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Attenuation Correction of PET/MR Imaging

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SYNOPSIS

PET/MR is a new promising multi-modality imaging approach. Attenuation is by far the largest correction required for quantitative PET imaging. MR based attenuation correction have been extensively pursued, especially for brain imaging in the past several years. In this article, we will focus on reviewing atlas and direct imaging MR based PET attenuation correction methods. The technical principles behind these methods are detailed and the advantages and disadvantages of these methods are discussed.

Keywords

PET; MR; attenuation correction; atlas; UTE; ZTE

Introduction

Simultaneous Positron Emission Tomography (PET) and Magnetic Resonance (MR) imaging offers unprecedented opportunities to synergize the physiological and molecular imaging capability of PET and the excellent anatomical and functional imaging capability of MR. This instrument opens up many possibilities for investigation in oncology, Alzheimer's disease, Parkinson's disease, and epilepsy, which are discussed in David Lalush's article, "MR-Derived Improvements in PET Imaging," in this issue. Simultaneous PET/MRI is emerging as potential clinical and research tools for the development of noninvasive imaging biomarkers.

In PET imaging, an annihilation of an emitted positron with an electron produces two 511 KeV photons that move in opposite directions. These photons travel through the tissue

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before reaching PET detectors. The absorption and scatter caused by the photon-tissue interaction leads to photon attenuation[1]. The effect of photon attenuation on PET signal is described in the form of a mono-exponential function as follows,

$$\frac{I}{\mathrm{I}_0}=\mathrm{e}^{-\mu \mathrm{L}}$$

where I and I_0 are the non-attenuated and attenuated PET signals, respectively, μ and L represent the linear attenuation coefficient (LAC) and thickness of a tissue. Photon attenuation depends on the spatially varying electron density and tissue thickness. Photon attenuation can result in as high as 90% signal reduction in some regions[2]. Therefore, attenuation is by far the largest correction required for quantitative PET imaging. Small errors in estimating the attenuation correction factors may lead to significant qualitative and quantitative errors in PET images, (i.e. bias and artifacts)[3]. PET attenuation correction methods require knowledge of the spatial distribution of tissue attenuation coefficients within the PET field of view. This information is represented in the form of an attenuation map (a.k.a. μ map) whose intensities represent the LAC values. In addition to tissue attenuation, some other sources of attenuation are from various hardware, such as patient table and radiofrequency coils that are placed within the PET field of view. A comprehensive review regarding hardware attenuation correction methods can be found in reference[4]. In this review, we will focus on methods to generate patient attenuation correction maps using MRI.

In stand-alone PET systems, attenuation maps are usually estimated from a transmission scan. An external long half-life radionuclide source such as ^{68}Ge/^{68}Ga that emits gamma photons at a similar energy level (511 KeV) is used to acquire a transmission scan. The attenuation maps can be estimated by dividing the reference scan (blank scan I_0) with the transmission scans. Since the number of photons emitted by the external radionuclide source is relatively low, a considerable acquisition time (~10–45 minutes) is needed just for an attenuation map with an adequate signal-to-noise ratio (SNR).

Since the introduction of the first commercial PET/CT scanner in early 2001, combined PET/CT replaced PET-only scanners at a rapid pace[5]. In combined PET/CT systems, a CT scan is used to provide the PET attenuation correction information[6]. The attenuation of x-rays transmitted through a patient is the source of CT contrast, and also directly related to electron density. Since the higher energy (511 keV) gamma photons in PET have a lower probability of being attenuated than the lower energy x-ray photons (80–140 keV) in CT, a piecewise linear transformation has been utilized to transform the CT Hounsfield Unit (HU) to PET LAC values[7,8]. Compared to the PET transmission scans, CT images have higher SNR and can be acquired much faster. However, it has been reported that CT based AC led to PET quantification errors in bones[9,10]. Nevertheless, CT based PET attenuation correction has been widely accepted as the clinical standard.

Unlike PET/CT, MR based attenuation correction (MRAC) in simultaneous PET/MR is very challenging. MR imaging provides information on proton density and MR relaxation rates. It does not provide direct information on electron density needed by PET attenuation correction. While PET/MRI is FDA approved for clinical use, MRI-based attenuation

correction (MRAC) methods have not been well accepted for clinical trials. Bone has near-zero signal in conventional MR images due to low spin density and a rapid T2 relaxation rate while it causes the most photon attenuation per unit volume. On the other hand, air space appears similarly as the bone in conventional MR images, while it does not cause photon attenuation. Therefore, the most difficult tasks of MRAC are to separate bone from other tissue and air, and assign correct linear attenuation coefficients accordingly. It has been demonstrated that improperly accounting for bone leads to large underestimation of PET signal, particularly in tissue near bone[11,12].

In the past several years, numerous approaches have been proposed to develop attenuation correction for PET/MR imaging. There is one class of method that relies primarily on PET emission data to directly estimate attenuation information through iterative joint estimation based on maximum likelihood (ML)[13]. This class of method is dubbed as ML reconstruction of attenuation and activity (MLAA). More recently, PET time-of-flight information has been incorporated into the MLAA method to improve PET attenuation correction[14–16]. MR imaging is not essential in the MLAA approaches. Regarding MR-based PET attenuation correction, there are two major categories of methods to generate CT like images for PET/MRI attenuation correction. The first category consists of an atlas-based approach[17–20]. This typically relies on a precompiled atlas of paired MR and CT images and an algorithm to generate a pseudo-CT image from patient MR images. These pseudo-CTs are subsequently converted to PET attenuation maps through the same scaling operation used in PET/CT attenuation correction. The second category of MRAC consists of direct MR imaging using Dixon, ultra-short echo (UTE) or zero echo time (ZTE) without using complex imaging registration and processing procedures[20–30]. In the latter approach, individual patient MR images are segmented into several tissue classes. Early efforts assigned a constant attenuation value to each tissue class. More recently, advanced methods have been proposed to derive conversion factors to convert MR signal/relaxation rates to CT HU for continuous LAC[25,28]. In this review article, we will focus on the MR based PET attenuation correction methods. The advantages and disadvantages of these methods will be discussed.

Atlas-based approaches

The atlas-based methods usually derive a computational relationship from a group of observed CT and MRI image pair using population data, which can be generalized for future deployment when only MRI is available. Atlas based approaches usually involves two main steps. The first step is to align target patients MR images with atlas MR/CT images. The second step is to use the aligned atlas MR/CT images to synthesize a pseudo-CT for the target patient. Various methods have been proposed and these methods differ either in the image registration step or in the pseudo-CT generation step. Depending on how pseudo-CT were generated, we roughly categorize these methods into three sub-groups: voxel based, patch based, and machine learning based methods. We will briefly introduce the technical aspects of these methods and summarize their performances.

Image Registration

In the atlas based methods, image registration is usually employed first to achieve alignment of the same anatomy from different subjects through transforming the anatomical geometry of the original acquired image. If an image alignment can be represented by a multiplication of the entire image volume with a matrix (including translating, rotating, stretching and scaling), this image registration is classified as a linear transformation (affine registration). A rigid registration is a special case of an affine registration that only consists of translation and rotation transformation. Nonlinear registration (deformable registration) can improve registration accuracy by utilizing flexible local transformation. Usually, linear registration is employed for same subject multimodal image registration, while a non-linear registration is utilized for atlas to subject image alignment where local geometry differences are expected.

Voxel based pseudo-CT generation

Schreibmann et al proposed a multi-step approach to register atlas CT images directly towards the patient MRI without going through intermediate MR image registration[18]. Their method employed a three-step CT-MR image registration, including 1) an initial approximate CT-MR matching using a rigid registration; 2) a B-Spline registration to solve large deformation between atlas CT and individual patient MR; and 3) an optical flow deformable registration to refine BSpline registration. The aligned atlas CT signal voxel by voxel were then directly used for patient's PET attenuation correction. The mean distance between the aligned atlas CT and the actually acquired CT was 1.26 and 2.15 mm, respectively, for the external contour and bone. The mean Hounsfield Units difference across all voxels was less than 2 in 17 brain tumor patients. Due to lack of PET/MR/CT tri-modality data, PET attenuation correction accuracy was not evaluated in this study. Accurate image registration is crucial to this method. Since CT and MR images have very different image intensity and tissue contrast, an accurate deformable registration between atlas CT and patient MR might be challenging.

Burgos et al used a B-Spline transformation to register patient MRI to a group of atlas MRI/CT pairs. A local normalized correlation coefficient was used to assess similarity between the patient's and an atlas subject's MR images for each voxel[31]. A ranking scheme was used on the voxel similarity measure to assign more weight to an atlas subject's images better registered to the patient MR images. An estimate of the target subject's CT was then obtained by a weighted averaging of all atlas CT images. This method can tolerate registration inaccuracy through this similarity based weighting. Relative absolute error was computed as the percent absolute PET signal difference between attenuation corrected PET using the estimated CT and the actually acquired CT. This method achieved a relative absolute error of 2.87+0.90% in PET reconstruction.

Izquierdo-Garcia et al used SPM8 to improve the registration accuracy via tissue segmentation. MRI images were first segmented into gray matter, white matter, CSF, bone, soft tissue and air with a Gaussian mixture model considering the prior spatial probabilities of each voxel belongs to different tissue types. This segmentation was performed through an imbedded processing pipeline in SPM for a tissue specific registration. A patient T1 was also followed through the same steps to be aligned to this template. Due to the

diffeomorphic nature of the registration, the CT template could be inversely warped into the subject's native space for the estimated CT[32]. The voxel- and ROI-based comparisons yielded an error of 3.87+5.0% and 2.74%+2.28% in reconstructed PET images, respectively.

Patch based pseudo-CT generation

In the method proposed by Chen et al[19], a nonlinear symmetric diffeomorphic registration algorithm was employed to align patient's T1 weighted MR images to atlas subject's T1 weighted MR images and CT images. This method utilized an air distribution probability map obtained from all the atlas subjects' CT images to assist air space segmentation from MR T1w images. To estimate the patient's tissue CT images, a patch based method is employed. Compared to voxel based method, a patch based method allows for an incorporation of neighborhood information for a better description of the local intensity distribution. In this study, patches of 5×5×5 cubes located in the vicinity of the voxel were combined using weights derived from a sparse regression. Since the CT estimation was performed using neighborhood patches, the performance of this method is less dependent on the image registration accuracy. This method had an absolute percent error of 2.42+1.0% in the whole brain PET and 85.8% ± 12.9% of all voxels had a below 5% PET errors from 20 subjects. The limitation with this approach is that sparse regression is very computational intense and parallel acceleration is needed for prompt CT estimation.

Andreasen et al employed patched based method for pseudo-CT estimation using an affine registration[33]. In this method, a patch based database was formed for each voxel location and the k nearest neighbors. Patch similarity weighting was used to regress the CT value. This method outperformed a method that used deformable registration, multi-atlas and Gaussian mixture regression[34] with dual echo ultrashort TE images. This method delivered high dosimetric accuracy with an average deviation of less than 0.5% compared to target coverage in 5 patients.

In a patch-based approach proposed by Roy et al, patches were matched between the reference and target MR images. The corresponding CT patches were then combined via Bayesian estimation[35]. This approach did not require image registration. This approach assumed the patches following a mixture of two Gaussian distributions and maximized the probability of the observed subject patch through the expectation-maximization (EM) algorithm. The reconstructed PET images with the synthesized CT was highly correlated to the reconstructed PET with the acquired CT (ρ=0.99, R^2 = 0.99).

Torrado-Carvajal et al implemented non-local patch based CT estimation using GPUs[36]. It propagated MR patch derived similarity to CT patches for weighted linear combinations. After non-local estimations, the estimated CT was regularized as a median within a local neighborhood. Standardized uptake value (SUV) error was lower than 10% in most voxels in simulation. The reconstructed SUV was highly correlated with the gold standard (R^2=0.998) in simulation. In the only one clinical scan, the correlation is reduced to 0.8919.

Machine learning based pseudo-CT generation

Machine learning methods utilized training data to derive a relationship between CT Hounsfield unit and MR signal using features such as signal intensity and geometrical

metrics. These learned relationship can then be applied to patients to generate pseudo-CT. Machine learning methods including Gaussian process regression (GPR), support vector regression (SVR) and random forest (RF) have been proposed. Gaussian process assumes the random variables have a joint Gaussian distribution, which can be fully specified by its mean and covariance functions. Gaussian process regression refers the inference of continuous values with a Gaussian process prior. GPR is a kernel-based method for nonlinear regression problem interpreted in a Bayesian context of Gaussian process. To infer the unknown function, GPR calculates a prior from training samples for a posterior generalization. The learning of GPR is realized through determining covariance or kernel function parameters. SVR solves a constrained optimization problem. SVR can tolerate small errors between the predicted and true values within a small bound ε (a.k.a, ε-insensitive SVR) while controlling the complexity of the regression function. Furthermore, a nonlinear regression can be transformed into a linear regression using a kernel function (such as a radial basis function (RBF)) to map the problem into a higher dimensional space. RF is an ensemble learning methods which grows a set of decision trees through partitioning the data orderly into either left or right branches (like a tree). The input to each tree is a set of bootstrapped samples of the original input data. The final estimation is performed via either averaging or majority voting of the outputs from each individual tree.

Hoffman et al have developed a Gaussian process regression for pseudo CT estimation[17]. The Gaussian process modeled a mean function and a kernel function for covariance of the Gaussian process. The authors used a multiply of two Gaussian functions considering both the similarity of the MR patches and the distance from an atlas patch to the voxel location where CT is being estimated. In this work, the authors estimated CT as the average of the surrounding patches after deformable image registration. This method was applied for brain PET attenuation correction in three patients. A mean percentage error of 3.2%±2.5% were obtained in manually defined ROIs in the dorsal cortex, frontal cortex, lateral cortex, caudate nucleus, thalamus, and white matter. This method was later adapted for whole body PET/MR attenuation correction[37]. The mean percent error was 7.7% ± 8.4% for the whole body PET/MR.

Johnansson et al employed a Guassian mixture regression model with T2 and dual echo UTE images to estimate CT from the joint distribution of MR and CT[38]. Two dual-echo UTE sequences were acquired with 10 and 60 degree flip angle. In addition, 3D T2 weighted images were also acquired. MR signal intensity at a voxel plus the mean and standard deviation from a 3×3×3 neighborhood around this voxel from UTE and T2 weighted MR images were jointly modeled with CT using Gaussian mixtures. To estimate a pseudo CT, the conditional probability density given the MR information was maximized to estimate CT. PET attenuation correction was not performed in this study, only CT estimation accuracy was reported in[38]. The average error for estimated CT was137 HU. This method was evaluated later by Larsson et al for PET attenuation correction in eight patients[39]. The mean and standard deviation of the percent error in brain were −1.9% ± 4.1% with a range from −61% to 34%.

Support vector machine was used for CT prediction from Dixon-volume and UTE images[40]. As in the conventional support vector regression based approaches, a radial basis kernel

function between the features was chosen in this study to be tuned for optimal performance. The features included mean, median, variance, minimal and maximal values across a 3×3×3 window from 3D Dixon-VIBE fat, 3D Dixon-VIBE water and difference volumes. When compared to PET reconstructed using the CT based attenuation correction, the epsilon-insensitive support vector regression (SVR) yielded an error of 2.4% and 2.16% in complete brain and regions close to the cortical bone.

Chan et al have employed random forest classifiers to achieve an accuracy in Dice similarity coefficients of 0.83+0.08 and 0.98+0.01 in air and bone segmentation respectively[41]. This method used both MR anatomical and PET images without attenuation correction, and it took advantage of gradient, texture (metrics quantifying the perceived textures of image) and context features (relationship between image information at different locations). An interesting finding was that features from the uncorrected PET could replace the contextual features from MRI without sacrificing the segmentation accuracy. This finding suggests that PET images without AC can be used as an input to a machine learning algorithm to further improve AC accuracy.

Huynh et al employed a structured random forest to predict CT values[42]. The features included spatial location, pairwise differences, Haar-like features and discrete consine transform (DCT) coefficients, and the auto-context model. These features allowed the random forest based learning method to account for the anatomical location, T1 intensity, T1 image intensity difference using voxel pairwise difference (at the voxel-level), Haar-like features (at sub-region level), and DCT coefficients (at whole patch level), and the occurrence of CT intensities between different anatomical regions (auto-context model). The CT patch difference was computed as the summation of the squared difference between the Principle component analysis (PCA) coefficients of the CT patches. The final CT patch was averaged across all the voxels for a smoothed CT prediction. In brain region, this method achieved an average mean absolute difference 99.9 ±14.2 HU between the synthesized CT and actually acquired CT. Because PET data were not available, PET attenuation correction accuracy was not evaluated.

Summary

In summary, atlas based AC methods can provide accurate CT estimations and PET attenuation maps in brain for patients with normal anatomy. Depending on how pseudo-CT images were generated, the atlas based methods can be roughly classified into voxel based, patch based, and machine learning based pseudo-CT generation subgroups in this review. The pros and cons of these methods are summarized in Table 1. The basic premises of atlas based AC approaches are 1) each individual patient's anatomy can be well represented by the population data; 2) morphological similarity of patient's MR images to the atlas images can result in CT HU similarity. Data with either abnormal anatomy and/or unusual tissue density (e.g. bone density) that is very different from population average may lead to large AC errors. Moreover, atlas based methods usually involves complex computation which may be time consuming. Thus far, atlas based methods have been well tested in neuro-imaging. Due to difficulty in image registration, atlas based MRAC method has not been well developed and used for whole body imaging. The following clinical utility discussion is only

limited to neuroimaging applications. If a nonlinear registration can be performed fairly well, the voxel based pseudo-CT generation method is recommended due to its simplicity and speed. This class of method is more clinical flow friendly at a reasonable PET attenuation correction accuracy. In cases that non-linear registration is challenging or high accuracy is needed for subtle signal abnormality detection, either patch based or machine learning based method should be considered at the expense of computational cost.

Direct imaging methods

The direct MR imaging based methods derive attenuation maps from patient specific MR images without using population derived image atlas. Dixon, UTE or ZTE MR images have been widely used for this purpose. Since MR signal is not directly associated with electron density, MR images are usually used for tissue segmentation. Depending on whether a constant or continuous LAC values are assigned to each tissue class, the direct imaging based methods can be further divided into two sub-categories: 1) Direct imaging with Segmentation only; and 2) Direct imaging methods with segmentation and continuous LAC value conversion. In this section, we will introduce these methods and discuss their performances.

Direct imaging with segmentation only

Early direct imaging based MRAC used either T1weighted or Dixon MR images to segment voxels into 3 (air, lung, soft tissue) or 4 classes (air, lung, soft tissue and fat)[21,22,26,43] for whole body PET attenuation correction. A constant LAC value was assigned to all voxels within each class. This group of methods provides an approximation of tissue densities for soft tissue and fat. Since bone, especially cortical bone with high density, appears ‘invisible’ in conventional MR images, bone was not included in these early methods. Therefore, there was significant quantification error in the brain and pelvis due to the presence of large osseous structures. A particular challenging problem is to delineate bone from air; both have similar MR signal but very different attenuation effects. Ignoring bone may lead to 20% underestimation of PET activity in the head, especially in the cerebral cortical regions due to their spatial proximity of skull[12,19,44–46].

Given the limitations of conventional approaches in obtaining bone signal, there has been the development of numerous sequences that allow for the imaging of bone in order to improve the patient specific attenuation correction maps. The majority of these approaches rely on UTE or ZTE MR techniques that have very short or zero echo times[23,24,27,30,47,48]. These approaches potentially will provide lung, bone and soft tissue maps allowing for accurate patient specific attenuation correction.

In the method proposed by Keereman et al.[30], a background and air mask was first determined using a region-growing approach on the first echo of DUTE. This mask was then applied to the R2* map computed from the first and second echoes of a DUTE to mask out air region. Subsequently, the masked R2* was used to segment bone and soft tissue. A whole brain average error was about 5%[30].

Catana et al. used (DUTE1−DUTE2)/(DUTE2)^2 and (DUTE1+DUTE2)/(DUTE1)^2 to enhance and segment the bone and air regions, respectively[23]. Soft tissue was then identified as non-background regions not classified as bone or air. No quantitative AC accuracy was provided in this work[23].

In the method proposed by Berker et al.[24], a triple-echo UTE sequence was employed. Air and bone were identified using the phase information of the first echo and a dual-echo UTE, respectively. Soft tissue and adipose tissue were separated using a 3-point Dixon decomposition with all three echoes. Eight ROIs with volumes ranging from 2–9 ml were manually placed to cover various brain regions with different proximities to skull. In the 48 evaluated brain regions (8 ROIs for each of 6 patients) mean PET errors ranged from −4.8% and 7.6%[24].

The method proposed by Poython et al combined an atlas generated probabilistic maps to improve MR tissue segmentation. Bone/soft tissue/air probabilistic maps were generated using the aligned CT atlas. These probabilistic maps were then utilized for tissue segmentation using MR T1 and UTE images[48]. The Dice similarity coefficients for air, bone and soft tissue segmentation were respectively 69%, 81% and 96%. Averaged relative difference between the reconstructed PET using estimated CT and the ground truth CT was 2.45%. The evaluation of this approach was performed using the so called “silver standard” in which segmented CT was used for comparison reference.

Paupus et al have developed a model-based estimation for appending the bone information with the attenuation correction map obtained with the Dixon method[49]. The bone model was constructed using pre-aligned MRI and CT pairs, which were further transferred to each individual subject to add the lacked bone information in AC map with the Dixon method. This method can reduce the underestimation of the bone lesion SUV to 2.9%.

Delso et al have developed a posterior probability based approach to segment dual-echo UTE images into air, soft tissue and bone using the CT and UTE image pair[50]. This approach transferred the threshold based CT HU segmentation for the optimal thresholds to segment UTE images into tissue, air and bone. This study reported good overlaps between the estimated tissues classes and the ground truth.

In these methods[23,24,30,48], a predefined constant LAC value was assigned to all voxels in each class to generate patient specific μ maps[30]. As summarized in reference[2], LAC values of bone range from 0.110 to 0.172 depending on the density of bone. Apparently, a single LAC to represent all bone voxels leads to PET AC errors. It has been demonstrated that CT segmentation based AC method still had about 5% whole brain errors when compared to the gold standard piecewise scaling CT based AC[19]. The AC errors of the CT segmentation based method are caused by the under-representation of a wide range of LAC values in tissues. The CT segmentation based AC errors in the whole brain are larger than those of the atlas based MRAC method. Of note, bone, air and soft tissue segmentation using MR images have less accuracy when compared to the silver standard CT segmentation. Therefore, it is expected that the MR segmentation based AC typically produces less accurate PET reconstructions compared to atlas-based methods.

The advantages of the segmentation based method include easy implementation, shorter computation time and better accounting for anatomical variation. However, due to inaccurate segmentation and under-representation of a wide range of LAC values, the direct imaging with segmentation only methods produce less accurate PET reconstructions when compared to atlas-based methods, particularly in head.

Direct imaging methods with segmentation and continuous LAC value conversion

More recently, there are several direct imaging methods that have made efforts to convert MR signal/relaxation rate to continuous CT HU, and then continuous LAC values.

In the method proposed by Cabello et al.[29], air mask was generated using histogram-based thresholding methods. R_2^* maps were computed and used to extract bone from voxels not identified as air. R2* of the bone voxels is linearly equalized to the corresponding CT signal intensity from the same voxels after MR and CT images alignment. The scaled R2* was then used to generate LAC values in bone. A constant LAC of 0.096 cm^{-1} was used for all soft tissue. Mean percent errors for various ROIs were from −5.8% to 2.5%.

In the method proposed by Juttukonda et al.[25], an air mask was generated using a histogram determined threshold on an inverted and normalized image of the first echo of DUTE (TE=0.07 ms). R_2^* maps were computed using the dual echoes of DUTE. Since bone has a much more rapid R2* decay than other tissues, bone was delineated in voxels with a R2* above a certain threshold. Aligned Dixon images were used to identify fat and soft tissue. The generated tissue mask from the Dixon mask was also used to clean up noise-induced misclassification of bone. A sigmoid-of-best-fit regression was performed to convert R2* to continuous CT HU. A leave-one-out method was employed to evaluate the performance of this conversion in 98 patients. A continuous LAC was used in bone and a constant LAC value was used for each of the fat and soft tissue classes to generate μ maps. Regional PET absolute percent errors ranged from 0.88% to 3.79% in 24 brain ROIs.

In the method proposed by Ladefoged et al.[28], R_2^* computed from DUTE was also used to extract bone regions. Bone R2* to CT HU conversion was performed using a 3rd order polynomial fitting to a set of R_2^*-CT relationship pairs from 10 training patients. A non-linear registration of the individual UTE TE2 to an ICBM 152 2009a template was performed. Predefined regional masks drawn in the frontal sinus, the nasal septa and ethmoidal sinus, the skull base, and the rest of the patient volume on the ICBM template was then mapped to individual patient UTE images. Several empirically determined LAC values were assigned to voxels within these challenging noisy or mixed air-tissue regions based on the aligned ICBM masks. A LAC of 0.096 cm^{-1} and 0.099 cm^{-1} was used for CSF and the other brain tissue, respectively. The mean absolute error and mean error over the full brain was 3.4% and 0.1%, respectively. The mean error is less than 1.2% in any region of the brain. This method is a mixed direct imaging and template registration method.

Wiesinger et al proposed a ZTE method to image bone[47]. Imaging parameters of the ZTE protocol were chosen to generate proton density weighted images. A histogram based signal bias-correction was first applied and then an image signal normalization was performed. Two thresholds were used on the normalized inverse logarithmic scaled ZTE dataset to

segment images into three classes: air, soft-tissue, and bone. A linear correlation between inverse log-scaled ZTE and CT signal has been observed for HU between −300 and 1500 HU (corresponding to soft-tissue and bone). Sekine et al employed the ZTE method proposed by Wiseinger et al and evaluated its utility in PET MRAC[27]. Continuous attenuation values were assigned to the bone-tissue using a linear regression between CT and ZTE MR values. A fixed attenuation value was assigned to soft tissue. The relative errors and absolute relative errors were −0.09% and 1.77%.

Summary

In summary, direct imaging methods utilize MR images acquired using Dixon, UTE or ZTE images to derive PET AC maps without atlas alignment and complex pseudo-CT generation. The proposed methods can be roughly classified into two sub-groups: segmentation-only and segmentation+MR-CT conversion. The pros and cons of several representative methods in each sub-group are summarized in Table 2. The direct imaging methods are fast and can account for patient variability. However, the direct imaging can be negatively impacted by image artifacts. Dixon images are very quick to acquire (<20 seconds). However, since it does not provide bone information, large errors are expected, especially in brain or pelvic PET imaging. It usually take several minutes to acquire UTE or ZTE images. Both of UTE and ZTE can be used for bone segmentation. However, the direct imaging with segmentation only methods under-represent the continuous electron density in PET attenuation correction. Direct imaging methods with segmentation and continuous LAC value conversion can achieve PET AC accuracy on par with the atlas based MRAC. This class of method relies on direct UTE or ZTE MR imaging for tissue segmentation and a conversion using either DUTE R2* or the inverse of logarithm of ZTE signal to CT HU for continuous LAC values in bone. Since the MR-to-CT conversion is predefined, these methods are much faster than the atlas based method. These methods can account for individual subject variations better than the atlas based methods. Of note, the MR-to-CT conversion relationship are potentially sequence and scanner dependent. For example, DUTE R2* computation might depends on the employed TEs. A water-fat in-phase or out-of-phase TE for the second echo might yield different R2*. The ZTE signal may vary from scanner to scanner. A consistent imaging protocol is needed. Given the published results, we recommend the segmentation + MR-CT conversion methods over the segmentation only methods for their improved accuracy at a minimal additional computation cost.

Conclusions

PET/MR attenuation correction have been extensively pursued, especially for brain imaging in the past several years. A summary of the atlas and direct imaging based methods is provided in Table 3.

Atlas based methods have shown high accuracy and robustness in adult brain PET AC. In atlas based methods, continuous LACs are available and the population averaged information provide robustness to imaging artifacts and noise. However, atlas based approaches cannot account for inter-subject variations. Since age, gender and race can impact bone thickness and density significantly, a single atlas based CT estimation may not

be adequate for all patients[51]. Separate MR-CT pair database is needed for AC in children. Because the inter-subject image registration of whole body is very difficult, atlas based MR-AC in the body may not be as successful as that in brain. Finally, the complex computation makes atlas based methods time consuming.

Direct imaging based methods can account for variations across patients. They can be easily translated to whole body. These methods can be directly applied to any age group, including children. μ map generation is rapid. Due to imaging noise and artifacts, they are not as robust as the atlas based method. Direct imaging with segmentation only approaches have large AC errors due to discrete LAC values. The direct imaging with segmentation and MR-CT conversion address this problem and have improved PET AC accuracy.

Regional variations of AC errors are observed. Cortical region and regions near the skull base usually demonstrate larger errors. Caution needs to be used when interpreting results in these regions. Future technical development should focus on challenging brain skull regions and whole body MRAC. Clinical evaluation across vendors and centers are also needed.

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KEY POINTS

- Atlas and direct imaging based methods are two major categories of MR based PET/MR attenuation correction (AC).
- Atlas based methods are accurate and robustness in brain PET AC.; however, atlas based approach cannot account for inter-subject variations and is time consuming.
- Direct imaging based MRAC methods are rapid and can account for variations across patients.
- Direct imaging with segmentation only approaches have large AC errors due to discrete linear attenuation coefficient linear attenuation coefficient values.
- Direct imaging with segmentation and MR-CT conversion has similar PET AC accuracy as the atlas based MRAC.

Table 1

Pros and Cons of the atlas based methods

	Voxel Based	Patch Based	Machine Learning
REFERENCES	18,31,32	19,33,35,36	17,38,40–42
PROS	Simple and quick	Account for neighborhood	Inter-subject registration is not crucial
	Low computational cost	Less subjective to registration inaccuracy	Quick in applying trained relationship
CONS	Highly depends on image registration accuracy	Computational intense and time consuming	Computational intense and time consuming in training
	Cannot handle patient specific variability	Cannot handle patient specific variability	Cannot handle patient specific variability

Table 2

Pros and Cons of the direct imaging based methods

	Segmentation only	**Segmentation+MR-CT coversion**
REFERENCES	21,23,24,30,43	25,28,29,47
PROS	Quick and low computational cost	Quick and low computational cost
	Account for patient specific variability	Account for patient specific variability
	No need for image registration	No[25,29,47] or simple[28] image registration
		Continuous LAC in bone
CONS	No continuous LACs	Possible Sequence and scanner dependent conversion relationship
	Subjective to image noise and artifacts	Subjective to image noise and artifacts

Table 3

Summary of atlas based and direct imaging based PET attenuation correction

	Atlas based	Direct Imaging (segmentation only)	Direct imaging (Segmentation+MR-CT conversion
Relative PET Error (whole brain)	<3%	5–20%	<3%
Robustness	high	Low	Low
Continuous LACs	Yes	No	Yes
Whole body applicable	Difficult	Yes	Yes
Pediatric applicable	Need separate pediatric atlas	Yes	Yes
Abnormal anatomy	No	Yes	Yes
Speed	Minutes-hours	Seconds	Seconds