Chapter 1

General Introduction
1.1 Positron emission tomography (PET)

Positron emission tomography (PET) is a commonly used medical imaging technology for measuring organ and tissue metabolism or function, such as blood flow, oxygen use and glucose consumption. To perform a PET study, a radiotracer, which is a molecule of interest labelled with a positron emitting radionuclide, is administered to the patient. The emitted annihilation radiation, resulting from the positron emission, can be measured with a PET system. Finally, these acquired data are reconstructed into an image representing the distribution of the radiotracer within the body [1].

1.2 PET data acquisition principle

After the administration (either injection or inhalation) of a radiotracer, the decaying radionuclide emits a positron ($\beta^+$) that, after losing its kinetic energy, annihilates with an electron. Each annihilation produces a pair of 511 keV photons traveling in nearly opposite directions, and can be detected by the detectors in the PET system surrounding the subject. If both photons are detected, a coincidence will be recorded. The line connecting the detectors after a coincidence has been detected is called a line of response (LOR). State of the art PET scanners can also measure the difference in arrival time between both annihilation photons in order to calculate the position of the positron emission along the LOR with a certain accuracy. The use of this difference in arrival time of both annihilation photons for more accurate localisation of the positron emission is called time of flight (TOF). The coincidence detection resulting from these 2 annihilation photons is referred to as a true coincidence. However, in practice, not only true coincidences are detected. When ‘accidentally’ two photons from two simultaneously occurring but different positron emissions are detected a so-called random detection or random count is recorded. Moreover, if one or both annihilation photons are scattered within the body, mainly by Compton scattering, the photon loses energy and is deflected from its original path. The latter will result in an incorrect location of the LOR and a scattered coincidence is recorded. Scatter is also the main cause for photon attenuation resulting in a loss of possible coincidence detections. The effects from randoms, scatter and attenuation on PET data acquisition need to be accounted for during the PET acquisition and image reconstruction process in order to obtain quantitatively accurate PET images. Finally, the quantitative accuracy of PET images is affected by the limited spatial resolution of the PET system. The effects of the relative low spatial resolution (<4 to 5 mm full width at half maximum [FWHM] for clinical systems) is indicated as partial volume effects (PVE) and are more pronounced in small lesions and brain structures. Because of PVE, small brain structures and tumors with diameters less than 2 or 3 times the resolution (specified by
the full width at half maximum, FWHM) of the imaging system [2] show a negative bias in radiotracer uptake. In the next section some of the required corrections, relevant for this thesis, will be discussed in more detail.

1.3 PET image reconstruction

Image reconstruction is the process of generation an image representing the activity distribution (of the radiotracer) in the body from the measured projection (coincidence) data. The two most popular reconstruction algorithms for image reconstruction are filtered back-projection (FBP), an analytical algorithm, and ordered subsets expectation maximization (OSEM) [3], an iterative algorithm. Both reconstruction algorithms produce an image with different noise characteristics. OSEM produce higher signal to noise ratio (SNR) of the data compared to FBP [4–6]. As mentioned above latest generation of PET systems are able to capture TOF information. The inclusion of TOF information in the reconstruction process can improve image contrast, reduce the image acquisition time [7–9] and/or reduce patient radiation dose [10]. Moreover, the latest versions of image reconstruction methods include the scanner specific resolution model, expressed by the point spread function (PSF), thereby accounting for the limited spatial resolution of the system and reducing PVE. Incorporating both TOF and PSF into the PET image reconstruction proved to increase the accuracy of quantification in several studies [11–14]. However, it has been shown that it can also cause quantification errors due to Gibbs artefacts [15, 16].

1.3.1 Random and random correction in PET

Random coincidences occur when two photons with an energy of 511 keV from two different positron annihilation location are detected by a detector pair within the width of the time window. The contribution from random coincidences increases with activity. The most common method for correcting random coincidences is the subtraction of a randoms contribution estimate measure by the so-called delayed time window technique. Other methods used are e.g. smoothed delayed coincidences and randoms estimates that are calculated from single photon rates. Each method makes different trade-offs between noise amplification, bias, and data processing requirements [17].
1.3.2 Scatter correction in PET

When annihilation photons travel through the body, one or both photons can interact with tissue and, as a consequence, energy and direction may alter. If the deflected photons are then detected and registered as counts, this will be called a scatter event. Since the direction of the photon is changed during the scattering process, it is highly likely that the resulting coincidence event will result in a wrong LOR and thus would degrade the image quality. To reduce the impact of scatter in the final reconstructed image, several scatter correction methods have been proposed, such as the energy window based approach [18, 19] and the calculation of scatter distribution based on the single scatter simulation (SSS) method [20–22]. SSS only models the contribution of single scatter events (i.e. those that result from annihilation photon pairs in which a photon has been scattered only once before being detected) and typically uses tail fitting to estimate the amplitude of the modelled scatter data with the measured data. In 2D SSS only takes scatter coincidences in non-oblique imaging planes into account while 3D SSS takes also the oblique scatter into consideration.

1.3.3 Attenuation correction in PET

Photon attenuation is the loss of coincidence events through scatter or absorption of one or both of the annihilation photons in the body, which depends on tissue density. The attenuation of photons inside the body reduces the accuracy of reconstructed PET images. In order to correct for attenuation an attenuation map needs to be created that represents the spatial distribution of linear attenuation coefficients. The attenuation map is incorporated into PET reconstruction algorithm to correct the emission data for the errors that originate from photon attenuation.

Attenuation correction can be achieved with or without a transmission scan. Transmission less or free attenuation correction has been developed recently to estimate the attenuation sinogram in TOF PET using emission data only [23]. In contrast, transmission based methods require an external transmission scan such as computed tomography (CT) in PET/CT [24, 25], or a $^{137}$Cs point source or $^{68}$Ge rod source that rotates around the patient as in High-Resolution Research Tomography (HRRT; Siemens Healthcare, Knoxville, USA) and HR+ (Siemens Healthcare, Knoxville, USA) PET only scanners, respectively. In CT, different tissue densities correspond to different Hounsfield unit (HU) values that basically depend on the attenuation properties of the tissues. To derive a correct attenuation correction for the PET photons, scaling of the CT data is required to convert the data obtained using the energy spectra of CT and that obtained with the $^{137}$Cs point source to data corresponding to the (mono-energetic) 511 keV photons of PET.
1.4 PET quantification

After image reconstruction, while applying all corrections, an emission image is obtained where each voxel value quantitatively represents the activity concentration of the radiotracer. Quantitative PET studies can be performed in several ways, such as static and dynamic scans. A static scan is performed at a certain uptake time interval after tracer injection and provide the radiotracer concentration at that uptake time only, while a dynamic scan is typically started simultaneously with the tracer injection and measures the tracer uptake over an extended time, for example from 0 to 60 or 90 min p.i., depending on the radiotracer kinetics. Dynamic scans are made to follow the fate of the tracer in tissue over time and allow for full quantitative kinetic analysis of the PET study.

1.4.1 Segmentation of PET images

A typical first step for the quantification of radiotracer uptake is the segmentation or delineation of the structures of interest such as lesions or brain regions. Segmentation or delineation of e.g. brain structures or tumours may be performed manually or by using automated region definition methods such as threshold-based methods for tumours [26] or those based on human brain atlases [27, 28]. The latter generates volumes of interest (VOI) to delineate the anatomical structures of the brain with the help of MRI data. Once VOIs have been defined and projected onto the PET data information on the radiotracer concentration within that VOI can extracted from the PET data. In case of dynamic studies, PET data are collected sequentially over time and time activity curves (\(TAC_{\text{PET}}\)) are generated by projecting the VOIs on all image frames of the dynamic scan. The TAC represents the mean activity concentration within the VOI as function of the uptake time.

1.4.2 SUV based quantification

Standardized Uptake Value (SUV) is defined as the ratio between activity concentrations at a specific uptake time, in a voxel or the average value within the VOI, \(C_{\text{tissue}}\), and injected activity (\(C_{\text{inj}}\)) normalized to e.g. the subject weight, lean body mass or body surface area. Apart from the average SUV within a VOI other metrics such as the maximum SUV and peak SUV are being used and additional corrections, such as for plasma glucose levels may be applied.
1.4.3 Kinetic modelling and parametric method

Kinetic models can be used to mathematically describe the fate of the radiotracer in tissue. By performing kinetic analysis quantitative information on physiological processes, such as perfusion, or specific (binding) information can be obtained. Full kinetic analysis requires dynamic PET scanning to measure the temporal course of the tracer in tissue and a so-called arterial input function. The input function describes the radiotracer concentration in plasma over time and can be measured during the dynamic PET study by e.g. arterial sampling. The PET TAC is then fitted by a kinetic compartment model in combination with the input function. An example of a compartment model is given in Fig. 1.1, where each compartment represent the tracer in a certain physiological state. In Fig. 1.1, $C_p$, $C_f$, $C_b$ and $C_n$ are compartments for plasma, free, bound tracer and non-specific binding respectively. The transport parameters between the compartments are referred to as “rate constants”. $K_1$ is the plasma to tissue rate constant and it can be defined as the product between perfusion and first pass extraction has a unit of ml/min/ml. The $k_2$, $k_3$, $k_4$, $k_5$ and $k_6$ are kinetic rate constants and has min$^{-1}$ as unit. The distribution volume ($V_T$), net influx rate ($K_i$) and binding potential (BP) can be calculated from the estimated or fitted rate constants. Pharmacokinetic analysis is based on fitting a model to the tissue TAC measured with PET ($\text{TAC}_{\text{PET}}$) using e.g. non-linear least square (NLLS) fitting algorithms. The fitted model then provides information on individual compartments and rate constants. Various different models may be fitted to the data. The model that fits the data best can be identified using goodness of fit criteria such as the Akaike information criteria (AIC) [29].

![Figure 1.1](image).

**Figure 1.1** – Three tissue compartments model. The dashed line corresponds to what the PET system measures ($C_{PET}$).
1.4.4 Parametric method

Voxel by voxel analysis could be of interest when pharmacokinetic data at the highest possible spatial resolution is desired to explore uptake heterogeneity by voxel wise comparison on a subject group using statistical parametric mapping approaches. Voxel wise or parametric kinetic analysis requires (linearized) algorithms to cope with high noise levels and large amounts of calculations as typically an image contains millions of voxels. Typical or most common parametric methods are the Logan graphical analysis [30] providing estimates for $V_T$ and Patlak plots [31] providing the net influx rate from plasma ($K_i$). Other linearized parametric methods exist such as Spectral Analysis (SA) and Basis Function methods (BFM) [32]. The performance of the various different parametric methods depends on noise and tracer kinetics. Therefore, the applicability and accuracy of parametric methods need to be carefully evaluated before being used to analyse the PET studies.

1.5 Aim of the thesis

This thesis covers broad aspects of PET imaging, starting from optimizing PET instrumentation to the full quantitative assessment of a new tracer developed for clinical use. First, we compared the performance of two different PET systems for brain PET studies: one specifically developed for high-resolution human brain studies (Siemens HRRT) and one used clinically as human whole body scanner (Siemens HR+). In these studies we tried to optimize the performance of the HRRT scatter correction for several different tracers with vastly different kinetic behaviour. In addition, we experimentally studied the precision of PET data for a clinical PET/CT system (Philips Ingenuity TF), investigating effects of noise, data analysis methods, phantom repositioning, and reconstruction settings. Finally, the optimal pharmacokinetic model and parametric method for the quantification of a novel tracer, $[^{11}C]$phenytoin, were investigated.

1.6 Thesis outline

Chapter 2 compares the performance between HRRT and HR+ scanners for several quantitative brain studies using three tracers with vastly different tracer distributions, i.e. for $\text{(R)}-[^{11}C]$verapamil, $[^{11}C]$raclopride and $[^{11}C]$flumazenil. In chapter 3 we studied the impact of different scatter correction strategies on quantification of HRRT brain studies using three tracers covering a wide range in kinetic profiles. Errors in the scatter correction scaling caused by patient motion-induced mismatch between transmission and emission scans, could
be minimized by applying a spatial margin to the attenuation sinogram, resulting in more reliable scatter correction. In chapter 4 we investigated the impact of data analysis methods, image reconstruction settings, noise and phantom repositioning on the accuracy and precision of quantitative uptake metrics for an oncology/image quality and anthropomorphic brain phantom. Chapter 5 covers the assessment of an optimal plasma kinetic model for quantification of a novel tracer, $[^{11}\text{C}]$phenytoin. Next in chapter 6, the performance of various parametric methods for this novel tracer was evaluated. Finally, chapter 7 provides a summary of this thesis and discusses future research opportunities.