Quantification and Kinetic Analysis of Brain PET Studies
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Chapter 7

Summary, general discussion and future perspectives
7.1 Summary

In this thesis various quantitative aspects of positron emission tomography (PET) studies were assessed. The first part investigated some PET instrumentation related aspects, focussing mainly on the performance of a high resolution brain PET scanner, the High-Resolution Research Tomograph (HRRT). This performance evaluation was followed by an assessment of the impact of analysis methods, reconstruction settings and repositioning on the quantification of oncology and brain PET studies. Finally, an optimal pharmacokinetic model was developed for analysis of $^{11}$Cphenytoin studies in humans.

More specifically, in Chapter 2, a direct comparison between HRRT (high-resolution brain) and HR+ (standard whole-body) PET only scanners for quantitative brain studies using three tracers with vastly different tracer distributions was performed. After resolution matching, HRRT-derived kinetic parameter values correlated well with those of HR+ for all tracers (intra-class correlation coefficients $\geq 0.78$), having a good absolute inter-scanner test-retest variability ($\leq 15\%$). However, systematic differences can be seen for HRRT-derived kinetic parameter values (range $-13$ to $+15\%$). Quantification of kinetic parameters based on plasma-input models leads to comparable results when spatial resolution between HRRT and HR+ data is matched. When using reference-tissue models, differences remain that are likely caused by differences in attenuation and scatter corrections and/or image reconstruction.

In Chapter 3, the impact of different scatter correction strategies on quantification of HRRT data for three tracers covering a wide range in kinetic profiles were evaluated. To reduce the effects of patient motion on scatter scaling factors, a margin in the attenuation correction factor (ACF) sinogram was applied prior to 2D or 3D single scatter simulation (SSS). Some ($R$-$[^{11}]C$verapamil studies showed prominent artefacts that disappeared with an ACF-margin of $10\ mm$ or more. Use of 3D SSS for ($R$-$[^{11}]C$verapamil showed a statistically significant increase in volume of distribution compared with 2D SSS ($p<0.05$), but not for $[^{11}]C$raclopride and $[^{11}]C$flumazenil studies ($p>0.05$). When there is a patient motion-induced mismatch between transmission and emission scans, applying an ACF-margin resulted in more reliable scatter scaling factors but did not change (and/or deteriorate) quantification.

Chapter 4 describes the assessment of PET/CT repeatability dependencies on reconstruction settings, analysis methods, scan duration (or image noise) and phantom position in the field of view (FOV). In this study, multiple (repeated) scans have been performed using a $^{68}$Ge uniformity phantom, a NEMA image quality (IQ) phantom and a 3D Hoffman brain phantom filled with $^{18}$F solution. Studies were performed with and without repositioning the phantom and all scans (12 replicates for IQ phantom and 10 replicates for Hoffman brain phantom) were performed using equal count statistics. For the $^{68}$Ge uniformity phantom, the coefficient of variation (COV$\%$) and variance of the voxel values across the phantom were studied as function of scan statistics and reconstruction settings. For the NEMA IQ phan-
tom we studied the maximum, peak and mean recovery coefficients (RC) in each sphere as function of experimental conditions (noise level, reconstruction settings and phantom repositioning). For the 3D Hoffman phantom the mean activity concentration was determined within several volumes of interest and activity recovery and its precision was studied as function of experimental conditions. As a result, we found that for all phantom studies voxel noise (expressed by variance and COV) and repeatability of RC (RC$_{\text{max}}$ or RC$_{\text{mean}}$) depended on reconstruction settings and frame duration, as expected. When exploring RC$_{\text{max}}$, RC$_{\text{peak}}$ or RC$_{\text{mean}}$ of the spheres in the NEMA IQ phantom, it was observed that repeatability depended largely on phantom position, with RC$_{\text{max}}$ being most (up to 30%, $p<0.05$) and RC$_{\text{peak}}$ being least (up to 9%, $p>0.05$) sensitive to phantom repositioning. Moreover, impact of phantom repositioning on SUV metrics also depended on sphere size. For the brain phantom, regional average activity concentrations or RC were only minimally affected by phantom repositioning (<5% repeatability). The repeatability of quantitative PET metrics depends on the combination of reconstruction settings, data analysis methods and scan duration (scan statistics). Moreover, repeatability was also affected by phantom repositioning but its impact depended largely on the data analysis method (max, peak or mean) being used. In conclusion, the study suggests that for oncological PET studies use of SUV$_{\text{peak}}$ may be preferred over SUV$_{\text{max}}$ because SUV$_{\text{peak}}$ seems less sensitive to patient positioning/tumor sampling effects.

Chapter 5 describes the assessment of an optimal plasma kinetic model for quantification of a novel P-glycoprotein (Pgp) tracer, $[^{11}\text{C}]$phenytoin. Overexpression of Pgp is thought to be an important mechanism of pharmacoresistance in epilepsy. Recently, $[^{11}\text{C}]$phenytoin has been evaluated preclinically as a tracer for Pgp. The aim of the study was to assess the optimal plasma kinetic model for quantification of $[^{11}\text{C}]$phenytoin studies in humans using non-linear regression (NLR) analysis of time activity curves. Dynamic $[^{11}\text{C}]$phenytoin PET scans of 6 healthy volunteers with arterial sampling were acquired twice on the same day and analyzed using single- and 2-tissue-compartment models with and without a blood volume parameter. Global and regional test–retest (TRT) variability was determined for both plasma to tissue rate constant ($K_1$) and volume of distribution ($V_T$). According to the Akaike information criterion, the reversible single-tissue-compartment model with blood volume parameter was the preferred plasma input model. Mean TRT variability ranged from 1.5% to 16.9% for $K_1$ and from 0.5% to 5.8% for $V_T$. Larger VOI showed better repeatabilities than smaller regions. A 45 min scan provided essentially the same $K_1$ and $V_T$ values as a 60 min scan. A reversible single-tissue-compartment model with blood volume seems to be a good candidate model for quantification of dynamic $[^{11}\text{C}]$phenytoin studies. Scan duration may be reduced to 45 min without notable loss of accuracy and precision of both $K_1$ and $V_T$, although this still needs to be confirmed under pathologic conditions.

In Chapter 6, the performance of various methods for generating quantitative parametric
images of dynamic $^{[11]C}$phenytoin PET studies were evaluated. Parametric images were generated using Logan plot analysis, a basis function method (BFM) and spectral analysis (SA). Parametric $V_T$ and $K_1$ were compared to those obtained from NLR. In addition, global and regional TRT variability was determined for parametric $K_1$ and $V_T$ values. Biases in $V_T$ observed with all parametric methods were less than 5%, For $K_1$, SA showed negative bias of 16%. Mean TRT variabilities of $V_T$ and $K_1$ were less than 10% for all methods. Shortening the scan duration to 45 min provided similar $V_T$ and $K_1$ with comparable TRT performance compared to 60 min data. Among the various parametric methods tested, BFM provided parametric $V_T$ and $K_1$ values with the least bias compared to NLR data and showed TRT variabilities lower than 5%, also for smaller VOI sizes (i.e. higher noise levels) and shorter scan duration.

### 7.2 General discussions and future perspectives

The first part of this thesis compared the performance of HRRT scanner to the HR+ scanner using three different tracers with vastly different tracer distributions. The HRRT has a higher intrinsic spatial resolution compared to HR+ which results in smaller partial-volume errors than seen in the clinical PET system (HR+). Even though quantification of the HRRT scanner is comparable to HR+, there is still a room for improvement in reconstruction (settings), and attenuation and scatter correction, especially for quantification based on reference tissue models. The HRRT is no longer commercially available. Nevertheless, the findings and recommended improvements to the software may also be applicable to the more modern clinical multimodality PET scanners, e.g. PET/CT and PET/MRI. As research is aimed at improving the spatial resolution of PET scanners, the acquired data will likely be sparse and, consequently, may suffer from bias using iterative reconstructions with non-negativity constraints. In addition, since bone tissue cannot easily be accounted for during MRI-based attenuation correction, PET/MRI quantification may be hampered in the vicinity of the skull. Therefore, validating modern PET systems against more quantitatively robust PET systems using clinical studies with various tracer distributions is of utmost importance, particularly for quantitative studies.

When there is a mismatch between transmission and emission scans due to patient motion, applying an ACF-margin results in more reliable scatter scaling factors but does not change (and/or deteriorate) quantification. Current and future state-of-the-art clinical PET/CT systems may be equally sensitive to inaccurate scatter scaling factors (e.g. due to patient motion) when an SSS algorithm is used, which is similar to that currently in use for the HRRT. Therefore, a relatively easy to implement, fast and low cost method, such as the one presented here, to avoid scatter scaling issues when low levels of patient motion are present is relevant for all PET systems.
As for the HRRT, there are various alternatives to the current tail-fitting SSS algorithm for estimating scatter. An accurate way to estimate scatter would be to perform a full Monte Carlo (MC) simulation. However, such a method may be computationally expensive. Recently, a new hybrid scatter correction strategy has been proposed for PET/CT studies to overcome scatter scaling issues due to incorrect tail fitting. This method uses SSS to approximate the shape of the scatter contribution but scales it based on a low-count MC simulation. Although initial results are promising, MC-SSS is sensitive to outside FOV scatter as well, since it estimates the scatter scaling factor per bed position (i.e. not plane by plane). Another promising new alternative avoiding spatial mismatch between emission and transmission data and thereby scatter scaling issue is the use of the so-called maximum likelihood for activity and attenuation (MLAA) reconstruction algorithm. MLAA is a promising reconstruction algorithm that could enable future time-of-flight (TOF) PET/CT and PET/MR scanners to estimate attenuation and scatter without the need for a transmission scan. Furthermore, MLRR [33], a recent reconstruction algorithm that iteratively reconstructs the activity image while registering the available attenuation image, so that the pair of activity and attenuation images maximize the likelihood of the TOF emission sinogram, could also compensate for a patient-induced mismatch between transmission and emission data. Unfortunately, the HRRT is not capable of TOF measurements. Nevertheless, full MC simulations to estimate scatter and MC-SSS might be interesting to explore their capacity to further reduce bias that is still observed in HRRT reference tissue model studies.

In the study presented in chapter 4 increased bias and variation of data were seen when SUV\textsubscript{max} was used for regional assessment. The use of the maximum uptake value as a metric tends to have larger biases for the bigger spheres, both in TOF and TOF+PSF reconstructions. This findings indicate that more accurate and reliable tumour uptake quantification metrics are needed for studies in cancer patients. A drawback of this study is that only data from a single scanner were assessed, therefore more data are needed to compare the results with those from other systems. In addition, different scanner systems, acquisition protocols, and reconstruction settings may yield more variability and thus it requires a complete assessment of variability using multiple repositioned phantom scans at different sites, with different scanners and clinically used protocols.

[^11C]phenytoin has been developed to measure the Pgp up-regulation in epilepsy subjects [34]. This thesis describes a complete pharmacokinetic assessment of[^11C]phenytoin in order to find optimal kinetic analysis approach for such studies. The tracer shows promising results compared to other Pgp tracers such as (R)-[^11C]verapamil and[^11C]-N-desmethylloperamidethat are currently used in clinical studies [35, 36]. We found that[^11C]phenytoin provides a stable metabolism during the whole duration of the scan that is comparable between subjects. This provides the possibility for either the use of a plasma input function without additional metabolite analysis, or use of a population based correction for tracer metabolites. The tracer
has a relatively high $V_T$ in the brain with a low efflux ($k_2$) values when compared to other tracers such as $(R)$-[\(^{11}\)C]verapamil and \([^{11}\)C]-N-desmethylloperamide. Based on the findings in this thesis, it can be concluded that study time can be reduced without a notable loss of quantitative accuracy. The parametric methods showed pharmacokinetic values comparable to NLR. However, a future study should be performed to first validate the parametric methods for patients with epilepsy and subsequently compare the pharmacokinetic values between epilepsy patients and healthy subjects to investigate the clinical applicability of the tracer.


volumes of interest in human brain PET images using probability maps. Neuroimage. 24: 969-979


