8 Summary, general discussion and future perspectives

8.1 Summary

Positron emission tomography (PET) is an accurate technique for in vivo quantification of tissue function. PET tracers are molecules that are labelled with positron emitting radionuclides. The annihilation photons resulting from these decaying radionuclides can be detected accurately using PET and various physiological and pharmacokinetic parameters can be derived from the acquired data using tracer kinetic models. To date, various PET tracers are available for studying different tissue functions and there is an ongoing search for new tracers.

This thesis describes various methods for improving parameter estimation during pharmacokinetic analysis, such as various filtering techniques, the use of weighting factors and non-linear regression optimisation algorithms. Furthermore, in this thesis applicability of various pharmacokinetic models, together with simplified methods, was evaluated for tracers that play a role in the study of Parkinson’s disease ([\(^{18}\)F]FP-\(\beta\)-CIT) and Alzheimer’s disease ([\(^{18}\)F]FDDNP and [\(^{11}\)C]PIB).

Brain studies using PET are often concerned with detecting differences in neuroreceptor binding between subjects. Neuroreceptor binding is determined using a PET tracer which shows high affinity for that neuroreceptor. First, a dynamic PET scan is made, which are a series of consecutive PET scans, in order to accurately measure the tracer uptake and clearance. Next, for each anatomical region of interest, the average time activity curve is determined (TAC). Finally, TACs are analyzed using pharmacokinetic models in order to determine the pharmacokinetic parameters. During analysis, pharmacokinetic models are fitted to the TACs using non-linear regression. Non-linear regression algorithm adjusts iteratively the pharmacokinetic parameters until a best fit is found.
Pharmacokinetic models used in PET (brain) studies describe the tracer binding in mathematical terms. Pharmacokinetic models are highly simplified versions of reality and different simplifications are used for each tracer. The parameters of interest in these studies are the volume of distribution ($V_T$) and the binding potential ($BP_{ND}$). $V_T$ is the ratio of the tracer concentration in tissue relative to that in blood at equilibrium and $BP_{ND}$ is a measure of binding that takes into account both neuroreceptor density and affinity of the ligand for the receptor. In general, two main types of PET pharmacokinetic models can be identified: plasma input and reference tissue models. Plasma input models require accurate arterial blood sampling during a PET scan. Arterial plasma data are then used as input function for kinetic analysis. Reference tissue models do not require arterial sampling, but rather a reference region is used as input for the regions under study. A suitable reference tissue should be similar to the region under study, but be devoid of the receptors of interest. Reference tissue models avoid the need for arterial sampling and, therefore, are more patient friendly and better suited for routine clinical studies. However, the accuracy of reference tissue models for a new tracer needs to be evaluated by comparison with plasma input models. In this thesis the most common pharmacokinetic models were evaluated such as: single tissue (reversible) ($1T2k$), irreversible two-tissue ($2T3k$) and reversible two tissue ($2T4k$) plasma input models, together with simplified ($SRTM$) and full ($FRTM$) reference tissue models. $BP_{ND}$ is the pharmacokinetic parameter of interest for $SRTM$, $FRTM$ and (sometimes) $2T4k$, and $V_T$ for $1T2k$ and (usually) $2T4k$. The plasma input models can also be used to estimate $BP_{ND}$ indirectly, i.e. from the volume of distribution ratio ($DVR$), according to $BP_{ND} = DVR - 1$, where $DVR = \frac{V_{T,\text{target}}}{V_{T,\text{reference}}}$ . This indirectly estimated $BP_{ND}$ is comparable with $BP_{ND}$ obtained with the reference tissue models and requires the same assumptions for the reference tissue.

Most pharmacokinetic models are also available in linearised versions. Linearised models may be less accurate, but are much faster and more robust with respect to noise than their non-linear counterparts. Linearised models are therefore ideal for rapid evaluation of kinetic parameters across the brain (i.e. at the voxel level), in particular if it is not known where abnormalities in binding can be found or when tracer binding is so hetero-
geneous that abnormalities might be missed in an ROI analysis. For each application, however, accuracy of these linearised or simplified methods needs to be evaluated.

Finally, very simple semi-quantitative methods are available that can give a measure of the binding if tracer uptake has reached equilibrium. Although suffering from bias, these methods can also be useful for example in larger clinical trials or for routine clinical (e.g. diagnostic) use. In this thesis semi-quantitative methods, such as standardised uptake value ($SUV$) and $SUV$ normalized to that of the reference region ($SUV_r$), were evaluated.

All studies included simulations in order to evaluate pharmacokinetic models under fully controlled conditions, such as effects of variation in relative flow ($R_1 = K_{target}^{1}/K_{reference}^{1}$), fractional blood volume ($V_b$), binding potential ($BP_{ND}$), and TAC noise. These simulation studies are also important because it is the only way to determine accuracy and precision, as the true pharmacokinetic parameters in clinical data are unknown.

Chapter 2 describes the evaluation of the effects of pharmacokinetic analysis using incorrect weighting factors, the performance of optimisation algorithms commonly used in PET (i.e. interior-reflective Newton methods), and a newly developed simulated annealing (SA) based method. Only reversible plasma input models (i.e. $1T2k$ and $2T4k$) were investigated and data were taken from $[15O]H_2O$, $[11C]Flumazenil$ and $(R)-[11C]PK11195$ studies. SA is a method that automatically produces appropriate new starting parameters for repeated optimisation. Therefore, in contrast to the commonly used interior-reflective Newton method, SA was able to produce accurate results without the need for selecting appropriate starting values for (kinetic) parameters. The Newton method yielded biased results, unless it was modified to restart over a range of initial parameter estimates. For patient studies, where large variability can be expected, both SA and the extended Newton method provided accurate results. Small to intermediate mismatches between variance in data and weighting factors used did not significantly affect the outcome of the fits. Therefore approximately correct weighting models are required for good accuracy. It was concluded that selection of specific optimisation algorithms and weighting factors can have a large effect on the accuracy and precision of PET pharmacokinetic analyses.
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In chapter 3, improvements by wavelets based denoising of \( (R)-[^{11}C]PK11195 \) TACs are discussed. Wavelets allow for filtering frequency components at selected time intervals and could therefore be ideal for filtering TACs, because TAC noise levels are time dependent. In simulations, when using optimised settings, all wavelet filters tested reduced noise without biasing TACs. Furthermore, for both clinical and simulated data, plasma Logan \( V_T \) values increased after filtering. This increase in plasma Logan \( V_T \) suggests a reduction of noise-induced bias by wavelet based denoising, as was seen during simulations. However, after filtering, no improvements were seen for reference Logan \( DVR \) outcomes. Wavelet denoising of TACs for \( (R)-[^{11}C]PK11195 \) PET studies might therefore be especially useful when parametric Logan based \( V_T \) is the parameter of interest.

Chapter 4 describes a study on the quantification of \( [^{18}F]FP-\beta\text{-CIT} \), a tracer of the dopamine transporter used for human PET studies. Simulation studies showed poor fits (Akaike criterion) for plasma input models at typical noise levels (\( COV \sim 2.5\% \)) and scan durations (< 90 min). These poor fits are due to the relatively slow kinetics of \( [^{18}F]FP-\beta\text{-CIT} \), which approaches irreversible kinetics for short scan times. However, reference tissue models provided more reliable fits, which were nearly independent of noise and scan duration. Similar results were obtained in clinical studies. \( SRTM \) provided best discrimination between patients and controls. When differentiating between patients and controls, \( SUV_r \) performed almost equally well as \( SRTM \), although contrast between striatum and background was lower. Therefore, \( SRTM \) is the method of choice for quantitative \( [^{18}F]FP-\beta\text{-CIT} \) studies. \( SUV_r \), however, might be an alternative for larger clinical trials.

Chapter 5 describes a study on the quantification of \( [^{18}F]FDDNP \), a tracer of amyloid deposition. Blood data showed rapid metabolism of \( [^{18}F]FDDNP \), with a large number of polar metabolites being formed. Recently, it has been demonstrated that the latter metabolites may enter the brain and, therefore, they should be accounted for. To do so, evaluation of analytical methods included a modified \( 2T4k \) plasma input model with an additional compartment for metabolites (\( 2T1M \)). In clinical studies, based on the Akaike criterion, the \( 2T1M \) model was preferred over the standard \( 2T4k \) model. \( SRTM \) showed better correlation with \( 2T1M \) then with \( 2T4k \). Furthermore, in simulations, \( SRTM \) showed relatively
constant bias with best precision, even when it was assumed that metabolites could enter the brain. It was concluded that SRTM is the method of choice for quantitative analysis of $[^{18}\text{F}]$FDDNP studies, even if it is unclear whether labelled metabolites enter the brain.

In chapter 6 various reference tissue based parametric methods for improving quantification of $[^{11}\text{C}]$PIB studies are evaluated. The following parametric methods were evaluated: receptor parametric mapping (basis function implementation of the simplified reference tissue model with and without fixed $k'_2$), reference Logan, and several multi-linear reference tissue methods (again with and without fixed $k'_2$). In addition a semi-quantitative method, $SUV_r$, was evaluated. For clinical studies, most parametric methods showed comparable performance, with poorest results for $SUV_r$. Best performance was obtained for receptor parametric mapping ($RPM2$) and one of the multi-linear reference tissue models ($MRTM2$), both with fixed (reference tissue clearance constant) $k'_2$. $BP_{ND}$ was least affected by noise and generated images showed better contrast than with other methods. In addition, $RPM2$ and $MRTM2$ provided the most accurate and precise $BP_{ND}$ estimates. Therefore, $RPM2$ and $MRTM2$ are the methods of choice for parametric analysis of clinical $[^{11}\text{C}]$PIB studies.

Finally, in chapter 7 the evaluation of several parametric methods for improving quantification of $[^{18}\text{F}]$FDDNP studies is described. This study was similar in design to the $[^{11}\text{C}]$PIB study of the previous chapter. In clinical studies, again best performance was obtained using $RPM2$ and $MRTM2$. Both methods showed good correlation with SRTM, $BP_{ND}$ was least affected by noise and parametric images showed good contrast. Similar results were found in the simulations. Therefore, $RPM2$ and $MRTM2$ also are the methods of choice for parametric analysis of clinical $[^{18}\text{F}]$FDDNP studies.

8.2 General discussions and future perspectives

This thesis describes two studies in which various algorithms were evaluated for improving parameter estimation in general and that are of relevance for any PET tracer. The first study, evaluated various optimisation algorithms and schemes for weighting data. This study showed that
weighting factors and optimisation algorithms need to be selected carefully to obtain the highest possible accuracy for the derived pharmacokinetic parameters. Furthermore, a procedure for finding optimal non-linear TAC fits was defined. Subsequently, this procedure was used in all quantification studies described in this thesis and future studies should use similar methods to avoid poor quality fits. The second study evaluated different wavelet based filtering algorithms for denoising TAC. Only recently wavelet based filtering has been introduced into PET. In practice, wavelet based filtering may be difficult due to the many parameters that need to be optimized for each tracer. For example, in evaluating various available wavelet functions, large differences in the outcome were seen. In future studies an extensive evaluation of different existing wavelet functions together with novel wavelet functions to be designed specifically for PET TACs is needed, in order to achieve optimal separation of noise from the specific signal in the wavelet domain. As a specific example, it was shown that wavelet denoising of \((R)\text{-[}^{11}\text{C}]\text{PK11195 TACs}\) is useful when Logan based \(V_T\) is the parameter of interest. Logan analysis is one of the fastest methods for generating parametric \(V_T\) images, but it can suffer from noise induced bias. In this particular case, wavelet filtering reduce bias and improved accuracy. This type of filtering could also be useful for other tracers with relatively low cerebral uptake, because noise induced bias is a general problem of the plasma Logan method.[13, 55]

In previous \([^{18}\text{F}]\text{FP-}\beta\text{-CIT}\) and \([^{18}\text{F}]\text{FDDNP}\) studies, analyses were performed using either simple measures such as \(SUV\) or (parametric) reference tissue models without properly validating against a plasma input model. However, for new tracers such a validation is required to guarantee accurate quantification. This thesis describes a general approach for determining the most appropriate model, which was applied to \([^{18}\text{F}]\text{FP-}\beta\text{-CIT}, \ [^{11}\text{C}]\text{PIB}\) and \([^{18}\text{F}]\text{FDDNP}\) studies. This approach can be sub-divided into the following steps: (1) assessment of pharmacokinetic models that describe the underlying kinetic behaviour best, i.e. reversible models, irreversible models and the number of pharmacokinetic compartments and parameters to describe; (2) use of both clinical and simulated data to assess of accuracy and precision; (3) evaluation of accuracy and precision of reference tissue models against the optimal plasma input method in order to avoid arterial sampling; (4) assessment whether even simpler methods,
such as $SUV_r$, can be used. In addition to this general approach, some tracer specific analyses might be required, such as the analysis of the effects of the slow kinetics of $[^{18}F]$FP-$\beta$-CIT on outcome accuracy, and the effects of metabolites entering the brain for $[^{18}F]$FDDNP. Using this approach the most appropriate model for clinical use could be determined for all 3 ligands. Furthermore, simulations provided estimates of accuracy and precision under various conditions, such as metabolite levels in brain tissue, tracer delivery, level of binding, noise levels and scan duration. In the future, these procedures could be combined into an even more generalised approach by including linearised methods for irreversible binding and spectral analysis based methods.

In the study on quantification of $[^{18}F]$FP-$\beta$-CIT, both SRTM and $SUV_r$ were validated for use in larger future clinical trials in Parkinson’s disease. Both methods do not require arterial sampling, making studies less invasive. In addition, due to the longer half-life of $^{18}F$, $[^{18}F]$FP-$\beta$-CIT could be produced centrally and delivered to scanners in hospitals without an on-site cyclotron. To improve future studies, a more sensitive and a higher resolution scanner (such as the HRRT) is needed for better delineation of sub regions in the striatum. Furthermore, due to disease related movements, patient motion monitoring and correction techniques should be evaluated and implemented. Finally, $[^{18}F]$FP-$\beta$-CIT suffers from very slow tissue kinetics and a related tracer with faster kinetics would be advantageous for reducing scanning time.

Both $[^{11}C]$PIB and $[^{18}F]$FDDNP are rapidly metabolised in the human body. Consequently, a more extensive study is needed to investigating whether labelled metabolites enter brain tissue. If the metabolites do enter the brain than the increased number kinetic parameters would degrade the quantification, therefore new amyloid binding tracers would be necessary. Furthermore, so far receptor-ligand models have been used to analyse data. These models, however, have some limitations when used to quantify amyloid binding. A receptor ligand can bind to receptors without physical restrictions, only its selectivity to the receptor or competition with endogenous ligands can reduce its specific binding. However, in case of amyloid tracers, binding to the outer surface of the amyloid plaques is much easier than binding sites in the inner (shielded) core, reducing the effective binding seen with PET\cite{106}. Further evaluation of this potential
underestimation in binding is needed.

Overall, \textit{SRTM} is the best kinetic method for analysing both \(^{11}\text{C}\)PIB and \(^{18}\text{F}\)FDDNP scans and should be used in future studies. \(^{18}\text{F}\)FDDNP is less suited for diagnosing Alzheimer’s disease, but may be better for following disease progression, as shown elsewhere.[100] \(^{11}\text{C}\)PIB, on the other hand, is better suited for diagnosing AD.[108] Labelling with \(^{11}\text{C}\) makes distribution of PIB to remote scanners impossible. On the other hand, \(^{11}\text{C}\) labelled tracers are better suited for response studies than \(^{18}\text{F}\) labelled tracers, because of the lower radiation dose to the patient. Future amyloid tracers preferably should have low levels of non-specific binding, and limited peripheral metabolism with labelled metabolites not entering the brain. Ideally, such a tracer should be useful both for diagnosing Alzheimer’s disease at its earliest stage and for following disease progression, enabling monitoring the effects of novel treatment strategies.

Further optimisation of quantifying \(^{11}\text{C}\)PIB and \(^{18}\text{F}\)FDDNP studies focussed on parametric imaging. Most parametric methods are ‘linearised versions’ of the corresponding (non-linear) compartment model. These methods are much faster and less sensitive to noise than methods that are based on non-linear regression, usually at the cost of additional bias in the parameters of interest. Although most previous studies have used reference Logan to generate parametric images of \(^{11}\text{C}\)PIB and \(^{18}\text{F}\)FDDNP binding, this thesis has shown that this is not the optimal parametric method for these two tracers. For both tracers best accuracy and precision was obtained using \textit{RPM2} and \textit{MRTM2}, in which the efflux rate constant \(k'_{2}\) of the reference tissue is fixed to the median value obtained from a first run with free \(k'_{2}\).
Bibliography


Bibliography


[34] Thijssen, J.M., Computational Physics, Cambridge University Press, 1999


Bibliography


Bibliography


Bibliography


190
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191
Bibliography


