PET/MR attenuation correction: where have we come from and where are we going?

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PET/MR attenuation correction: where do we come from and where are we going

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The advent of clinical multimodality imaging with the development of Positron Emission Tomography (PET) / Computed Tomography (CT) scanners [1] has presented us with ample opportunities in harvesting the benefits of combining functional and anatomical imaging. These benefits concern improved PET quantitative accuracy, overall patient management (improved diagnostic accuracy and therapy response assessment), but also increased patient throughput. It is indeed this latter point that has substantially contributed to the rapid acceptance of PET/CT imaging in clinical practice eclipsing PET only systems. Indeed one of the major reasons behind the improved patient throughput achieved with PET/CT has been the use of CT images for the attenuation correction (AC) of the acquired PET emission datasets. Within this context CT images possess two desirable properties. Firstly, CT acquisitions are very fast, removing the need for long radionuclide based transmission imaging that was traditionally used in PET (~50% of the overall acquisition times). Secondly, CT intensity values represent the attenuation properties of the tissues in the imaging field of view, albeit at X-ray photon energies. The necessary transformation of CT images into attenuation maps at 511keV can be obtained through a bilinear transformation [2]. Although such a transformation represents a certain approximation, CT based AC of PET datasets using such attenuation maps has been shown to lead to the same level of quantitative accuracy and superior contrast in the reconstructed PET images compared to radionuclide based transmission scanning [3].

In the last couple of years clinical PET/MR devices have become reality and the first results concerning their potential interest in terms of patient management are beginning to emerge. Different issues however persist with respect to the quantitative accuracy of this new modality, concerning in particular the question of PET attenuation correction based on the use of MR derived attenuation maps. A recent study published in this journal clearly reinforces these issues for neurological imaging [4]. In contrast to CT imaging, MRI does not provide direct information concerning tissue attenuation properties and as such there is no direct way to obtain the required information for PET attenuation correction purposes. Most of the approaches currently proposed in clinical PET/MR systems for PET AC are based on the combination of specific MR sequences and subsequent image segmentation.

Amongst them the approach implemented in the first generation of clinical systems is based on the two-point Dixon gradient echo sequence [5]. This sequence, which involves a few seconds of acquisition time, allows the separation of water and fat tissue by using the chemical shift of fat relative to water. This information facilitates in turn the segmentation of MR images in four to five different classes (lung, fat tissue, non-fat tissue, mixture of fat/non-fat tissue, air) [6]. One has to highlight that once segmented, fixed 511keV linear attenuation coefficients (LACs) are assigned to each of the considered tissue types, largely ignoring tissue heterogeneities. However, the biggest drawback of this approach is the lack for consideration of bone structures which are considered as soft tissue for the purpose of reconstructing PET AC maps. As such the use of this approach may introduce severe quantitative errors depending clearly on the location of the region of interest. In terms of quantitative accuracy it is generally accepted that the inclusion of bone in the attenuation correction of brain PET images is essential. On the other hand, the inclusion of bone structures in whole body imaging introduces quantitative errors mostly in the case of osseous lesions. Compared to CT based attenuation correction in whole body PET/MR imaging standardised uptake value (SUV) underestimation may vary from few percent up to 30% depending not only on the lesion location but also on the composition of bone lesions [7]. This result further highlights the need for using a continuous scale in the LACs rather than a fixed value assigned in segmented tissue regions. In the case of brain imaging, a recent publication in EJNMMI [4] has also shown variable mean regional activity concentration underestimation of 10%-22% compared to CT based attenuation correction, with the smaller differences measured in structures such as the striatum, thalamus and hippocampus.

In order to account and improve the overall accuracy of segmentation based attenuation correction, more recent implementations of PET AC in clinical PET/MR consider the use of an ultrashort echo time (UTE) sequence [8]. UTE sequences have been proposed in MRI for the visualisation of bone which has a very short spin-spin relaxation time T2. UTE based attenuation correction involves acquisitions at two echo times; one visualising bone while the signal for other tissue types is the same in both images. Different methodologies have been subsequently proposed in order to provide a three tissue class (air, soft tissue, bone) segmentation approach for PET AC [9] or alternatively use a triple-echo sequence combining UTE and Dixon

to distinguish four tissue classes (air, soft tissue, bone, fat tissue) [10]. These approaches have been almost exclusively evaluated in brain imaging showing mean activity concentration differences in the entire brain of ~5% relative to CT based AC, although maximum differences could be up to 20-40% [8,9,10]. Similarly, a more detailed study on a region by region basis, considering 25 FDG PET brain patients, has shown that despite a decrease in the measured mean activity underestimation resulting from the use of a three tissue class UTE based approach compared to Dixon based AC, there are still substantial underestimations compared to CT based AC. These differences (up to an average of 20%) were also region dependent, with the worst results at the level of the cerebellum which is located at the level of sinuses, where the mixture of air, soft tissue and bone structures represents a substantial challenge for all approaches, including UTE. In general terms average percentage differences of 10%-15% relative to CT based AC were measured in the frontal, temporal and parietal lobes. This regional variability in the measured differences throughout the brain is a clear issue for neurological applications. Furthermore, there seems to be a lack of standardisation with respect to the UTE protocols for AC currently in use both in terms of overall acquisition times and selection of individual parameters. On the other hand, there are only few reports on the use of UTE sequences in whole body MR imaging, since its application is hampered by long acquisition times and field inhomogeneities associated with an extended field of view. Therefore the extension of this approach for whole body imaging represents real challenges.

There is therefore a clear need for improved AC in PET/MR not only for neurological but also whole body imaging applications. This improvement should be both in terms of accuracy in determining the spatial extent of the structures of interest but also in the use of attenuation maps with continuous LACs. There are different approaches based on the use of atlas combined with machine learning techniques that have been proposed in order to improve both of these aspects. The basic idea behind these approaches is to explore a database of paired CT and MR patient images. These images in combination with the acquired MR datasets for a given patient are subsequently used in order to derive a patient specific pseudo-CT map. Another advantage for these approaches is that in principle can provide attenuation maps with continuous LACs, eliminating issues associated with the use of single tissue

values that do not account for tissue heterogeneities. Different MR sequences can be considered in the MR-CT paired datasets used in the atlas in order to improve the overall accuracy of the identified structures of interest. One of these approaches uses a combination of atlas derived information and pattern recognition to obtain patient specific pseudo-CT maps [11]. This approach has been evaluated in brain images showing average activity concentration differences of <4% relative to CT based AC in different brain areas without reporting on inter-regional differences. A clear issue with any atlas based approach for brain and whole body applications is the accurate handling of pathology, inter-patient lung density variations, or the presence of metallic implants. In an attempt to improve overall robustness, a modified version of this same approach including atlas based artefacts detection, has been more recently applied to whole body imaging leading to mean activity underestimations of <6% [12]. Variants of this approach consider the use of multiple MR sequences in order to better identify different tissues classes and hence improve the overall atlas registration process and the subsequent pseudo-CT prediction model [13,14]. Although such alternatives have been only tested on brain imaging, since they mostly use UTE sequences, they are clearly associated with longer MR acquisition times which may compromise their clinical utility in PET/MR. What is currently missing is large scale clinical evaluation studies for these atlas and machine learning approaches in order to clearly demonstrate their robustness with respect to the presence of anatomical abnormalities which are largely patient specific and as such hard to account for in any atlas based approach.

One has to finally consider the truncation issues associated with MR based attenuation correction maps which can be important in whole body imaging given that the patients are scanned arms down due to multiple practical issues. Different solutions have already been implemented on current generation PET/MR devices based either on information from uncorrected PET images [15] or using a modified iterative maximum likelihood reconstruction of attenuation and activity (MLAA) for estimating the missing part of the attenuation map from the PET emission data [16]. Despite the lack of resolution in bone structures in the arms, both approaches have been reported to reduce errors to <5%, but clearly larger scale clinical studies are necessary to demonstrate their performance and associated robustness in clinical

practice. On the other hand, both approaches will clearly benefit from time of flight (ToF) information improving further their accuracy.

An alternative that has more recently emerged is the use of non-MR information for PET AC in PET/MR. The first such approach is based on the use of transmission scanning within the PET/MR device [17], using radionuclide sources and the acquisition of both emission and transmission datasets during the PET acquisition. In order to be able to carry out such simultaneous acquisitions the PET device requires ToF capabilities. Although theoretically feasible, the question of limited space available with combined PET/MR devices poses certain associated engineering challenges for the clinical implementation of such an approach, which may therefore be more appropriate for sequential PET/MR systems only. The second option is based on purely exploring information inherent in the acquired PET emission datasets about tissue attenuation without the need for any explicit transmission data acquisition. If one assumes that the true emission data distribution is known there will be only a single attenuation map that can be consistent with that emission distribution and can be therefore estimated. However, the problem is poorly determined and as such previous attempts have led to poor results with emission data structures contained in the estimated attenuation correction maps. More recently Defrise et al [18] have demonstrated that the spatial constraints provided by the ToF information in the emission datasets may allow a more robust exploitation of the consistency conditions in order to determine the attenuation images from the acquired emission datasets. Despite the fact that current devices are limited in terms of ToF resolution to 400-500ps, this study has also shown that this ToF resolution is sufficient to obtain good results for clinical applications. Although this initial proof of principle work was performed in 2D using an analytical algorithm, current studies in this active field are concentrating on an extension to 3D and the use of iterative algorithms that allows better noise modelling [19].

In conclusion, the development of combined PET/MR devices has brought to the forefront of scientific interest the issue of PET attenuation correction, after CT largely contributed to its solution in multimodality PET/CT imaging. Current clinical AC implementations are moving towards the inclusion of bone structures which are clearly essential in quantitative neurological PET imaging, in principle one of the

flagship applications of PET/MR. However, substantial quantitative differences compared to CT based AC persist, which appear to be also region dependent with the largest differences in areas at the vicinity of dense bone and/or a substantial mixture of bone, air and soft tissue. There is now clearly a need for larger patient population studies with protocol standardisation in the MR sequence parameters used in order to further evaluate these latest developments for quantitative brain imaging in clinical practice. Atlas and machine learning approaches offer the possibility to correct for AC including bone structures both in brain and whole body PET/MR applications. However, these approaches need also to be further assessed in clinical practice in order to demonstrate their robustness to different patient specific pathology types. Finally, the calculation of attenuation maps directly from emission datasets is the most promising solution for future ToF based PET/MR devices.

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