Is MR-guided Attenuation Correction a Viable Option for Dual-Modality PET/MR Imaging?[1]

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This is an exciting time for molecular imaging because molecular medicine is expected to lead to a revolutionary paradigm shift in health care. While the nuclear medicine community is witnessing a revolution in the practice of this specialty with the introduction of dual-modality positron emission tomography (PET) and computed tomography (CT), many groups in academic and corporate settings are focusing their efforts on the development of promising multimodality imaging technologies that will combine magnetic resonance (MR) imaging and PET components in a single gantry. One such preclinical system is described by Judenhofer et al (1) in this issue of *Radiology,* and different design trends have been reported in the literature (2–8). Similar design concepts are also being investigated for combined single photon emission CT (SPECT) and MR imaging instrumentation (9).

The recent interest in simultaneous PET/MR imaging is not the consequence of controversies surrounding the role and clinical benefits of PET/CT (10,11) but will likely be the subject of similar critique and debates. The development of PET/MR imaging has been motivated by various factors and has several important incentives (12). First, MR imaging is used to obtain anatomic and structural images with submillimeter spatial resolution that offers better soft-tissue contrast sensitivity than that offered by CT. MR imaging has excellent contrast between white and gray matter and allows for functional imaging in brain studies, and, more importantly, it can be used to assess flow, diffusion, perfusion, and cardiac motion in one examination (13). In addition, MR imaging can be combined with MR spectroscopy to measure the regional biochemical content and to assess the metabolic status or the presence of neoplasia and other diseases in specific tissue areas.

Finally, MR imaging does not involve the use of ionizing radiation; thus, it can be used without restrictions in serial studies, for pediatric studies, and in many other situations where radiation exposure is a concern. PET imaging is used to record the regional distribution of radiolabeled tracers; however, unlike MR spectroscopy, it cannot be used to distinguish the specific molecular species to which the radionuclide is attached, and, unlike MR imaging, it provides little anatomic information.

While many technical problems have recently been solved, there are still several important challenges to the implementation and operation of a PET/MR imaging system that must be overcome. In comparison with x-ray CT, MR imaging typically is more costly, involves longer examination times, and produces anatomic images from which it is more difficult or at least not as straightforward to derive attenuation maps for photon correction of the emission data (14). The latter issue was not described by Judenhofer et al (1), as it has received only limited attention in the scientific literature and few investigators have addressed the problem of the use of segmented MR data to construct an attenuation map for attenuation correction purposes with PET (15). However, interest in PET/MR imaging has been the driving force behind many worthwhile research efforts recently undertaken by different research groups. The major difficulty lies in the fact that the MR signal or tissue intensity level is not directly related to electronic attenuation, which renders conversion of MR images to attenuation maps less obvious when compared with CT. It is worth emphasizing that the optimal transmission scanning technique for PET/CT (ie, CT versus radionuclide sources) is still an open issue that remains to be addressed (16). This is not an issue for PET/MR imaging because of the limited space available, and thus, placement of external

radionuclide sources is difficult or even impossible.

The basic problem of attenuation map determination with MR imaging is locating and mapping the major attenuating structures in the body. Theoretically, this can be achieved in two steps: *(a)* segmentation into regions of tissues and organs that have different attenuating properties and *(b)* assignment of corresponding linear attenuation coefficients at 511 keV to the segmented tissues and organs. Whereas image segmentation has been identified as the key problem of medical image analysis and remains a popular and demanding area of research (17), the latter issue is more challenging to resolve. The former issue is also tricky, as different types of tissues can have identical signal intensities, and similar types of tissue can have different signal intensities. In addition, signal intensity varies strongly between MR images.

An article on the use of MR imaging for attenuation correction purposes with thoracic SPECT imaging was published by Rowell et al in 1992 (18). Although the method described in this article was based on approximations, it was clearly shown that use of the conventional value of an effective linear attenuation coefficient resulted in substantial over-correction for attenuation and that more accurate results could be obtained by using anatomic information derived from CT or MR images. This was followed by attempts to construct a nonuniform attenuation map from MR imaging data for brain SPECT imaging (19). In this approach, MR imaging data were segmented into bone and soft-tissue classes to yield a nonuniform attenuation map by modifying the uniform attenuation map to model bone of the skull according to the water thickness that would result in the same attenuation (eg, $\mu = 0.153$ cm^{-1} at 140 keV). A nonuniform water envelope was then added to the surface of the brain to account for the nonuniform bone compartment. This method, however, ignored the hollow spaces of the sinus and air cavities that are inevitably present in the head.

A more sophisticated approach based on coregistered T1-weighted three-dimensional MR images has been proposed for brain PET imaging (15). The MR images are first realigned (after brain extraction) to preliminary reconstructions of PET data obtained by using calculated attenuation correction. They are then segmented with a fuzzy clustering technique by identifying tissues that have a substantially different density and composition. The voxels that belong to different regions are classified as bone, brain tissue, or sinus cavities. These voxels are then assigned theoretical tissue-dependent attenuation coefficients, as reported by the International Commission on Radiological Units and Measurements (20), and the resulting image is smoothed by using a Gaussian kernel.

One of the limitations of this method is that the difficulties associated with automatic segmentation of the skull on T1-weighted spin-echo images with the fuzzy clustering algorithm led to manual intervention by the operator. This consisted of filling the complex-shaped skull base by using a morphologic closing operation to make it more uniform. The technique was further refined by automating the skull segmentation procedure of T1-weighted MR imaging with a sequence of mathematic morphologic operations (14). Prior to segmentation of the skull, the algorithm was used to segment the scalp and brain from the MR image. The scalp mask allows background voxels with signal intensities similar to those of the skull to be eliminated quickly, while the brain mask ensures that the brain does not intersect the skull segmentation (21). The inner and outer skull boundaries can be computed with thresholding and morphologic closing and opening operations. The results are then masked with the scalp and brain volumes to guarantee closed and nonintersecting skull boundaries. The techniques described previously were originally developed to be used with dedicated high-spatial-resolution brain PET cameras that were not equipped with transmission scanning devices and when subjects' MR images were readily available for brain research studies (22). The method is also useful for the simultaneous PET/MR imaging system dedicated for brain research that is currently being developed by one manufacturer (8).

Attenuation properties of bone structures, including the skull; lung regions; and unpredictable benign or malignant anatomic abnormalities that have various electronic densities can be difficult to depict with whole-body imaging. Bones are intrinsically undetectable with MR imaging (with use of conventional MR sequences) because they have void signal intensity, so it is difficult to distinguish air from bones. The skull, however, is covered by subcutaneous fat and encloses the brain. Incorporation of a priori anatomic knowledge enables sufficient information to be collected to precisely segment MR images and provide an accurate attenuation map.

Another appealing approach for segmentation of the skull and bone structures is to use multispectral MR data acquisition with varying contrast characteristics to provide additional information for the purpose of distinguishing between different tissues. For example, T1-weighted images show better soft-tissue contrast, whereas T2-weighted images show bone structures more clearly. The development of more refined MR sequences with which to label the bone structure more precisely will certainly result in a quantum leap in methodologic developments aimed at deriving attenuation maps from MR images (23). Careful optimization of the MR sequences is a prerequisite for successful implementation of the technique and needs to be investigated further. However, long acquisition times make performance of more than one MR sequence (as needed for some segmentation algorithms) almost impossible in practice. Another possibility would be to exploit the potential of rapid dual-tracer PET (24) where combination of fluoride 18 PET for bone scanning with the tracer of interest (eg, carbon 11 methionine) should allow both tracers to be scanned in a single examination. The preliminary results obtained with dynamic dual-tracer imaging with staggered injections appear to allow recovery of overlapping signals through the

use of information from kinetics and radioactive decay. Provided the additional absorbed dose is reasonable, the bone scan should allow mapping of bone structures in the body through segmentation.

Segmentation of lung regions with thoracic MR imaging is another challenging issue that received little attention owing to its limited clinical value until this modality became feasible as a result of developments in enhanced pulse sequences, reduced examination time, and introduction of new contrast media (eg, hyperpolarized gas). Segmentation of lung regions has been performed through merging of multiple active contours (25), region-based segmentation (26), and edge- and model-based techniques (27) successfully partitioning the image volumes into major anatomic structures, including the lungs, heart, cardiac ventricles, and thorax outlines. However, despite successful segmentation, a noteworthy difficulty is that some tissue regions have continuously varying densities that may not be correctly represented by a discrete set of a priori established tissue models. The lungs are the most representative organ, as it has been demonstrated that the attenuation of lung tissue is considerably different from subject to subject, depends on breathing patterns, and varies with age and in the event of respiratory diseases by as much as 30% (28).

Another approach is to use representative anatomic atlas registration, where the MR imaging atlas is registered to the patient's MR imaging data and prior knowledge of the attenuation properties of the atlas (eg, through coregistration to CT or transmission atlas) is used to yield a patient-specific attenuation map (29). The critical and crucial part of the algorithm is the registration procedure, which might fail in some patients with large deformations. The second fundamental question that remains to be addressed is whether the global anatomy depicted with atlas registration can really be used to predict an individual attenuation map. The use of support vector machines to predict the attenuation coefficients directly from the local image information by training a machine learning algorithm with small image patches has been reported recently (30). Combining this approach with the atlas registration technique described previously might be appealing. Unfortunately, the results reported so far are unconvincing, and more research is needed. Moreover, the clinical applicability of this approach remains to be demonstrated.

Predicting the future is difficult, and any attempt to do so is fundamentally flawed; nonetheless, it appears that plenty of opportunities remain for creative advances in MR-guided attenuation correction of PET data if PET/MR imaging is to become a multimodality platform for molecular imaging (31). At this time, it is unclear whether a viable solution is possible. In my opinion, inhomogeneity of the lungs and the presence of unpredictable anatomic abnormalities with varying attenuation properties will remain the critical issues for accurate MR-guided attenuation correction in whole-body PET imaging.

Noticeable progress in quantitative image analysis is expected to be made during the next few years. The main opportunities will arise from innovative and faster image processing algorithms, given the unlimited imagination of active researchers in the field. It is hoped that this will permit the implementation of more ambitious MR-guided attenuation correction algorithms that will address not only brain imaging but also the full range of whole-body imaging with dedicated PET/MR imaging systems.

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