Optimal Reconstruction Algorithms for High-Resolution Positron Emission Tomography

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9.1 Summary

The ECAT High Resolution Research Tomograph (HRRT) is a dedicated human brain positron emission tomography (PET) scanner, with design features that enable high image spatial resolution combined with high sensitivity. The HRRT is the first commercially available scanner that utilizes a double layer of LSO/LYSO crystals to achieve photon detection with depth-of-interaction information. At present, iterative reconstruction methods are the method of choice for reconstructing HRRT studies. However, the currently available 3D iterative reconstruction algorithms, i.e. ordinary Poisson ordered subsets expectation maximization (OP-OSEM) and attenuation and normalization weighted OSEM (ANW-OSEM), show bias in short time frames due to non-negativity constraints. Consequently, implementation of analytical 3D filtered backprojection (3D-FBP) is of interest. To apply 3D-FBP, however, all missing data due to gaps between detector heads need to be estimated. Further improvements in HRRT image reconstruction might be expected using a new method of variance reduction on randoms (VRR), in which random events are estimated based on coincidence histograms instead of a delayed window technique (DW). In previous studies, new iterative reconstruction algorithms such as shifted Poisson OSEM (SP-OSEM) and ordered subsets weighted least squares (OSWLS) showed promising results in bias reduction compared with OP-OSEM reconstruction, which is currently recommended by the supplier of the scanner. In this thesis, quantitative accuracy of various 3D iterative reconstruction and correction methods for the HRRT were assessed. The correction methods primarily concerned different random estimation techniques and attenuation correction methods. Quantitative accuracy was assessed directly using both phantom and patient data. In addition, impact on pharmacokinetic analyses was assessed. Finally, performance of the HRRT was compared directly to that of a standard clinical whole body PET scanner (ECAT EXACT HR+).

In **chapter 2**, performance of the commercial LSO/LYSO HRRT was characterised, using the NEMA NU-2 2001 and 1994 protocols as guidelines. Apart from measuring spatial resolution, energy resolution, sensitivity, scatter fraction, count rate performance, attenuation and scatter corrections, hot spot recovery and image quality, a clinical evaluation was performed by comparing brain scans with those acquired on a standard clinical scanner (ECAT EXACT HR+). Point source resolution varied across the FOV from approximately 2.3 to 3.2 mm (full width at half maximum, FWHM) in trans-axial direction and from 2.5 to 3.4 mm in axial direction. Absolute line source sensitivity ranged from 2.5 to 3.3% and the NEMA-2001 scatter fraction was 45%. Maximum NECR was 45 kcps and 148 kcps according the NEMA NU-2 2001 and 1994 protocols, respectively. Attenuation and scatter correction led to a volume uniformity of 6.3% and a system uniformity of 3.1%. Reconstructed values deviated up to 15 and 8% in regions with high and low count densities, respectively, which possibly can be attributed to inaccuracies in scatter estimation. Hot spot recovery ranged from

60 to 94% for spheres with diameters of 1 to 2.2 cm. High quantitative agreement was met between HR+ and HRRT clinical data. In conclusion, the ECAT HRRT has excellent resolution and sensitivity properties, which is an important advantage in many research studies involving smaller brain structures.

In **chapter 3**, quantitative accuracy of different attenuation correction strategies, presently available for the HRRT, was investigated. These attenuation correction methods differ in reconstruction and processing (segmentation) algorithms used for generating μ-images from measured 2D transmission scans, an intermediate step in the generation of 3D attenuation correction factors. Available methods are maximum-*a-posteriori* reconstruction (MAP-TR), unweighted OSEM (UW-OSEM) and NEC-TR, which transforms sinogram values back to their noise equivalent counts to restore Poisson distribution. All methods can be applied with or without μ-image segmentation. However, for MAP-TR a μ-histogram is *a prior* during reconstruction. All possible strategies were evaluated using phantoms of various sizes, simulating preclinical and clinical situations. Furthermore, accuracy of various attenuation correction strategies was studied in case the transmission scan was contaminated contamination by residual (emission) activity. Finally, accuracy of various attenuation corrections strategies and its relative impact on reconstructed activity concentrations were evaluated using small animal and human brain studies. For small structures, MAP-TR with human brain priors showed smaller differences in μ-values for transmission scans with and without emission contamination ($< 8\%$) than the other methods ($< 26\%$). In addition, it showed the best agreement with true activity concentrations (deviation $< 4.5\%$). A specific prior designed to take into account the presence of small animal fixation devices improved activity concentration slightly to 4.3%. All methods scaled μ-values of a large homogeneous phantom to within 4% of the water peak, but MAP-TR provided most accurate activity concentration after reconstruction. However, for clinical data MAP-TR overestimated the thickness of the skull when using default prior settings, resulting in overestimations of μ-values in regions near the skull and thus in incorrect activity concentrations. NEC-TR with segmentation or MAP-TR with an adjusted human brain prior showed less overestimation in both skull thickness and activity concentrations for these structures and are therefore the recommended methods for human brain studies.

In **chapter 4**, various gap filling strategies for 3D-FBP reconstructions of HRRT data were investigated, such as linear and bilinear interpolation or constraint Fourier space gap filling (confosp). Furthermore, missing planes were estimated using segment 0 image data only (non-iterative) or by using reconstructed images based on all previous segments (iterative method). Use of bilinear interpolation showed the worst correspondence between reconstructed and true activity concentrations, especially for small structures. Moreover, phantom data indicated that linear interpolation resulted in artifacts in planes located near the edge of the field-of-view. Use of confosp did not show these artifacts. Iterative estimations of missing planes for all segments except segment 0 improved image quality at the cost of more computation time. Therefore, use of confosp for filling sinogram gaps with both iterative and non-iterative estimation

of missing planes are recommended for quantitative 3D-FBP reconstructions of HRRT studies.

In **chapter 5**, a new randoms estimation method, called VRR, in combination with 3D-OP-OSEM and 3D-FBP reconstruction techniques was evaluated. Obtained results were compared with reconstructions in which randoms were estimated using the routinely used DW method. For most phantom studies, 3D-OP-OSEM showed higher accuracy of observed activity concentrations with VRR than with DW. However, both positive and negative deviations in reconstructed activity concentrations and large bias in grey to white matter contrast ratios (up to 88%) were still observed as function of scan statistics. Moreover, compared with 3D-FBP+VRR, 3D-OP-OSEM+VRR also showed bias up to 64% in some pharmacokinetic parameters derived from clinical data. In case of 3D-FBP, VRR showed similar results as DW for both phantom and clinical data, except that VRR resulted in better standard deviations of 6–10%. Therefore, VRR should be used to correct for randoms in HRRT studies.

In **chapter 6**, the use of image derived input functions (IDIF) as an alternative for arterial sampling for HRRT human brain studies was validated. To this end, IDIFs were extracted from 3D OP-OSEM and reconstruction based partial volume corrected (PVC) OP-OSEM images. IDIFs, either derived directly from regions of interest or further calibrated using manual samples taken during scans, were evaluated for dynamic [^{11}C]flumazenil data (n = 6). Results obtained with IDIFs were compared with those obtained using blood sampler input functions (BSIF). These comparisons included areas under the curve (AUC) for peak (0–3.3 min) and tail (3.3–55.0 min). In addition, slope, intercept and Pearson's correlation coefficient of tracer kinetic analysis results based on IDIF and BSIF were calculated for each subject. Good peak AUC ratios (0.83±0.21) between IDIF and BSIF were found for calibrated IDIFs extracted from OP-OSEM images. This combination of IDIFs and images also provided good slope values (1.07±0.11). Improved resolution, as obtained with PVC OP-OSEM, changed AUC ratios to 1.14±0.35 and, for tracer kinetic analysis, slopes changed to 0.95±0.13, showing the advantage of the high resolution of the HRRT scanner itself, with little additional value of PVC OP-OSEM. For all reconstructions, non-calibrated IDIFs gave poorer results (>61±34% higher slopes) compared with calibrated IDIFs, indicating that calibration is necessary for IDIFs derived from HRRT scans to compensate for quantification errors in low count regions due to inaccuracies of the scatter correction algorithm. Bias in iterative reconstruction techniques might also be of influence in obtaining correct IDIFs. Although manual samples were still necessary, these are needed anyway for calculating plasma to whole blood ratios and metabolite fractions. In summary, the feasibility of deriving accurate IDIFs from dynamic HRRT studies was demonstrated.

In **chapter 7**, quantitative accuracy of various 3D iterative reconstruction algorithms in comparison with 3D filtered backprojection (3D-FBP) was evaluated. ANW-OSEM, OP-OSEM, SP-OSEM and OSWLS methods were implemented on the HRRT. In order to study the various 3D iterative reconstruction techniques quantitatively, several phantoms and a human brain study (n = 5)

were performed and analysed. OSWLS showed low and almost linearly increasing coefficients of variation (SD divided by average activity concentration) with decreasing noise equivalent count (NEC) rates. In decay studies, OSWLS also showed good agreement with 3D-FBP grey (GM) to white (WM) matter contrast ratios (within 4%), while OP-OSEM and SP-OSEM showed agreement within 6 and 7%, respectively. For various frame durations, both SP-OSEM and OP-OSEM showed the smallest errors in GM to WM contrast ratios, varying 75% between different NEC rates. This variability was much higher for the other iterative methods (>92%). 3D-FBP showed least variability (34%). Visually, OSWLS hardly showed any artefacts in parametric images and agreement well with 3D-FBP data for parametric images, especially in case of reference tissue kinetic methods (slope: 1.02, Pearson's correlation coefficient: 0.99). OP-OSEM, SP-OSEM and OSWLS showed good performance for phantom studies. In addition, OSWLS showed better results for parametric analyses of clinical studies and it is therefore recommended for quantitative HRRT brain studies.

In **chapter 8**, quantitative accuracy of the HRRT was compared with that of a clinical HR+ scanner. In addition, effects of differences in spatial resolution between both scanners (~2.7 mm and 7 mm for HRRT and HR+, respectively) were assessed. This assessment was performed by paired [^{11}C]flumazenil scans in 7 healthy volunteers. For each volunteer, dynamic scans (including arterial sampling) were acquired on both scanners on the same day, thereby minimising intersubject variability. Volume of distribution (V_T) was generated using Logan plot analysis with plasma input. In addition, other plasma input, reference tissue (with pons as reference tissue) and parametric methods were included in this interscanner comparison. Logan V_T analysis of HRRT data showed higher values than those of HR+ data (slope with intercept fixed at origin of 1.14±0.10 to 1.19±0.10, depending on the HRRT reconstruction method used). Smoothing HRRT reconstructions with a 6 mm full width at half maximum Gaussian kernel reduced this slope towards the line of identity (1.04±0.11 to 1.07±0.11), retaining good correlation between HR+ and HRRT data (r: ~0.98). Similar trends were observed for other plasma input, reference tissue and parametric methods. However, the reference tissue models showed lower HRRT kinetic parameter values after resolution matching than for the HR+ (slope with fixed intercept: 0.90±0.10 to 0.94±0.13). The higher values of pharmacokinetic parameter values with the HRRT scanner indicate improved quantification primarily because of a reduction in partial volume effects.

In conclusion, attenuation and randoms correction methods for the HRRT are very accurate. Analytical 3D-FBP reconstructions in combination with constraint Fourier space gap filling can accurately predict activity concentrations in HRRT studies, but still show high noise levels. In contrast, 3D iterative reconstruction techniques for the HRRT result in bias in short frames, which are typical for the early phase of a dynamic scan. Nevertheless, accurate image derived input functions can be obtained, which can be attributed to the high spatial resolution of the HRRT. In summary, even with presently available software, the HRRT has excellent spatial resolution, sensitivity and reconstruction properties, with clinical results that are similar to those obtained with the

HR+ scanner when resolution is matched. As the HRRT can be operated at a much higher spatial resolution, results for smaller structures will be more accurate and, therefore, the HRRT should be the scanner of choice for human brain studies.

9.2 Future perspectives

Although dynamic HRRT brain studies were reasonably accurate, as compared with HR+ brain studies, further improvements are still needed to obtain accurate reference tissue values and to obviate the need for calibrating image derived plasma input functions. Systematic bias is still observed in short frames reconstructed with 3D iterative reconstruction algorithms. This systematic bias might be removed by using iterative reconstruction algorithms that allow both negative sinogram and image values, such as OP-OSEM in combination with either the NEG-ML algorithm (NEG-OP) [18, 124] or the lower bounded AB-OSEM (AB-OP) [19]. For some studies, additional anatomical information is known from MRI or CT scans (ideally from a hybrid scanner). Using this *a-priori* anatomical information, maximum *a-posteriori* (MAP) reconstructions [125] could be used to reduce partial volume effects and/or reduce the level of noise. Third, OSEM and OSWLS reconstruction algorithms can incorporate information about the spatial image resolution of the scanner to reduce partial volume effects [101], which may be important for correct estimation of IDIFs [99], especially in small animal imaging. Although already characterised for clinical studies, the use of different OSEM and OSWLS strategies, either with or without partial volume corrections, should also be investigated and validated for small animal studies. Finally, kinetic modelling typically is performed after image reconstruction. Application of kinetic models during image reconstruction (using intermediate smoothing) might also benefit quantitative accuracy of high-resolution PET imaging. These models could either be used as update functions in OSEM-based reconstructions or they could be used on the raw data to create parameter sinograms that can be used for image reconstruction [126, 127]. Although previously some studies were performed using mainly linear models, most of these methods need further improvement and validation, especially for the HRRT.