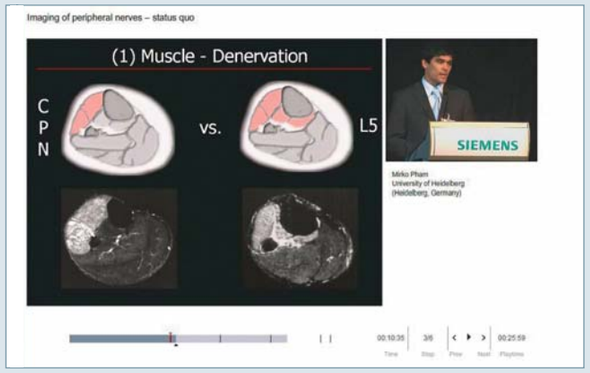

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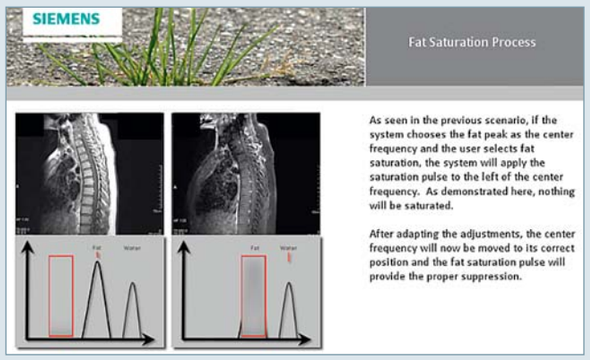

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MR/PET – Hybrid Imaging for the Next Decade

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Dual-modality imaging

Traditionally, medical imaging is dominated by anatomical imaging, such as X-ray, ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI). Functional imaging plays a minor, albeit important role. Most functional imaging modalities, including positron emission tomography (PET), are operated in the realms of nuclear medicine, sometimes mockingly referred to as 'unclear' medicine, so as to point to the fact that nuclear medicine images are comparatively noisy and of lower spatial resolution than, for example, CT or MR images. Nonetheless, PET in particular has been demonstrated to be of particular value in a number of disease staging and follow-up regimens.
Despite the clinical usefulness of standalone nuclear medicine and radiology imaging, the desire to combine anatomical, functional (e.g. perfusion) and especially metabolic imaging has been pursued since the 1960's when physicians manually added body contours to planar scintigraphy images of the thyroid. Subsequent approaches to image fusion included side-by-side viewing of complementary image sets on film and on light boxes; image fusion was performed in the head of the physicians and mainly dominated by the personal experience and expertise. The first reliable approaches to computer-assisted image co-registration and fusion were presented in the mid 1980's in an attempt to align brain studies from MR and PET. While retrospective image alignment and fusion works usually well for the brain, similar approaches do not work as well for extra-cerebral studies that are affected by multiple degrees of patient motion.
The introduction of combined, dual-modality imaging systems in the late 1990's offered for the first time the acquisition of high quality anatomical and functional / metabolic image information within a single examination. This was a unique stimulus for non-invasive diagnosis, and has resulted in an extraordinary rapid growth and commercial adoption of imaging systems such as SPECT (single photon emission tomography)/CT and PET/CT. A decade after its prototype introduction, PET/CT, for example, has become the modality-of-choice for a variety of clinical indications in oncology. Today, over 5,000 PET/CT systems are installed worldwide and up to 90% of all PET-investigations are performed for oncology indications with ^{18}F-FDG (fluorodesoxyglucose) being the tracer-of-choice in most of these indications. As discussed in this article, an alternative combination of MR with PET, while technically challenging, has a number of advantages compared to existing dual-modality imaging systems. Prototype MR/PET systems were first proposed for small animal imaging in the 1990's. Recently first prototype MR/PET systems were proposed for imaging humans and case reports and initial pilot studies have promoted a rising interest in this combination of two well-established diagnostic modalities.

MR/PET: From a PET attached to a CT to a PET inside an MR

Tracer principle

The origins of positron emission tomography date back more than 30 years. PET is a functional / metabolic imaging technique based on the detection of coincident photons originating from the annihilation of emitted positrons with electrons from surrounding tissues. PET employs biomolecules that are labeled with neutron-deficient nuclei, i.e. positron emitters. As such, the whole-body distribution of positron-emitting biomarkers can be followed and imaged with high sensitivity using PET (Fig. 1).
Upon decay of a neutron-deficient radioisotope (e.g. ^{18}F) attached to the biomolecule being traced (e.g. glucose) a positron is emitted. After traveling a mean path of

less than a mm in tissue the positron annihilates with an electron, thus creating two 511 keV photons that are emitted in opposite direction. PET scintillation detectors arranged around the patient register the annihilation photons in coincidence and store the events in sinograms from which PET activity distributions are reconstructed following the emission acquisition.

PET detector

PET detector arrangements are based on Anger readout (Fig. 2) which is based in turn on light sharing and mapping many small scintillation crystals to few light detectors (in clinical PET/CT scanners usually photomultiplier tubes (PMT)). The annihilation photon (Fig. 1) is stopped in the scintillator (Fig. 2) and the energy is transformed into secondary scintillation light pulses, which produce photoelectrons at the first cathode level of the PMT, next to the entrance window. These photoelectrons are directed and amplified (multiplied) by an electric field applied to the PMT. For each annihilation photon stopped an electric pulse is generated from the scintillator-PMT detector and stored with respect to the location of the crystal depending on the Anger localization. In the 1990's, bismuth germanate (BGO) was the crystal material of choice for almost all PET systems. Today, BGO is replaced mainly by lutetium oxyorthosilicate (LSO), or variations thereof; a scintillator material that combines fast timing properties with high light output and good stopping power for 511 keV photons. Modern PET system designs include several detector rings that fully surround the patient providing an axial field-of-view (FOV) of 15–22 cm with a measured transverse FOV of up to 70 cm. Most whole-body PET systems yield an intrinsic spatial resolution of 4–6 mm. Sensitivity and spatial resolution are key parameters for PET systems and both depend directly on the properties of the scintillation crystals as part of the PET detector system.

PET/CT systems

Today, close to 70% of all installed PET units are combined PET/CT devices. All but 2 of 8 PET system vendors, who offer standalone PET systems designed for dedicated clinical tasks, offer PET systems for clinical use that are combined with a CT system. The main advantages of combined PET/CT are the intrinsic availability of co-registered functional and anatomical information from PET and CT, for local and whole-body examinations respectively alike. Second, the ability to use available CT transmission images to replace lengthy PET transmission images using 511 keV rod sources, thus reducing overall examination time significantly and limiting noise propagation from measured attenuation correction.

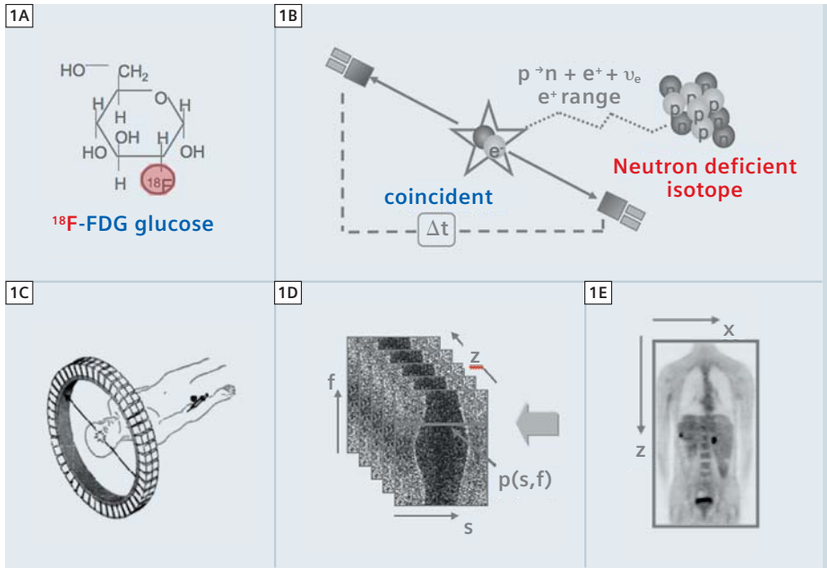
Dual-modality PET/CT systems combine a whole-body PET and a standard multi-slice CT within a single gantry. Various design concepts exist (Fig. 3), all aiming at reducing footprint and bringing the PET and CT components closer together. No fully-integrated, single-detector PET/CT exists today, however, because of the challenges to manufacture a detector system that is capable of CT (40–140 keV) and PET (511 keV) imaging. By using novel patient handling systems, patients are positioned accurately and reproducibly for co-axial imaging. Reports on residual displacements between CT and PET along the co-axial imaging range in combined PET CT indicate a maximum displacement of error of 0.5 mm. Thus, PET/CT yields the best possible alignment of extensive, complementary image volumes. With the benefits of intrinsically aligned PET and CT data, shorter overall scan times and the logistical advantages for patients and staff, combined PET/CT imaging has become a modality-of-choice for patient management in clinical oncology.

Challenges and drawbacks of PET/CT

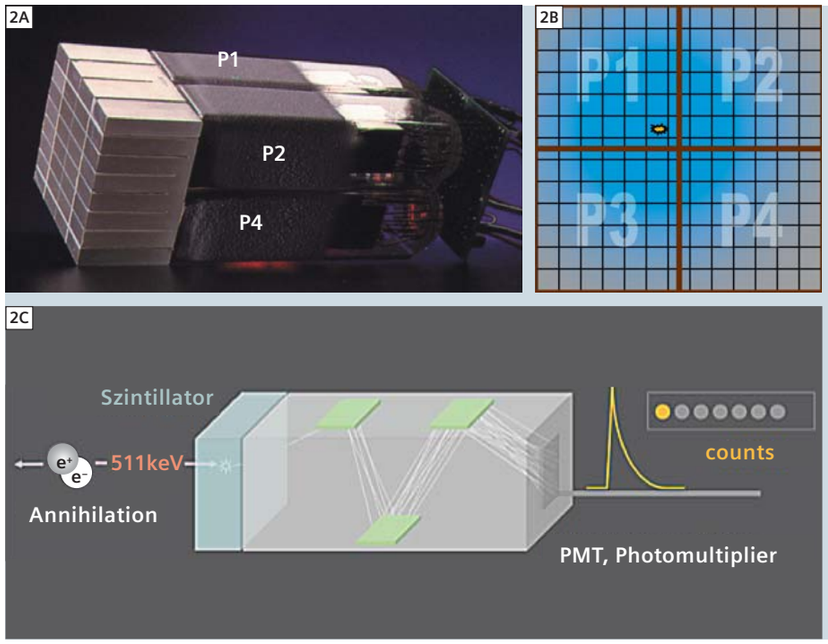
There are a few challenges when designing a PET/CT imaging system and making it clinically viable. First, the axial displacement of the CT and PET components (Fig. 3) is unavoidable as long as no single PET and CT detectors are available, thus allowing for only sequential rather than simultaneous acquisition modes. Sequential imaging holds the risk of involuntary patient motion in between the two examinations and, therefore, may increase the chance of local misalignment of the two studies. Second, residual patient motion is unavoidable in combined PET/CT imaging. Involuntary patient motion from, for example, respiration, cardiac motion, or muscle relaxation leads to PET–CT misregistration that may translate into artifacts on PET images following CT-based attenuation correction. Optimized imaging protocols are required to minimize these types of artifacts and image distortions. Third, the overall exposure from a whole-body PET/CT examination performed with ^{18}F-FDG is rather high at 20–25 mSv per study and 370 MBq of ^{18}F-FDG injected. This dose is justified whenever a clinical indication for a combined contrast-enhanced PET/CT study exists, but at the same time it limits the use of PET/CT in selected patients that undergo repeat studies or in subjects for pharmaceutical trials.

Rise of MR/PET

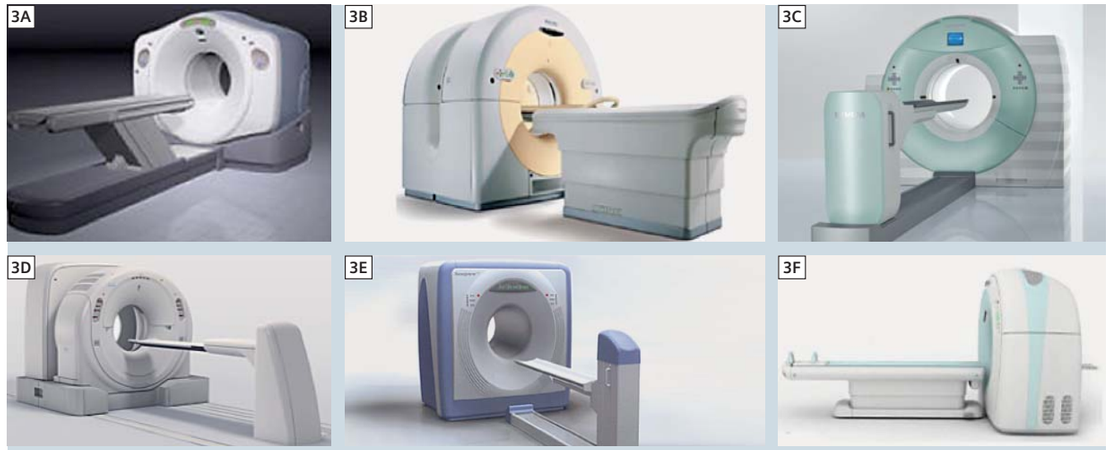
The development of hybrid MR/PET systems started in the late 1990's. CT is not the only available anatomical complement to PET. In comparison to CT, MRI offers a multitude of endogenous contrasts and a superb capability of differentiating soft tissues. With a sensitivity in the picomolar range, PET is ideally suited for the visualization of specific molecules in living organisms. However, PET lacks the spatial resolution offered by MRI, which in turn lacks sensitivity compared to PET. Therefore, the combination of PET and MRI is highly complementary. MRI also offers anatomical image information with the advantage of causing no risk to the patient from ionizing radiation and by offering much higher soft tissue contrast than CT, even in the absence of MR contrast agents. But MRI goes beyond plain anatomical imaging. MR spectroscopy, for example, can be used to dissect the molecular composition of tissues by applying selective radiofrequency excitation pulses. The Fourier transformation of the acquired signal provides a spectrum that allows for discrimination between various metabolites.



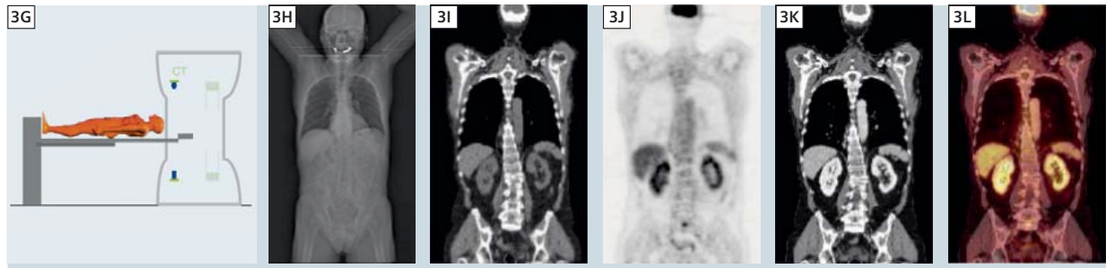
1 PET is based on the tracing of radioactively labeled metabolites. A radiotracer, e.g. ^{18}F-FDG **(A)**, is injected into the patient **(B)**: ^{18}F decays by emitting a positron, which annihilates with an electron, thus resulting in two annihilation photons along a straight line-of-response (LOR), **(C)** annihilation events are registered in coincidence and stored in raw sinogram space **(D)**. PET images are reconstructed following a number of physical and methodological corrections **(E)**. *(Figure adapted from DW Townsend, Singapore.)*



2 Block detector. **(A)** Example of PMT-bismuth germanate block detector from a clinical PET system (Fig. 1C). Readout is performed using only the 4 PMTs that are connected to pixilated scintillator block. Light sharing is used to distribute light originating from single pixel between the 4 readout PMTs (P1, P2, P3, P4). **(B)** Depending on crystal position, scintillation light will be uniquely distributed to readout PMTs. Using Anger weighting algorithm on measured signals, position of incident annihilation photon (i.e. the activated crystal) can be calculated. **(C)** Schematics of detection process from annihilation to stopping the annihilation photons in the crystal and signal transformation inside the photomultiplier.



3A–F Current commercial PET/CT systems: **(A)** Discovery series from General Electrics Healthcare, **(B)** Gemini series from Philips Healthcare, **(C)** Biograph mCT from Siemens Healthcare, **(D)** Acquiduo series from Toshiba Medical Systems, **(E)** Sceptre series from Hitachi Medical Systems, **(F)** Anyscan from Mediso (this device can be combined with a SPECT to form a triple-modality imaging system). Variations apply to the individual performance parameters of PET and CT.

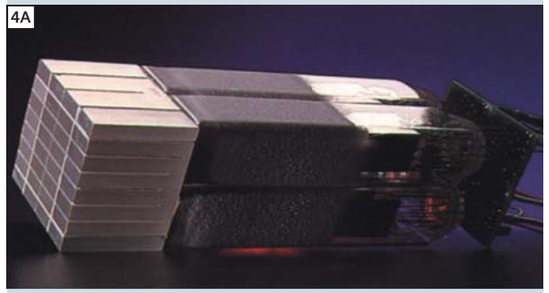


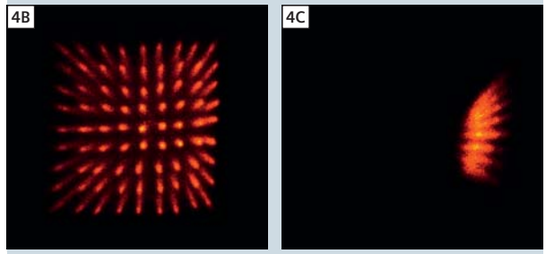
3G–L Schematic illustration of a standard PET/CT investigation: tracer injection, uptake time and patient positioning **(G)**, topogram and scan range definition **(H)**, CT acquisition for attenuation correction **(I)**, emission scan **(J)**, contrast-enhanced CT scan **(K)** and image reconstruction/fusion **(L)**.

Spectroscopic images of extended anatomical volumes can be generated for preoperative staging of gliomas, pH imaging, monitoring of temperature, or the evaluation of lactate changes during brain activation.
Functional processes in living subjects can also be studied via diffusion-weighted MRI. Here, the magnetic field, generated by different gradients, is used to map phase differences in the MRI signal that are caused by diffusing molecules. Many MRI sequences can be made sensitive to diffusion by using adequate gradient pulses. Diffusion MRI has various potential clinical applications ranging from diagnosing ischemia, cancer, multiple sclerosis, or Alzheimer's disease to general fiber tracking via diffusion tensor imaging. Diffusion imaging is not restricted to the brain; it has also been applied to other regions of the body (e.g., for oncologic diagnosis), where it provides qualitative and quantitative understanding of the tumor microenvironment and the integrity of cell membranes.
Functional MRI (fMRI) studies are frequently based on the BOLD (blood oxygen level dependent) effect. This technique is based on the fact that the magnetic properties of oxygenated and deoxygenated hemoglobin in the blood are different and, therefore, produce different signals when imaged with T2*-sensitive MRI sequences. Unlike contrast-enhanced MRI, BOLD effect is a non-invasive technique based on endogenous information. The BOLD effect also has certain applications in cancer imaging, such as the study of tumor angiogenesis, tumor oxygenation and brain activation in eloquent areas prior to surgical resection.
Lately, MRI has become a whole-body imaging modality thanks to the advent of Tim (Total imaging matrix) and parallel imaging techniques. Image acquisition times have been shortened, thus allowing whole-body MRI examinations with high spatial resolution in less than one hour. Initial results show that whole-body MRI is a promising modality in oncology, especially for the detection of metastases and hematologic malignancies. In summary, MRI holds a great potential in replacing CT as the complementary modality to PET in dual-modality tomographs and in selected indications where MR already outperforms CT.

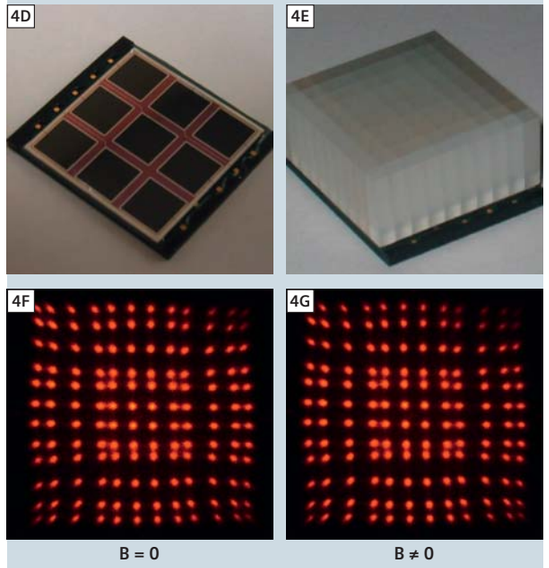
Challenges of combined MR/PET
Traditional PET systems use PMTs to detect the scintillation light. However, PMTs are sensitive to magnetic fields and are therefore not functional inside an MRI system. To overcome this problem, various approaches to the combination of PET and MRI have been established. For example, optical fibers can be used to lead the light from the scintillation crystals outside the fringe field of the magnet to the PMTs. Alternatively, split magnets with the PET detector positioned between the two magnet halves and connected via light fibers have been proposed. In either design, long optical fibers result in a loss of light and consequently in lower performance of such a PET system operated in the vicinity of an MR scanner.
This loss can be overcome by the use of magnetic field-compatible solid state light detectors, such as APDs (Fig. 4). This approach also permits easier expansion of the axial FOV of the PET system. The mutual interference between PET and MR is a critical problem; MR can affect PET performance because of the high static magnetic field, gradient fields, and radiofrequency field. MR image quality, however, can be impaired by either radiofrequency noise introduced by the PET electronics or magnetic field inhomogeneities caused by the presence of different materials in the PET insert and eddy currents induced from the gradient system in the conducting structures of the PET housing and circuit boards. Moreover, the operating temperature needs to be stabilized to ensure reliable PET and MR performance.
Finally, any combined MR/PET system must offer alternative approaches to deriving the necessary attenuation correction factors for the emission data. While in PET/CT attenuation data can be derived from transforming available CT transmission images into maps of attenuation coefficients at 511 keV, no such transmission data are available in MR/PET. This is due to the lack of physical space in general to host a transmission source. Secondly, a rotating metal-encased transmission

Conventional PET detectors

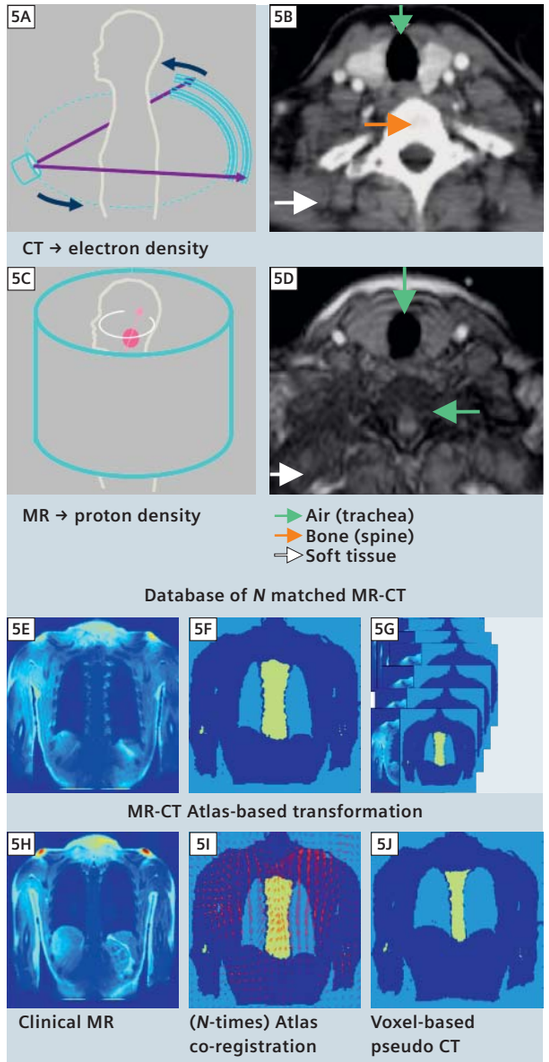




APD-based PET detectors



4 Conventional PET detectors **(A)** are based on scintillation crystals and Anger-logics readout. They work only outside magnetic fields **(B)**. If a PMT is operated inside a magnetic field (B ≠ 0) then the multiplier step is construed and the readout map severely distorted **(C)**. Avalanche photodiodes (APD) based detectors **(D, E)** are semiconductors that can be operated in magnetic fields, even at ultra-high field strengths **(F, G)**. *(Image courtesy of Prof. B. Pichler, University of Tübingen, Germany.)*



5 The challenges of MR-based attenuation correction: unlike CT images, that represent the attenuation of ionizing radiation (from an external source) by tissues in the field-of-view **(A)**, MR produces maps of proton densities **(C)**. Reconstructed images are different in the sense that highly attenuating tissues (e.g. bone) appear bright on CT and can be separated easily from low-attenuating tissues (e.g. air) **(B)**, which is not the case for MR images where air and bone have frequently similar appearances **(D)**. Therefore, segmentation-based algorithms for MR-based attenuation correction may fail to produce accurate PET attenuation maps. An alternative approach would be an atlas algorithm **(E–J)**: pairs of CT **(F)** and MR image volumes **(E)** are aligned and used to create a database of MR-CT data pairs **(G)**. The MR images **(H)** of a patient undergoing an MR/PET examination are compared voxel-by-voxel with the MR-database and a corresponding CT image is composed **(I)** and used to calculate the PET attenuation coefficients **(J)**.

source, whether X-ray tube, rod or point sources would lead to grave crosstalk effects with the MR magnetic field. And finally, the available MR images represent, in essence, proton densities that cannot be transformed to maps of electron densities as obtained from CT transmission measurements. Therefore, MR/PET requires novel approaches to MR-based attenuation correction. Segmentation-based approaches have been proposed and seem to work in brain imaging. However, MR-based attenuation correction in extracranial applications is much more demanding (Fig. 5).

Clinical prototype MR/PET

The development of combined MR/PET tomographs has been the reverse experience to that of PET/CT. The first PET/CT design emerged from industry-academia collaboration and was a prototype for human clinical use that stimulated a commercial response and later led to the development of PET/CT for imaging small animals. In contrast, MR/PET in the mid 1990's began with small animal designs.

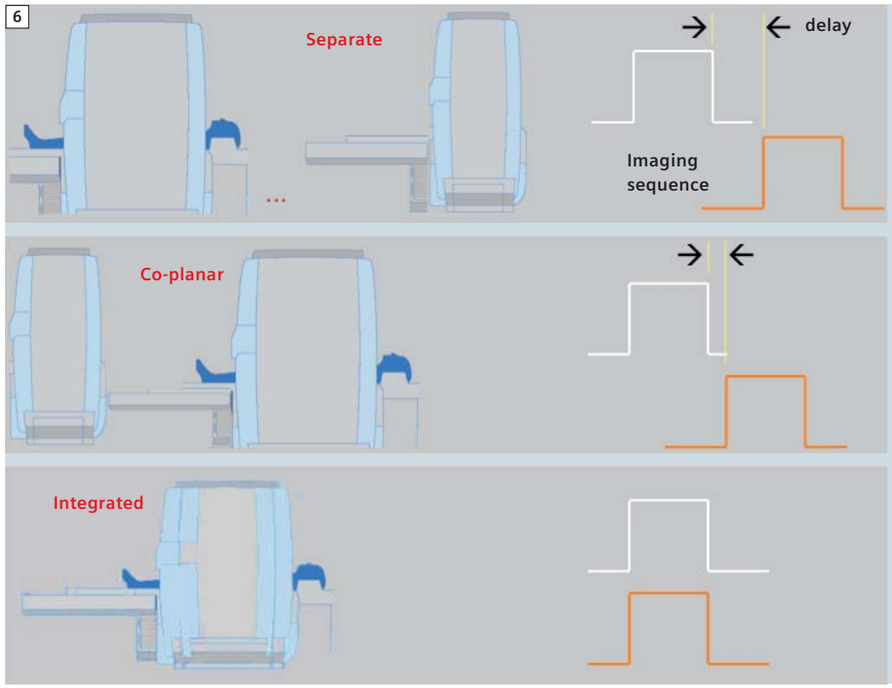
Then, over a decade later, a prototype MR/PET was developed for human brain scanning that acquired the first images in November 2006. This prototype design is based on a PET insert for a 3T MR, and offers a transverse FOV limited to scanning the brain, or the extremities (Fig. 6). As of today four brain insert MR/PET systems have been installed worldwide; industrial backing for this human MR/PET prototype development is impressive and exceeds that of the early PET/CT developments.

This insert design is one of three general approaches to MR/PET being discussed today. An alternative design encompassing a co-axial arrangement of a 3T MRI and a TOF (time-of-flight) PET with a rotating patient handling system in between within one room was proposed in early 2010 (Fig. 6). A comparable system but with separate cabins for MRI and PET has been in existence for brain research since 2007. Again, several prototype systems were installed for clinical testing. A third, much simpler approach is also illustrated in figure 6. While the integrated MR/PET is the most sophisticated and perhaps ideal solution to combined imaging, the third design is that of a standalone PET and a standalone MR with a unified table docking station.

First experiences with MR/PET

First results of clinical simultaneous MR/PET

We received a prototype MR/PET system in 2008 and have evaluated the system since then. Our patient studies, as approved by the Ethic Committee, aim at demonstrating the feasibility of simultaneous MR/PET imaging of the human brain by using APD-based PET



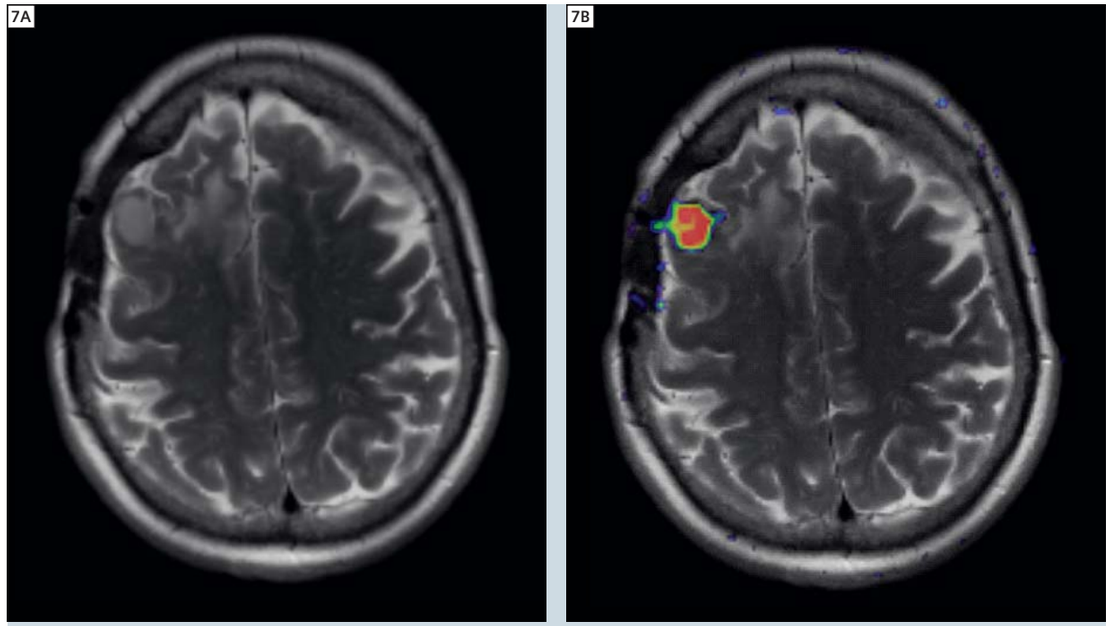
6 Different designs for combined MR/PET systems. Separate operations in different rooms is suggested as a low-budget approach to combined MR/PET; however, several practical challenges exist. An alternative approach to combine MR and PET information is to use a PET and an MR in tandem with a joined table platform. A third, and most challenging approach, is pursued by Siemens Healthcare and tested as a prototype at our institution with a PET insert that is slim fit into a whole-body 3T MR offering simultaneous MR/PET acquisitions.

detector technology integrated into a clinical 3T MAGNETOM Tim Trio system. The PET system consists of blocks of a 12 x 12 LSO matrix with an individual crystal size of 2.5 x 2.5 x 20 mm^3. The block is displayed on a 3 x 3 APD array with individual diodes that have an active surface of 5 x 5 mm. Six LSO-APD block detectors form a cassette; the cassettes are arranged along the z (main) axis of the tomograph, thus forming 72 crystal rings. The entire PET system consists of 32 radially arranged cassettes and has an axial FOV of 19.2 cm and an inner ring diameter of 35.5 cm. The system has a time resolution of 5.6 ms (full width at half maximum, FWHM) and a mean energy resolution at 511 keV of 22% (FWHM). All PET detector components such as amplifiers, resistors, shielding material and housing were selected to minimize interference with the MR imaging B field, gradients, and radio-frequency.

MR examinations are performed during PET data acquisition. Conventional MR imaging of the brain includes axial T2-weighted turbo spin-echo (TSE), fluid-attenuated inversion recovery sequence (FLAIR) and 3D T1-weighted fast low-angle shot sequence (FLASH) sequences. For diffusion-weighted imaging (DWI), a single-shot echo-planar imaging (SS-EPI) sequence is applied.

For PET imaging, the patients fast for at least 4 hours prior to the intravenous injection of ^{18}F-FDG. Body-weight adjusted, we inject in mean 370 mBq of ^{18}F-FDG. The distribution of the tracer is recorded during the entire MRI acquisition (time-range for simultaneous MR/PET from 20 to 40 minutes in most cases) at a steady state at 120 min post injection. The extended uptake time is due to the fact that all patients first undergo a clinically indicated PET/CT. PET data are acquired in 96-bit list mode containing complete information for each coincident event and stored on a disk, accumulating approximately 20 GB of raw data during a 40 min of PET acquisition. Emission data set is reconstructed iteratively (6 iterations and 16 subsets). The image volume consists of 153 transaxial image planes with a voxel size of 1.25 mm^3. Reconstructed resolution is 2.5 mm (FWHM) in the center and 4.5 mm at 10 cm off axis (for a line source in air reconstructed by using OPOSEM3D).

Our experience and studies indicate that – following system set-up and quality control - simultaneous MR/PET of intracranial tumors using ^{18}F-FDG, ^{11}C-methionine or ^{68}Ga-DOTATOC can be performed reliably. The image quality and quantitative data achieved using MR/PET is similar to that using PET/CT. An example MR/PET study is shown in Figure 7.



7 MR/PET imaging of a 65-year-old patient with a meningioma in the right frontal lobe. **(A)** Axial T2w MR images. **(B)** The intrinsic fusion of the simultaneously acquired MR and ^{68}Ga-DOTATOC PET images highlights the advantage of hybrid imaging regarding the accurate spatial coregistration without distorting artifacts. Data have been acquired using the integrated BrainPET MR/PET system (Siemens Healthcare, Erlangen, Germany).

The development of a prototype integrated MR/PET imaging system with no detrimental effect on the performance of PET and no degradation of MR images for a number of standard clinical MR images has put MR/PET imaging on the verge of being applied to clinical neurosciences. The combined system will certainly broaden the impact and possibilities of simultaneous imaging of morphologic, functional and metabolic information. First patient data are promising and highlight the scientific and clinical potential of the integrated system.

Challenges of (simultaneous) MR/PET: Quantification

Together with the clinical and performance evaluation of the prototype MR/PET at our hospital, we have initiated the development of versatile approaches to MR-based attenuation correction (AC) for clinical use. Performing PET attenuation correction with MR image information is challenging. Various approaches for predicting the attenuation maps from MR images have been proposed by several groups. MR image segmentation works well for the brain but can fail on extra-cerebral images, mainly due to the similar appearance of air and bony tissues as well as artifacts towards the edge of the FOV of MR images. If a separation of bone and air is required, torso MR/PET imaging in particlular requires more sophisticated methodologies. We focus on a combination of an atlas approach and machine-learning algorithm to estimate a PET attenuation map from the available MR images (Fig. 5), which was shown to work well in our hypothesized whole-body MR/PET data. In general, MR-AC must address adequate transformation of MRI pixel value information to appropriate PET attenuation values and account for additional pitfalls, such as truncation effects from patients extending beyond the transverse FOV of the MR system and the presence of MR surface coils typically not seen on MR imaging. In latter cases, dedicated MRI sequences using ultra-short echo times appear as promising adjuncts to MR imaging for the purpose of MR-AC.

Challenges of simultaneous MR/PET: workflow

In terms of workflow aspects and logistics, integrated imaging techniques – in theory – can outperform any separate or sequential imaging. This has direct implications on patient comfort and compliance. Nonetheless, a number of questions remain with respect to the overall integration of this new combined modality into clinical workflow, be it as an adjunct or as a replacement method; this needs to be addressed by prospective studies. In the interim there are indications for numerous research applications that benefit from simultaneous MR/PET imaging, currently for brain application only, in the near future for larger imaging areas. Simultaneous imaging functionalities must comprise hardware and software tools. As hardware integration of the combined system progresses, so must the integration with respect to software and data processing. Current viewing tools need to be expanded to allow efficient screening, accurate analysis and quantification, where needed, of data sets that comprise 3D images, dynamic data and additional information, such as spectra, perfusion maps or multiple metabolic pathways.

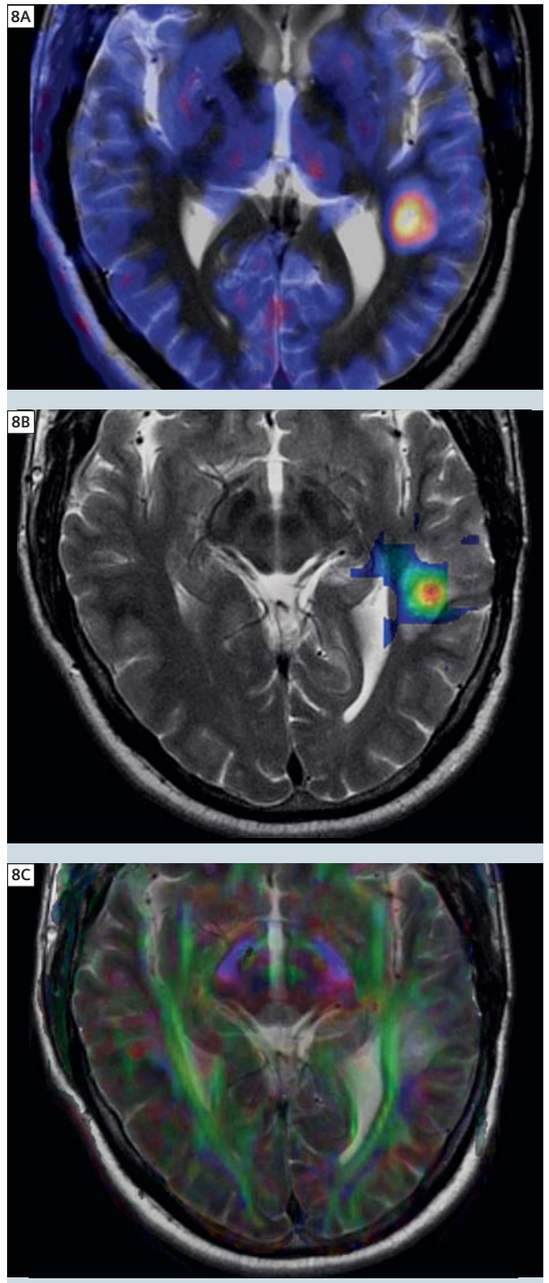
Simultaneous versus sequential MR/PET imaging

It may be too early to predict a prevalence of one over another acquisition mode. The question of sequential over simultaneous imaging is the subject of an ongoing debate. From a technical perspective simultaneous imaging allows for a number of advanced data processing steps that are not straight forward in sequential MR/PET (and PET/CT imaging). This includes motion correction for involuntary patient motion and any subsequent quantification that may be biased from patient motion during the examination. MR-based motion correction is work-in-progress.

To correct for patient motion, special MRI sequences can be applied by either 1-dimensional navigator scans or in 2 to 3 dimensions to detect the motion of the subject. Ideally, these protocols can be combined with the MRI sequence already running to provide motion information about the subject in intervals of as short as 1 s. The motion vectors may be extracted from the motion-sensitive MRI scans and made available to the PET system, allowing either online or post acquisition motion correction of the PET images. General advantages of simultaneous data acquisition include temporal correlation of PET and MR imaging data, reduced imaging time compared with sequential imaging, and the option for cardiac and respiratory motion correction of PET data.

MR/PET – What can be expected in the near future?

With the success of PET/CT in mind, the expectations for any new combination, such as MR/PET are very high. Obviously, MRI provides excellent soft tissue contrast without using ionizing radiation. Thus, it seems a perfect anatomical complement to PET (Table 1). The main idea behind merging PET and MRI is to combine the functional / metabolic information provided by PET with the high soft-tissue contrast and the func-



8 Simultaneously acquired and superimposed on ^{11}C-methionine-PET and MR imaging avid tracer uptake of the atypical neurocytoma on the left side in a 42-year-old patient **(A)**. Simultaneously acquired chemical shift imaging (CSI) MR spectroscopy provides a map of choline to N-acetyl-aspartate ratio **(B)** indicating the high proliferating index of the tumor, while simultaneous diffusion tensor imaging **(C)** shows the clear relationship to the adjacent optic radiation.

tional information offered by MRI. However, the potential areas of application of combined MR/PET extend far beyond high-contrast image fusion. This is supported by our in-house studies where the pre-clinical and clinical prototypes have convincingly demonstrated that the APD-based PET system can be operated simultaneously with the MRI without sacrificing the performance of either modality.

Brain studies, for example, benefit greatly from the additional morphologic information provided by MRI. Simultaneous data acquisition will allow the addition of kinetic, functional and metabolic information for real time multi-parametric functional imaging; to name just two applications:

- MRS can provide additional metabolic information to regional metabolic data from PET in stroke, gliomas, and degenerative disorders;
- MR-based perfusion-weighted imaging (PWI) can be correlated with hypoxic markers (^{18}F-MISO PET) for correcting PET results and also for further understanding of tumor microenvironment.

For complex studies of brain functions combinations of modalities or additional functional techniques will open new insights into the organization of the brain and the changes in disease. For example, diffusion tensor imaging can be added to activation studies and therefore, effects on transmitter release, receptor occupancy and metabolism in connected areas can be analyzed as substrates of connectivity in networks (Fig. 8). The list of conceivable research topics and clinical applications of MR/PET is extensive. It could be particularly useful for early tumor detection and functional therapy monitoring in oncology. It will likely be used to investigate the effect of novel drugs, such as inhibitors of angiogenesis or modulators of the immune system. Integrated information on individual cell metabolism and microenvironment and their response to therapy will help elucidate the mechanism of action and optimize treatment schedules.

In the field of cardiology, the potential of MRI to assess cardiac function can be combined with the possibilities offered by cardiac PET; this combination would allow clinicians to assess the metabolic viability of the heart muscle, its perfusion and functional impairment. Initial studies combining MR spectroscopy with PET have already been performed on isolated perfused rat hearts, but may also elaborate cardiac MR/PET studies involving cardiac stress simultaneously assessed with PET and MRI. Dual functional studies correlating the same parameters (e.g. perfusion in PET via radioactive water or ammonia and in MRI using arterial spin labeling or MRI contrast agents) can help to cross correlate and validate different acquisition techniques. Using the strengths of each individual modality, one can simultaneously assess different molecular parameters. For instance, diffusion processes may be tracked simultaneously with PET tracer uptake, or PET perfusion can be correlated with the MRI BOLD effect. Because of the large number of existing PET probes and the various functional imaging capabilities of MRI, the number of possible combinations for molecular imaging readouts is virtually unlimited. The advantage of truly simultaneous MR/PET is that the same subject is scanned at the same time with identical environmental parameters and stimuli. It is likely that such functional studies will further push the limits for basic biologic research and will open new realms for studying biology in vivo.

Finally, applications of MR/PET imaging in oncology are likely to expand. Recent clinical studies comparing whole-body MRI and PET/CT have indicated the potential advantages of a combination of MR and PET. The superior soft tissue contrast of MR is in general relevant for all types of soft tissue tumors regarding detection, delineation, characterization, and staging. Nonetheless, CT is still more sensitive than MR in revealing smallest lung nodules. On the other hand, dynamic MR studies that yield various parameters for quantification of perfusion without additional radiation exposure, and PET studies that may be performed simultaneously visualize in whole the tissue and the vascular components of the tumor.

One of the primary strengths of MRI is its ability to provide anatomical detail in addition to detect abnormalities within boney structures (e.g. marrow, joint spaces). ^{18}F-FDG PET is useful in the diagnosis of acute infections and is an accurate imaging modality to exclude the diagnosis of osteomyelitis. When combined and clinically available, MR/PET may provide a more accurate diagnosis of patients with osteomyelitis including those with complicated diabetic foot disease.

The complementary morphological and metabolic data can be relevant for defining biopsy targets, particularly by differentiating areas of active tumor involvement from inflammatory disease, fibrosis or necrosis. Combined morphological and metabolic imaging is also important for the evaluation of early treatment response. Metabolic information assessed e.g. by ^{18}F-FDG (marker for glucose consumption and therefore energy consumption) or ^{18}F-FLT (fluorothymidine; marker for nuclide acid synthesis and therefore proliferation) is more sensitive for detecting therapy-induced metabolic and necrotic tissue damage. Additional high-resolution morphologic information may be potentially helpful in the planning of subsequent surgery and radiotherapy.

A decade of hybrid imaging

A mere two years after the advent of commercial PET/CT, Johannes Czernin from UCLA commented: "PET/CT is a technical *evolution* that has led to a medical *revolution*". Today, at the dawn of MR/PET imaging, we may extend his phrase by "integrated MR/PET is a medical *evolution* based on a technical *revolution*". PET/CT appears to have replaced stand-alone PET for nearly all oncologic indications. Ongoing and future studies using first prototype and clinical systems will show how much MR/PET could supplement PET/CT imaging in the clinic. We believe that MR/PET is a required and valuable adjunct to modern healthcare and that there will be indications for which MR/PET may become a primary or secondary diagnostic test during work-up or follow-up of a variety of patients.

Nevertheless, MR/PET will not replace PET/CT as a molecular imaging modality in the near future. Both modalities are here to stay because both platforms incorporate the diagnostic power of PET. In fact, with PET/CT being a "*dual*-modality imaging" platform by virtue of combining functional (PET) and anatomical (CT) imaging only MR/PET offers true "*multi*-modality imaging" by virtue of combining function (PET) and anatomy and function (both MR). This will open, without a doubt, new avenues in non-invasive imaging as part of clinical patient management and clinical research.

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Table 1: Assessment of biological properties by MR and PET.

MR	PET
Morphology	Flow ($H_2{}^{15}O$)
Water diffusion capacity (DWI)	Metabolism (^{18}F-FDG)
Vascular anatomy (MRA)	Blood volume ($C^{15}O$)
Perfusion (PWI, DCE-MRI)	Oxygen consumption (^{15}O)
Tissue metabolites (MRS)	Hypoxia (^{18}F-MISO)
Functional activation (fMRI)	Vascular permeability (labeled AA)
Cerebral fiber tracts (DTI)	Nuclide acid synthesis (^{18}F-FLT)
Oxygen consumption (^{17}O)	Transmitters (e.g. ^{18}F-DOPA)
Migration of cells (Fe labeling)	Enzymatic activity (e.g., MP4A)
	Angiogenesis (e.g. ^{18}F-RGD)
	Distribution and kinetics of tracers and drugs (labeled compounds)
	Enzymatic activity in transfected cells

The Siemens MR/PET Hybrid System requires US FDA 510(k) review. It is not commercially available in the US and its future availability cannot be ensured.