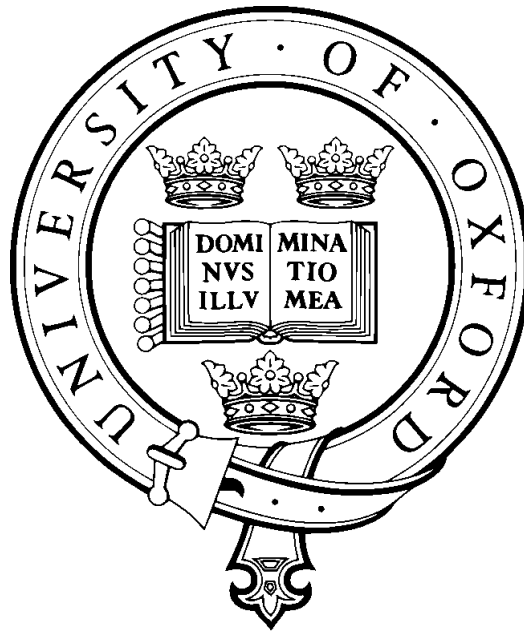


Spatio-temporal Registration of dynamic PET data



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This thesis is submitted to the Department of Engineering Science,
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degree of Doctor of Philosophy

Declaration

I declare that this thesis is entirely my own work, and except where otherwise stated, describes my own research.

Jieqing Jiao,
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Dedication

To the incredible four years in my life.

Abstract

Medical imaging plays an essential role in current clinical research and practice. Among the wealth of available imaging modalities, Positron Tomography Emission (PET) reveals functional processes *in vivo* by providing information on the interaction between a biological target and its tracer at the molecular level. A time series of PET images obtained from a dynamic scan depicts the spatio-temporal distribution of the PET tracer. Analysing the dynamic PET data then enables the quantification of the functional processes of interest for disease understanding and drug development. Given the time duration of a dynamic PET scan, which is usually 1-2 hours, any subject motion inevitably corrupts the tissue-to-voxel mapping during PET imaging, resulting in an unreliable analysis of the data for clinical decision making. Image registration has been applied to perform motion correction on misaligned dynamic PET frames, however, the current methods are solely based on spatial similarity. By ignoring the temporal changes due to PET tracer kinetics they can lead to inaccurate registration. In this thesis, a spatio-temporal registration framework of dynamic PET data is developed to overcome such limits. There are three scientific contributions made in this thesis. Firstly, the likelihood of dynamic PET data is formulated based on the generative model with both tracer kinetics and subject motion, providing a novel objective function. Secondly, the solution to the optimisation based on the generic plasma-input model is given, leading to the availability of a variety of biological targets. Thirdly, reference-input models are also incorporated to avoid blood sampling and thus extend the coverage of PET studies of the proposed framework. In the simulation-based validation, the proposed method achieves sub-voxel accuracy and its impact on clinical studies is evaluated on dopamine receptor data from an occupancy study, as well as breast cancer data from a reproducibility study. By successfully eliminating the motion artifacts as shown by visual inspection, the proposed method reduces the variability in clinical PET data and improves the confidence of deriving outcome measures on a study level. The motion correction algorithms developed in this thesis do not require any additional computational resources for a PET research centre, and they facilitate cost reduction by eliminating the need of acquiring extra PET scans in cases of motion corruption.

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Chapter 1

Introduction

This thesis is on the topic of dynamic positron emission tomography (PET) motion correction, which is one of the fundamental issues in PET imaging. Over the last three decades, the development of PET has provided scientists with a unique tool to investigate the functional activities of the human body *in vivo*, and commercial PET scanners have been used in clinical practice for improved diagnosis and therapy monitoring. More importantly, quantitative PET image data at the molecular level allow a new kind of "precision pharmacology", shedding light on a number of essential questions in drug development.

PET imaging is based on recording the spatial distribution of the molecule of interest labelled with a radioactive nuclide (tracer) following its intravenous injection into the subject. Each tracer has its own distinct behaviour *in vivo*, and the ever increasing library of these tracers allows for imaging of a range of biochemical, physiological and pharmacological processes. The tracer concentration changes over time due to the underlying physiology and biological processes. Quantification of the

biological process of interest is achieved by performing tracer kinetic modelling on the PET time activity data to determine the biological parameters of interest. The integrity and validity of PET data analyses is dependent on the accuracy of the time activity data, which can be corrupted by subject motion that alters the voxel-to-tissue mapping in a PET scan. The scan duration is usually one or two hours long, during which some subject motion is inevitable. Therefore, motion correction is of fundamental importance in PET imaging.

This thesis will present a novel dynamic PET motion correction method based on groupwise registration with the incorporation of kinetic modelling, in a spatio-temporal registration framework. Figure 1.1 outlines the thesis structure.

Following the introductory Chapter 2 on PET imaging and kinetic analysis, and Chapter 3 on the existing motion correction approaches, in Chapter 4 the framework of the proposed registration approach for PET motion correction will be described. Chapter 4 involves the incorporation of a plasma input based kinetic model into the groupwise image registration approach, and in Chapter 6 this framework is extended to incorporate reference input based models. The simulation based validation and clinical evaluation for both the plasma input and reference tissue input approaches are presented in Chapter 5 and Chapter 7 respectively. In Chapter 8 the overall contributions of this work, together with the future directions will be discussed.

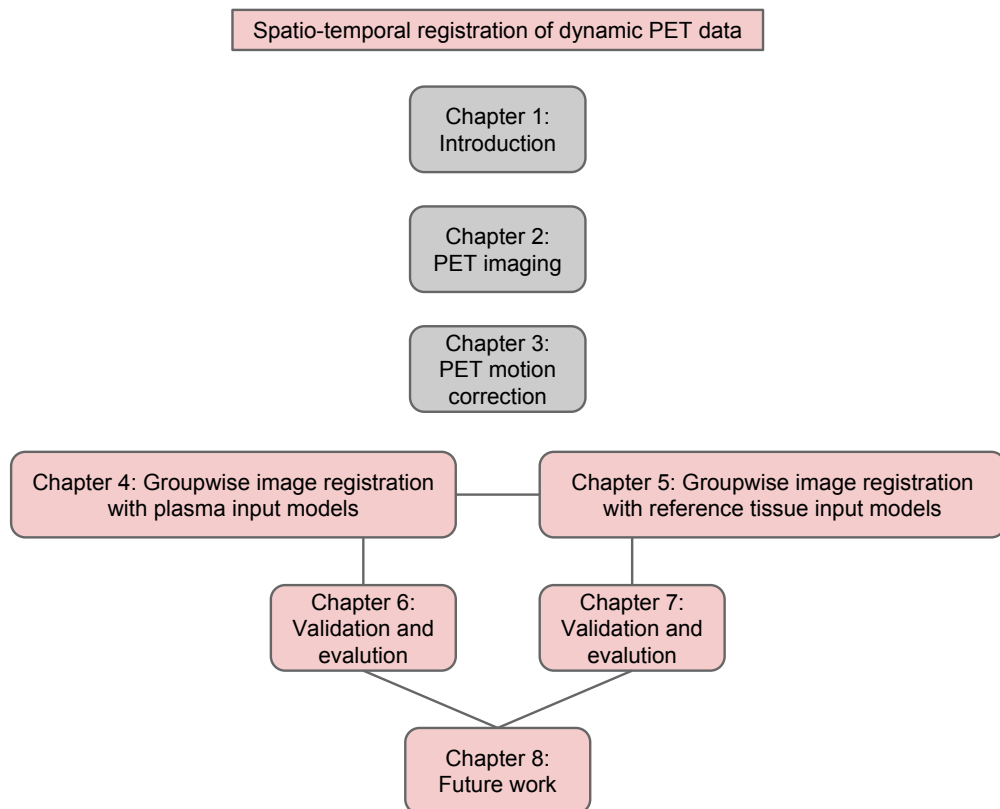


Figure 1.1: *Thesis structure.*

Chapter 2

PET imaging and applications

In this Chapter, the principles of PET imaging, the reconstruction of PET images will be firstly introduced. Then kinetic modelling of the dynamic PET data and the associated clinical applications will be presented.

2.1 Medical imaging techniques and basic concepts

Medical imaging is the technique and process of non-invasively producing images of the human body to provide *in vivo* anatomical or functional information for clinicians and medical scientists in disease understanding, diagnosis and therapy. There are various imaging modalities developed based on particular acquisition mechanisms, some of which are currently commercialised and used in both clinical and scientific practice, facilitating the measurement of disease processes and therapeutic development in humans. The principle is to collect a signal of how the human body reacts to an external stimulation. The spatial difference in the response from inside the body is contained within the collected signal, from which images can be reconstructed, with the inten-

sity variation corresponding to the spatial difference inside the body. The formed image can be of two dimensions (2D), three dimensions (3D) or four dimensions (4D) as a time sequence, dependent on the type of image acquisition. The basic element of a medical image is a voxel in a 3D volume (or pixel in 2D images), representing a single intensity value on a grid position. The size of the voxel is typically close in dimensions to the intrinsic resolution of the imaging device. The physical limitation of the imaging mechanism determines the intrinsic resolution that the modality can achieve. In practice, the resolution is also affected by the design of the instrumentation and its operation. A detailed introduction can be found in (Smith and Webb 2010).

Computed Tomography (CT) is the most common volumetric imaging modality that provides structural information (Kalender 2011). In a CT scan, X-rays, which are high energy electromagnetic radiation, are emitted and, when passing through the subject, attenuate due to absorption by the tissue. Therefore in a CT image the structures can be distinguished according to their capacity to attenuate X-ray. The typical resolution is $0.2mm$. A concern with the use of CT is the ionising radiation.

Magnetic Resonance Imaging (MRI) is another imaging technique that can provide anatomical information based on the phenomenon of nuclear magnetic resonance (Haacke et al. 1999). The intensity of a voxel in the image depends on the proton density, and also the inherent properties of the tissue which affect the relaxation times T_1 and T_2 for the protons. The stimulation originates from a magnetic field and thus carries a lower risk than the ionising radiation of CT and PET. MRI can also achieve sub- mm resolution and has excellent contrast in soft tissues, but its scan time is longer than CT. Another two tissue variables, namely flow and spectral

shifts, can also be used to construct images, as in functional MRI (fMRI), to measure the change in blood flow and in diffusion MRI, to measure water diffusion. With the injection of contrast agent which can change the proton relaxation times, dynamic contrast-enhanced MRI (DCE-MRI) is capable of imaging perfusion.

Positron Emission Tomography (PET) is a molecular imaging technique that can image functional processes in the body (Bailey et al. 2005). Molecules of interest are labelled with a short lived radioactive isotope that is injected into the subject, and the subsequent radioactive decay is monitored via external capture of co-linear gamma rays which then allows for image reconstruction of the molecules' spatial distribution. A key feature of PET imaging is its high sensitivity. However, the lower resolution and insufficient anatomical definition in PET images often require a complementary structural image to localise the activity. The combination of two imaging scanners within a single gantry had led to the recent development of PET/CT and PET/MRI scanning systems to achieve near simultaneous dual-modality scanning. As the photons also get absorbed by tissues like X-rays, the low dose CT scan along side is often used to correct PET attenuation before image reconstruction. Another drawback of PET imaging is that the scan time can be hours long due to the half-life time of the labelling isotope, leading to degraded image quality due to subject motion.

2.2 PET imaging: principles and measurements

Figure 2.1 provides a summary of dynamic PET imaging and data analysis, and each component will be introduced in this Section.

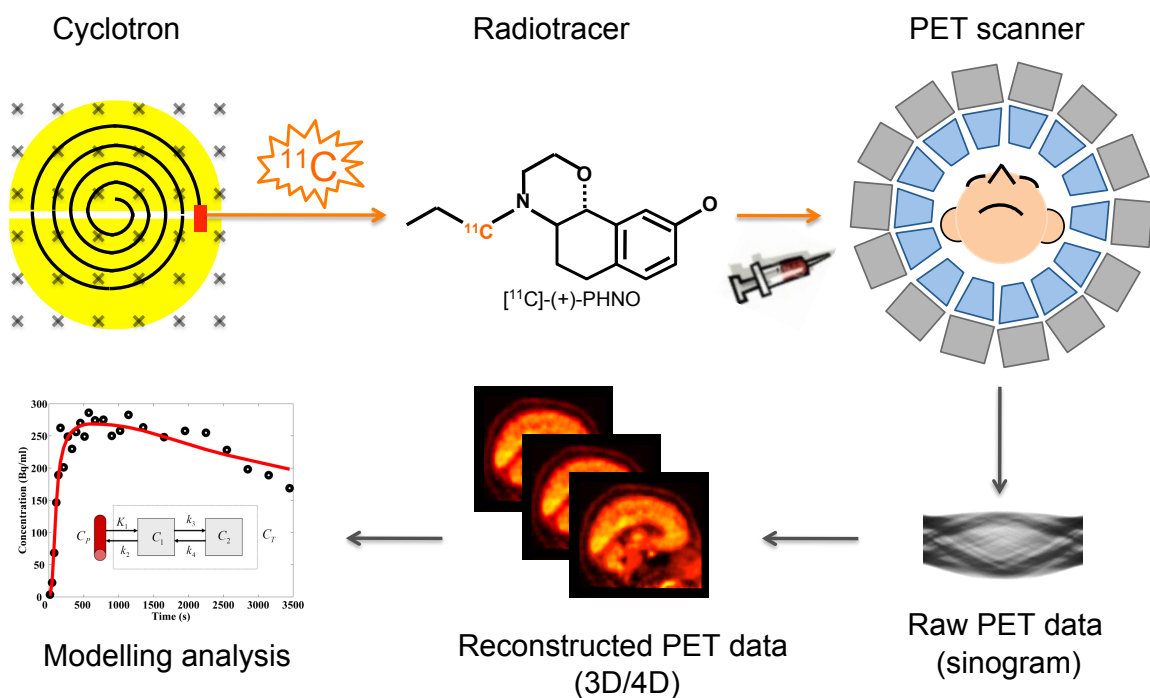


Figure 2.1: *Molecular imaging with PET*

2.2.1 The physical principle

The physics underlying positron emission tomography involves a radionuclide emitting, during decay, a positron which will annihilate with a nearby electron, to produce a pair of high energy photons (γ rays). The process of positron emission and subsequent positron-electron annihilation is described in Figure 2.2.

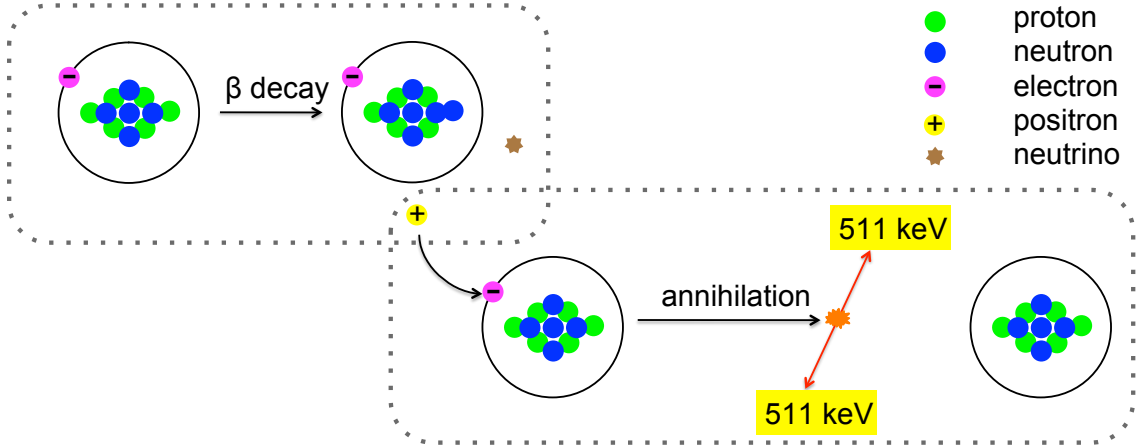


Figure 2.2: Positron emission and annihilation with a nearby electron leading to the production of two co-linear gamma rays.

In nuclear physics, there is a type of radioactive decay known as β decay during which a β particle (electron β^- or positron β^+) is emitted from an atomic nucleus to allow the atom to reach a stable ratio of protons and neutrons. In β^+ decay, or positron emission, the nucleus converts one proton into a neutron while emitting one positron and one electron neutrino:

$${}^A_Z N \rightarrow {}^A_{Z-1} N' + e^+ + \nu_e, \quad (2.1)$$

where e^+ and ν are positron and neutrino respectively.

In electron-rich tissue the emitted positron loses its kinetic energy rapidly (normally in the range of 10^{-1} to $10^{-2} cm$) due to the inelastic interaction with atomic electrons in the tissue (Cherry and Dahlbom 2006). This distance is a factor of uncertainty in determining the location of the radioactive decay. Once its kinetic energy is mostly dissipated, the positron will undergo with an electron a process known as annihilation when the mass of positron and electron converts into energy, in the form of

a pair of photons (γ rays). For the conservation of energy and near-zero momentum, the photons have the same energy of 511 keV and travel in opposite directions.

2.2.2 Radionuclides and PET tracers

Many radioisotopes decay with positron emission. For PET imaging to provide functional information, the radioactive isotope has to be coupled chemically with the biologically relevant molecule in order to be useful as a tracer. The commonly used radionuclides for PET imaging are listed in Table 2.1 along with their half-lives.

Table 2.1: *Radioactive isotopes used in PET imaging*

Radionuclide	Half-life
Oxygen 15 (^{15}O)	122sec
Nitrogen 13 (^{13}N)	10min
Carbon 11 (^{11}C)	20min
Fluorine 18 (^{18}F)	110min

The radioactivity levels drop by 50% within the time of the half life. Given their short half lives, the radioisotopes suitable for PET imaging are produced by a cyclotron. Normally a particular radioisotope allows for a PET scan of up to five times the duration of its half time. Therefore with a half life of 110min, ^{18}F is considered as the most convenient radioisotope, as it is possible to obtain the ^{18}F -labelled radio tracer from an off-site centralised manufacturer and have it delivered to the imaging facility, whereas other radioisotopes for PET imaging often require an on-site cyclotron to produce.

2.2.3 Photon detection and image reconstruction

The photon detection elements in a PET scanner are scintillators made of certain materials. A photon (γ ray) hits a scintillator and transfers part of its energy to the electron, and during ionisation and excitation, lower-energy photons are induced and then converted to an electrical signal by a photomultiplier tube (PMT) connected to the scintillator. This process typically takes place on a time scale of nanoseconds to microseconds. Currently inorganic scintillator materials are used, e.g. $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ (BGO) by GE Healthcare, $\text{Lu}_2\text{SiO}_5[\text{Ge}]$ (LSO) by Siemens, and $\text{Lu}_{1.8}\text{Y}_{0.2}\text{SiO}_5[\text{Ce}]$ (LYSO) by Philips (Moskal et al. 2013).

After the co-linear pair of photons are produced by annihilation, each photon travels through the subject's body before being detected by a PET scintillator. Due to the interaction between the photon and tissue, there are a number of factors that may degrade the measurement quality. The photon can change its direction of travel by colliding with electrons, an effect called Compton scattering. The photon may also lose its energy as it gets absorbed while passing through the subject's body due to attenuation. The magnitude of attenuation varies with the density of the material the photon has to pass through. Any high density anatomical areas such as bones lead to underestimated activity in the subject. Such effects can be corrected for in the reconstruction process.

The activity is reconstructed from raw PET data in the form of recorded events of photon detection. This is an inverse problem that determines the localisation of the annihilation (cause), given the measurement of emitted photons (effect). Mathematically it is not straightforward to solve. The collinearity of the photons produced in an annihilation event is used to localise the radioactivity. In a PET scanner the scin-

tillators are arranged to form concentric rings next to each other so that the photon pair can be detected by two PET scintillators on a line, called the line of response (LOR). There are two ways of determining the annihilation events by the radioactivity using LORs. Figure 2.3 illustrates the use of intersecting LORs for radioactivity localisation.

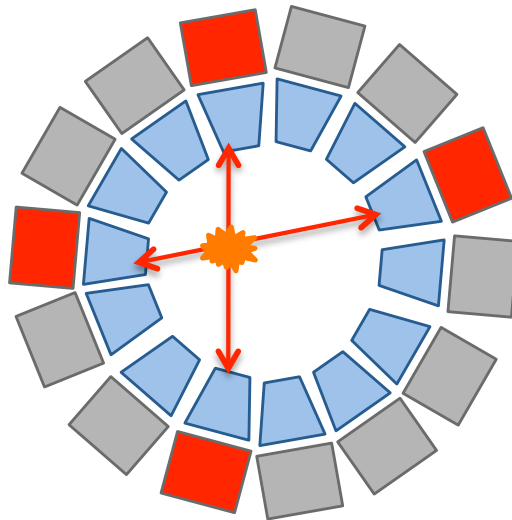


Figure 2.3: *Line of Response (LOR): the detection of near-collinear pairs of 511keV photons. Multiple LORs allow for the tomographic reconstruction of the annihilation events.*

The other way to localise the radioactivity is to use the difference in the arrival times of the pair of photons. After being emitted, the 511keV photon travels at the speed of light up to 30cm/ns , and if the time resolution of the system is sufficiently high, it is possible to determine on the LOR where the annihilation has happened based on the difference of photon arrival times, as illustrated by Figure 2.4. Time-of-Flight (ToF) PET systems have been developed over the recent years based on this concept. Currently there are systems with $< 300\text{ ps}$ time resolution. The full-width-at-half-maximum (FWHM) time resolution of two detectors in coincidence Δt

corresponds to the uncertainty in localising on the LOR Δx is $\Delta x = c^* \Delta t / 2$, where c^* is the photon speed.

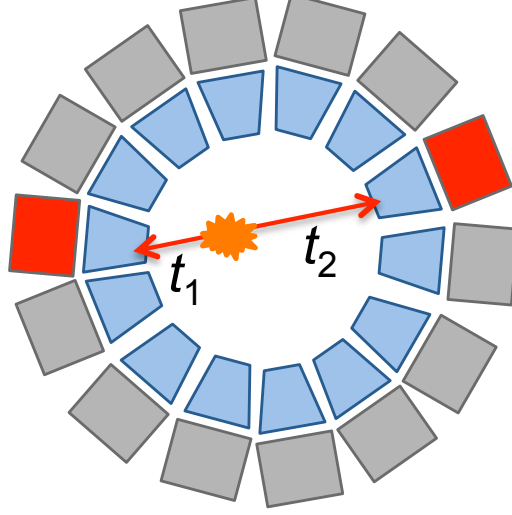


Figure 2.4: *Time-of-Flight (ToF): the determination of annihilation events based on the difference in times of arrival of the near-collinear pairs of 511keV photons.*

The raw data collected by a PET scanner is in the form of a list of coincidence events of detecting the annihilation photons within a time window of 6 – 12 nanoseconds by paired PET scintillators. The coincidence events can be grouped based on the LORs into projection images called sinograms. In a sinogram, each point represents a LOR, and the intensity indicates the number of annihilation photons detected on this LOR. If the activity distribution is known, the sinogram can easily be generated by performing a Radon transform. The three dimensional Radon transform is:

$$\mathcal{S}(\rho, \theta, \phi) = \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} I(x, y, z) \delta(\rho - x \cos \phi \sin \theta - y \sin \phi \sin \theta - z \cos \theta) dx dy dz, \quad (2.2)$$

where $I(x, y, z)$ is the activity in Cartesian coordinates (x, y, z) and $\mathcal{S}(\rho, \theta, \phi)$ is the sinogram intensity in, for example, spherical coordinates (ρ, θ, ϕ) , and δ stands for

the Dirac δ function. Figure 2.5 shows a two dimensional example of the sinogram generated from activity.

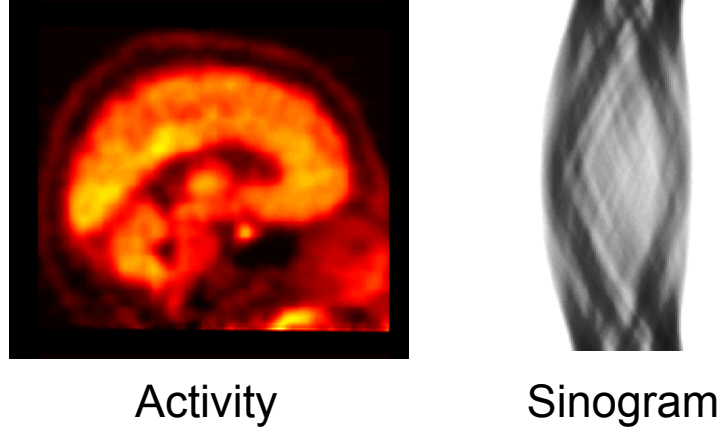


Figure 2.5: *Generation of sinogram from activity via Radon transform*

It is straightforward to see that, given the projection data $S(\rho, \theta, \phi)$, by performing the inverse Radon transform, the original activity $I(x, y, z)$ can be obtained. Filtered Backforward Projection (FBP) (Kinahan and Rogers 1989) is the analytical method that reconstructs the activity $I(x, y, z)$ based on this principle, with a filtering process in practice to cut off high frequencies to account for the Nyquist sampling theorem as the activity distribution is sampled with a finite width in the space. This filtering can lead to artefacts in the reconstructed PET image where the activity value is underestimated or even negative, especially at high contrast areas such as edges. Another drawback of FBP is that it treats the PET data deterministically and does not account for the measurement noise, resulting in streak artefacts. In addition it can be seen that FBP cannot be applied to ToF PET data.

Alternatively, statistical methods (Vardi et al. 1985; Leahy and Qi 2000) can be applied to address the variations during the image acquisition, by modelling and

maximising the likelihood function (probability) of the measured PET data.

The activity y can be resampled in space to facilitate discretising the reconstruction algorithm in practice, so that the radioactivity in the imaged volume can be approximated using a set of point sources spaced at j , $j = 1 \dots N_{vox}$ on a regular grid, as y_j . For each point source, the number of photons y_j observed over a given interval follows a Poisson process, and given the expected number of emissions $\bar{y}_j$, the probability of y_j is

$$p(\bar{y}_j, y_j) = \mathcal{P}(\bar{y}_j, y_j) = \frac{\bar{y}_j^{y_j} e^{-\bar{y}_j}}{y_j!} \quad (2.3)$$

For each detector i , the probability $\mathbf{P}_{i,j}$ of detecting the emissions y_j is determined by the geometry of the system and the attenuation in the imaged volume. Considering all voxels, based on the sum property of the Poisson distribution, the total photon counts in i follows a Poisson distribution with expected value

$$\bar{z}_i = \sum_{j=1}^{N_{vox}} \mathbf{P}_{i,j} \bar{y}_j \quad (2.4)$$

The probability of the system observing counts z given the activity y is

$$p(z|y) = \prod_{i=1}^{N_{det}} \mathcal{P}(\bar{z}_i, z_i) = \prod_{i=1}^{N_{det}} \mathcal{P}\left(\sum_{j=1}^{N_{vox}} \mathbf{P}_{i,j} \bar{y}_j, z_i\right) \quad (2.5)$$

where

i	-	index of the detector
j	-	index of the voxel
N_{det}	-	number of the detectors
N_{vox}	-	number of the voxels
y_j	-	activity in voxel j
z_i	-	observed counts in detector i
$\mathbf{P}_{i,j}$	-	probability of the photon emitted in voxel j is detected by the detector i .

The reconstruction of y can be then considered as a maximum likelihood problem (ML) to estimate z that maximises the system observation z , as

$$\hat{y} := \underset{y}{\operatorname{argmax}} p(z|y) \quad (2.6)$$

The expectation-maximisation (EM) algorithm gives an iterative solution as:

$$y_j^{(n+1)} = \frac{y_j^{(n)}}{\sum_{i=1}^{N_{det}} \mathbf{P}_{i,j}} \sum_{i=1}^{N_{det}} \mathbf{P}_{i,j} \frac{z_i}{\tilde{z}_i} \quad (2.7)$$

The matrix constructed by $\mathbf{P}_{i,j}$ is referred to as the system matrix. It possesses features of the Fisher information matrix. Corrections of the data due to for example attenuation and scattering can be accounted for in the system matrix.

2.3 Quantitative analysis of dynamic PET data

After injection, the radiotracer interacts with the biological target of interest. It should be noted that in PET studies there is the tracer assumption that the physiological processes and molecular interactions are not influenced by the PET tracer because it is administered at such low concentration that it does not perturb the system under investigation. Analysis of the process provides information directly reflecting the biological targets that are essential for disease understanding and drug development (Lassen and Perl 1979). In practice, dynamic PET data recorded over a period of time allow to capture this process to be measured and analysed. Typically, the raw PET data is rebinned into separate time frames to reconstruct PET temporal images individually, obtaining a four dimensional (4D) data set of the spatio-temporal distribution of the radiotracer. Then the kinetic analysis can be conducted either on a regional or voxel-wise basis for the time activity curves (TACs) extracted from the 4D PET data on a region or voxel of interest. Also, the kinetic analysis can be performed directly on the raw PET data during the reconstruction process, by modelling the activity using the kinetic parameters in the likelihood function (Matthews et al. 1997; Meikle et al. 1998; Tsoumpas et al. 2008).

Kinetic analysis involves applying mathematical models to fit the measured TACs. This kinetic modelling describes how radiotracer concentration changes over time due to the underlying biochemical/physiological process, and by fitting the model, parameters that quantify this process are thus estimated.

2.3.1 PET kinetic modelling

PET measures the concentration time course of radioactive tracer in the subject. This allows the measurement of a specific biochemical or pharmacological function by analysing the relationship between the input data from blood and the output PET data, as shown in Figure 2.6. Note that for the tracer in blood, only the fraction that is in the plasma is able to transfer into the tissue, and participate in the process of interest if not metabolised. Therefore from here on the tracer concentration in plasma with metabolism correction $C_P(t)$ is used to represent the blood input.

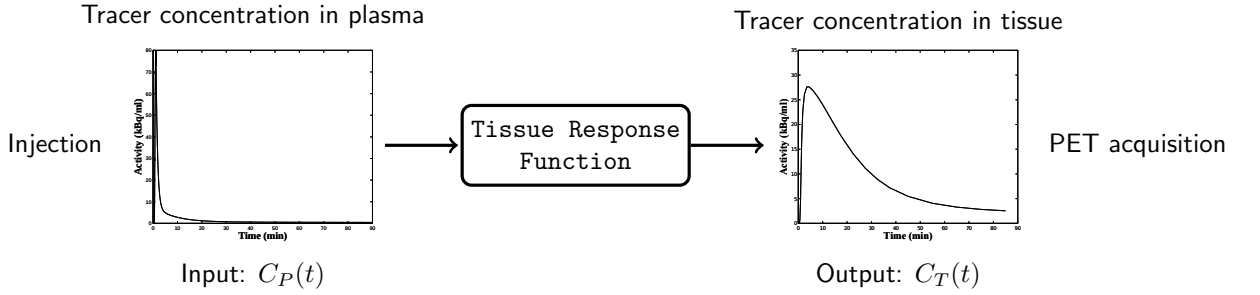


Figure 2.6: *PET measurement as a function of the plasma input function and the tissue response function*

Compartmental system

The response of the tissue to the injected tracer in plasma is characterised by the underlying biochemical or physiological function. The functional processes can be captured mathematically by describing the tracer kinetic behaviour using a compartmental system. A compartmental system is constructed from a series of interacting compartments (Landaw, DiStefano, et al. 1984). Each individual compartment is considered as a homogeneous well mixed entity with possible influx and efflux of

tracer between itself and other compartments in the overall system. For PET tracer-tissue interaction, the tissue compartments are distinct by the tracer's status in the tissue, such as being free, non-specifically bound, specifically bound or a combination thereof. For tracer systems, the concentration of the radiotracer is low enough not to disturb the underlying biology, and the transfer of tracer between compartments in the system is determined by rate constants, which describes the rate at which the tracer transitions between the compartments. With the simultaneous measurement of the dynamic tracer concentrations in plasma and tissue, a compartmental model can be constructed to characterise the relationship between them.

In this thesis the majority of the work will focus around using radioligands to quantify receptors in the brain and thus the description of compartmental models in the following is presented within the context of this biology.

One-tissue compartment model (1TC)

The simplest compartment model (Kety and Schmidt 1948) is illustrated in Figure 2.7. It comprises the plasma input, and one tissue compartment where the tracer exchanges so rapidly between the free (F), non-specifically bound (NS) and specifically bound (SP) compartments such that the individual compartments are not kinetically distinguishable.

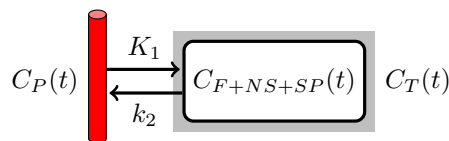


Figure 2.7: *One-tissue compartment model (1TC)*

Considering the conservation of mass, time differential equations can be written

as:

$$\begin{aligned}\frac{dC_{F+NS+SP}(t)}{dt} &= K_1 C_P(t) - k_2 C_{F+NS+SP}(t) \\ C_T(t) &= C_{F+NS+SP}(t)\end{aligned}\tag{2.8}$$

The system variables are defined as:

t	- time
$C_P(t)$	- tracer plasma concentration
$C_T(t)$	- tracer concentration in tissue - the PET tomographic measurement
$C_{F+NS+SP}(t)$	- free, non-specifically bound, specifically bound tracer concentration in tissue
K_1	- rate constant from plasma to tissue
k_2	- rate constant from tissue to plasma

Specific binding and multi-compartment model

In the clinical application of these radiotracers, it is the quantification of the specific binding which is the most important endpoint as this is the purpose for which these tracers are developed. The specific binding is determined by tracer-target interaction in the functional process, such as the receptor binding in neurotransmitter systems. For some tracers the kinetics between the free and bound compartments are slow enough such that a separate compartment for specific binding is distinguishable. Under these conditions, this can lead to the need for a two-tissue compartment (2TC)

model (Mintun et al. 1984) which is depicted in Figure 2.8.

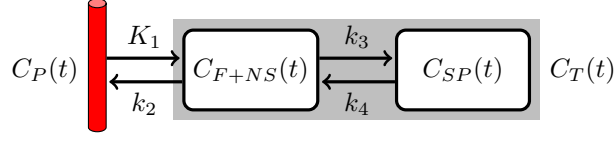


Figure 2.8: *Two-tissue compartment model (2TC)*

The differential equation system is correspondingly derived as:

$$\begin{aligned} \frac{dC_{F+NS}(t)}{dt} &= K_1 C_P(t) - (k_2 + k_3) C_{F+NS}(t) + k_4 C_{SP}(t) \\ \frac{dC_{SP}(t)}{dt} &= k_3 C_{F+NS}(t) - k_4 C_{SP}(t) \\ C_T(t) &= C_{F+NS}(t) + C_{SP}(t) \end{aligned} \quad (2.9)$$

where

- $C_{F+NS}(t)$ - tracer concentration in the non-displaceable compartment
(sum of free and non-specifically bound tracer)
- $C_{SP}(t)$ - specifically bound tracer concentration in tissue
concentration in tissue
- k_3 - rate constant from the non-displaceable to the specifically
bound compartment
- k_4 - rate constant from the specifically bound to the non-displaceable
compartment

Note that, when specific binding is present, due to the tracer-target interaction, the tracer behaviour can be reversible when the transport rate from the specifically

bound compartment is not zero ($k_4 \neq 0$), or the tracer behaviour is irreversible where $k_4 = 0$. In practice, for ligand-receptor binding one would always expect some level of reversibility with the ligand able to dissociate from the receptor, however, it may be that the off rate to dissociate is so slow when compared to the duration of the imaging session (up to 2 hours) that it is effectively zero.

From the two-tissue compartment model, if in addition the kinetics between the free and non-specifically bound compartment are kinetically distinguishable as well, then this leads to a three-tissue compartment configuration (3TC) (Mintun et al. 1984) which is depicted in Figure 2.9.

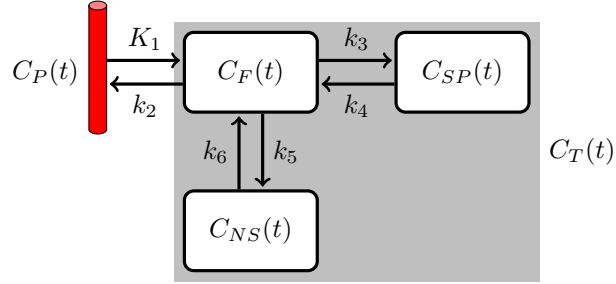


Figure 2.9: *Three-tissue compartment model (3TC)*

The associated differential equation system then becomes:

$$\begin{aligned}
 \frac{dC_F(t)}{dt} &= K_1 C_P(t) - (k_2 + k_3 + k_5) C_F(t) + k_4 C_{SP}(t) + k_6 C_{NS}(t) \\
 \frac{dC_{SP}(t)}{dt} &= k_3 C_F(t) - k_4 C_{SP}(t) \\
 \frac{dC_{NS}(t)}{dt} &= k_5 C_F(t) - k_6 C_{NS}(t) \\
 C_T(t) &= C_F(t) + C_{NS}(t) + C_{SP}(t)
 \end{aligned} \tag{2.10}$$

Laplace transform and the operational equation

To solve the set of ordinary differential equations generated from a compartment model, an efficient and well established approach is to transform the system in the time-domain (with functions of time) to the frequency-domain (with functions of frequency), where the mathematical operations become simpler (Godfrey 1983).

Taking the one-tissue compartment model for example, the Laplace transform of Equation 2.8 is

$$s\mathcal{L}_{C_T}(s) = K_1\mathcal{L}_{C_P}(s) - k_2\mathcal{L}_{C_T}(s) \quad (2.11)$$

By rearranging it becomes

$$\mathcal{L}_{C_T}(s) = \frac{K_1}{s + k_2}\mathcal{L}_{C_P}(s) \quad (2.12)$$

The operational equation for PET can then be obtained by applying the inverse Laplace transform to yield

$$C_T(t) = K_1e^{-k_2t} \otimes C_P(t) \quad (2.13)$$

where $\otimes$ is the convolution operator.

The tracer concentration in tissue $C_T(t)$ is measured by the PET scanner, and the tracer plasma concentration $C_P(t)$ can be obtained by simultaneous arterial blood sampling. With known $C_T(t)$ and $C_P(t)$, nonlinear regression techniques that minimise the sum of squared differences between the model and the data can then be used to find the best fit to the data points, resulting in optimal estimates for the rate constants K_1 , k_2 .

For multi-tissue compartment models, similar techniques can be applied to derive the operational equations, with the tissue's impulse response function.

2.3.2 Linearisation

So far it can be seen that a selected compartment model leads to a set of first order linear differential equations, from which the analytical solution can be derived. Weighted non-linear least squares can then be used to estimate the micro-parameters, however the computational issues (potential low efficiency and convergence problem) of nonlinear regression could impose a problem. Therefore methods that enable the use of linear least-squares fitting procedures for parameter estimation with their associated computational simplicity and robustness have been proposed (Gjedde 1982; Patlak et al. 1983; Blomqvist et al. 1990; Logan et al. 1990; Hoff et al. 1993).

One approach to develop more efficient estimation techniques for parametric imaging has been to linearise the solution to the compartmental system by transforming the data. For linearisation, there are graphical methods (Blomqvist et al. 1990; Logan et al. 1990; Patlak and Blasberg 1985), e.g. Logan plot for reversible tracers and Patlak plot for irreversible tracers. They make use of the asymptotic properties of the tissue response and provide information on the main macro-parameters of interest, e.g. total volume of distribution V_T for reversible tracers or metabolic rates K_I for irreversible tracers.

Other methods derive the complete set of rate constants for the model and allow the determination of the full system kinetics (Ichise et al. 2002; Gunn et al. 2001; Gunn et al. 2002). Ichise multi-linear analysis (Ichise et al. 2002) is one of the approaches that uses a two-tissue compartmental (2TC) model to describe the kinetics, and the

linearisation is performed as described in the following section.

2.3.2.1 Ichise multi-linear analysis

Ichise multi-linear analysis was developed to interpret the measured data using a 2TC model. The linearisation is carried out by integrating the differential equation system in Equation 2.9, which results in:

$$\begin{aligned} C(T) = & \gamma_1 \int_0^T \int_0^s C_p(t) dt ds + \gamma_2 \int_0^T \int_0^s C(t) dt ds \\ & + \gamma_3 \int_0^T C(t) dt + \gamma_4^* \int_0^T C_p(t) dt + \gamma_5 C_p(T) \end{aligned} \quad (2.14)$$

where $C(t)$ is the measured PET signal and $C_p(t)$ is the measured blood activity at time point t . The unknown linear coefficients γ_1 , γ_2 , γ_3 , γ_4^* and γ_5 can be expressed in terms of the system micro-parameters K_1 , k_2 , k_3 , k_4 .

This then reduces to a linear regression problem involving five parameters and takes the form:

$$Y = \Gamma X + \epsilon \quad (2.15)$$

where Γ is the matrix of unknown parameters $\gamma_1, \dots, \gamma_5$. Y and X are the observed data $C(T)$ and $[\int_0^T \int_0^s C_p(t) dt ds]$ respectively, and ϵ is the error term to minimise.

2.3.2.2 Basis function approach

The basis function approach is another technique that linearises the problem to provide a better conditioned parameter estimation method for voxel based model fitting. Basis function approaches are based on the general equation that describes a tracer compartmental system and generates a comprehensive set of kinetic basis functions

that yields a linearised optimisation problem (Cunningham and Jones 1993; Gunn et al. 2001; Gunn et al. 2002). The nonlinear terms in the solution are precalculated for discrete values in a possible range of basis functions, so that the solution becomes a linear combination of the basis functions, making the problem a linear system to solve. Given the number of basis functions generated, the problem is ill-posed and requires additional constraints for its solution.

The linear compartmental systems for PET tracer kinetics lead to a set of linear first order differential equations. Instead of writing out these equations explicitly, the whole system can be represented in terms of state space (Gunn et al. 2001). In this representation, a time-invariant linear compartmental system is defined as

$$\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t) + \mathbf{B}\mathbf{u}(t)$$

$$\mathbf{y}(t) = \mathbf{C}\mathbf{x}(t) + \mathbf{D}\mathbf{u}(t)$$

$$\mathbf{x}(0) = \mathbf{x}_0$$

where

$\mathbf{x}(t)$ - p -vector of state variables

$\mathbf{y}(t)$ - q -vector of observations

$\mathbf{u}(t)$ - r -vector of input functions

$\mathbf{A}$ - $p \times p$ state transition matrix

$\mathbf{B}$ - $p \times r$ input matrix

$\mathbf{C}$ - $q \times p$ observation matrix

$\mathbf{D}$ - $q \times r$ feedthrough matrix

$\mathbf{x}_0$ - p -vector of initial conditions

Without explicitly determining the compartmental system configuration, this set of equations corresponds to the compartment model depicted in Figure 2.10.

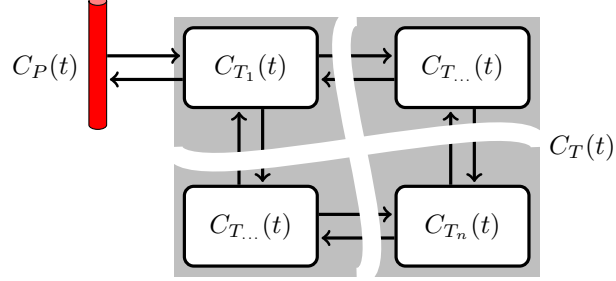


Figure 2.10: *General compartment model*

In PET, $\mathbf{x}(t)$ contains the time courses for all tissue compartments, $\mathbf{y}(t)$ is the observation corresponding to tomographic PET signal, and $\mathbf{u}(t)$ is the blood input function. The state transition matrix $\mathbf{A}$ has elements in the form of simple combinations of the transport rate constants k_n ($n = 2, \dots$) denoting the tracer transferring between compartments, $\mathbf{B}$ is typically the delivery rate K_1 of the tracer into the tissue, $\mathbf{C}$ is a vector of ones indicating that observation is the sum of all the compartments, and $\mathbf{D}$ denotes the blood fraction that presents in the volume of interest to account for the blood volume contribution for all models.

Based on these definitions, $\mathbf{A}$ takes the form of a diagonally dominant matrix with non-positive diagonal elements and non-negative off diagonal elements. For the large majority of linear compartmental systems which are non-cyclic, $\mathbf{A}$ is negative semidefinite (Schmidt 1999).

Spectral analysis (Cunningham and Jones 1993)

From the previous derivation of the solution using Laplace transforms in Sec. 2.3.1, it can be seen that the operational equation of such a system is written as the con-

volution of a sum of exponentials with the input function, where the coefficients of the exponentials are unknown and determined by the micro-system parameters K_1 , k_n ($n = 2, \dots$), as:

$$C_T(t) = \sum_{i=1}^N \phi_i e^{-\theta_i t} \otimes C_P(t), \quad (2.16)$$

where $\otimes$ denotes convolution, and the system impulse response function (IRF) is:

$$IRF = \sum_{i=1}^N \phi_i e^{-\theta_i t}, \quad (2.17)$$

where N is the number of tissue compartments, and ϕ_i and θ_i are the unknown coefficients relating to K_1 , k_n ($n = 2, \dots$).

The basis function approach performs linearisation by precalculating a possible range of basis functions in discrete values in the form of:

$$\begin{aligned} \Psi_i &= e^{-\theta_i t} \otimes C_P(t) \\ i &= 1 \dots N \end{aligned} \quad (2.18)$$

so that the PET observation $C_T(t)$ becomes a linear combination of the basis functions as:

$$C_T(t) = \sum_{i=1}^N \phi_i \Psi_i \quad (2.19)$$

where θ_i ($i = 1 \dots N$) are pre-chosen from a physiologically plausible range, and ϕ_i ($i = 1 \dots N$) are the unknown kinetic parameters to be solved.

In PET, $C_T(t)$ is measured as discrete tomographic time series data y , from F

PET time frames that

$$y = [y_1 \dots y_F]^T \quad (2.20)$$

$$y_k = \frac{1}{t_k^e - t_k^s} \int_{t_k^s}^{t_k^e} C_T dt$$

The corresponding matrix of kinetic basis functions Ψ , defined by Equation 2.18 is:

$$\Psi = \begin{pmatrix} \Psi_{11} \dots \Psi_{1N} \\ \vdots \dots \vdots \\ \Psi_{F1} \dots \Psi_{FN} \end{pmatrix} \quad (2.21)$$

$$\Psi_{ki} = \frac{1}{t_k^e - t_k^s} \int_{t_k^s}^{t_k^e} e^{-\theta_i t} \otimes C_P dt$$

where t_k^s and t_k^e are the start and end frame times for each frame ($k = 1, \dots, F$), respectively.

This linearisation leads to the least squares problem:

$$\min_{\phi} ||y - \Psi\phi||_2^2 \quad (2.22)$$

To elicit a suitable coverage of the kinetic spectrum, the values for θ_i ($i = 1 \dots N$) are typically spaced in a logarithmic manner with a sufficiently large value for N , which is normally $N = 32$ values for θ_i from $10^{-8}s^{-1} \leq \theta_i \leq 10^{-2}s^{-1}$ for reversible tracers. This results in the underdetermined problem, where $N > F$ for a system with F data points, such as a PET measurement with F time frames. Standard least squares techniques are not suitable for solving the problem as it is underdetermined.

To impose the necessary constraint to solve the underdetermined problem for

$N > F$, spectral analysis (Cunningham and Jones 1993) assumes the IRF to be a positive sum of exponentials, and employs non-negative least squares to find the coefficients to fit the observed PET data as the convolution of the IRF and plasma input. In (Schmidt 1999) it is shown that this non-negativity assumption holds for PET kinetic modelling which considers the sum of all compartments.

This leads to the non-negative least squares (NNLS) problem:

$$\begin{aligned} \min_{\phi} \quad & \|y - \Psi\phi\|_2^2 \\ \text{s.t.} \quad & \phi_i \geq 0 \end{aligned} \tag{2.23}$$

Figure 2.11 illustrates how spectral analysis fits two TACs y_1 and y_2 with different kinetics.

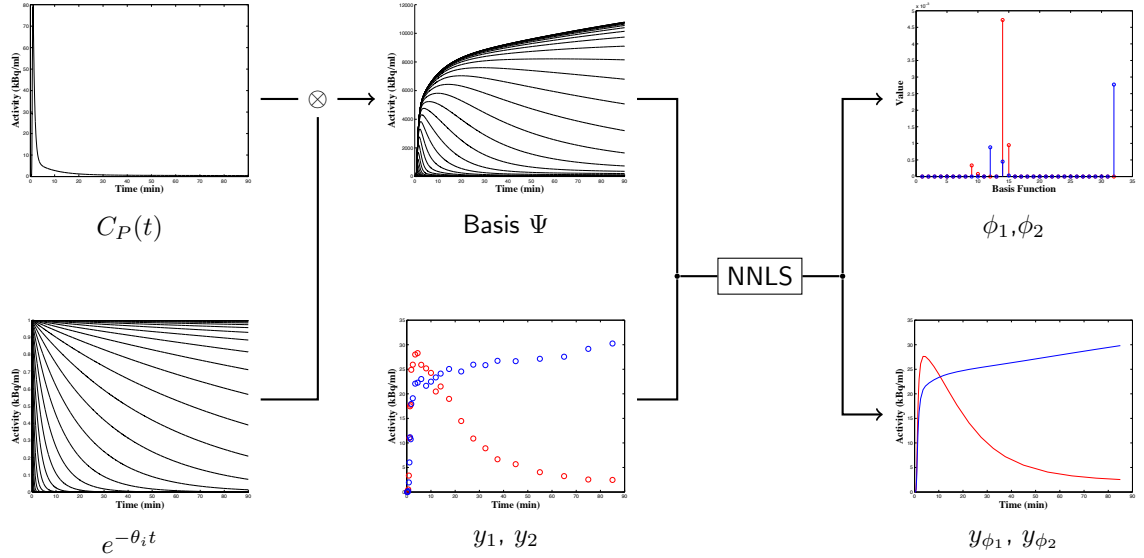


Figure 2.11: *Spectral analysis: a generalised model for various kinetics*

It can be seen that for tracer compartmental systems the impulse response function of the system is determined by a sum of N exponentials where N corresponds to the number of tissue compartments (Gunn et al. 2001). The model parameters k_n ($n = 2, \dots$) enter the solution in the coefficients and exponents of the exponential functions parameters K_1, k_n ($n = 2, \dots$), and can be estimated by nonlinear regression or linear regression after linearisation using the intermediate parameters. Once solved, the rate constants K_1, k_n ($n = 2, \dots$), as the micro-parameters of the system, or the intermediate parameters from a linearised system can be used to derive the macro-parameters, which are used as outcome measures of dynamic PET data.

2.3.2.3 Outcome measures of dynamic PET data

The terms macro- and micro-parameters are used to distinguish between the individual rate constants (micro) and global system parameters (macro) characterising the whole system. The macro-parameters are more stable with respect to the parameter estimation problem from dynamic PET data and as such are often the key parameters to estimate as they balance numerical identifiability with biological specificity. These macro-parameters can be derived from the compartmental system time differential equations as functions of the micro-parameters. In practice, the macro-parameters used as outcome measures of dynamic PET data are the total volume of distribution V_T (Ganong and Barrett 2005), binding potential BP (Innis et al. 2007), and the irreversible uptake rate constant to tissue K_I (Gjedde 1982; Patlak et al. 1983), as follows:

- 1) The total volume of distribution V_T is defined as the ratio of tissue concentration and the plasma concentration at equilibrium, i.e. $V_T = C_T/C_P$ when $dC_T/dt =$

0 and $dC_P/dt = 0$. Then from the differential equations, it can be solved that, $V_T = \frac{K_1}{k_2}$ for 1TC, $V_T = \frac{K_1}{k_2}(1 + \frac{k_3}{k_4})$ for 2TC and $V_T = \frac{K_1}{k_2}(1 + \frac{k_3}{k_4} + \frac{k_5}{k_6})$ for 3TC. The volume of distribution V_D of any compartment is also defined similarly as the ratio of this compartment concentration and plasma concentration at equilibrium, i.e. $V_{D_i} = C_{T_i}/C_P$.

- 2) Binding potential BP is the most common outcome measure for PET neuroreceptor studies as it quantifies the receptor availability of the target receptors by the radioligand, reflecting the receptor's density and the binding affinity. BP can be derived from V_D , and is defined as the concentration ratio of specific binding to non-displaceable, as in the 2TC, $BP_{ND} = \frac{V_T - V_{ND}}{V_{ND}}$, where the subscript ND stands for non-displaceable. V_{ND} is assumed to be homogeneous in the brain and is usually measured from a reference region devoid of the neuroreceptor for calculating the BP_{ND} values in other target regions.
- 3) Unlike V_T and BP , K_I is defined for irreversible systems. It quantifies the net transport rate from plasma to the irreversible compartment and is calculated as $K_I = \frac{K_1 k_3}{k_2 + k_3}$ in 2TC. For neuroreceptor ligands, the irreversibility comes with disadvantages and such ligands have very limited applications. However for cancer imaging, the proliferation and abnormal metabolism of tumour cells can often be well described by the irreversible model. In such applications, K_I is typically used as the metabolic rate or retention rate for quantifying tumour activities.

2.3.3 Reference tissue model

From the definition of the non-displaceable binding potential BP_{ND} , it can be seen that the quantification of receptor ligand binding requires the existence of a reference region that is devoid of the target receptor. Furthermore, it is possible to use the tracer activity (as a function of time) in this reference tissue region as an indirect input function to model the tracer kinetics in the target tissue (Blomqvist et al. 1989; Cunningham et al. 1991; Hume et al. 1992; Lammertsma et al. 1996; Lammertsma and Hume 1996; Gunn et al. 1997; Watabe H 2000).

Figure 2.12 illustrates an example of compartment model for the reference region, in which the tracer is free or non-specifically bound, described by a single tissue compartment.

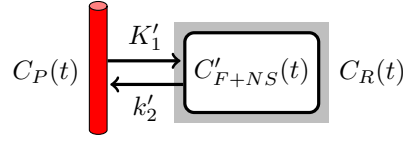


Figure 2.12: *Reference tissue*

The corresponding differential equation for the reference region is given as:

$$\frac{dC_R(t)}{dt} = K'_1 C_P(t) - k'_2 C_R(t) \quad (2.24)$$

where

- $C_R(t)$ - tracer concentration in reference tissue
- $C'_{F+NS}(t)$ - free, non-specifically bound tracer concentration in reference tissue
- K'_1 - rate constant from blood to reference tissue
- k'_2 - rate constant from reference tissue to blood

Equation 2.24 shows that the plasma input function $C_P(t)$ can be expressed in terms of the tracer concentration in reference tissue, namely the reference input function $C_R(t)$. As such, the arterial blood measurement can be avoided in modelling tracer kinetics in the target tissue by rearranging this equation to obtain the plasma time course described as a function of the reference tissue time course.

Full reference tissue model

In the target tissue with specific binding to the receptors, the tracer kinetics can often be described with the two-tissue compartments, as illustrated in Figure 2.13 together with the reference tissue region:

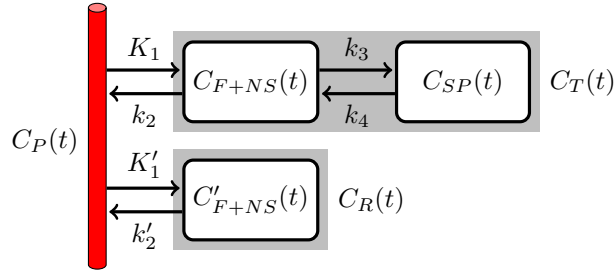


Figure 2.13: *Full reference tissue model*

This is the full reference tissue model (Blomqvist et al. 1989; Cunningham et al. 1991; Lammertsma et al. 1996) and the corresponding time differential equations are:

$$\begin{aligned}
\frac{dC'_{F+NS}(t)}{dt} &= K'_1 C_P(t) - k'_2 C'_{F+NS}(t) \\
C_R(t) &= C'_{F+NS}(t) \\
\frac{dC_{F+NS}(t)}{dt} &= K_1 C_P(t) - (k_2 + k_3) C_{F+NS}(t) + k_4 C_{SP}(t) \\
\frac{dC_{SP}(t)}{dt} &= k_3 C_{F+NS}(t) - k_4 C_{SP}(t) \\
C_T(t) &= C_{F+NS}(t) + C_{SP}(t)
\end{aligned} \tag{2.25}$$

To derive the operational equation between $C_T(t)$ and $C_R(t)$ without $C_P(t)$, from Equation 2.25 it can be seen that 6 parameters will remain in the equation (K_1 to k_4 in the target tissue, and K'_1 , k'_2 in the reference tissue), with the rate constants K_1 and K'_1 entering as a ratio accounting for the differences in delivery between the target and reference tissue, denoted as

$$K_1 = R_1 \cdot K'_1 \tag{2.26}$$

This leads to the reduction to 5 identifiable parameters with the deliveries from the plasma to the target and reference tissue being unidentifiable without a plasma input function.

Furthermore, assuming the non-displaceable volume of distribution of the non-specifically bound tracer in both tissues is the same (Cunningham et al. 1991), i.e.

$$V_{ND} = \frac{K_1}{k_2} = \frac{K'_1}{k'_2} \tag{2.27}$$

with the delivery ratio R_1 there is

$$k_2 = R_1 \cdot k'_2 \quad (2.28)$$

and this leads to the parameterisation requiring 4 parameters. The relationship between $C_T(t)$ and $C_R(t)$ can then be derived as (Lammertsma et al. 1996):

$$C_T(t) = R_1[C_R(t) + a \cdot C_R(t) \otimes e^{-ct} + b \cdot C_R(t) \otimes e^{-dt}] \quad (2.29)$$

where

$$\begin{aligned} a &= (k_3 + k_4 - c) \cdot (c - r)/p \\ b &= (d - k_3 - k_4) \cdot (d - r)/p \\ c &= (s + p)/2 \\ d &= (s - p)/2 \\ p &= \sqrt{(s^2 - q)} \\ q &= 4k_2 \cdot k_4 \\ r &= k_2/R_1 \\ s &= k_2 + k_3 + k_4 \\ \otimes &- \text{convolution operator} \end{aligned}$$

Using measured $C_T(t)$ and $C_R(t)$ in the tomographic PET data, the unknown parameters in the linear terms (R_1 , a , and b) and in the nonlinear terms (c and d) can be estimated using nonlinear least squares optimisation (nonlinear regression) techniques with Equation 2.29. Then the rate constants k_2 to k_4 can be solved with the intermediate parameters p , q , r , s , finally yielding the outcome measure of interest in neuro-receptor studies, $BP_{ND} = k_3/k_4$.

It should also be noted that, in the target and reference tissues, although the same non-displaceable volume of distribution V_{ND} is assumed, this model takes into account the differences between target and reference tissues in:

- 1) delivery as described by R_1 , the local rate of delivery in the target tissue relative to reference tissue;
- 2) free/non-specially bound concentration as $C_R(t) = C'_{F+NS}(t) \neq C_{F+NS}(t)$, although $\int_t C_R(t) = \int_t C'_{F+NS}(t) = \int_t C_{F+NS}(t)$.

Simplified reference tissue model

The simplified reference tissue model (SRTM) (Lammertsma and Hume 1996; Gunn et al. 1997) follows the compartmental structure illustrated in Figure 2.13 where the tracer kinetics in the target tissue are described by two tissue compartments, but is based on the further simplification that it is not possible to kinetically distinguish between the non-displaceable and specifically bound compartments. Therefore SRTM corresponds to the compartment structure shown in Figure 2.14, where a single compartment is sufficient to describe the time activity curve measured in the target tissue, without significant improvement when two compartments are used.

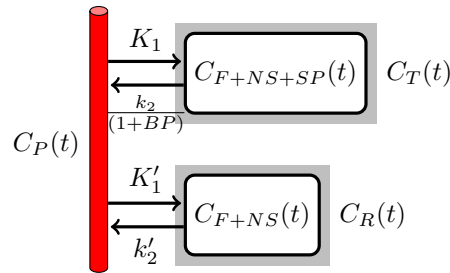


Figure 2.14: *Simplified reference tissue model (SRTM)*

It should be noted that because the specifically bound tracer in the target tissue is kinetically indistinguishable from the free/non-specifically bound tracer and also contributes to the efflux, the rate constant from tissue to plasma needs to account for this fraction. To keep the consistency with the two-tissue compartment model, the overall rate constant is written as $k_2/(1 + BP_{ND})$, where BP_{ND} is the binding potential that denotes the ratio of specific binding to non-specific binding.

The relationship between $C_T(t)$ and $C_R(t)$ can be directly solved as:

$$C_T(t) = R_1 C_R(t) + [k_2 - R_1 \frac{k_2}{1 + BP_{ND}}] C_R(t) \otimes e^{-\frac{k_2}{1 + BP_{ND}} t} \quad (2.30)$$

where $R_1 = K_1/K'_1$ is local rate of delivery in the target tissue relative to reference tissue.

It can be seen from Equation 2.30, that with SRTM and the measured tracer concentrations $C_T(t)$ and $C_R(t)$ in the target and reference tissues, the unknown parameters R_1 , k_2 and BP_{ND} can be estimated using nonlinear least squares optimisation (nonlinear regression) techniques. Thus computational issues (potential low efficiency and convergence problem) of nonlinear regression could impose a problem of employing SRTM. In (Gunn et al. 1997), the basis function approach was introduced to estimate R_1 , k_2 and BP_{ND} in a robust and fast way to avoid any such issues with convergence and sensitivity to noise.

Using the basis function approach, the operational equation of SRTM Equation 2.30 can be rewritten as:

$$C_T(t) = \phi_0 C_R(t) + \phi_1 C_R(t) \otimes e^{-\theta_1 t} \quad (2.31)$$

where

$$\begin{aligned}\phi_0 &= R_1 \\ \phi_1 &= k_2 - R_1 \frac{k_2}{1+BP_{ND}} \\ \theta_1 &= \frac{k_2}{1+BP_{ND}}\end{aligned}$$

It is straightforward to find that, Equation 2.31 is in the same form as Equation 2.32, and that only two basis functions (one is the reference tissue itself) are involved instead of a sum of basis functions due to the constraint of single compartment. Therefore, it is possible to implement a fast algorithm that, by pre-calculating the non-linear term $C_R(t) \otimes e^{-\theta_1 t}$ on a discrete spectrum of parameter values on θ_1 , allows for the values for ϕ_0 and ϕ_1 to be determined by standard linear least squares methods, finally leading to the determination of the optimal value for θ_1 from the solution that has the best fit (Gunn et al. 1997).

For quantification of the receptor kinetics, the parameters R_1 , k_2 and BP_{ND} can be calculated as:

$$\begin{aligned}R_1 &= \phi_0 \\ k_2 &= \phi_1 + R_1 \cdot \theta_1 \\ BP_{ND} &= \frac{k_2}{\theta_1} - 1\end{aligned}$$

Reference tissue compartmental structure

The full and simplified reference tissue models are only valid when the reference region can be described by a single tissue compartment (Hume et al. 1992) depicted in Figure 2.12.

In the reference region, when the free and non-specifically bound cannot be ki-

netically distinguished, the Watabe's reference tissue model (Watabe H 2000) uses a two-tissue compartment structure for the reference region, as illustrated in Figure 2.15. The operational equation for solving this system is also given in (Watabe H 2000).

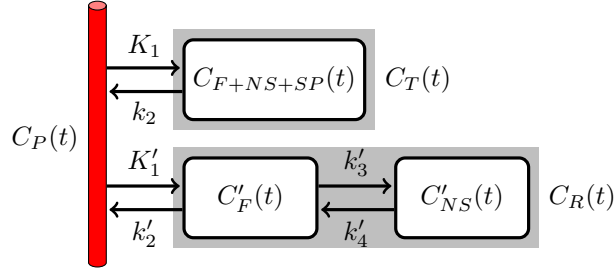


Figure 2.15: *Watabe's reference tissue model*

In (Gunn et al. 2001) the structures of both the reference tissue and the target tissue are generalised, as depicted by Figure 2.16, and the operational equation is derived as:

$$C_T(t) = \phi_0 C_R(t) + \sum_{i=1}^{m+n+1} \phi_i e^{-\theta_i t} \otimes C_R(t) \quad (2.32)$$

where the values for θ_i are predefined and the unknown ϕ_i s ($i = 1, \dots, m+n-1$) are solved by basis pursuit denoising (Gunn et al. 2002).

This equivalent generalised equation for reference tissue kinetics (equivalent to Equation 2.16 for the plasma input situation presented previously) that can be solved using basis function methods, with improved flexibility as compared to a fixed compartment model solved by non-linear regression. To elicit a suitable coverage of the kinetic spectrum, a suitably large value is usually chosen for the number of basis functions (≥ 32 as a minimum), usually making the linear system underdetermined.

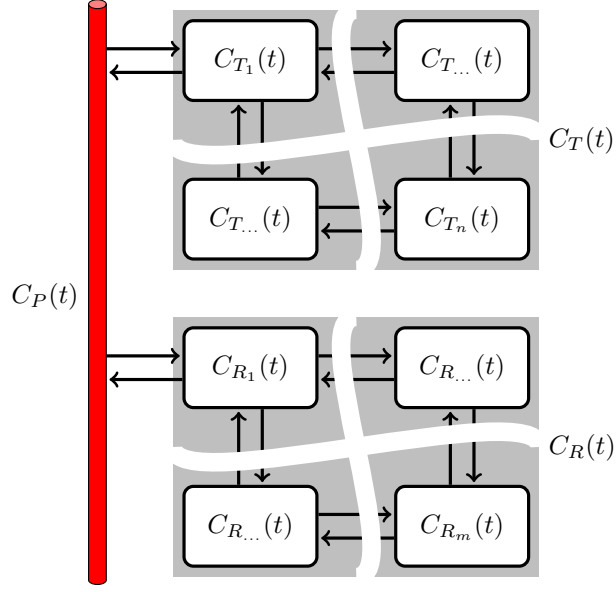


Figure 2.16: *Generalised reference tissue model*

Therefore, appropriate constraints are required to guarantee a unique solution is obtained for the underdetermined linear system. To impose such constraints when using the basis function approach, with plasma input, spectral analysis assumes the tissue response, in the form of an impulse response function (IRF), as a *positive* sum of exponentials and employs non-negative least squares to find the coefficients to fit the observed PET data as the convolution of the plasma input and IRF, as introduced in Chapter 4. However, for reference tissue models, negative coefficients can be encountered. Basis pursuit (Gunn et al. 2001) extends the concept of spectral analysis by allowing for negative coefficients for the basis functions to allow the use of a generalised reference tissue input, which leads to a more general framework.

When considering the fitting of the model 2.32 to measure tissue data it can be

expressed as an expansion on a basis,

$$C_T(t) = \phi_0 C_R(t) + \sum_{i=1}^N \phi_i \psi_i \quad (2.33)$$

where

$$\psi_i = e^{-\theta_i t} \otimes C_R(t) \quad (2.34)$$

A discrete set of N values for θ_i can be chosen from a physiologically plausible range spaced in a logarithmic manner to elicit a suitable coverage of the kinetic spectrum.

The tissue observation measured as PET data $\mathbf{Y}(\mathbf{x}_j, t_k)$, corresponds to $C_T(t)$ as

$$\mathbf{Y}(\mathbf{x}_j, t_k) = \mathbf{Y}_{k,j} = \frac{1}{t_k^e - t_k^s} \int_{t_k^s}^{t_k^e} C_T dt \quad (2.35)$$

where t_k^s and t_k^e are the start and end frame times ($k = 1 \dots F$).

Accordingly, the matrix of basis functions Ψ can be written as

$$\begin{aligned} \Psi_{0k} &= \frac{1}{t_k^e - t_k^s} \int_{t_k^s}^{t_k^e} C_R dt \\ \Psi_{ik} &= \frac{1}{t_k^e - t_k^s} \int_{t_k^s}^{t_k^e} e^{-\theta_i t} \otimes C_R dt \end{aligned} \quad (2.36)$$

Using the measured PET data $\mathbf{Y}$ and pre-calculated Ψ , the unknown Φ can be determined by

$$\mathbf{Y} \cong \Psi \Phi \quad (2.37)$$

In practice, to account for the uncertainty of the measurements, the weighted least

squares problem

$$\mathbf{W}^{\frac{1}{2}}\mathbf{Y} \cong \mathbf{W}^{\frac{1}{2}}\Psi\Phi \quad (2.38)$$

can be considered, where $\mathbf{W}$ is the inverse of the covariance matrix. The weighted least squares solution can be simply obtained by weighting both the measured data $\mathbf{Y}$ and the basis Ψ .

In solving for Φ from Equation 2.38, it is noted that the basis Ψ is typically overcomplete ($N > F - 1$) leading to an under-determined set of equations.

Solution to the underdetermined system

To solve the underdetermined system, the non-negativity constraint used previously by spectral analysis is no longer valid because of the need to allow for negative coefficients. In (Gunn et al. 2002), the problem is transformed by applying the technique proposed in (Chen et al. 1998). A regularising term on sparsity of the solution, is introduced which allows for the appropriate conditioning of the problem. The problem becomes

$$\min_{\Phi} ||\mathbf{W}^{\frac{1}{2}}(\mathbf{Y} - \Psi\Phi)||_2^2 + \mu||\Phi||_p \quad (2.39)$$

where $||\Phi||_p$ represents the L_p norm of the kinetic parameter in the basis space.

The regularisation parameter $\mu > 0$ balances the approximation error and sparseness of Φ to impose a unique solution. This is based on prior knowledge that the observed data can be accurately described by a few compartments. The L_p norm can be chosen as L_0 (atomic decomposition) and L_1 (basis pursuit denoising) (Chen and Donoho 1995) that satisfy the requirements of the sparsity of solution. For computational efficiency, $p = 1$ is chosen for solving the problem, leading to a basis pursuit

denoising solution that is given by

$$\min_{\Phi} ||\mathbf{W}^{\frac{1}{2}}(\mathbf{Y} - \Psi\Phi)||_2^2 + \mu||\Phi||_1 \quad (2.40)$$

Equation 2.40 can be rewritten as a bound constrained quadratic problem (Chen and Donoho 1995):

$$\begin{aligned} \min_{\Phi'} & \frac{1}{2} \Phi'^T \mathbf{H} \Phi' + \mathbf{c}^T \Phi' \\ \text{s.t. } & \phi'_i \geq 0 \end{aligned} \quad (2.41)$$

where

$$\begin{aligned} \mathbf{H} &= \begin{bmatrix} \Psi^T \mathbf{W} \Psi & -\Psi^T \mathbf{W} \Psi \\ -\Psi^T \mathbf{W} \Psi & \Psi^T \mathbf{W} \Psi \end{bmatrix} \\ \mathbf{c} &= \mu \mathbf{1} - \begin{bmatrix} \Psi^T \mathbf{W} \Psi \\ -\Psi^T \mathbf{W} \Psi \end{bmatrix} \\ \Phi' &= \begin{bmatrix} \Phi^+ \\ \Phi^- \end{bmatrix} \end{aligned} \quad (2.42)$$

Note that due to the bound constraint $\phi'_i \geq 0$, the non-negative least squares techniques employed by spectral analysis can be readily used to solve Φ' . The kinetic parameter, as the basis coefficients Φ is then given by

$$\Phi = \Phi^+ - \Phi^- \quad (2.43)$$

finally yielding $\mathbf{Y}_\Phi = \Psi\Phi$.

Figure 6.2.4 depicts how basis pursuit denoising fits two TACs y_1 and y_2 with different kinetics.

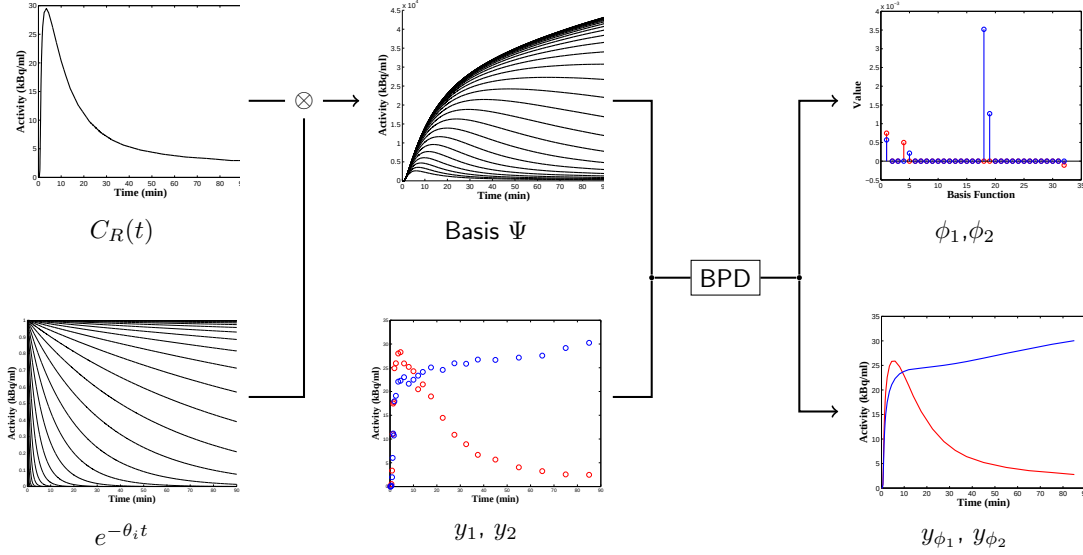


Figure 2.17: *Basis pursuit denoising*

Using the reference tissue models, it is impossible to quantify the volume of distribution due to the lack of the plasma input, and the binding potential is calculated directly with the reference tissue time activity as the outcome measure (Gunn et al. 2002).

2.4 PET applications

Potentially, PET is able to image *in vivo* biologic pathways and targets of any compound that can be radiolabelled by a PET isotope. Great endeavour has been put into

the development of new radiotracers, and PET imaging has been increasingly used in clinical and scientific research for disease understanding and drug development.

2.4.1 Clinical application of PET

PET is a valuable tool for a range of diseases and disorders as it is able to target radioactive chemicals used in particular body functions. In clinical research, it is used to localise and measure activities that can be used as biomarkers to evaluate normal biological processes, pathological processes, or pharmacological responses to a therapeutic intervention. PET was initially applied to clinical cardiology for measuring blood flow, and neurology for quantifying neurological disorders and dementia. It became quickly a standard diagnostic procedure in clinical oncology with the success of fluorodeoxyglucose (FDG), a fluorine-18 labelled glucose analog for localising and quantifying glucose metabolism. Table 2.2 gives a list of PET tracers of clinical interest.

PET tracer	Biological target	Pathophysiological process	Indication
$^{15}\text{O}_2$	oxygen metabolism	ischemia	stroke
$[^{15}\text{O}]\text{H}_2\text{O}$	blood flow	oligemia	stroke
$[^{18}\text{F}]\text{FDG}$	glucose metabolism	hyperexcitability metabolic impairment abnormal metabolism	epilepsy Alzheimer's disease cancer
$[^{18}\text{F}]\text{FML}$	apoptosis-specific alterations	apoptosis	cancer
$[^{18}\text{F}]\text{FLT}$	thymidine kinase 1	proliferation	cancer
$[^{18}\text{F}]\text{FMISO}$	misonidazole metabolism	hypoxia ischemia	cancer myocardial infarcts
$[^{18}\text{F}]\text{PBR111}$ $[^{11}\text{C}]\text{PBR28}$ $[^{11}\text{C}]\text{PK11195}$	translocator protein	inflammation	Huntington's disease Parkinson's disease Alzheimer's disease
$[^{18}\text{F}]\text{FDDNP}$ $[^{18}\text{F}]\text{florbetapir}$ $[^{11}\text{C}]\text{PIB}$	amyloid β	amyloid β aggregates	Alzheimer's disease
$[^{18}\text{F}]\text{T807}$	tau	tau aggregates	Alzheimer's disease
$[^{18}\text{F}]\text{DOPA}$	dopamine	dopamine storage	Parkinson's disease
$[^{11}\text{C}]\text{Raclopride}$ $[^{11}\text{C}]\text{PHNO}$	dopamine D2 receptor D3/D2 dopamine receptor	receptor synthesis	Huntington's disease Parkinson's disease

Table 2.2: PET tracers and their clinical applications

2.4.2 PET in drug development

For drug development, it is essential to know at an early stage whether a new drug molecule reaches the tissue of interest in pharmacologically active amounts, whether it interacts with the target and the quantitative relationship of this interaction with the administered dose. With the *in vivo* quantitative measurement of a radiotracer, PET is able to address such questions (Matthews et al. 2012).

Biodistribution studies with PET

After a drug compound gets into the circulation, its pharmaceutical capacity is dependent on the free concentration in the tissue. The radioactive version of the new drug can be used as the PET tracer for determining the tissue concentration. The drug compound is labelled by a positron-emitting isotope that does not change the compound's chemical structure or properties. Therefore using dynamic PET, the distribution and concentration of the drug candidate can be measured *in vivo*. In such a PET biodistribution study, the drug is injected at the tracer dose which is insufficient to have pharmacological effects (Bergström et al. 2003). With the associated measurement of its concentration in plasma after metabolism correction, the kinetic models described in Sec. 2.3.1 can be used to derive the estimate of the ratio of drug concentration in tissue to blood at equilibrium, as the total volume of distribution V_T . The free tissue concentration cannot be calculated from the total tissue concentration and requires additional equilibrium dialysis measurements. *In vitro* equilibrium dialysis assays that account for the non-specific binding in the tissue, in conjunction with the V_T values from PET data, allow for the estimation of the free concentration of the drug candidate in the tissue of interest (Gunn et al. 2012).

A PET biodistribution study provides evidence of the drug getting into the target tissue, therefore it is useful for evaluating drug candidates at early stage to terminate the unsuccessful ones. PET biodistribution studies have been widely used in developing central nervous system (CNS) drugs, and recently it is shown that anti-cancer drug development can also benefit as this analysis provides predictions on drug concentrations in normal and tumour tissues (Rosso et al. 2009).

Occupancy studies with PET

For a drug candidate, it is also important to know the relationship between the drug concentration in plasma and the extent of drug-target interaction to deduce the dose range that needs to be investigated. To assess the dose for a drug to have pharmacological effects, a target occupancy study can be conducted with a PET tracer that binds to the same target, where the drug itself is not radio-labelled (Farde et al. 1989; Howes et al. 2009; Abanades et al. 2011). This is based on the fact that, when injected at the "tracer dose", which is normally much lower than the pharmacological dose, the PET data reflect the density of receptors that are not occupied by the drug. At tracer doses, BP_{ND} calculated as the tracer concentration ratio of specific binding to non-displaceable is proportional to the available concentration of receptors. At tracer doses, it can be derived that $BP_{ND} = B_{avail}/K_d$, where B_{avail} represents the concentration of available receptor sites. The affinity is a property of the receptor and is assumed to be the same, therefore the changes in BP_{ND} are typically interpreted as changes in B_{avail} . A PET occupancy study consists of an initial PET scan with no drug and subsequent scans with therapeutic doses of drug on board. Although the PET tracer only occupies a small percentage of the receptors, the measured BP_{ND} values before and after dosing still reflect the total receptor density B_{avail} available

for binding to the PET tracer. The drug occupies some of the receptors, and this occupancy can be assessed by the change in BP_{ND} measured by PET. With the plasma concentrations (doses) of the drug measured along with the PET scans, the relationship between the drug dose and the target occupancy (reflected by BP_{ND}) can be characterised by a competitive binding model. This information is important for drug candidate selection. In practice, a drug is expected to have the target occupancy above a certain percentage to be pharmacologically effective, and the minimal plasma concentration can be assessed from the occupancy study. Meanwhile, the drug can be found to have dose limiting toxicities. Therapeutic index defined as the ratio of the toxic dose to the effective dose can be used for drug selection, the drug candidate with higher therapeutic index will be selected for further development.

To summarise, this chapter has introduced the principles of PET imaging and the reconstruction of PET images, and the associated clinical applications based on the kinetic modelling of the dynamic PET data. The next chapter will introduce subject motion which is one of the fundamental problems in PET imaging, and previous approaches developed to address the subject movements in the PET data.

Chapter 3

PET motion correction

As introduced in Chapter 2, kinetic analysis of the PET time activity curves (TACs) provides quantitative information on the underlying biological process of interest. The integrity and validity of analyses derived from a dynamic PET scan is therefore dependent on the accuracy of the TAC data, which can be corrupted by subject motion that alters the voxel-to-tissue mapping. The scan duration is usually one or two hours long, and subject motion is inevitable. Therefore, motion correction is of fundamental importance for PET imaging. In this Chapter, the influence of subject motion on the quantifying tracer kinetics from the dynamic PET data will be addressed, and previous techniques developed to correct for subject movements in the PET data will be reviewed.

3.1 Subject motion in PET data

In any imaging system, subject motion degrades the image quality. In a dynamic PET scan, the functional processes of interest are continuously recorded over a period of

time. Dependent on the tracer kinetics, the scan duration is typically 60 – 90 minutes. It is therefore impossible to avoid subject motion that corrupts the temporal consistency of PET data measured at a certain spatial position. Modern PET scanners have a typical voxel size of $2mm$, and the voxel-to-tissue mapping can be easily altered by the subject motion during a scan, such as a $2cm$ movement of the diaphragm during breathing. Motion due to the physiological activities, e.g. cardiac motion, respiratory motion, and peristalsis are of involuntary nature. Other motion types such as head motion and body motion are voluntary but are impossible to avoid for diseased subjects with movement disorders, and are still difficult for healthy subjects because of the long scan duration. Regarding the motion complexity, head movements are rigid, i.e. all the points on the head have the same translations and rotations with no local deformations. For other body parts where muscular movements are involved such as in the heart, the motion has by nature more degrees of freedom and requires more parameters to describe.

The subject motion affects the quality of dynamic PET data that are reconstructed into a series of temporal frames in three ways:

1. For attenuation correction, it introduces a mismatch between the PET emission data and the attenuation map. The attenuation map is a static image with values to scale the PET activity to account for the attenuation for each voxel. It is usually derived from a scan (such as CT) that is aligned to the PET emission data as a whole and the misalignment is therefore not accounted for between the PET data at different time points and the attenuation map. This leads to inaccurate attenuation correction for the dynamic PET data.

It should be noted that the motion correction techniques proposed in this thesis

can be applied to PET data before performing attenuation correction, thus this influence can be eliminated.

2. For the series of temporal frames, the spatial correlation is distorted by subject motion. As a consequence, all the data points on a time activity curve (TAC) do not represent the same voxel or the same region, therefore this inter-frame misalignment affects the kinetic analysis for parameter estimation. Figure 3.1 illustrates an example of this effect with the dynamic brain PET data obtained with $[^{11}\text{C}]\text{-(+)-PHNO}$, a dopamine D3/D2 receptor imaging ligand, from two different healthy subjects, one with no motion and the other with severe motion for kinetic analysis, as a comparison. The impact on the TACs derived on voxels from anatomical regions of interest is shown.

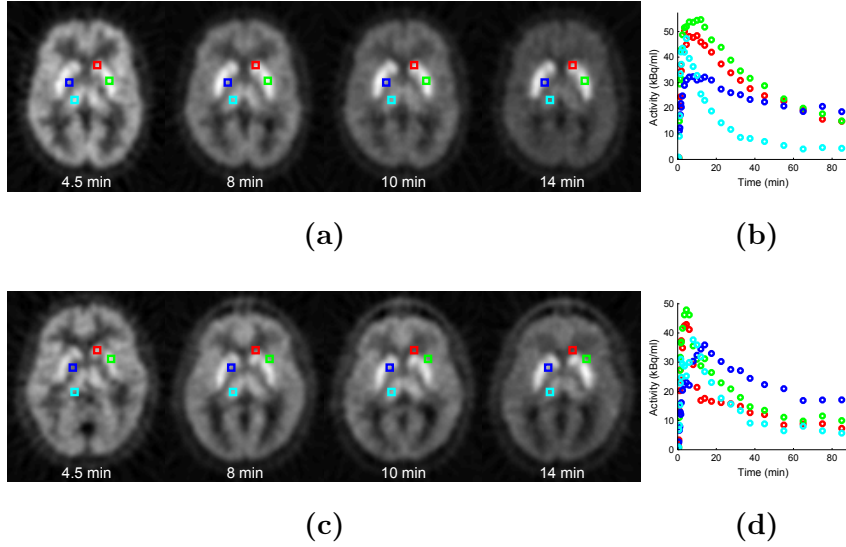


Figure 3.1: Subset of $[^{11}\text{C}]\text{-(+)-PHNO}$ PET temporal frames (times are mid-frame times) from an axial slice, for a subject with no motion (3.1a) and a subject with significant motion (3.1c), with voxels from various functional structures depicted in colours which are spatially fixed to demonstrate the displacement caused by motion. TACs from these voxels are shown in corresponding colours for both subjects in (3.1b) and (3.1d) respectively. The subject motion gives rise to altered functional TACs particularly in (3.1d).

3. For an individual PET temporal frame, the subject motion may also occur within the frame causing blurriness that degrades the data quality on each voxel. Even small amounts of movements have this effect as the spatial resolution of the scanners nowadays have reached a full-width-at-half-maximum (FWHM) of $2mm$ (Mourik et al. 2009; Rahmim et al. 2007). This leads to erroneous activity values on the voxels in a PET frame. For a TAC, this intra-frame motion introduces uncertainties in the data points.

In this thesis, for method validation and evaluation, the dynamic PET data are temporal frames reconstructed with attenuation correction, therefore the motion correction performance is directly demonstrated on reducing the inter-frame misalignments. In fact the proposed methodology can be applied to attenuation uncorrected PET data to account for the bias in attenuation correction, and the possibility of addressing the intra-frame motion using the same methodology will be discussed in the future work section.

Subject motion can be quantified with motion parameters solved as a mathematical problem. From this perspective, motion correction can be considered as establishing the spatial correspondences in the corrupted dynamic PET data, which fits the concept of image registration introduced in the following Sec. 3.2.1.

3.2 Medical image registration

3.2.1 Introduction to image registration

Image registration is the computational approach of estimating the geometrical transformation for one image to match the other based on the image intensity values or

image features such as lines and contours. In medical image analysis, registration is an essential post-processing technique that establishes anatomical or functional correspondences of related features between images taken at different times (e.g. before and after medical interventions), using different imaging modalities (such as CT and MRI with complementary structural information) or from different subjects (as in statistical analysis of group studies).

Mathematically it is the problem of finding an optimal coordinate transformation, which spatially aligns two images, or a group of images by minimising a given cost function. It is an N -dimensional optimisation problem where N is the number of parameters that characterise the transformation. At each iteration of the optimisation, one image is transformed and the cost function is calculated with the other image fixed. Optimisation terminates when the cost function reaches a minimum and the optimal transformation for the registration is obtained. It can be formulated as Equation 3.1:

$$\hat{\mathbf{T}} \leftarrow \arg \min_{\mathbf{T}} C(I_{target}, I(\mathbf{T}(\mathbf{x}))) \quad (3.1)$$

where I and I_{target} stand for the two images. The three aspects of registration, namely the transformation model $\mathbf{T}$ for the coordinate $\mathbf{x}$, the cost function C and the optimisation strategy are discussed in the following.

Transformation models describe how the coordinate of each voxel changes. The simplest transformation involves only spatial translations and rotations, known as rigid transformation. For 3D, there are 6 degrees of freedom (DOF), i.e. one translation parameter and one rotation parameter for each dimension. Head movement can be modelled by a rigid transformation. An extension to this adds scaling and shearing known as an affine transformation with 12 DOFs. Both rigid and affine are

linear and they account for global changes of position. The transformation is the same for all voxels, and can be represented using a matrix as shown in Equation 3.2:

$$\begin{pmatrix} x' \\ y' \\ z' \\ 1 \end{pmatrix} = \mathbf{T}_{global} \begin{pmatrix} x \\ y \\ z \\ 1 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} & a_{13} & a_{14} \\ a_{21} & a_{22} & a_{23} & a_{24} \\ a_{31} & a_{32} & a_{33} & a_{34} \\ 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} x \\ y \\ z \\ 1 \end{pmatrix} \quad (3.2)$$

where $\mathbf{T}_{global}$ is calculated by combining the rotations $\mathbf{R}$, translation $\mathbf{T}$, scaling $\mathbf{S}$ and shearing $\mathbf{H}$ as

$$\mathbf{T}_{global} = \mathbf{H} \cdot \mathbf{S} \cdot \mathbf{T} \cdot \mathbf{R} \quad (3.3)$$

$$\mathbf{T} = \begin{pmatrix} 1 & 0 & 0 & t_x \\ 0 & 1 & 0 & t_y \\ 0 & 0 & 1 & t_z \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

$$\mathbf{R} = \mathbf{R}_x \mathbf{R}_y \mathbf{R}_z$$

$$= \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & \cos \theta_x & -\sin \theta_x & 0 \\ 0 & \sin \theta_x & \cos \theta_x & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} \cos \theta_y & 0 & \sin \theta_y & 0 \\ 0 & 1 & 0 & 0 \\ -\sin \theta_y & 0 & \cos \theta_y & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} \cos \theta_z & -\sin \theta_z & 0 & 0 \\ \sin \theta_z & \cos \theta_z & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

$$\mathbf{S} = \begin{pmatrix} s_x & 0 & 0 & 0 \\ 0 & s_y & 0 & 0 \\ 0 & 0 & s_z & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

$$\mathbf{H} = \begin{pmatrix} 1 & h_{xy} & h_{xz} & 0 \\ h_{yx} & 1 & h_{yz} & 0 \\ h_{zx} & h_{zy} & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

In addition to the global transformation, in many medical applications one needs to account for local deformations, such as the movements of cardiac tissues, or the structural changes caused by progression of disease. A further level of complexity is introduced for the nonlinear voxel-dependent coordinate transformation. Nonlinear transformation models can be broadly classified into two groups, parametric and non-parametric. In a parametric model the transformation is parameterised as a linear combination of basis functions, whereas in a non-parametric model each voxel has its own displacement vector that is solved independently. The most popular non-rigid models used in medical image registration are

- Parametric: Free-Form Deformation (FFD) B-splines (Rueckert et al. 1999), which has a compact support of the basis function making it suitable to model local deformations.

In FFD B-splines the approximation of local deformation is characterised by

the following equation:

$$\mathbf{T}_{local}(x, y, z) = \sum_{l=0}^3 \sum_{m=0}^3 \sum_{n=0}^3 B_l(u) B_m(v) B_n(w) \phi_{i+l, j+m, k+n} \quad (3.4)$$

where $\phi_{i+l, j+m, k+n}$ are the control points in the $n_x \times n_y \times n_z$ mesh with uniform spacing in the domain of image volume, $i = \lfloor x/n_x \rfloor - 1$, $j = \lfloor y/n_y \rfloor - 1$, $k = \lfloor z/n_z \rfloor - 1$, $u = x/n_x - \lfloor x/n_x \rfloor$, $v = y/n_y - \lfloor y/n_y \rfloor$, $w = z/n_z - \lfloor z/n_z \rfloor$ and B_l represents the l th basis function of the B-spline:

$$B_0(u) = (1 - u)^3 / 6$$

$$B_1(u) = (3u^3 - 6u^2 + 4) / 6$$

$$B_2(u) = (-3u^3 + 3u^2 + 3u + 1) / 6$$

$$B_3(u) = u^3 / 6$$

- Non-parametric: demons (Thirion 1998), where the deformation is driven by image force as flow.

In contrast to parametric methods, these methods do not employ a parametric model of the deformation. Instead a displacement field s is used to model to spatial mapping of points from the fixed image space to the moving image space. For each voxel a displacement vector is added to an identity transformation to describe the deformation:

$$\mathbf{s} : x \leftarrow x + \mathbf{s}(x)$$

Thirion proposed to consider the nonlinear registration as a diffusion process (Thirion 1998). He introduced *demons* that push the image according to the

local characteristics in a way similar to what Maxwell did for solving the Gibbs paradox. The forces are inspired from the optical flow equations (Barron et al. 1994) and the method iteratively computes the forces and regularises the deformation by Gaussian smoothing, resulting in a computationally efficient algorithm. The basic assumption is that in a local neighbourhood, the intensities of the two images I_1 and I_2 in a motion sequence do not change: $I_1(x) = I_2(x+\mathbf{s}(x))$. To avoid the nonlinear dependency of $I_2(x+\mathbf{s}(x))$ on s , higher order terms in the Taylor series are eliminated such that $I_2(x+\mathbf{s}(x)) \approx I_2(x) + \nabla I_2(x) \cdot \mathbf{s}(x)$.

Cost function Mathematically, registration is formulated as an optimisation problem where an optimal transformation is found by minimising a cost function that includes the discrepancy between the moving and fixed images, and the regularisation on the transformation. The measure of discrepancy, or inversely the similarity can either be evaluated in a voxel-wise fashion based on the image intensities, or it can be derived from higher level information such as features in terms of anatomical landmarks or surfaces. In general, feature-based methods depend greatly on the structural information, which is limited in PET due to its low spatial resolution and signal-to-noise ratio (SNR). In contrast to that, intensity-based similarity metrics are frequently considered in PET image registration. In addition, the degrees of freedom increase in non-rigid transformation to allow local deformations, and this in turn requires an appropriate regularisation term to be incorporated in the cost function to keep the transformation physically meaningful and improve the stability. The most common similarity metrics are:

- **sum of squared difference (SSD)** is the basic similarity metric that assumes

identical intensities in images I_1 and I_2 as:

$$SSD = \sum_{all \text{ voxels}} (I_1 - I_2)^2, \quad (3.5)$$

and it is only suitable for intra-modality registration.

- **normalised cross correlation (NCC)** assumes a locally linear intensity relation and can be computed as:

$$NCC = \frac{\sum(I_2 - \bar{I}_2) \cdot (I_1 - \bar{I}_1)}{\sqrt{\sum(I_2 - \bar{I}_2)^2 \cdot \sum(I_1 - \bar{I}_1)^2}} \quad (3.6)$$

and is suitable for images of the same modality but of different contrasts.

- **normalised mutual information (NMI)** is a measure of statistical dependence based on the concept of information theory and is unaffected by the amount of image overlap (Studholme 1999). The definition is:

$$NMI(I_1, I_2) = \frac{H(I_1) + H(I_2)}{H(I_1, I_2)} \quad (3.7)$$

$$H(I_1) = - \sum_{i_1} p_{I_1}(i_1) \log p_{I_1}(i_1)$$

$$H(I_2) = - \sum_{i_2} p_{I_2}(i_2) \log p_{I_2}(i_2)$$

$$H(I_1, I_2) = - \sum_{i_1} \sum_{i_2} p_{I_1, I_2}(i_1, i_2) \log p_{I_1, I_2}(i_1, i_2)$$

where $H(I_1)$ and $H(I_2)$ are the marginal entropies of image I_1 and I_2 , $H(I_1, I_2)$ is the joint entropy of I_1 and I_2 calculated from their joint histogram. NMI does not depend directly on the intensities of the images but gives a measure of the

information shared by the two images. Therefore it is suitable for measuring the similarity between images coming from different modalities such as PET and CT, and is also suitable for images from the same modality which differ in intensity such as individual PET time frames and the averaged PET.

Optimisation method In order to solve Equation 3.1, usually an iterative updating procedure is employed such that in each step k , the current transformation parameters $\mathbf{T}_k$ are updated by taking a step in the search space with a step size of a_k in the direction $\mathbf{d}_k$:

$$\mathbf{T}_{k+1} = \mathbf{T}_k + a_k \mathbf{d}_k. \quad (3.8)$$

According to different definitions of a_k and $\mathbf{d}_k$ there are a wide range of optimisation methods. The step size a_k can be a user-defined constant or a decaying function of k . Another way is to use a *line search* that tries to minimise the cost function along the search direction $\mathbf{d}_k$:

$$a_k = \arg \min_a C(\mathbf{T}_k + a \mathbf{d}_k). \quad (3.9)$$

However the *exact* line search requires additional evaluations of the cost function or/and its derivative and more often an *inexact* line search is used that finds an a_k which gives sufficient reduction of C . Based on the expression for $\mathbf{d}_k$, the most commonly used methods are:

- **Gradient descent (GD)** takes steps in the direction of the negative gradient of the cost function:

$$\mathbf{T}_{k+1} = \mathbf{T}_k - a_k \mathbf{g}(\mathbf{T}_k) \quad (3.10)$$

where $\mathbf{g}(\mathbf{T}_k)$ is the derivative of cost function evaluated at $\mathbf{T}_k$. Various determi-

nations of a_k lead to variants of GD, where a_k is mostly defined as a decaying function of k or achieved by an inexact line search.

- **Quasi-Newton (QN)** is inspired by the Newton-Raphson algorithm which is given by:

$$\mathbf{T}_{k+1} = \mathbf{T}_k - [\mathbf{H}(\mathbf{T}_k)]^{-1} \mathbf{g}(\mathbf{T}_k) \quad (3.11)$$

where $\mathbf{H}(\mathbf{T}_k)$ is the Hessian matrix of the cost function at $\mathbf{T}_k$. The use of second order information gives better theoretical convergence than GD. However, the computation of $H(\mathbf{T}_k)$ and its inverse is expensive. There are a number of methods for approximating $H(\mathbf{T}_k)$, and the Broyden-Fletcher-Goldfarb-Shanno (BFGS) formula is the most popular to update the Hessian as the following:

$$\mathbf{H}_{k+1} = \mathbf{H}_k + \frac{\mathbf{q}_k \mathbf{q}_k^T}{\mathbf{q}_k^T \mathbf{s}_k} - \frac{\mathbf{H}_k^T \mathbf{s}_k^T \mathbf{s}_k \mathbf{H}_k}{\mathbf{s}_k^T \mathbf{H}_k \mathbf{s}_k} \quad (3.12)$$

$$\mathbf{s}_k = \mathbf{T}_{k+1} - \mathbf{T}_k \quad (3.13)$$

$$\mathbf{q}_k = \nabla C(\mathbf{T}_{k+1}) - \nabla C(\mathbf{T}_k) \quad (3.14)$$

- **Levenberg-Marquardt (LM)** can be thought of as a combination of Gauss-Newton and gradient descent methods for nonlinear least-squares problems in which the cost function is written as sum of squares, such as a similarity metric using SSD. When the solution is far from the correct one it behaves like a gradient descent and when near the correction solution it becomes Gaussian-Newton to have faster convergence.

3.2.2 Image registration of PET

PET-related image registration is largely conducted in the context of aligning a three dimensional PET image with functional information to images from another imaging modality with structural information and higher spatial resolution, such as CT and MRI, to localise the activity within anatomy for the purposes of tumour segmentation, blood flow estimation, ligand bio-distribution analysis as well as for attenuation correction (Klein et al. 1997; Slomka et al. 2003; Mattes et al. 2003; Slomka 2004; Townsend 2008; Slagmolen et al. 2009). The deformation involved in intra-subject PET to CT or PET to MR registration is physical in nature, thus it is straightforward to employ transformation models based on physical theories, such as linear elastic transformation (Tai et al. 1997; Slomka et al. 2003; Shekhar et al. 2005). Registration with a linear elastic model is driven by the body force that causes deformation and its accuracy limits it to small deformations and biological material with linear stress-strain relationship (Bajcsy and Kovacic 1989). Another option is optical flow (Klein et al. 1997; Dawood et al. 2008), which is used to track small motion in time sequences of images assuming intensity conservation and therefore its application is usually limited to correct for intra-frame motion within a short period of time that the intensity is assumed to have negligible change. There are other transformation models that do not describe the physical/biological processes that cause anatomical changes; instead they model the deformation by approximating/interpolating functions, such as B-spline Free-Form Deformations (FFDs) (Rueckert et al. 1999). These models have been used in PET to CT registration (Mattes et al. 2003; Slagmolen et al. 2009), as well as PET to MRI registration (Fox et al. 2007).

Image registration can use fiducial markers or the inherent image similarities to

achieve alignment. Due to the lack of anatomical definition and low resolution in PET images, the use of landmark-based similarity measures is problematic. In the inter-modality registration of PET to CT or MRI images, where the intensities do not follow a linear relationship, a spatial similarity based on information shared by the images is frequently used to measure the discrepancy, and is quantitatively optimised with respect to the transformation parameters to obtain an image match. The most commonly used is normalised mutual information (NMI) which does not rely on the amount of image overlap (Studholme 1999), and it can be formulated as a continuous and differentiable function of the transformation parameters using Parzen Windows (Thevenaz and Unser 2000). The differentiability provides great advantage for gradient-based optimisers to have superlinear convergence near the optimum (Marquardt 1963). Optimisation in a multi-resolution fashion is shown to produce robust results in PET-related registration (Studholme et al. 1995; Studholme et al. 1998). Both the capture range and the shape of the cost function can be improved with blurring at each resolution level (Studholme 1999).

3.3 Methods for PET motion correction

As pointed out in Sec. 3.1, subject motion is one of the fundamental issues in PET imaging. The simplest solution is to use fixation devices to reduce the motion in the first place. Head restraints are available to constrain the rigid head motion, but they are very uncomfortable over long scanning time (too much restraint can actually induce greater movement due to discomfort) and are not applicable to subjects for example with brain injury or obsessive-compulsive disorder (Mourik et al. 2009). The

development of motion correction methods dated back to the early 1990s (Daube-Witherspoon et al. 1990; Woods et al. 1992; Menke et al. 1996). Motion correction of PET data involves compensating the motion information in the PET data. So the task can be divided into two steps: motion measurement (or estimation) and motion compensation. Estimation of the motion information can be broadly divided into two categories: by PET data itself or by an external motion tracking system. Image-based motion estimation is typically based on applying the image registration techniques introduced in Sec 3.2.1 to the PET data, whereas the tracking-based estimation derives the motion parameters from extra data recorded by another device simultaneously with the PET scan. In the following the review of motion compensation methods, tracking-based and image-based methods for motion estimation will be given.

3.3.1 Motion compensation methods

Once the subject motion during the scan is known, the motion compensation can be either applied to the reconstructed PET images post-reconstruction, or as an integrated component in the PET image reconstruction from raw data, depending on which form the PET data is available. When the motion information is measured as motion events at different time points, it is possible to determine the frame timing based on these time points, and apply the motion transformation to each of the frames as by the multiple acquisition frames (MAF) method (Picard and Thompson 1997). However when the individual frames contain limited photon counts, the reconstruction of the PET images can become very challenging. Therefore LOR-based methods were developed (Menke et al. 1996; Bloomfield et al. 2003; Carson et al. 2003). The principle is to alter the LOR data in the projection space by the

spatial transformation in an event-by-event fashion, so that after the motion compensation, the "motion-free" raw data can be obtained before temporally rebinning the data. However it is difficult to establish the validity of altering the LOR data with deformable spatial transformations (for rigid transformation this is straightforward because a LOR is still a LOR after a rigid transformation). To overcome this, the motion information can be incorporated into the system matrix (Rahmim et al. 2004). To do so, the motion transformation can be combined with the system information matrix (in the form of a matrix or an operator). The system information matrix provides a forward mapping from the image space to the projection space, and the motion transformation provides a mapping from the image space to the image space, and it is straightforward to combine the two. To use this motion-incorporated system matrix in an iterative reconstruction algorithm (such as the maximum likelihood expectation maximisation MLEM algorithm), one only needs to work out the transpose of the motion transformation (the adjoint operator) and combine it with the transpose of the system matrix to have the motion-incorporated backward projector. In the following sections different ways of measuring the motion during a PET scan will be presented.

3.3.2 Tracking-based methods

Electromagnetic and acoustic systems were firstly used for motion monitoring (Rahmim et al. 2007), but had limited application either due to the interferences with the eddy currents in metal in the PET scanner or due to the dependence on the audible signals which are not acceptable for neurological studies. Later the optical motion tracking systems using optical cameras have been developed for estimating rigid head

motion, cardiac motion, respiratory motion, and other unwanted motion. Markers were initially used in these systems to place on a subject's surface at selected positions and record the positions of the markers during the PET scan. Algorithms were then applied, either to extract global motion (Raghunath et al. 2009; Koshino et al. 2010), or to decompose motion according to sources (Woo et al. 2003; Juslin et al. 2007). Since the motion is only measured on the surface of the subject, the deformation occurring inside is difficult to estimate with such approaches. Later the optical systems were used as a surface tracking method without markers and applied to estimate mostly the head motion in neurological studies (Carson et al. 2003; Bloomfield et al. 2003; Olesen et al. 2012). One example of these markerless optical motion tracking system is demonstrated with the neurological PET imaging system for freely moving lab animals (Kyme et al. 2011; Kyme et al. 2012). Also Microsoft Kinect, which is a motion-sensing device based on infrared projector and camera developed initially for gaming, has been shown to be able to offer high positional accuracy for markerless motion tracking in brain PET studies (Noonan et al. 2011; Noonan et al. 2012a), and in whole-body PET studies (Noonan et al. 2012b). A more extensive review on tracking-based methods can be found in (Noonan 2014).

The tracking-based methods mentioned above obtain the motion information purely from the motion tracking system and are therefore independent of the PET data. Such an approach can be applied for any tracer, but only in brain studies with rigid motion. For nonrigid motion correction, registration of the PET data to external reference data was investigated. In the case of cardiac and respiratory movements where the motion is periodic, a gating scheme is usually employed to divide the collected data into frames according to their phase in the motion cycle, and then data

are reconstructed individually (Cao et al. 2003; Mair et al. 2006; Lang et al. 2006; Kokki et al. 2007). By eliminating the motion between different phases, the blurring of final images can therefore be removed to some degree. The motion is estimated by conducting nonrigid registration of the individual PET frames or by registering the PET frame to images from another scan by other modality such as CT or MRI based on mutual information (Slomka et al. 2003; Juslin et al. 2007; Grgic et al. December 2009). One major issue of using gated scheme arises from the poorer statistics in gated frames than in the entire dataset and the reconstructed images contain more noise (Rahmim et al. 2007). Such methods are only capable of removing blurring caused by intra-frame motion to reduce resolution degradation and would not correct for the inter-frame misalignments. Also these methods can be affected by the noise and artefacts in the PET data. Very recently the development of a hybrid PET-MR imaging system allows for the estimation of nonrigid motion from the high quality MR data acquired simultaneously in the PET scan by registering the motion-deformed MR images (Chun et al. 2012; Grimm et al. 2013). Since the intensity of the MR image is consistent with the PET scan, such approaches present improved estimation of the non-rigid motion. Furthermore for the simultaneous PET-MR scanner in (Pedemonte et al. 2012) it is proposed to estimate the rigid brain motion jointly from both the MR and PET data, however it assumes a steady-state activity of the PET tracer and is therefore inappropriate for dynamic PET data.

3.3.3 Image-based methods

For tracking-based motion correction, when the motion information is obtained from the tracking system as the motion events, the correction can be regarded as conducted

in an event-by-event fashion. For the image-based methods, the motion correction is operated on time frames of PET data and is usually considered as a frame-by-frame approach based on pairwise image registration techniques. Registration strategies with different references and similarity measures were investigated to correct for the rigid motion between the dynamic PET brain images (Costes et al. 2009; Mourik et al. 2009). It is shown that the use of PET data before attenuation correction is more advantageous for the reason that 1) it eliminates the activity intensity bias in the reconstructed images caused by transmission-emission mismatch; 2) the cupping effect in attenuated PET images strengthens the head contour as a favourable feature for registration. In most brain PET studies the motion correction is performed using a mutual information-based frame-by-frame registration (Kreisl et al. 2010; Bohnen et al. 2012; Petrou et al. 2012; Bailer et al. 2013). However such a frame-by-frame registration method does not account for the changing tracer distribution in the dynamic PET frames and can cause inaccurate registration due to the limited spatial similarity.

To overcome the limitations of the conventional frame-by-frame registration methods that are based on only the spatial similarity measures, in this thesis the objective was to develop a kinetic model based registration framework for dynamic PET motion correction. The tracer kinetics is incorporated into the likelihood of tomographic PET data along with the subject motion via the generative model of dynamic PET data, and both kinetic parameters and motion parameters are estimated iteratively by maximising the likelihood function.

Chapter 4

PET spatio-temporal registration with blood-input kinetic model

The objective of this thesis was to develop a novel registration framework for dynamic PET motion correction, and overcome the limitations of the conventional frame-by-frame registration based solely on spatial similarity measures. To achieve this, the pharmacokinetic model which describes the underlying PET tracer kinetics is incorporated into the registration framework. This chapter describes the generative model for 4D PET data using a generalised pharmacokinetic model and subject motion model to formulate the likelihood of measured PET data. The generative model then allows for the solution of the maximum likelihood (ML) problem, which enables groupwise registration of the dynamic PET data constrained by the permissible kinetic behaviour of the radiotracer.

4.1 Modelling PET tracer kinetics in registration

To incorporate tracer kinetic information into the registration process, it is necessary to specify a tracer kinetic model that is able to describe the behaviour of the tracer data. This kinetic model should be able to describe differing tracer behaviour across all voxels in the image and ideally generalise to different radiotracers. In addition, the model should be robust to noise and computationally efficient as the kinetic information will be calculated at each step in which the cost function is evaluated.

However, when the voxel-by-voxel estimates of the parameters are required for the motion correction task, nonlinear regression as a time-consuming process becomes inappropriate. Thus, alternative PET data quantification approaches are required to estimate the tracer kinetic parameters on a per voxel basis.

As introduced in Sec. 2.3.2, graphical methods, Ichise multi-linear analysis and spectral analysis are based on linearised kinetic models and can be solved using linear regression, the applicability of these methods for the purpose of describing the tracer kinetics in the spatio-temporal registration framework will be discussed here.

The graphical methods make use of the asymptotic properties of the tissue response and provide only restricted information on the macro-parameters of interest, Such information is not sufficient for deriving the full description of the tissue response system. Therefore these graphical methods are not suitable for modelling the tracer kinetic in the registration framework proposed in this work.

In Ichise multi-linear analysis, the model fitting error can be expressed analytically in terms of measured $C(t)$ and $C_p(t)$, the gradient of the model fitting error in the cost function can be derived with respect to the transformation parameters, which is desirable for optimisation. However, a crucial drawback of this linearisation method

is that it is based on linear regression of a transformation of the measured data, which integrates the data over time, thus any noise and motion artefacts during the scan will weaken the validity of the estimation by propagating into the regression.

Spectral analysis generalises the tissue compartment structure for various kinetics as depicted by Figure 2.11, providing a way to describe PET data without *a priori* specification of the particular compartmental structure by solving the non-negative least squares problem. There are different algorithms for solving non-negative least squares. A concern here is whether the solution obtained is unique. In (Gunn 1996) a condition for uniqueness is presented using the NNLS algorithm proposed in (Lawson and Hanson 1995) based on double loops (one loop nested). The solution was discussed in the context of the Kuhn Tucker theorem which guarantees that a local minimum is obtained on termination of the algorithm. This theorem guarantees that, if a solution to the spectral analysis problem with F data points has N compartments and $N < F/2$, then the solution is unique.

To summarise, spectral analysis provides the ideal kinetic modelling approach for the registration framework. It is capable of describing nearly all linear compartmental systems with fast and slow kinetics, therefore characterises equally well the time course at individual voxel level with no need for *a priori* specification of the particular compartmental structure. It linearises the problem and achieves a fast modelling process. The use of basis functions also improves the robustness to noise and motion artefacts.

To perform parameter estimation, it is not necessary to use spectral analysis; other kinetic modelling techniques can be applied when appropriate.

4.2 Generative model of PET data

It can be seen that the tracer activity which generates the measured PET signal can be described by the tracer kinetics which are characterised by the blood input and the system impulse response function. Using the general compartment framework without explicitly choosing the configuration, spectral analysis can model the tracer activity at all voxels within the image.

To incorporate this tracer kinetic model into the registration framework for dynamic PET data, here the relationship between the underlying tracer activity and the measured PET data based on the imaging physics is introduced.

In PET imaging, the localisation of the annihilation enables the determination of the spatio-temporal distribution of the PET tracer and the detection of the two gamma photons facilitates the determination of absolute tracer concentration. The rate of emission of Gamma rays is a continuous function over the spatial domain of the patient's body and proportional to the local density of radioactive tracer.

For a given voxel at position $\mathbf{x}_j$, after the acquisition of multiple lines of response (LORs) data recorded by the PET scanner enables reconstruction of the tracer concentration at this voxel. The image intensity measured over time $\mathbf{Y}(\mathbf{x}_j)$ corresponds to the tracer concentration time course, and is related to the underlying tissue-target functional interaction which can be described by spectral analysis. Given the hidden state of the activity denoted by spectral analysis, with the parameters for this voxel as $\Phi(\mathbf{x}_j)$ and the basis function matrix Ψ , the generative model (Roche et al. 1999) describing this random process is:

$$\mathbf{Y}(\mathbf{x}_j) = \Psi\Phi(\mathbf{x}_j) + \epsilon(\mathbf{x}_j) \quad (4.1)$$

based on the assumption that there is additive measurement noise $\epsilon(\mathbf{x}_j)$.

4.2.1 Multivariate Gaussian model

For a voxel with coordinate $\mathbf{x}_j$, the probability density function $p(\mathbf{Y}(\mathbf{x}_j)|\Phi(\mathbf{x}_j))$ depends on the activity and the noise model for ϵ . The noise model here is random, related to counting statistics. The pure photon counts along the line of response (LOR) follow the Poisson process with expected value given by the activity. For reconstructed PET image data, however, the Poisson distribution is not appropriate to describe the total measurement noise. There are a number of noise sources in the PET image during the reconstruction and correction processes, and several additive sources of errors tend to form a Gaussian distribution. For this reason, a Gaussian distribution with zero mean is widely assumed in PET studies (Chen et al. 1991; Logan et al. 2001; Ichise et al. 2002), so

$$\epsilon(\mathbf{x}_j) \sim \mathcal{N}(0, \sigma^2(\mathbf{x}_j)) \quad (4.2)$$

where σ^2 is the variance.

Let $\mathbf{Y}_\Phi(\mathbf{x}_j)$ denote $\Psi\Phi(\mathbf{x}_j)$, which is the PET activity modelled by spectral analysis. The probability density function becomes:

$$p(\mathbf{Y}(\mathbf{x}_j)|\Phi(\mathbf{x}_j)) = \frac{1}{\sqrt{2\pi\sigma^2(\mathbf{x}_j)}} \exp\left(-\frac{(\mathbf{Y}(\mathbf{x}_j) - \mathbf{Y}_\Phi(\mathbf{x}_j))^2}{2\sigma^2(\mathbf{x}_j)}\right) \quad (4.3)$$

In the registration framework, motion is described by considering the movement of the hidden state for activity. Motion transforms the tissue location, thus the activity in a voxel $\mathbf{x}_j$ is correspondingly altered as a result of distorted tissue-to-voxel

mapping. Denote the motion function by $\mathbf{T}$, it operates on the voxel's coordinates, mapping from $\mathbf{x}_j$ to $\mathbf{T}^{-1}(\mathbf{x}_j)$. In reality $\mathbf{T}$ describes the subject motion during the PET scan and therefore is continuous over time. For reconstructed dynamic PET frames, however, $\mathbf{T}$ can be simplified as the misalignment between the temporal frames, to represent the inter-frame subject motion.

Considering the frame-dependent motion function $\mathbf{T}_k$, and the discrete temporal PET data points in the reconstructed images binned into a series of time frames, the probability density function is a multivariate Gaussian:

$$p(\mathbf{Y}(\mathbf{x}_j)|\Phi(\mathbf{x}_j)) = \prod_{k=1}^F \frac{1}{\sqrt{2\pi\sigma^2(\mathbf{x}_j, k)}} \exp\left(-\frac{(\mathbf{Y}(\mathbf{T}_k^{-1}(\mathbf{x}_j), t_k) - \mathbf{Y}_\Phi(\mathbf{x}_j, t_k))^2}{2\sigma^2(\mathbf{x}_j, k)}\right) \quad (4.4)$$

4.2.2 Formulation of the joint likelihood function

When the tracer kinetics that generates the measured PET image data is determined, the voxels of the image are conditionally independent, i.e.

$$p(\mathbf{Y}|\Phi) = \prod_{j=1}^M p(\mathbf{Y}(\mathbf{x}_j)|\Phi(\mathbf{x}_j)). \quad (4.5)$$

While the frame-dependent motion function $\mathbf{T}_k$ alters the coordinates, the likelihood of the measured data $\mathbf{Y}$ can be written as:

$$L(\Phi, \mathbf{T}; \mathbf{Y}) = \prod_{j=1}^M \prod_{k=1}^F \frac{1}{\sqrt{2\pi\sigma^2(\mathbf{x}_j, k)}} \exp\left(-\frac{(\mathbf{Y}(\mathbf{T}_k^{-1}(\mathbf{x}_j), t_k) - \mathbf{Y}_\Phi(\mathbf{x}_j, t_k))^2}{2\sigma^2(\mathbf{x}_j, k)}\right) \quad (4.6)$$

where $\mathbf{Y}$ is the decay-corrected radioactivity measured for the whole image, Φ is the parameter describing the tracer kinetics in Equation 2.16, and $\mathbf{Y}_\Phi$ is the predicted

PET data determined by Φ . $\sigma^2(\mathbf{x}_j, k)$ denotes the variance in the PET data because of the measurement noise. $\mathbf{T}_k$ is the time-dependent motion function to be estimated, $\mathbf{x}_j$ are the coordinates of voxel j , t_k is the middle time point for the k -th frame, and M and F are the numbers of voxels and time frames, respectively.

Neglecting the normalisation term for simplicity, the negative log-likelihood then becomes

$$-\log L(\Phi, \mathbf{T}; \mathbf{Y}) = \sum_{j=1}^M \sum_{k=1}^F \frac{(\mathbf{Y}(\mathbf{T}_k^{-1}(\mathbf{x}_j), t_k) - \mathbf{Y}_\Phi(\mathbf{x}_j, t_k))^2}{2\sigma^2(\mathbf{x}_j, k)} \quad (4.7)$$

4.3 Iterative optimisation

The negative log-likelihood can then be minimised iteratively using the iterated conditional modes (ICM) approach (Besag 1986). The iterations are illustrated in Figure 4.1. The iterative optimisations are equivalent to performing a spatial similarity minimisation to update $\mathbf{T}$, and a kinetic model fitting to update Φ .

4.3.1 Weighted least squares problem

For both the registration and kinetic model fitting steps, the noise variance term σ^2 allows for weighting of the data in order to minimise the variance on the estimates. There are various models proposed for σ^2 in PET data, to ensure the data points are weighted equally well with appropriate approximations. In this work modifications are made based on the model in (Yaqub et al. 2006) for decay corrected PET data:

$$\sigma^2(\mathbf{x}_j, k) = c \frac{\mathbf{Y}(\mathbf{x}_j, t_k)}{t_k^e - t_k^s} dcf(k) \quad (4.8)$$

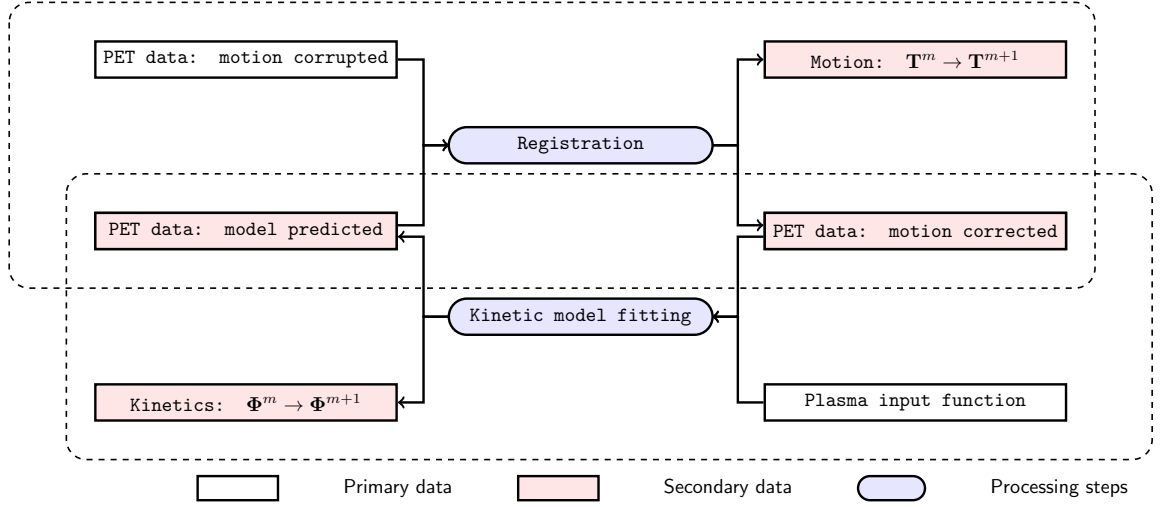


Figure 4.1: Flow diagram of iterations in the spatio-temporal registration algorithm. In the registration step, the motion function $\mathbf{T}$ for all temporal frames is updated, and the motion-corrected PET data is thus obtained as $\mathbf{Y}(\mathbf{T}^{-1}(\cdot))$ in Equation 5.1; in the kinetic model fitting step, the tracer kinetics parameter Φ is determined for all spatial voxels, and the model-predicted PET data is obtained as $\mathbf{Y}_\Phi$ in Equation 5.1.

where c is a constant that determines the noise level, $\mathbf{Y}(\mathbf{x}_j, t_k)$ is the average decay-corrected radioactivity of frame k with start time t_k^s and end time t_k^e . The decay correction function (for each frame) is given by $dcf(k) = \lambda(t_k^e - t_k^s) / [\exp(-\lambda t_k^s) - \exp(-\lambda t_k^e)]$, where λ is the decay constant of the isotope. At iteration $m + 1$, in the registration step, the subject motion function is updated from $\mathbf{T}^m$ to $\mathbf{T}^{m+1}$ in a groupwise fashion based on the minimisation of the differences between $\mathbf{Y}$ and $\mathbf{Y}_{\Phi^m}$. For the groupwise registration, Equation 4.8 is modified and $\sigma^2(\mathbf{x}_j, k) = c\mathbf{Y}_\Phi(\mathbf{x}_j, t_k)$ is used to provide a more equitable weighting of the PET frames to improve convergence of the optimisation problem. The activity used for weighting should be noise free, so $\sigma^2(\mathbf{x}_j, k) = c\mathbf{Y}_\Phi(\mathbf{x}_j, t_k)$. The possibly erroneous weighting by variances close to zero is avoided by employing a mask that excludes voxels that are considered to

contain mainly noise, with intensities averaged over time being lower than 10% of the maximum time-averaged value in the measurement. This allows for all the voxels to contribute similarly to the overall metric. By weighting according to its radioactivity, a voxel with low intensity can have a comparable impact to a voxel that has a high intensity value, which is expected to produce higher accuracy in estimating the motion function. In the kinetic model fitting step, weighting is introduced into the solution of the NNLS problem by the weighting matrix $\mathbf{W}$. Given the statistical independence of the frames, $\mathbf{W}$ is diagonal. These diagonal elements can be approximated from the total activity in the frame and the frame duration (Mazoyer et al. 1986), and $\mathbf{W}$ is calculated as $W_{kk} \propto \sum_{j=1}^M \mathbf{Y}((\mathbf{T}_k^{m+1})^{-1}(\mathbf{x}_j), t_k)/(t_k^e - t_k^s) dcf(k)$.

4.3.2 Simultaneous solution to the non-negative least squares problem

Here, the iterative image space reconstruction algorithm (ISRA) (Daube-Witherspoon and Muehllehner 1986) is used to solve the NNLS problem for multiple TACs simultaneously. For M TACs in the form:

$$\mathbf{Y} = \begin{pmatrix} y_{11} \cdots y_{1M} \\ \vdots \ddots \vdots \\ y_{F1} \cdots y_{FM} \end{pmatrix} \quad (4.9)$$

the iteration for the solution is written as:

$$\begin{aligned}\Phi_{ij}^{[l+1]} &= \Phi_{ij}^{[l]} \cdot \frac{[\Psi^T \mathbf{Y}]_{ij}}{[\Psi^T \Psi \Phi^{[l]}]_{ij}} \\ i &= 1 \dots N \\ j &= 1 \dots M\end{aligned}\tag{4.10}$$

The proof of convergence is given in (Scherzer 2011). In practice it is initialised by $\Phi_{ij}^{[0]} = 1$ (non-negative) and the iteration is stopped when $\forall i, j : |\Phi_{ij}^{[l+1]} - \Phi_{ij}^{[l]}| < 10^{-6}$. To account for different levels of noise at each time point, weighting is used to modify the data and basis functions accordingly. The NNLS problem is solved with $\mathbf{Y}$ replaced by $\mathbf{W}^{\frac{1}{2}} \mathbf{Y}$, Ψ replaced by $\mathbf{W}^{\frac{1}{2}} \Psi$, where $\mathbf{W}$ is the inverse of the covariance matrix. Calculation of $\mathbf{W}$ has already been discussed in Sec. 4.3.1.

4.3.3 Optimisation of the groupwise registration

Considering the weighting term in Equation 4.8:

$$\sigma^2(\mathbf{x}_j, k) = c \frac{\mathbf{Y}(\mathbf{x}_j, t_k)}{t_k^e - t_k^s} dcf(k)\tag{4.11}$$

$\mathbf{Y}(\mathbf{x}_j, t_k)$ should be noise free, so $\mathbf{Y}(\mathbf{x}_j, t_k) = \mathbf{Y}_\Phi(\mathbf{x}_j, t_k)$, and the negative log-likelihood in Equation 5.1 can be written as:

$$-\log L(\Phi, \mathbf{T}; \mathbf{Y}) = \frac{1}{2c} \sum_{k=1}^F \sum_{j=1}^M \left(\frac{t_k^e - t_k^s}{dcf(k)} \right) \cdot \frac{(\mathbf{Y}(\mathbf{T}_k^{-1}(\mathbf{x}_j), t_k) - \mathbf{Y}_\Phi(\mathbf{x}_j, t_k))^2}{\mathbf{Y}_\Phi(\mathbf{x}_j, t_k)}\tag{4.12}$$

To update $\mathbf{T}$ with a fixed estimate of Φ , the maximum likelihood problem becomes a

groupwise image registration problem. The cost function is a sum of a large number of squared residuals based on the formulation of the negative likelihood function. This special structure of nonlinear least squares for the cost function allows for optimisation using a Newton-like algorithm, which approximates the cost function using a quadratic function based on its gradient (first-order derivatives) and Hessian (second-order partial derivatives) at the current parameter estimate, and the parameters are updated as the quadratic's minimum. In practice, computing the Hessian is not always feasible thus approximations of the Hessian matrix are applied to improve the performance. Here in this work the Levenberg-Marquardt algorithm is used, which is a variation of the Newton method that approximates the Hessian by the product of gradient of residuals and uses the identity matrix for the Hessian to improve stability when the search of parameter goes into the negative curvature regions of the cost function.

For this purpose the gradient of the residuals needs to be calculated for the image registration. The transformation $\mathbf{T}_k$ ($k = 1 \dots F$) for all F PET frames is optimised simultaneously. If $\mathbf{T}_k$ is parameterised by vector $\mathbf{q}_k = [q_{k,1} \dots q_{k,R}]^T$, then the parameter space is constructed with $F \times R$ dimensions, with the parameter vector for all PET frames $\mathbf{Q} = [\mathbf{q}_1; \dots; \mathbf{q}_F]$.

Based on the negative log-likelihood, the residual vector $\mathbf{b}$ is constructed as:

$$\mathbf{b} = \begin{bmatrix} b_{1,1} \\ \vdots \\ b_{k,j} \\ \vdots \\ b_{F,M} \end{bmatrix} \quad (4.13)$$

where

$$b_{k,j} = \alpha_k [\mathbf{Y}_\Phi^{-1}(\mathbf{x}_j, t_k)]^{\frac{1}{2}} \cdot [\mathbf{Y}(\mathbf{T}_k^{-1}(\mathbf{x}_j), t_k) - \mathbf{Y}_\Phi(\mathbf{x}_j, t_k)] \quad (4.14)$$

$$\alpha_k = \left[\frac{(t_k^e - t_k^s)}{dcf(k)} \right]^{\frac{1}{2}} \quad (4.15)$$

α_k is the transformation-independent term.

The gradient matrix $\mathbf{A}$ can be written as

$$\mathbf{A} = \begin{bmatrix} \frac{\partial b_{1,1}}{\partial q_{1,1}} & \dots & \frac{\partial b_{1,1}}{\partial q_{F,R}} \\ \vdots & \ddots & \vdots \\ \frac{\partial b_{k,j}}{\partial q_{1,1}} & \dots & \frac{\partial b_{k,j}}{\partial q_{F,R}} \\ \vdots & \ddots & \vdots \\ \frac{\partial b_{F,M}}{\partial q_{1,1}} & \dots & \frac{\partial b_{F,M}}{\partial q_{F,R}} \end{bmatrix} \quad (4.16)$$

Then the update equation for $\mathbf{Q}$ using the Levenberg-Marquardt algorithm is:

$$\mathbf{Q}^{(n+1)} = \mathbf{Q}^{(n)} - (\mathbf{A}^T \mathbf{A} + w_{LM} \mathbf{I})^{-1} \mathbf{A}^T \mathbf{b} \quad (4.17)$$

where $\mathbf{A}^T \mathbf{b}$ is equal to 1/2 of the gradient, $\mathbf{A}^T \mathbf{A}$ is approximately equal to 1/2 of the Hessian matrix, $\mathbf{I}$ is the identity matrix and w_{LM} is the weight to enforce a steepest-descent step in the cost function regions of negative curvature where the Hessian approximation is not very good.

To update the transformation parameters $\mathbf{Q}$ for all PET frames, it is straightforward to see that $\mathbf{A}$ is sparse, i.e. $\frac{\partial b_{k,j}}{\partial q_{l,m}} = 0$ when $k \neq l$. This leads to an alternative optimisation in the groupwise registration.

Considering the residual $b'_{k,j}$ in the form of

$$b'_{k,j} = [\mathbf{Y}_\Phi^{-1}(\mathbf{x}_j, t_k)]^{\frac{1}{2}} \cdot [\mathbf{Y}(\mathbf{T}_k^{-1}(\mathbf{x}_j), t_k) - \mathbf{Y}_\Phi(\mathbf{x}_j, t_k)] \quad (4.18)$$

and

$$b_{k,j} = \alpha_k b'_{k,j} \quad (4.19)$$

Then

$$\mathbf{A} = \begin{bmatrix} \alpha_1 \frac{\partial b'_{1,1}}{\partial q_{1,1}} & \cdots & \alpha_1 \frac{\partial b'_{1,1}}{\partial q_{F,R}} \\ \vdots & \ddots & \vdots \\ \alpha_k \frac{\partial b'_{k,j}}{\partial q_{1,1}} & \cdots & \alpha_k \frac{\partial b'_{k,j}}{\partial q_{F,R}} \\ \vdots & \ddots & \vdots \\ \alpha_F \frac{\partial b'_{F,M}}{\partial q_{1,1}} & \cdots & \alpha_F \frac{\partial b'_{F,M}}{\partial q_{F,R}} \end{bmatrix} \quad (4.20)$$

Let

$$\boldsymbol{\alpha} = \begin{bmatrix} \alpha_1 & \cdots & 0 \\ \vdots & \alpha_k & \vdots \\ 0 & \cdots & \alpha_F \end{bmatrix} \quad (4.21)$$

$\boldsymbol{\alpha}$ is a diagonal matrix, with elements being the time/frame-dependent weighting.

Using $\mathbf{b}'$ and the corresponding $\mathbf{A}' = \nabla \mathbf{b}'$, $\mathbf{A}$ and $\mathbf{b}$ can be written as:

$$\mathbf{A} = \alpha \mathbf{A}' \quad (4.22)$$

$$\mathbf{b} = \alpha \mathbf{b}' \quad (4.23)$$

Then the update equation for $\mathbf{Q}$ in Equation 4.17 becomes

$$\mathbf{Q}^{(n+1)} = \mathbf{Q}^{(n)} - (\mathbf{A}'^T \mathbf{A}' + w_{LM}(\alpha^T \alpha)^{-1} \mathbf{I})^{-1} \mathbf{A}'^T \mathbf{b}' \quad (4.24)$$

This indicates when using Levenberg-Marquardt algorithm, if the steep-descent is not enforced, minimising the residuals $\mathbf{b}$ is mathematically equivalent to minimising the residuals $\mathbf{b}'$, and the negative log-likelihood function reduces to be

$$-\log L(\Phi, \mathbf{T}; \mathbf{Y}) = \sum_{k=1}^F \sum_{j=1}^M \frac{(\mathbf{Y}(\mathbf{T}_k^{-1}(\mathbf{x}_j), t_k) - \mathbf{Y}_\Phi(\mathbf{x}_j, t_k))^2}{\mathbf{Y}_\Phi(\mathbf{x}_j, t_k)}. \quad (4.25)$$

Then it is straightforward to find that for $\hat{\mathbf{T}}$ given by

$$\hat{\mathbf{T}} := \underset{\mathbf{T}}{\operatorname{argmin}} -\log L(\Phi, \mathbf{T}; \mathbf{Y}), \quad (4.26)$$

$\hat{\mathbf{T}}$ can be written as the set of $\hat{\mathbf{T}}_k$, i.e.

$$\hat{\mathbf{T}} = \{\hat{\mathbf{T}}_k\} \quad (4.27)$$

where $\hat{\mathbf{T}}_k$ is the estimated motion for the time frame k given by

$$\hat{\mathbf{T}}_k := \underset{\mathbf{T}_k}{\operatorname{argmin}} -\log L(\Phi, \mathbf{T}_k; \mathbf{Y}) \quad (4.28)$$

and

$$-\log L(\Phi, \mathbf{T}_k; \mathbf{Y}) = \sum_{j=1}^M \frac{(\mathbf{Y}(\mathbf{T}_k^{-1}(\mathbf{x}_j), t_k) - \mathbf{Y}_\Phi(\mathbf{x}_j, t_k))^2}{\mathbf{Y}_\Phi(\mathbf{x}_j, t_k)} \quad (4.29)$$

Thus the groupwise registration is equivalent to registering individual pairs of measured PET frames and the corresponding PET frames predicted by the kinetic model, when steep-descent is not enforced and Levenberg-Marquardt reduces to the Gauss-Newton algorithm, with a weighting term determined by the kinetic model-predicted PET frame $\mathbf{Y}_\Phi(\mathbf{x}_j, t_k)$.

Instead of using the image intensities directly, the proposed spatio-temporal registration framework scales both the moving and reference PET images by introducing the weighting term resulting from the measurement noise variance. The possible erroneous scaling by $\mathbf{Y}_\Phi(\mathbf{x}_j, t_k)$ close to zero is avoided by employing a mask that rules out voxels, which are considered to contain mainly noise, with intensities averaged over time being lower than 10% of the maximum time-averaged value in the measurement. This allows for all the voxels to contribute evenly to the overall metric. By scaling according to its radioactivity, a voxel with low intensity can have a comparable impact to a voxel that has a high intensity value, which is expected to produce higher accuracy in estimating the motion parameters.

4.3.4 Robust registration for brain PET images

For brain images, $\mathbf{T}$ represents the rigid transformation consisting of three translations and three rotations, for each time frame. The registration of scaled $\mathbf{Y}$ and $\mathbf{Y}_\Phi$ using sum of squared differences (SSQ) as the cost function yields the estimation of the rigid motion parameters. In order to achieve an efficient and accurate registration, a multi-

resolution approach is adopted in combination with a local optimisation method. This multi-resolution approach involves computing the cost function for resampled volumes with cubic voxel sizes from large to small. At each resolution level, the local optimisation takes the parameter estimates from the preceding resolution level as the initial transformation, and returns an estimate of the nearby local minimum of the cost function calculated on the current resolution level, to be passed on as the initial transformation to the next resolution level. To account for any possible drifting motion (large translations) of a subject, the registration is initialised using the spatial difference between centres of mass in $\mathbf{Y}$ and $\mathbf{Y}_\Phi$ for each dynamic PET frame. The centre of mass of a PET frame is defined as:

$$\mathbf{x}_c = \frac{\sum_{\mathbf{x} \in \Omega} \mathbf{Y}(\mathbf{x}, t) \cdot \mathbf{x}}{\sum_{\mathbf{x} \in \Omega} \mathbf{Y}(\mathbf{x}, t)} \quad (4.30)$$

where Ω is the imaged volume.

4.3.5 Summary

The **Algorithm 1** gives the overview of the spatio-temporal registration framework proposed in this Chapter for the dynamic PET data. The tracer kinetics is incorporated into the registration framework by the generative model, and by maximising the likelihood function in alternation between the kinetic parameters and motion parameters, the motion-corrected PET data is obtained for the subsequent analysis. The simulation-based validation and clinical evaluation will be presented in Chapter 6.

Algorithm 1: Spatio-temporal pharmacokinetic model based registration of 4D PET data

Input: Motion-corrupted PET data $\mathbf{Y}(\mathbf{x}, t)$ and measured plasma input function $C_P(t)$, with which the matrix of kinetic basis functions Ψ is computed using Equation 2.21.

Output: Motion-corrected PET data $\mathbf{Y}(\mathbf{T}^{-1}(\mathbf{x}), t)$. The estimated motion function $\mathbf{T}$ and tracer pharmacokinetic parameter Φ .

Initialization $\mathbf{T} = \mathbf{Id}$, $\mathbf{Id}(\mathbf{x}) = \mathbf{x}$, i.e. $\mathbf{Y}(\mathbf{T}^{-1}(\mathbf{x}), t) = \mathbf{Y}(\mathbf{x}, t)$;

while not converged do

- Do kinetic model fitting using $\mathbf{W}^{\frac{1}{2}}\mathbf{Y}(\mathbf{T}^{-1}(\mathbf{x}), t)$ and $\mathbf{W}^{\frac{1}{2}}\Psi$, calculating the kinetic parameter Φ by Equation 4.10 in Sec. 2.11, and the model-predicted PET data $\mathbf{Y}_\Phi = \Psi\Phi$;
- Selectively scale $\mathbf{Y}$ and $\mathbf{Y}_\Phi$ using $\sigma(\mathbf{x}_j, k) = \mathbf{Y}_\Phi(\mathbf{x}_j, t_k)^{\frac{1}{2}}$, ruling out the voxels containing mainly noise;
- Do image registration on scaled $\mathbf{Y}$ and $\mathbf{Y}_\Phi$ using SSQ as the cost function to obtain motion function $\mathbf{T}$ and the motion-corrected PET data $\mathbf{Y}(\mathbf{T}^{-1}(\mathbf{x}), t)$;

end

Chapter 5

Groupwise Image Registration of dynamic PET data in the absence of blood data

So far in this thesis the tracer kinetics have been described using a compartmental system and a measured plasma input function, which requires arterial cannulation and sometimes complex metabolite measurements. To avoid the need for arterial blood sampling and metabolite corrections, reference tissue methods have been developed which obviate the need for blood sampling and are well established for the quantification of receptor ligand binding.

In this Chapter, the registration framework proposed in Chapter 4 and evaluated in Chapter 6 is extended to allow for the application of reference tissue based pharmacokinetic models, widening the applicability of the registration approach to PET scans that only acquire dynamic tissue data. A generalised reference tissue

modelling approach is introduced and the subsequent technical issues of using the reference region-based model in the registration framework are considered, i.e. the performance of the cost function and the robustness of the optimisation.

5.1 Reference tissue models

5.1.1 General reference model and solution with basis pursuit denoising

In Sec. 2.3.3 it has been demonstrated that the plasma input function can be replaced by reference input obtained from the tomographic PET data on its own to model the tracer activities measured by the PET scanner in the imaged volume, thus avoiding the invasiveness and additional costs of arterial blood sampling and metabolite measurements. However, the analytical solution given by Equation 2.29 for a two-tissue compartment model leads to the need for linearisation to improve the computation and convergence, as discussed in Sec. 2.3.2. Further, it may not be the appropriate model order to describe the observed kinetics which will vary between tracers and regions.

Due to such reasons, similarly one can use the generalised reference model solved with basis pursuit denoising as introduced in 2.3.3. However for the purpose of incorporating it into the registration framework, a suitable strategy for determining the relaxation parameter μ in the model 2.32 is needed.

Determination of the relaxation parameter

μ regularises the number of compartmental components and should be determined

based on appropriate parsimony criteria. In (Gunn et al. 2002), μ is selected by leave-one-out cross-validation (LOOCV) using measured $\mathbf{Y}$. For the motion correction task, if determined by LOOCV using data with motion artefacts, μ could be too small, which would lead to overfitting of unwanted motion artefacts. Therefore, in the PET data registration framework μ is optimised using a different approach:

Firstly a numerical phantom is needed for the given tracer to provide reconstructed noiseless motion-free 4D PET data $\mathbf{Y}_0$ as the ground truth. In the volume, $\mathbf{y}_0$ can be sampled from $\mathbf{Y}_0$ for each voxel, and Gaussian noise can be added to simulate the measured data $\mathbf{y}$. Then a set $\mathbb{T} = \{z_1 \dots z_n\}$, $z_i = (\mathbf{y}, \mathbf{y}_0)$ can be obtained. For $\mathbf{y}$, the basis pursuit denoising regularised by μ can predict a fitted $f_\mu(\mathbf{y})$. For $\mathbb{T}$, the average squared error of f_μ is $R_\mu = \mathbb{E}(f_\mu(\mathbf{Y}) - \mathbf{Y}_0)$. Then the μ that minimises R will be chosen.

5.1.2 Simplified reference tissue model (SRTM)

As has been demonstrated in Sec. 2.3.2.2 and 5.1.1, the basis function approach using spectral analysis or basis pursuit provides an effective way of describing the tracer kinetics, with computational efficiency that allows the modelling on a voxel-basis to be incorporated into the registration framework, as well as the flexibility of describing the tracer-target interaction determined by any (arbitrary) compartmental structure. Due to the over completeness of the basis functions that guarantees the coverage of tracer kinetics, additional constraints are required to ensure a meaningful and robust solution. When a plasma input is available, spectral analysis imposes the non-negative solution on the basis function coefficients to lead to the unique solution, whereas with the reference input approach, basis function denoising relies on the introduction of a

penalty term, leading to a relaxation parameter that balances the fitting error and the sparseness to be determined. The relaxation parameter can be determined directly by the measured PET data, as proposed in (Gunn et al. 2002) using leave-one-out cross-validation (LOOCV), but this may potentially result in overfitting of the data with motion artefacts, causing the registration to fail in eliminating the motion artefacts. Although in this work an alternative way is proposed for determining the relaxation parameter based on the knowledge estimated from the PET data on the number of compartments involved in the underlying tracer-target interaction, it is extremely difficult to mathematically prove that this approach is completely robust against the motion. This motivates the option of employing a more parsimonious model such as the simplified reference tissue model (SRTM) (Lammertsma and Hume 1996), in which the tracer-target interaction is described by a single tissue compartment model, to describe or approximate the tracer kinetics in the registration framework.

It should be noted that SRTM is based on the assumption of a single tissue compartment to describe the kinetics in reference and target tissues, and neglects any blood volume contribution. Also the non-displaceable volume of distribution (V_T) is assumed to be homogeneous and the reference tissue is devoid of specific binding. According to (Salinas et al. 2013), bias in the estimated parameters can be introduced when these assumptions are not met, particularly when the compartmental topology of either the target tissue or the reference region is invalid. In practice, depending on the radioligand and the region, for a certain neuroreceptor study, it may be that additional compartment(s) would be required. The misrepresentation of measured PET data by SRTM due to these factors could affect the performance when the oversimplified model is incorporated in the registration framework. However,

SRTM may provide improved robustness against motion artefacts as compared to basis pursuit denoising which could suffer from overfitting if the relaxation parameter is sub-optimal. If the approximation of tracer kinetics using the single compartment is satisfactory, it is likely to be beneficial to use SRTM in the registration framework.

5.1.3 Extraction of reference input

So far, this Section introduces the tracer kinetic modelling approaches that avoid the invasiveness and cost associated with plasma input function sampling by using a reference region. Based on the fact that the reference tissue shares the same plasma input with the target tissue, a direct relationship can be formed between them to eliminate the plasma input in the modelling process. In order for the reference-based approach to be valid, the identification of a reliable reference region in the field of view of the imaged subject is crucial.

In principle the reference region has to be devoid of specific binding for quantification of specific binding outcome measures, however in practice this condition can be loosened if the goal is mainly image registration. Depending on the underlying biological/functional interaction in the study, there may be a number of regions that meet the criteria for a valid reference region. Often the cerebellum is used as it is mostly devoid of particular protein targets. The cerebellum is a separate structure attached to the bottom of the brain, making it easy to delineate this region anatomically. The delineation of the cerebellum and extraction of its time activity curve from the PET image data can be performed as follows: firstly align the subject's structural image (such as MRI) to the PET image, secondly warp a pre-segmented structural atlas to the subject's structural brain image and propagate the segmentation of cerebellum

to the subject's aligned structural image; finally apply this segmentation on the PET image and extract the reference input as the volume-averaged time activity curve in the cerebellum region.

For some PET tracers, however, a valid anatomically defined reference region does not exist. It can be that voxels devoid of specific binding do not construct a homogeneous structure that can be easily segmented as a whole, or even such voxels do not exist. In the first case, data clustering techniques can be applied to extract the reference input (Gunn et al. 1998). In the second case, for the purpose of describing the tracer kinetics, rather than estimating the absolute parameters for receptor binding quantification, a region with low specific binding is mathematically appropriate for deriving the reference input.

5.2 Generalised spatio-temporal PET registration

The reference tissue models discussed in the previous Section obviates the need for arterial sampling. These can be incorporated into the groupwise image registration framework introduced in Chapter 4 to widen the applicability and generalise the method.

5.2.1 Incorporation of basis pursuit denoising and SRTM

In Sec. 4.2, the negative log-likelihood function of measured PET data under the tracer kinetic parameter Φ and subject motion $\mathbf{T}$ is formulated as:

$$-\log L(\Phi, \mathbf{T}; \mathbf{Y}) = \sum_{j=1}^M \sum_{k=1}^F \frac{(\mathbf{Y}(\mathbf{T}_k^{-1}(\mathbf{x}_j), t_k) - \mathbf{Y}_\Phi(\mathbf{x}_j, t_k))^2}{2\sigma^2(\mathbf{x}_j, k)}$$

The model-predicted PET data generated by a reference tissue model (such as basis pursuit denoising or SRTM) as $\mathbf{Y}_\Phi$ can then be incorporated into this function to drive the registration. The calculation of the weighting term from the noise variance $\sigma^2(\mathbf{x}_j, k)$, the iterative optimisation, and the groupwise image registration can be performed in the same way that was described in Sec. 4.2. As discussed in Sec. 5.1.2, SRTM can be used in the registration framework for the whole algorithm for certain tracers for which the assumptions of SRTM are met, or for the initial steps to reduce the magnitude of motion artefacts, and as such to reduce the potential over fitting by basis pursuit denoising, to improve the registration performance for other tracers. Figure 5.1 shows the schematic illustration of the spatio-temporal PET registration algorithm with reference tissue model to correct for subject motion. To depict the 4D data, PET frames in the dynamic image are fused and a sagittal slice is shown for each data set.

Steps of the algorithm are denoted with numbers:

- Step 1 initialise the motion estimation using the identity function for $\mathbf{T}$;
- Step 2 extract the discrete reference data from the motion-corrected PET data $\mathbf{Y}(\mathbf{T}^{-1}(\mathbf{x}), t)$,
and generate the reference input function $C_R(t)$;
- Step 3 calculate the basis functions which are convolutions of the interpolated reference
input and pre-defined exponentials;
- Step 4 solve the kinetic model fitting;
- Step 5 register the original motion-corrupted PET data $\mathbf{Y}(\mathbf{x}, t)$ to the model-predicted
PET data $\mathbf{Y}_\Phi$ to update the motion estimation $\mathbf{T}$ and motion-corrected PET
data $\mathbf{Y}(\mathbf{T}^{-1}(\mathbf{x}), t)$;

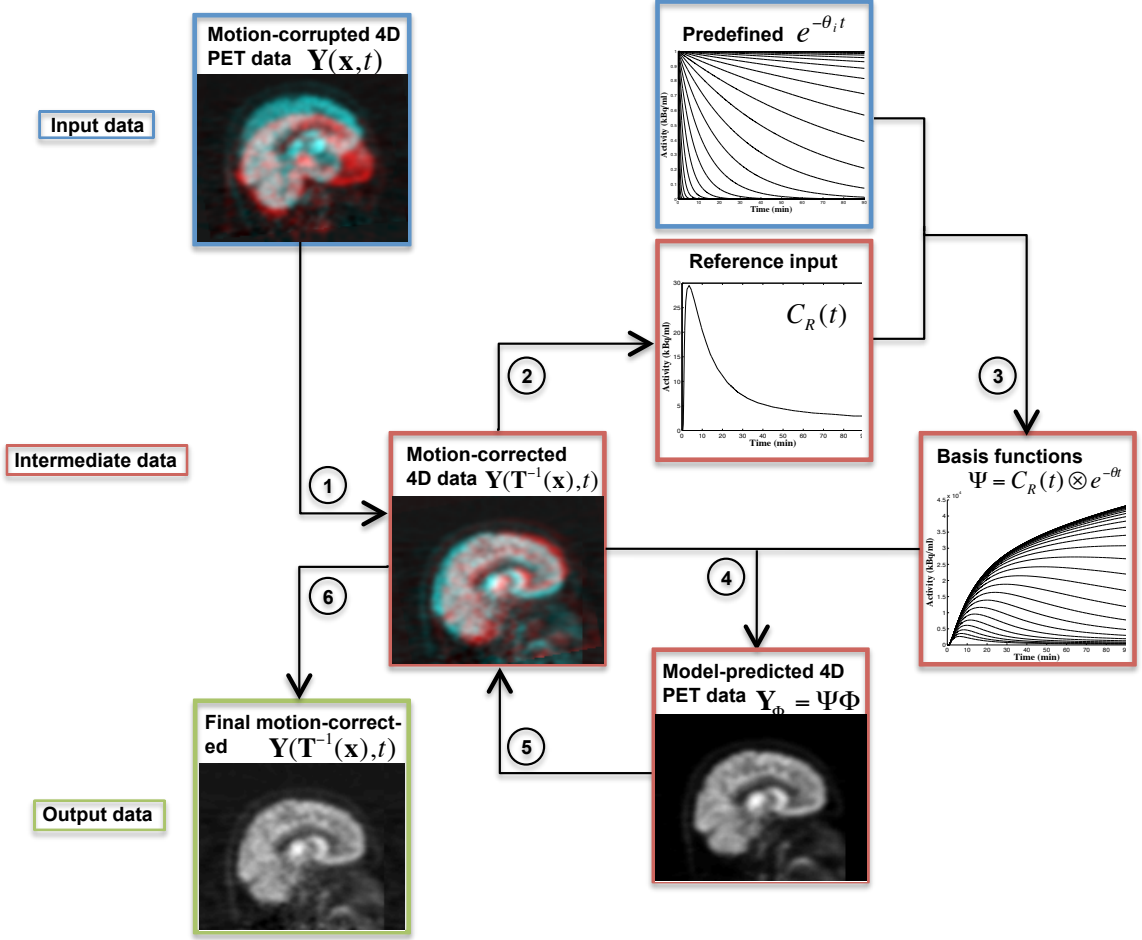


Figure 5.1: Spatio-temporal PET registration with reference tissue model

Step 6 obtain motion-corrected PET data $Y(T^{-1}(\mathbf{x}), t)$ when convergence is reached.

5.3 Conclusion

In this Chapter, two different reference tissue models to be incorporated into the groupwise image registration framework have been presented, namely basis pursuit denoising that uses a generalised model to apply different model order at each voxel,

and SRTM which employs an *a priori* selected compartmental model. The extension to allow for the application of reference tissue based pharmacokinetic models widens the applicability of the registration approach to PET scans that only acquire dynamic tissue data without arterial blood sampling and metabolite corrections to obtain a measured blood input function. The performance of incorporating these two different reference tissue models into the spatio-temporal registration framework is validated in Chapter 7.

Chapter 6

Simulation-based validation and clinical evaluation of PET spatio-temporal registration with blood-input kinetic model

In this Chapter, the validation and clinical evaluation of the groupwise image registration incorporated with spectral analysis (GIR_{SA}) developed in Chapter 4 is presented. The validation data sets were simulated in the context of $[^{11}\text{C}]\text{-(+)-PHNO}$ dopamine receptor imaging with known subject motion, and the accuracy of motion correction and the impact on receptor binding estimate were compared between the proposed GIR_{SA} method and the standard frame-by-frame (FBF) methods that are applied in many PET studies for motion correction. The clinical evaluation was performed on measured $[^{11}\text{C}]\text{-(+)-PHNO}$ data from a neurological study as well as on $[^{11}\text{C}]\text{Choline}$

data from an oncology study.

6.1 Validation on simulated brain dopamine receptor PET data

The proposed groupwise registration method incorporated with spectral analysis (GIR_{SA}) was applied to simulated $[^{11}\text{C}]\text{-(+)-PHNO}$ data sets to correct for the subject motion and then performed pharmacokinetic analysis to derive the outcome measure of interest BP_{ND} that quantifies the receptor availability. Assessment of performance was based on known spatial deformations for the simulations and on intra-class variability of the non-displaceable binding potential BP_{ND} for both the simulations and measured data. For $[^{11}\text{C}]\text{-(+)-PHNO}$, the two-tissue compartment model has been shown recently in (Searle et al. 2010) to be an appropriate model for kinetic analysis and was applied to selected regions of interest to obtain BP_{ND} as the outcome measure following completion of the groupwise image registration process.

6.1.1 Dynamic human PET data with $[^{11}\text{C}]\text{-(+)-PHNO}$

Data from human dopamine D3 receptor imaging studies with $[^{11}\text{C}]\text{-(+)-PHNO}$ was used for validation. Dopamine D3 receptors are involved in the pathophysiology of a number of neuropsychiatric conditions such as addiction, schizophrenia, and Parkinson’s disease (PD). $[^{11}\text{C}]\text{-(+)-PHNO}$ is a D3 preferring PET radioligand which has recently opened the possibility of imaging D3 receptors in the human brain *in vivo* (Wilson et al. 2005; Willeit et al. 2006; Gallezot et al. 2009; Searle et al. 2010). Measured clinical data from 10 healthy subjects were used. Each subject received a

high resolution T1 MRI scan, and a dynamic [^{11}C]-(+)-PHNO PET scan. [^{11}C]-(+)-PHNO was injected as an intravenous bolus over approximately 30 seconds at the start of a 90 minute 3D-mode dynamic PET acquisition. The PET images were acquired using a Siemens Biograph 6 PET-CT with Truepoint gantry, and MRI images with a Siemens Tim Trio 3T scanner (Siemens Healthcare, Erlangen, Germany). PET data were reconstructed using 2D filtered back projection with corrections for attenuation (based on a low-dose CT acquisition) and scatter. Dynamic data were binned into 26 frames (durations: 8×15 s, 3×1 min, 5×2 min, 5×5 min, 5×10 min). The PET voxel dimension is $2 \times 2 \times 2\text{mm}^3$. Arterial blood and metabolite data were also acquired, for details see (Searle et al. 2013).

6.1.2 Generation of a realistic [^{11}C]-(+)-PHNO phantom and motion-corrupted data sets

The proposed method was first validated using simulated data sets with known rigid-body motion corruptions. A realistic software phantom was developed using measured [^{11}C]-(+)-PHNO data, thus the phantom covers all biologically relevant regions in this study, including substantia nigra (SN) and ventral striatum (VST) which are important regions of interest for [^{11}C]-(+)-PHNO but not defined in the other more commonly available phantoms (such as Zubal brain phantom (Zubal et al. 1994)). Data from one subject, with visually negligible motion (summarised in Figure 3.1a), was chosen and spectral analysis was performed to the 4D volume in order to derive a motion free phantom.

The subject motion during a scan can be continuous and introduces in practice intra-frame motion blur and inter-frame misalignments in reconstructed PET data.

For most clinical settings, the reconstructed PET frames are provided for performing motion correction, and thus the intra-frame motion blur was not addressed in this project. Therefore in the simulation-based experiments only the performance of the registration methods for removing inter-frame misalignments was assessed. Using the motion-free realistic phantom, random translations and rotations for rigid head movements were introduced in each temporal frame with large, medium and small levels of motion consistent with observations from measured PET data. The motion simulation will be described in details below. For each motion level, 10 simulations were conducted, related to different types of ground truth motion. The displacement produced by motion corruption at each motion level can be found in Figure 6.3. In addition to the noise free simulations, noise using Equation 4.8 with $c = 16$ (normal level of noise in clinical data) and $c = 64$ (high level of noise) was added for each of the motion-corrupted data sets, for carrying out 5 simulations at each noise level, therefore generating $3 \times 10 \times (1 + 5 + 5) = 330$ data sets. Examples of the data sets are shown in Figure 6.1. The simulated translations and rotations were sampled from Gaussian distributions. To generate simulation data that reflects the level of motion observed in clinical practice, firstly the estimation of the rigid head motion data from previous clinical brain studies including 33 dynamic PET scans was derived based on a mutual information based frame-by-frame registration and manual realignment. In left-right (L-R), anterior-posterior (A-P) and foot-head (F-H) directions, the maximum of the estimated translations and rotations are $19.5788mm$ (L-R), $8.3290mm$ (A-P), $34.6392mm$ (F-H), and 5.3348° (L-R), 3.6702° (A-P), 5.2302° (F-H). Based on the amount of misalignment introduced, the estimated translations and rotations are grouped into high, medium and small levels, and the mean and standard deviations

at these three motion levels were derived respectively, as below:

	L-R (mm)	A-P (mm)	F-H (mm)
high	0.51 ± 3.63	0.21 ± 3.74	1.02 ± 6.49
medium	-0.21 ± 1.83	-0.02 ± 2.76	-0.56 ± 2.95
small	0.05 ± 0.81	0.04 ± 0.75	0.11 ± 1.24
	L-R ($^{\circ}$)	A-P ($^{\circ}$)	F-H ($^{\circ}$)
high	0.07 ± 1.20	0.23 ± 1.07	-0.30 ± 1.47
medium	-0.09 ± 0.80	0.06 ± 0.64	0.04 ± 0.65
small	0.07 ± 0.42	0.06 ± 0.41	-0.09 ± 0.47

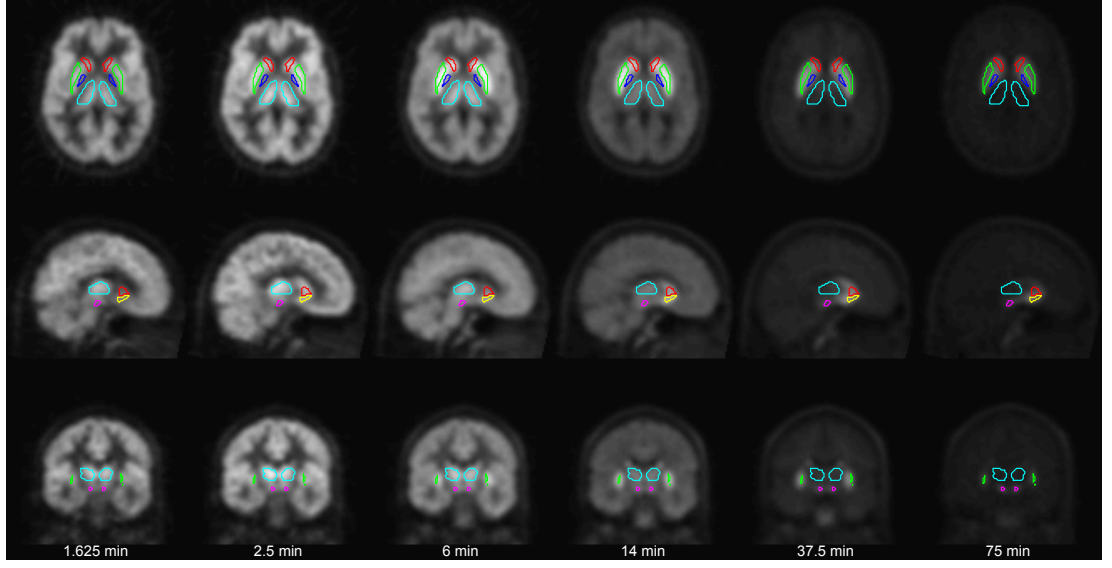
Table 6.1: *Head motion estimated from a previous study: mean $\pm$ std*

For each motion level, simulated translations and rotations were generated from the Gaussian distribution with the corresponding mean and standard deviation in Table 6.1. The simulated translations and rotations are combined and grouped again into high, medium and small levels and applied to individual PET frames. The 10 simulations therefore relate to different ground truth motions.

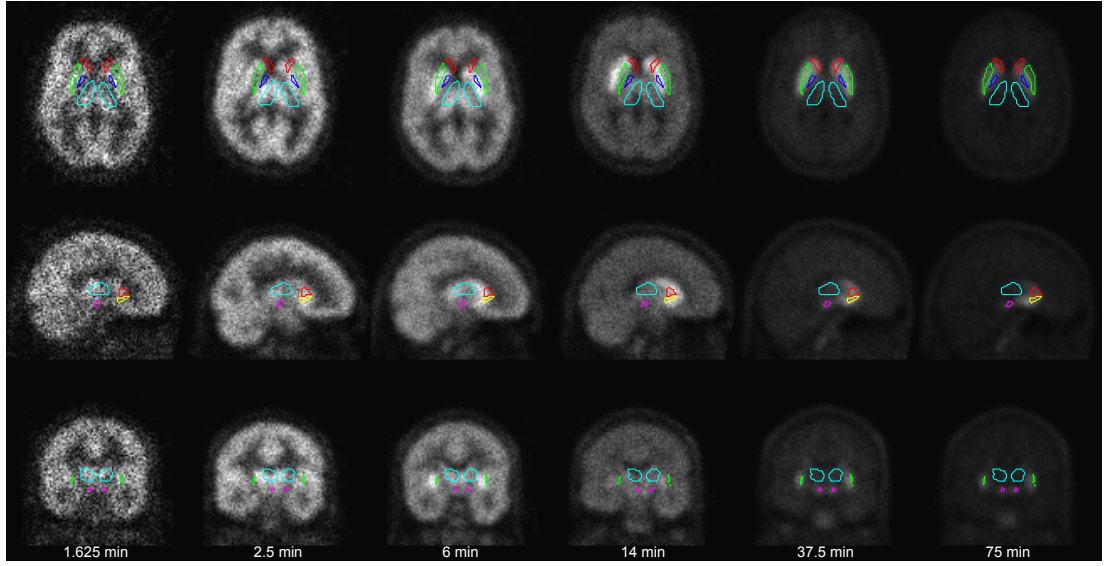
6.1.3 Measures for evaluation of registration

Registration error measurements

For a single frame k , the target registration error (TRE) (Fitzpatrick et al. 1998) is calculated as:



(a)



(b)

Figure 6.1: Two example data sets with motion corruption and noise generated using the phantom. Selected temporal frames (times are mid-frame times) are shown in orthogonal views for (6.1a) small motion with low noise, and (6.1b) large motion with high noise. Contours of the ROIs are depicted in colours as a reference to illustrate the motion misalignments. Colours corresponds to ROIs as: ■ SN, ■ VST, ■ CD, ■ PU, ■ GP and ■ TH.

$$\begin{aligned}
TRE_k &= \sqrt{\frac{1}{M} \sum_{j=1}^M \|\mathbf{x}_j - (\mathbf{T}_G^{-1} \circ \mathbf{T}_k \circ \mathbf{R}_k)(\mathbf{x}_j)\|^2} \\
\mathbf{T}_G &= \frac{1}{F} \sum_{k=1}^F (\mathbf{T}_k \circ \mathbf{R}_k),
\end{aligned} \tag{6.1}$$

where M is the number of voxels in the imaged volume, $\mathbf{x}_j$ is the coordinate of voxel j , $\mathbf{R}_k$ is the transformation for frame k determined from the simulated translations and rotations, $\mathbf{T}_k$ is the transformation for frame k obtained by the registration method, $\mathbf{T}_G$ describes the group transformation of all time frames, and $\circ$ denotes function composition. TRE_k is the root mean square distance between the motion-corrected position and the motion-free position of all voxels in frame k .

The purpose of the group transformation term can be explained with Figure 6.2. For frame k , the simulated motion $\mathbf{R}_k$ moves the original coordinate from $\mathbf{x}_j$ to $\mathbf{R}_k(\mathbf{x}_j)$ as in column b), and the registration $\mathbf{T}_k$ corrects the motion and moves the coordinate to $\mathbf{T}_k \circ \mathbf{R}_k(\mathbf{x}_j)$ as in column c). The registration realigns all the time frames and ideally the motion is corrected, but not necessarily moves $\mathbf{R}_k(\mathbf{x}_j)$ back to $\mathbf{x}_j$, i.e. $\mathbf{T}_k \circ \mathbf{R}_k(\mathbf{x}_j) \neq \mathbf{x}_j$, as illustrated in column c). In this case the target registration error calculated based on $\mathbf{T}_k \circ \mathbf{R}_k(\mathbf{x}_j) - \mathbf{x}_j$ will include a group transformation part that every time frame has in common but does not describe the amount of uncorrected motion. Therefore the group transformation term, calculated as the average of the transformation of all time frames during correcting the simulated motion, is applied to compensate the displacement between $\mathbf{T}_k \circ \mathbf{R}_k(\mathbf{x}_j)$ and $\mathbf{x}_j$, so that $\mathbf{T}_G^{-1} \circ \mathbf{T}_k \circ \mathbf{R}_k(\mathbf{x}_j) = \mathbf{x}_j$, $TRE_k = 0$ when the motion is perfectly corrected.

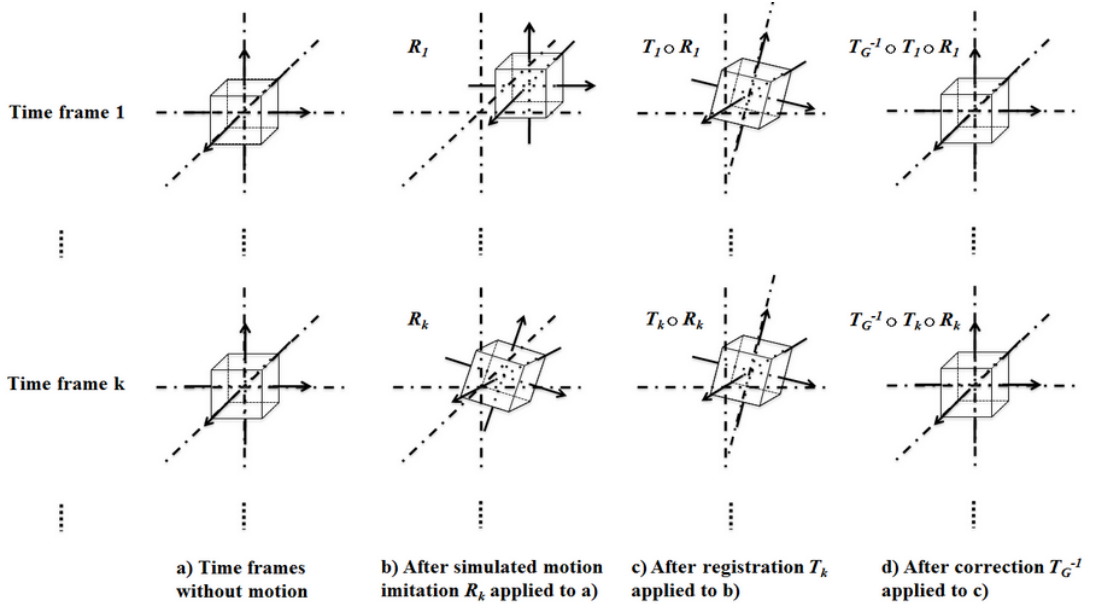


Figure 6.2: Group transformation to account for of dynamic images

6.2 Experiments and Results

For the purpose of evaluating the proposed groupwise image registration (GIR_{SA}) method, motion correction using GIR_{SA} and two conventional image similarity-based methods was performed on the $[^{11}\text{C}]\text{-(+)-PHNO}$ PET phantom data with noise and known motion artefacts that led to inter-frame misalignments. Both the registration errors and the recovery of the BP_{ND} estimates were investigated in comparison to the ground truth at various motion and noise levels to establish algorithmic performance in terms of robustness and precision. Additionally, all these methods were applied to clinical $[^{11}\text{C}]\text{-(+)-PHNO}$ PET data of 10 healthy subjects from a human dopamine D3 receptor imaging study, which included any motion that was present during acquisition. The intra-class variation of BP_{ND} across the subjects was examined as an indicator for removal of motion artefacts with reduced variability.

6.2.1 Registration of simulated PET data with motion

Registration methods

Firstly the proposed spatio-temporal GIR_{SA} registration method was applied to each data set. Secondly a frame-by-frame registration method using normalised mutual information (Studholme 1999) (FBF_{NMI} method) was also applied to benchmark the realignment performance. The FBF_{NMI} method registers all time frames to the one with highest tracer intensity.

Thirdly, another frame-by-frame registration method that registers consecutive time frames using the sum of squared differences SSQ (FBF_{SSQ} method) was also applied as a reduced version of the proposed GIR_{SA} method without the temporal constraints, to investigate the advantage of incorporating the kinetic modelling for temporal constraints.

All the methods were implemented in MATLAB 7.7 by extending functions available within Statistical Parametric Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm/>, 'spm_affreg' for GIR_{SA} and FBF_{SSQ} with the 'rigid' regularisation, and 'spm_coreg' for FBF_{NMI}). The default settings in SPM8 were used for the optimisation, interpolation, image smoothing and histogram smoothing, with details given in Table 6.2. All registrations were performed at 3 resolution levels with voxel sizes of 8mm , 4mm and 2mm .

6.2.2 Motion correction accuracy

With the known ground truth, the realignment performance can be quantified by the target registration error (TRE) (Fitzpatrick et al. 1998). Figure 6.3 illustrates the

cost function	SSQ	NMI
optimisation algorithm	Levenberg-Marquardt	Powell's Method
iteration limit	256	512
convergence criteria	δ cost function $< 10^{-4}\%$	δ translations and rotations $< [0.02, 0.02, 0.02, 0.001, 0.001, 0.001]$
interpolation algorithm	trilinear	to reduce the interpolation artefacts in the histogram the image is sampled with a random jitter to the sampled points
voxel size at resolution levels	8mm, 4mm, 2mm	8mm, 4mm, 2mm
filtering and smoothing	image smoothed before sampling	image is smoothed slightly, 256x256 joint histogram is smoothed

Table 6.2: *Details for the registration algorithms*

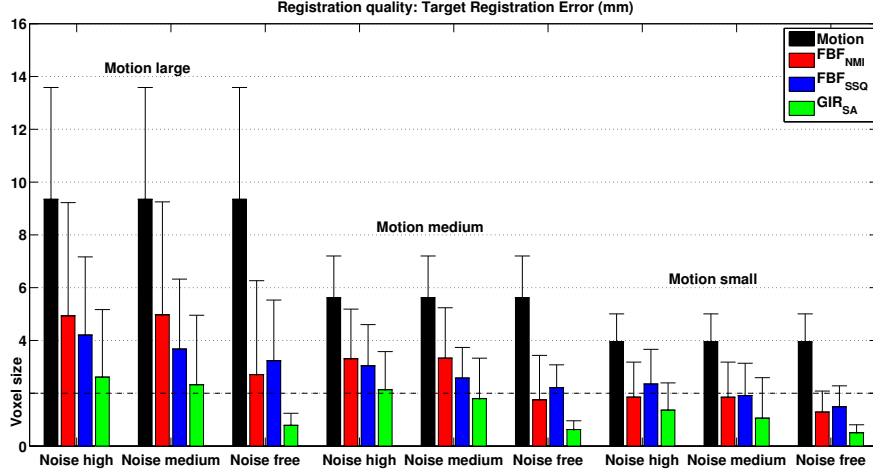


Figure 6.3: Registration performance of the proposed spatio-temporal GIR_{SA} in comparison with conventional FBF methods on simulated data sets. The dashed line indicates the voxel size. For each simulation, TRE_k from Equation 6.1 is averaged over all time frames. The mean TREs at each motion level and noise level before and after correction by GIR_{SA} and FBF methods are shown with the standard deviations as error bars. FBF_{NMI} denotes the frame-by-frame registration which registers all PET time frames to the one with highest tracer intensity using normalised mutual information (NMI). FBF_{SSQ} denotes the frame-by-frame registration which registers the time frames consecutively using the sum of squared differences. Compared to the FBF methods, the GIR_{SA} method achieves smaller registration error in all cases and achieves sub-voxel registration accuracy at low noise and motion levels.

performance of the spatio-temporal GIR_{SA} method and the FBF methods (FBF_{NMI} , FBF_{SSQ}). The TREs were first averaged for each simulation over all time frames, and then grouped into different noise levels and motion levels. The comparison between the motion artefacts and TREs indicates that the proposed method GIR_{SA} leads to more accurate registration results than the other frame-by-frame methods, with in general sub-voxel registration accuracy achieved in the low and medium noise cases.

In the proposed GIR_{SA} method, the introduction of the noise variance term in Equation 4.6 contributes to an improved registration accuracy, by scaling the images

by the noise term to provide each voxel with comparable impact in the calculation of the cost function regardless of its intensity. The incorporation of a pharmacokinetic model to capture the changing image information due to tracer kinetics helps to reduce the dependence on image intensity when registering the time frames. To further demonstrate this, Figure 6.4 shows the relationship between the sum of radioactivity in the frame across all voxels, and the registration performance which is assessed as:

$$R = \left(1 - \frac{TRE}{TRE_0}\right) \times 100\% \quad (6.2)$$

where TRE_0 and TRE are the registration errors before and after correction, respectively.

The spatio-temporal GIR_{SA} method showed much less dependence on the uptake of tracer with regard to registration performance, whereas the performance of a frame-by-frame registration of varying temporal images to a common reference depended heavily on the tracer activity in the frames. FBF_{SSQ} had smaller dependence on tracer activity and registration errors than FBF_{NMI} , however the registration errors were higher than those of the proposed GIR_{SA} with the temporal constraints imposed by the tracer kinetic model.

6.2.3 Influence of continuous motion on the motion correction performance

In practice the subject motion can be continuous and this results in motion blur within the reconstructed PET frames. Such artefacts degrade the image quality and would affect the performance of the developed motion correction methods in this

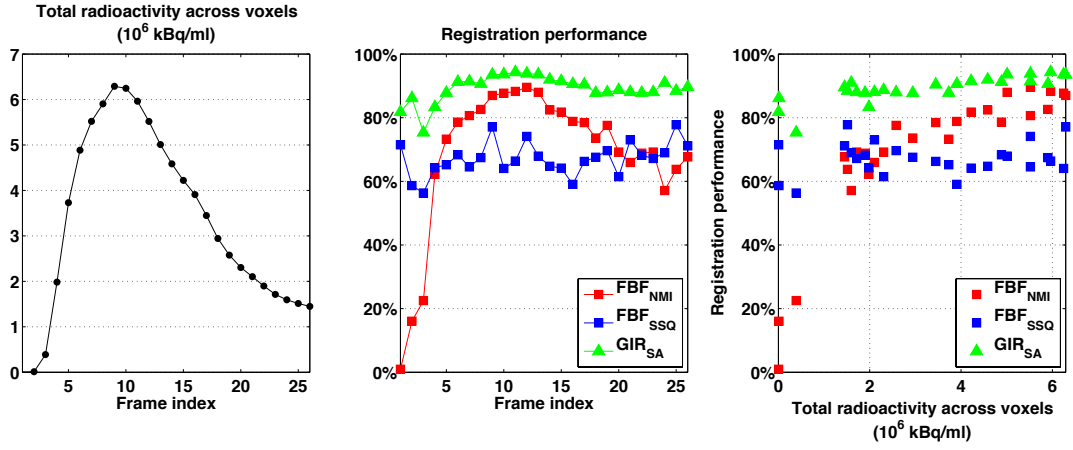


Figure 6.4: The dependencies of the spatio-temporal GIR_{SA} and FBF methods on the radioactivity in each frame. The results here are from the noise free simulations. Left: the total tracer radioactivity per time frame, showing the varying image intensities. Middle: the frame registration performance achieved by each method averaged over all motion levels, computed using Equation 6.2. The proposed GIR_{SA} method achieves on average $> 80\%$, the FBF_{SSQ} method $> 60\%$ and the performance of FBF_{NMI} decays with decreasing radioactivity. Note that in the first PET time frames there is tracer uptake in the blood only in a few voxels. Right: the registration performance versus frame radioactivity. The spatio-temporal GIR_{SA} method shows less dependence on the uptake of tracer with regard to registration performance.

thesis. Therefore the intra-frame motion was also added to the simulated data for assessing the motion correction performance.

Simulation of continuous motion

The motion blur caused by continuous intra-frame motion is introduced to the simulated dynamic PET data using a kernel-based method. The motion is represented by a kernel which describes the continuous trajectory of motion in the 3D space, and the convolution of a PET volume and this kernel produces the blurred PET volume with intra-frame motion, as illustrated in Figure 6.5, with 3 levels of blur (trajectory length equals to 10, 20 or 30 voxels respectively). The trajectory was generated as a random continuous path.

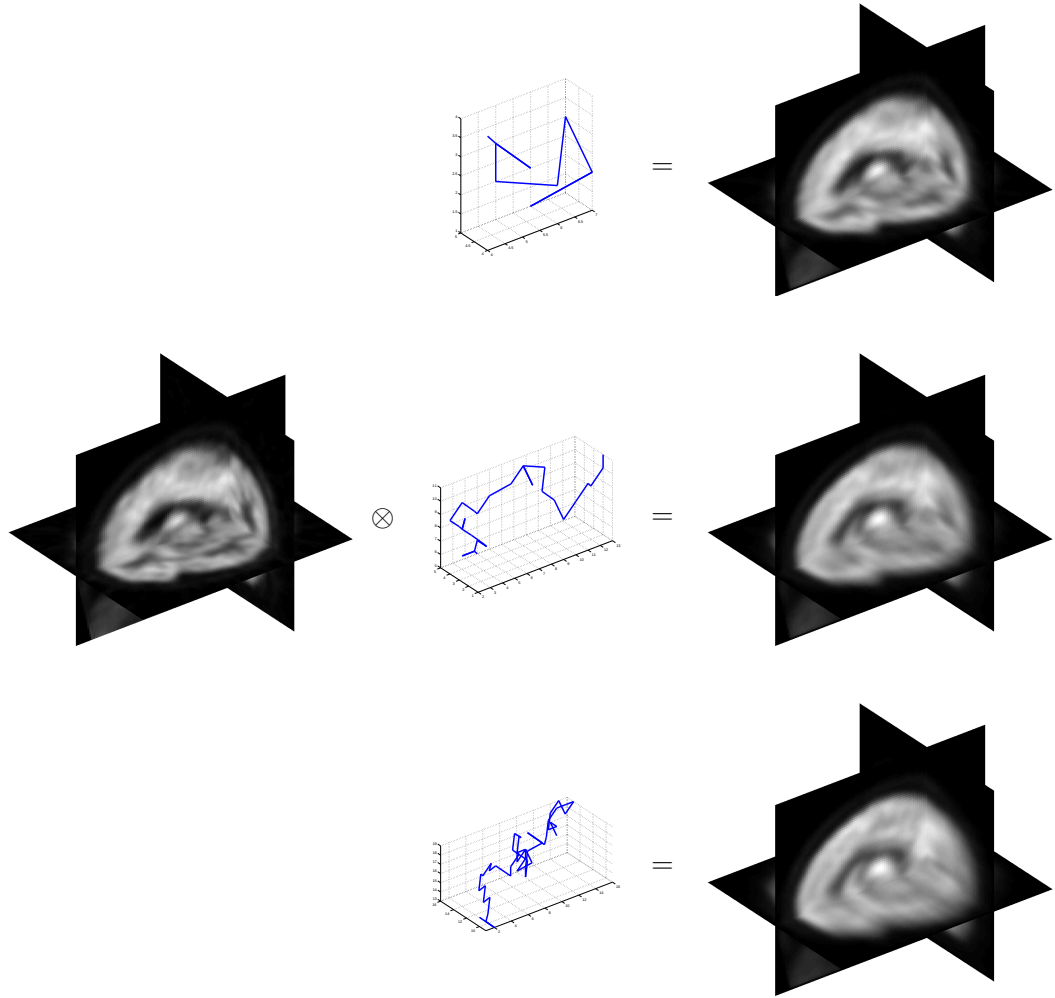


Figure 6.5: *Introduction of continuous motion blur using motion kernel. Left: PET volume with no motion blur. Middle: continuous motion trajectories, with length of 10, 20 and 30 voxels from top to bottom. Right: blurred PET volume after the convolution with the blur kernel.*

Motion correction in the presence of motion blur

For each frame of the simulated $[^{11}\text{C}]\text{-(+)-PHNO}$ data, in addition to the three

blur levels, which are low (L, with trajectory length 10), medium (M, with trajectory length 20) and high (H, with trajectory length 30), 3 noise levels (free, medium and high) were simulated as described by the previous experiment. The spatio-temporal GIR_{SA} method was applied to correct the inter-frame motion, and the FBF_{NMI} was performed as a comparison. The motion correction performance, quantified as the target registration errors (TREs), is shown in Figure 6.6.

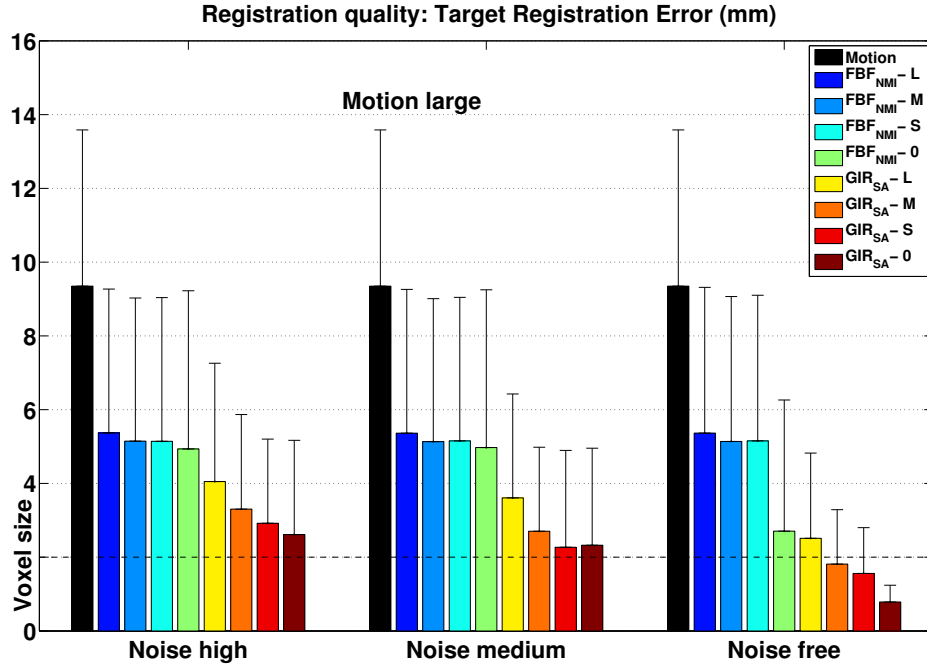


Figure 6.6: Registration performance of the proposed spatio-temporal GIR_{SA} in comparison with conventional FBF methods in the presence of intra-frame motion blur. The dashed line indicates the voxel size. L, M, S and 0 stand for large, medium, small and none continuous motion, with blur kernel length of 30, 20, 10 and 0 respectively.

It can be seen that the effect of the intra-frame motion can be described as blurring of the image. The degradation of the image quality due to this motion blur affects the performance of an image-based motion correction method. The proposed spatio-

temporal GIR method shows to be more robust than the conventional FBF method in the presence of intra-frame motion blur.

6.2.4 Impact on [^{11}C]-(+)-PHNO primary outcome measure (BP)

Delineation of brain regions of interest

In the [^{11}C]-(+)-PHNO PET images, six target ROIs relevant to dopamine receptor binding were analysed, as shown in Table 6.3.

Table 6.3: [^{11}C]-(+)-PHNO brain ROIs

ROI name	Abbr.
substantia nigra	SN
globus pallidus	GP
ventral striatum	VST
dorsal putamen	PU
dorsal caudate	CD
thalamus	THA

The target ROIs were manually defined based on the guidelines described in (Tziortzi et al. 2011). GP, VST, THA, CD and PU were delineated on the MR images whereas SN is defined on the integral of the subject’s dynamic PET image as its boundary is not evident on the T1 weighted MR image. The grey matter of the cerebellum (CER) was used as the reference region and is defined by applying a non-rigid registration of the ICBM152 template (<http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152Nlin2009>) using the normalised mutual information as a

cost function to the subject’s MR image, and applying the same non-rigid transformation to the corresponding brain atlas to match the subject’s MR image. Subsequently, the segmentation is propagated to the dynamic PET frames by rigidly registering the PET integral image to the MR with a mutual information cost function. The registration was implemented using Statistical Parametric Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm/>).

Dopamine receptor binding analysis

The two-tissue compartmental (2TC) plasma input model has previously been identified as an appropriate model for the quantification of basal ganglia ROIs with [^{11}C]-(+)-PHNO (Searle et al. 2013), and was applied to the time activity curves for each brain region.

The volume of distribution is derived using 2TC with a fixed blood volume correction of 5%. The binding potential relative to the nondisplaceable component, BP_{ND} is then calculated using cerebellar grey matter as the reference region devoid of specific binding (Tziortzi et al. 2011; Searle et al. 2013).

Binding analysis error

To investigate the impact of the motion correction methods on the tracer kinetic analysis, target and reference ROIs were applied on each motion-corrected data set to derive the regional TACs that then allowed for the estimation of V_T and BP_{ND} as described in Sec. 2.3.1. In order to consider only the influence of motion, the noise-free simulations were used here.

The impact of the motion corruption, as well as the motion correction on the binding potential BP_{ND} outcome measure are shown in Figure 6.7 for the six target

ROIs. Subject motion introduced a substantial error into the estimation of BP_{ND} for all ROIs, and the magnitude of the effect was dependent on the ROI's anatomical location, volume size, local neighbourhood, and the magnitude of the motion. After application of the motion correction approaches, the error in BP_{ND} was substantially reduced, with the spatio-temporal GIR_{SA} approach achieving the smallest bias and variance for ROIs SN, GP, CD, PU and TH.

For each ROI, the BP_{ND} recovery bias by the GIR_{SA} or FBF methods after correcting subject motion is quantified as:

$$BP_{ND}^{bias} = \frac{\mu(BP_{ND} - BP_{ND}^{true})}{BP_{ND}^{true}} \times 100\%, \quad (6.3)$$

where μ denotes the mean function, BP_{ND}^{true} is the ground truth value, BP_{ND} is obtained by applying either the conventional FBF methods or the spatio-temporal GIR_{SA} method to correct for the motion, for 30 noise free simulations at a range of motion levels.

The recovery bias in BP_{ND} estimation is plotted against the ROI volume in Figure 6.8, showing that the spatio-temporal GIR_{SA} method provided better results, especially for the smaller SN and GP ROIs for which the FBF methods had an underestimation of up to 25%. The small size and lower uptake in the local neighbourhood of these ROIs explain the underestimation of BP_{ND} . The target registration error obtained by the FBF methods as shown in Figure 6.3 in the noise-free simulations suggests that a registration error exceeding 2mm (the voxel size in this study) would be unsuccessful in recovering the BP_{ND} estimate in SN and GP from significantly motion-corrupted [¹¹C]-(+)-PHNO PET data.

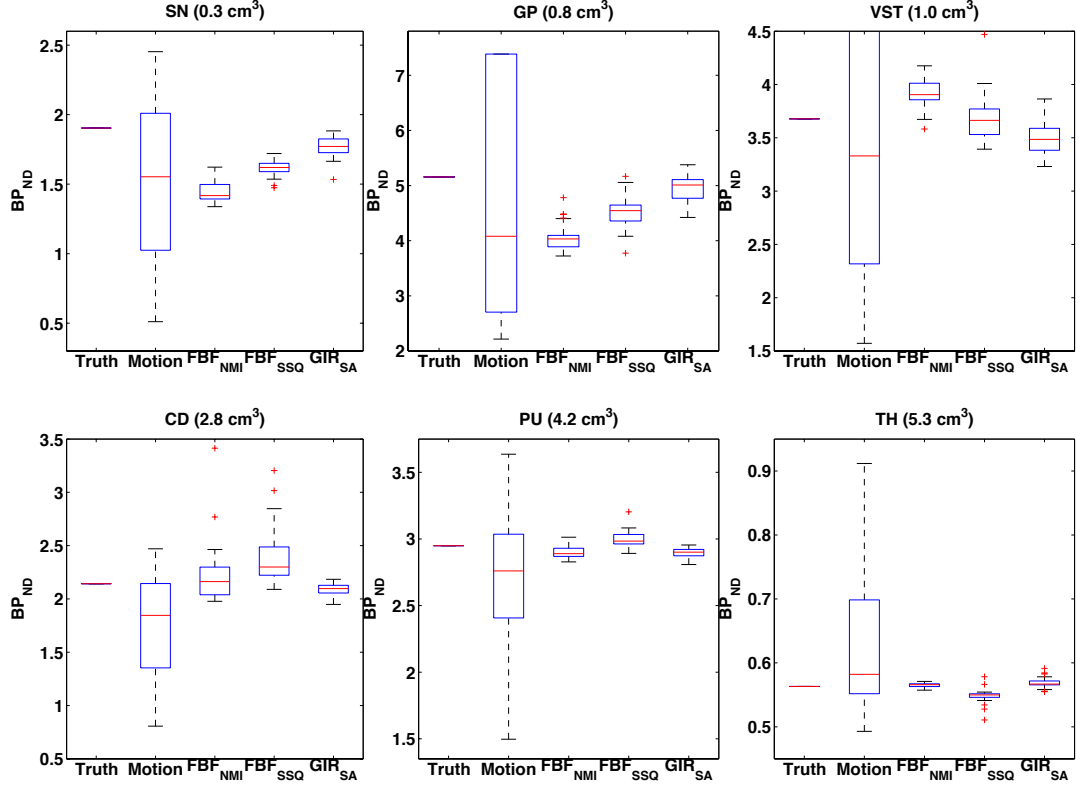


Figure 6.7: Binding potentials (BP_{ND}) of $[^{11}C]$ -(+)-PHNO within the function-related ROI of the simulated data sets. In each boxplot, the columns show from left to right the ground truth value in the motion-free phantom, the motion-corrupted estimates, and the values estimated after motion correction by FBF and GIR_{SA} methods. Apart from the variability for all regions, for smaller regions in the first row, subject motion introduces substantial bias in estimating BP_{ND} , which can be corrected quite successfully by the spatio-temporal GIR_{SA} method.

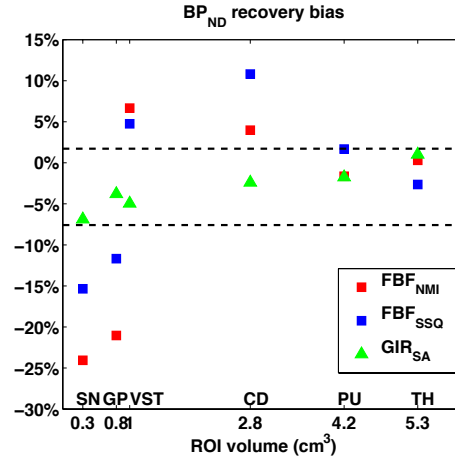


Figure 6.8: Bias of BP_{ND} recovery in motion-corrupted $[^{11}C]$ -(+)-PHNO PET data after applying FBF and GIR_{SA} methods. For substantia nigra (SN) and globus pallidus (GP), the inadequate reduction of motion artefacts by the FBF methods causes an underestimation of BP_{ND} . The dashed lines represent the narrow recovery bias for all ROIs achieved by the spatio-temporal GIR_{SA} method resulting from sub-voxel registration accuracy.

6.3 Evaluation on clinical dopamine receptor PET data

Following the validation of the proposed spatio-temporal GIR_{SA} method on the phantom data, the method was applied to clinical data from 10 healthy subjects (S1-S10) in which various motion patterns and noise levels are observed. Notably subject S8 exhibited a sliding motion of approximately 40mm downwards along the axial direction during the last 30 min of the PET scan. Without knowledge of the ground truth for the motion parameters in the time-dependent rigid transformation, the estimate of BP_{ND} was examined in the absence of any motion correction and following the application of the spatio-temporal GIR_{SA} , as well as the FBF methods. The motion correction was applied to the measured PET data directly. On a desktop workstation (CPU 3.20GHz, 16GB RAM) with MATLAB 7.7, the GIR_{SA} method took an average of 20 mins. The number of iterations for GIR_{SA} to converge depends on the amplitude of the motion and the noise level. Usually it takes 3 – 7 iterations to converge for a 26-frame dynamic image.

Figure 6.9 shows the BP_{ND} values obtained for the ROIs. The range of BP_{ND} in the absence of motion correction is shown to be well captured by the simulations in Sec. 6.2.1, as illustrated in Figure 6.7. For S8, in the uncorrected data, the overall underestimation of BP_{ND} in all ROIs was due to the subject movement that kept the ROIs out of the field of view in the last few frames. After applying the spatio-temporal GIR_{SA} method, as expected, there was an obvious reduction in the intra-class variation of BP_{ND} across the healthy subjects, which was evaluated by the

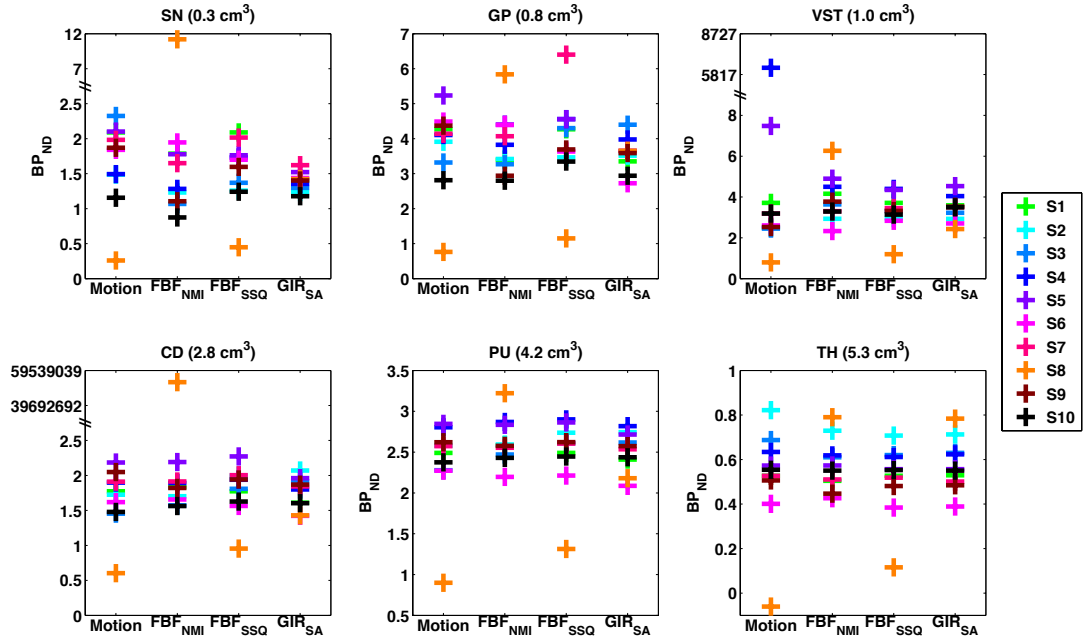


Figure 6.9: Binding potentials (BP_{ND}) of $[^{11}C]$ -(+)-PHNO within the six ROIs of the ten healthy subjects (S1-S10) before and after motion correction by the GIR_{SA} method, showing that the intra-class variability has been reduced after applying the GIR_{SA} method, especially for the small regions SN, GP and VST.

Table 6.4: Coefficient of variation of BP_{ND} before and after correction, for PET data from ten healthy subjects (S1-S10). The ROI abbreviations are presented in Table 6.3. Using the spatio-temporal GIR_{SA} method, the variability has been successfully reduced regardless of the ROI volume size.

ROI	SN ($0.3cm^3$)	GP ($0.8cm^3$)	VST ($1.0cm^3$)
w/o	0.3634	0.3295	3.1476
FBF _{NMI}	1.1261	0.2343	0.2857
FBF _{SSQ}	0.312	0.3342	0.2748
GIR_{SA}	0.0938	0.1338	0.1824
ROI	CD ($2.8cm^3$)	PU ($4.2cm^3$)	TH ($5.3cm^3$)
w/o	0.2646	0.2332	0.4501
FBF _{NMI}	3.1622	0.1069	0.2019
FBF _{SSQ}	0.1992	0.1841	0.3204
GIR_{SA}	0.1277	0.0950	0.1998

coefficient of variation (C_v) as:

$$C_v = \frac{\sigma(BP_{ND})}{\mu(BP_{ND})}, \quad (6.4)$$

where σ and μ are the standard deviation and mean across the ten subjects respectively, with values shown in Table 6.4 along with those from the FBF methods.

The unsuccessful realignment of PET data from subject S8 with substantial motion corruption by the FBF method led to unreliable BP_{ND} estimation, possibly because the registration algorithm failed as a result of being trapped in a local minimum since the overlap of information in the images is inadequate due to the lack of signal from part of the brain that was moving out of the scanner’s field of view. For this case the proposed GIR_{SA} method, which incorporates the temporal regular-

Table 6.5: *Coefficient of variation of BP_{ND} before and after correction with subject S8 removed as an outlier.*

ROI	SN ($0.3cm^3$)	GP ($0.8cm^3$)	VST ($1.0cm^3$)
w/o	0.2037	0.1700	2.9863
FBF _{NMI}	0.2704	0.1638	0.2180
FBF _{SSQ}	0.1865	0.2195	0.1598
GIR _{SA}	0.0993	0.1419	0.1566
ROI	CD ($2.8cm^3$)	PU ($4.2cm^3$)	TH ($5.3cm^3$)
w/o	0.1388	0.08155	0.2077
FBF _{NMI}	0.1103	0.07904	0.1703
FBF _{SSQ}	0.1143	0.0818	0.1664
GIR _{SA}	0.1144	0.08668	0.1708

isation through the tracer’s kinetic model, is more robust in mitigating the motion artefacts and gives a more accurate estimate of the outcome parameter of interest. In addition, Table 6.5 shows the intra-class variation of BP_{ND} with subject S8 removed as an outlier.

To relate the results to the simulation-based validation, Table 6.5 can be interpreted in relation to the BP_{ND} recovery errors in Figure 6.7. The pattern in reduction of the variation of BP_{ND} is consistent, with the GIR_{SA} method having greater reduction in smaller ROIs than the FBF method. However, the clinical data includes biological variability across the population of 9 individuals (subject S8 was excluded as an outlier) in contrast to the single subject simulation data.

6.4 Evaluation on clinical breast cancer PET data

When imaging neurological activities in the brain using dynamic PET, the subject's head motion is rigid without changes of the structure. For other parts of the body, such as below the neck, the motion is however more complicated in general because of the deformable nature of tissues. In other applications, such as for cancer imaging in the body, in a considerable amount of cases the tumour may change shape or morphology during the PET scan. Therefore, the validity of extending the proposed spatio-temporal registration framework for motion correction in the body for oncology PET data needs to be addressed. In this Section, the GIR_{SA} method proposed in this project is evaluated on a reproducibility study of breast cancer imaging using [¹¹C]Choline, previously published in (Kenny et al. 2010). It will be demonstrated that, for a solid tumour, when regional analysis is required instead of voxel-based analysis, the rigid approximation of the motion is effective to improve the reliability of the study.

6.4.1 Background of the clinical study

Choline is an essential component of cell membranes and is thus necessary for cell division. [¹¹C]Choline PET is a marker of choline kinase activity, which is upregulated in tumorigenesis, and as such is a promising imaging technique in cancer. The clinical study was designed to test the reproducibility of [¹¹C]Choline measurements in breast cancer.

Nine patients with histologic or cytologic evidence of breast cancer (American Joint Committee on Cancer stage II-IV) were recruited from the medical oncol-

ogy clinics at Charing Cross Hospital, London and had test and retest scans with $[^{11}\text{C}]\text{Choline}$. Ten lesions $\geq 2\text{cm}$ in total were found in these patients. Tumour $[^{11}\text{C}]\text{Choline}$ pharmacokinetics were characterised by K_1 , K_I and SUV_{max} , the parameters derived from kinetic modelling of the regional time activity curves from the segmented lesion, which represent the delivery of $[^{11}\text{C}]\text{Choline}$ from the plasma to tissue, the irreversible retention of $[^{11}\text{C}]\text{Choline}$ and the highest uptake of $[^{11}\text{C}]\text{Choline}$, respectively. The reproducibility of these parameters was evaluated using Pearson's linear correlation coefficient (r), the coefficient of variation (C_v) and the intra-class correlation coefficient (ICC).

6.4.2 Materials and Methods

Image data and motion correction

All patients were scanned on a CTI/Siemens HR+ ECAT962 tomograph. The field of view was centred on the target tumour lesion(s) that had been previously identified by clinical/radiological examination. Patients were scanned for 65 minutes in two-dimensional mode. Data were reconstructed by filtered back projection and binned into time frames as follows: 1×30 (background), 5×10 , 2×20 , 2×30 , 5×60 , 3×120 , 2×180 , 3×300 , and 3×600 seconds.

The motion correction was then performed on a cropped volume of the tomographic PET data that included the lesions, with the size of 20 to 30 voxels in each dimension. The concentration of $[^{11}\text{C}]\text{Choline}$ in arterial plasma was measured using continuous arterial blood sampling over time during the scan to quantify the arterial plasma input function and this enabled the application of spectral analysis. The rigid motion model was used with 3 translations and 3 rotations globally.

Regional analysis and reproducibility evaluation

Each lesion was delineated manually by visual inspection of 20 to 60 minutes summed image data. The time activity curve in each region of interest was extracted and normalised to the body surface area. With the regional time activity curve and the plasma input function, spectral analysis was used to perform kinetic analysis. The blood component estimated by spectral analysis was removed from the regional time activity curve for calculating K_1 , K_I and SUV_{max} . K_1 and K_I were calculated based on the basis function coefficients. SUV_{max} , which is the maximum standardised uptake value, was calculated by normalising the maximum [^{11}C]Choline activity data by the body surface area and injected dose.

Analysis of reproducibility of tumour [^{11}C]Choline pharmacokinetic parameters was done on a lesion-by-lesion basis. Individual parameter values for the test and retest scans were paired up to assess the reproducibility: the Pearson's correlation coefficient r as a measure of linear correlation (dependence), the coefficient of variation C_v as a normalised dispersion of the data, and the intra-class correlation ICC as a measure of the consistency of the measurements of the same subject (tumour).

6.4.3 Results

Realignment of the lesions

Figure 6.11 and 6.12 show an example of realigning the [^{11}C]Choline PET data with the proposed motion correction approach. The subject had large sliding motion for the later part of the scan. The motion is illustrated by manually segmenting the lesions on each of the PET frames and showing the contours of the delineated lesions on the time-averaged PET frames. The misalignment/alignment of lesions during

the scan is assessed using the Dice coefficient, a quantitative measure of how much the lesions moved during the scan. The Dice coefficient is a spatial overlap measure defined as:

$$Dice = \frac{2|X \cap Y|}{|X| + |Y|}$$

where X and Y are illustrated in Figure 6.10.

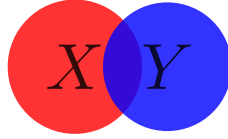


Figure 6.10: *Illustration of Dice coefficient as a measure of volume overlap*

From Figure 6.11 one can see that due to the subject motion, delineating the regions of interest (the lesions in this case) based on summed/averaged PET data can result in inaccurate time activity curves extracted for the subsequent kinetic analysis. For this specific study which was designed to evaluate the candidate tracer's capacity of imaging cancer, the time activity curves derived in this way can be unreliable in the sense that the corrupted tissue-to-voxel mapping causes normal tissue to move into the defined region and as such reduce the measured uptake of this tracer which could result in erroneous estimates of the tracer uptake or retention. In such cases, segmenting the lesions on a frame-by-frame basis could address this problem but is practically not only tedious and time consuming, but also subjective and prone to errors due to the low SNR of the data. Figure 6.12 shows that the misalignment is satisfactorily removed by the proposed motion correction method. The manual delineation of the lesions across the time frames is consistent, indicating the motion is well compensated, and the time activity curves derived are well recovered and preserve the tracer's behaviour in tumour cells.

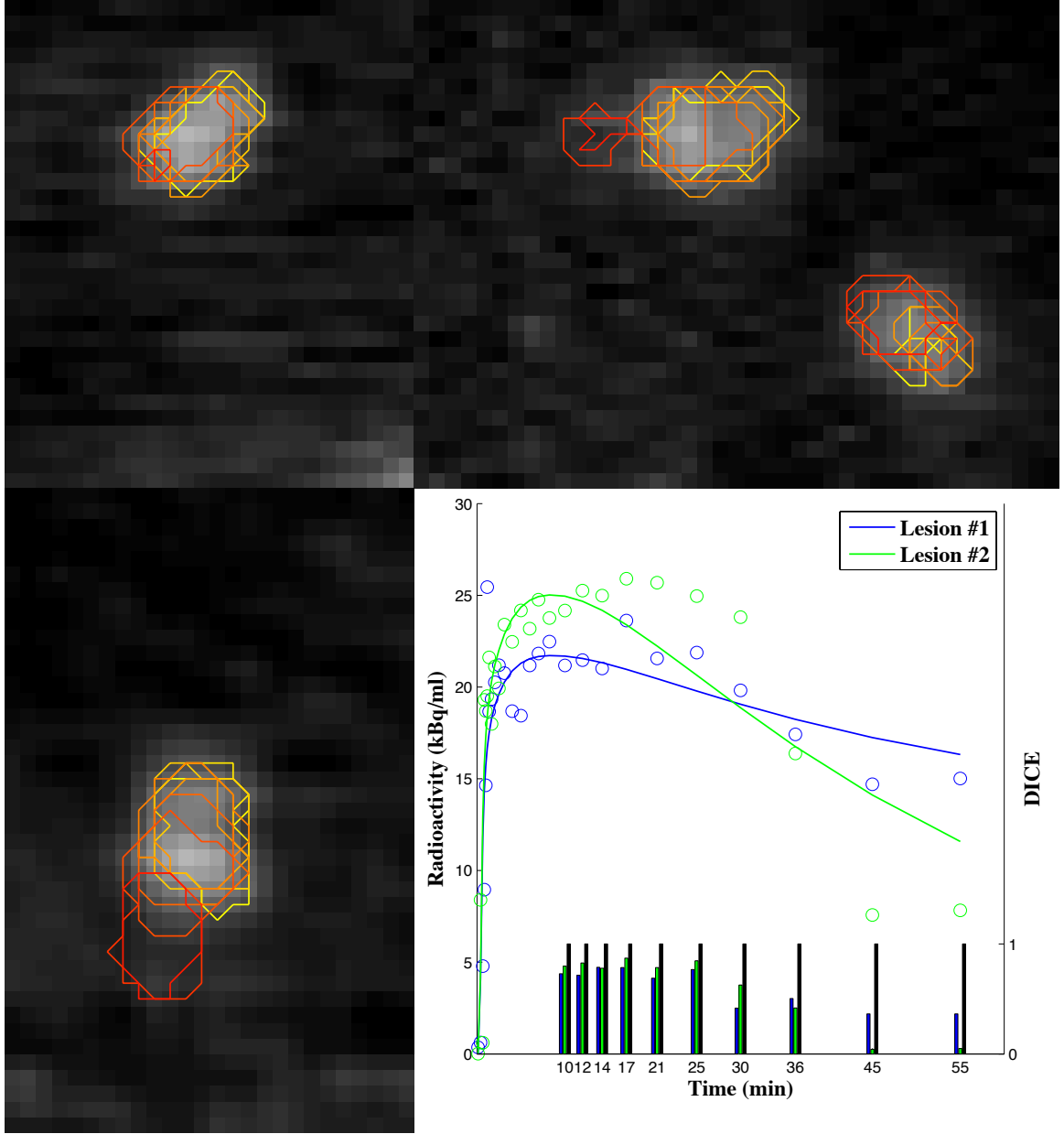


Figure 6.11: Tumour $[^{11}\text{C}]\text{Choline}$ data before motion correction. On the orthogonal views, $[^{11}\text{C}]\text{Choline}$ PET data averaged over 20 - 60 min is shown. The motion of lesions is illustrated by the contours of two lesions on each time frame. The colour of the contours changes from yellow to red during time. Bottom right: time activity curves of these two lesions in circles, with model fits shown in curves. The overlap of the lesion on each time frame with the manual delineation by clinicians based on the summed image is also shown as Dice, with the perfect overlap Dice value being 1.

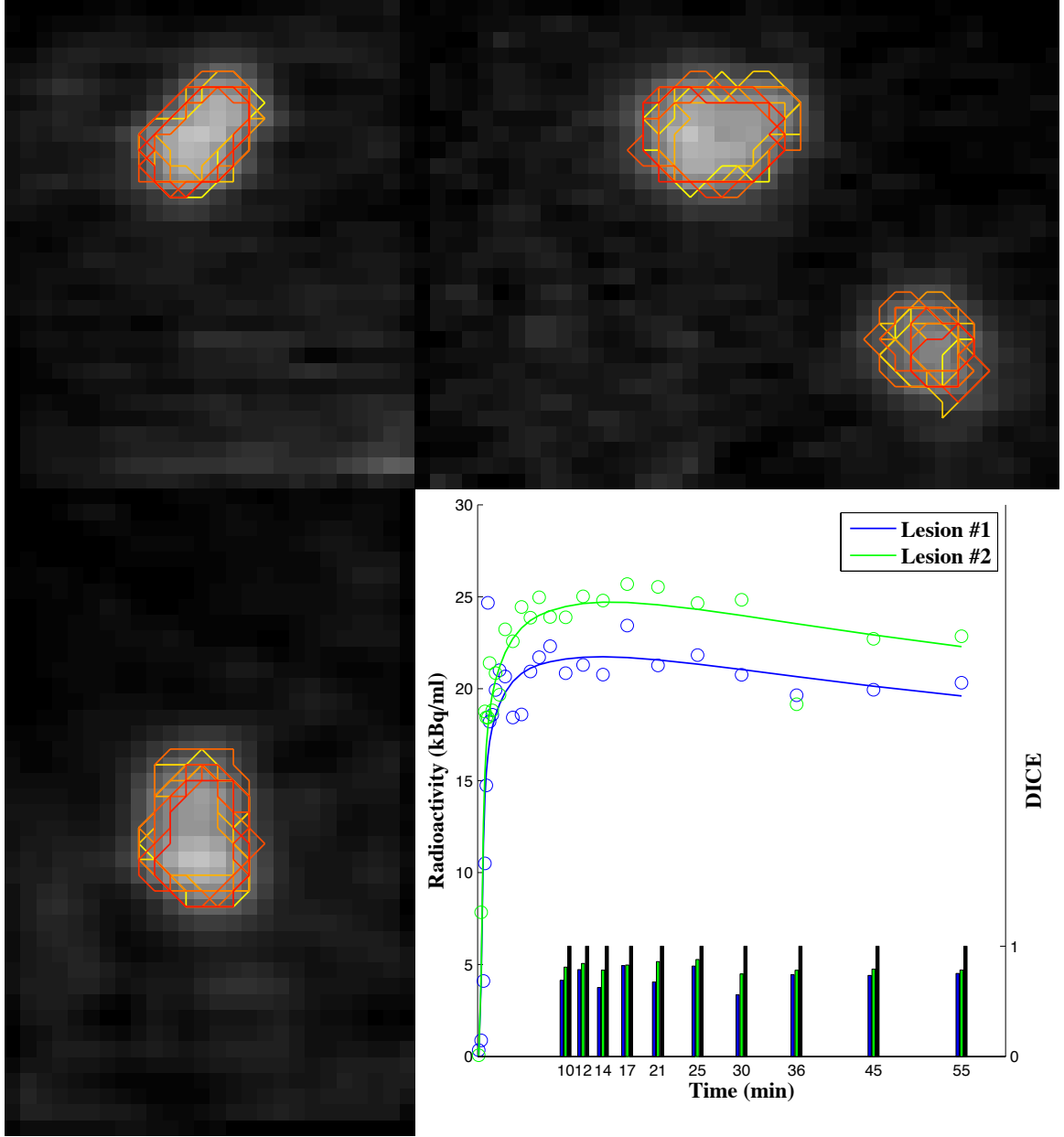


Figure 6.12: Tumour $[^{11}\text{C}]\text{Choline}$ data after the proposed motion correction. On the orthogonal views, $[^{11}\text{C}]\text{Choline}$ PET data averaged over 20 - 60 min is shown. The contours of two lesions on each time frame are illustrated. The colour of the contours changes from yellow to red over time. Bottom right: time activity curves of these two lesions in circles, with model fits shown in curves. The overlap of the lesion on each time frame with the manually delineation by clinicians based on the summed image is also shown as Dice, with the perfect overlap Dice value 1.

Improved reproducibility in tumour pharmacokinetic parameters

Table 6.6 shows the reproducibility of [^{11}C]Choline-PET in breast cancer before and after motion correction for the 9 subjects with 10 lesions.

Table 6.6: *Reproducibility of [^{11}C]Choline-PET in breast cancer lesions before and after motion correction by the proposed GIR_{SA} . The irreversible retention of [^{11}C]Choline K_I is the kinetic parameter of which the reproducibility is improved the most.*

	r		C_v		ICC	
	before	after	before	after	before	after
K_1	0.7047	0.6771	0.1080	0.1135	0.7119	0.6917
K_I	0.2139	0.8217	0.2990	0.0983	0.2233	0.7894
SUV_{max}	0.7285	0.7605	0.1126	0.0976	0.7051	0.7509

6.4.4 Discussion

In the [^{11}C]Choline PET study, it has been demonstrated that the proposed image-based motion correction method GIR_{SA} (groupwise image registration with spectral analysis) can effectively remove the subject motion. Given that the pharmacokinetic analysis on a regional basis is required, the rigid motion model is sufficient for re-aligning the regions of interest to generate reliable time activity curves for analysis, although in reality the lesion in flexible organs such as breast follows a deformable motion pattern. Attempts to apply affine or deformable motion models in this study (data not shown) in fact suggested further constraints are needed to regularise the complex motion model, given the poor SNR and resolution of the PET data. By reducing the variability in estimating the kinetic parameters by minimising motion artefacts, the reproducibility in this test-retest study is improved, thus increasing the

confidence of the study. Among the pharmacokinetic parameters, K_I which describes the retention of the tracer, is more sensitive to subject motion than K_1 and SUV_{max} as it depends mostly on the slow kinetics of the tracer in late frames which can be easily impacted by the subject motion.

6.5 Conclusion

A fully automated spatio-temporal image registration technique that was developed in Chapter 4, was shown to remove motion artefacts in reconstructed dynamic PET images, providing reliable estimation of the functional parameters of interest in neuroreceptor imaging studies. The method is embedded in a maximum likelihood framework, with the tracer kinetics described by spectral analysis, a data-driven pharmacokinetic modelling approach that estimates the appropriate compartmental equation from the data itself. For brain imaging, the subject motion is described by a rigid motion model of 3 translations and 3 rotations. The method reduces the misalignment of the time frames and updates the tracer kinetic modelling of a measured 4D PET data set during the iteration steps.

The validation using simulated $[^{11}\text{C}]\text{-(+)-PHNO}$ PET data with ground truth at a wide range of motion levels and noise levels demonstrates good quality registration of the misaligned time frames by the GIR_{SA} method. In contrast to the conventional frame-by-frame registration methods based only on image similarity measures, the ability to achieve sub-voxel registration error by incorporating the tracer kinetics allows for a more reliable estimation of the outcome measure of interest as indicated by the lower recovery bias and error. For regional kinetic analysis, the motion artefacts would impose a more substantial deviation for smaller ROIs. For $[^{11}\text{C}]\text{-(+)-PHNO}$ binding, the misalignment above 2 mm could lead to up to 25% underestimation in the receptor density for substantia nigra (SN) and globus pallidus (GP), as determined from the simulations. Segmentation of the ROIs is also important for regional kinetic analysis and segmentation errors will introduce inaccuracies in BP_{ND} estimation for $[^{11}\text{C}]\text{-(+)-PHNO}$. However, the purpose of this work was to develop and evaluate a

registration method for motion correction in dynamic PET data, therefore the method proposed in (Tziortzi et al. 2011) was adopted to delineate [^{11}C]-(+)-PHNO binding regions robustly and minimise the impact of segmentation errors.

In addition, the proposed method was applied to real clinical data from ten healthy subjects with [^{11}C]-(+)-PHNO to quantify its performance indirectly by measuring the intra-class variability in the biological outcome measure of interest across the population. [^{11}C]-(+)-PHNO is a challenging tracer for image registration as it does not have a large cortical signal as a spatial feature. It also has a range of kinetics as depicted in Figure 3.1, including particularly slow kinetics in the pallidum. The scans were affected by various types of subject motion and noise levels. The approximate 40mm sliding motion of a subject during the last 30 mins of the scan was successfully removed by the proposed method, as determined by visual inspection. The intra-class variation of the BP_{ND} values in these healthy subjects was reduced after applying the motion correction method, either with or without the inclusion of the subject mentioned above as an outlier. This provides additional indirect evidence of the appropriate realignment of the motion-corrupted PET images by the proposed spatio-temporal registration method.

Also in the [^{11}C]Choline PET reproducibility study, it has been demonstrated that the proposed method can effectively remove the subject motion that affects the regional kinetic analysis on breast tumours. By minimising motion artefacts, the variability in estimating the kinetic parameters is reduced and the reproducibility in this test-retest study is improved, thus increasing the confidence of the study.

The advantage of this approach relies on the incorporation of the tracer kinetics by the pharmacokinetic modelling technique. Spectral analysis was chosen here for its

ability to describe different tracer behaviour across the measured image. Notably, for parameter estimation, spectral analysis can be more susceptible to noise than more parsimonious models (e.g. two-tissue compartment model with only four parameters) and thus other models may be more appropriate for kinetic estimation of the outcome measures of interest. In practice, the spectral analysis method requires the measurement of the tracer concentration in arterial plasma to provide the input function for the model. To apply this approach to dynamic PET studies without arterial blood data using the technique developed in Chapter 5 will be presented in the following chapter.

Chapter 7

Validation and Clinical Evaluation of Groupwise Image Registration of dynamic PET data using reference tissue models

By incorporating reference tissue models, the groupwise image registration (GIR) methods for dynamic PET data developed in Chapter 5 obviate the need for invasive and costly arterial sampling. In this Chapter, the performance of the reference input-based registration approach for dynamic PET data is validated using simulated data sets and is also evaluated with real data from clinical studies. For validation of the GIR reference tissue based methods, the simulated data presented in Chapter 6 was used but now with the blood data no longer present. The clinical [^{11}C]-(+)-PHNO data used is also from the study presented in Chapter 6. In this Chapter

the data is further supplemented by additional scans post administration of a novel therapeutic drug, where the image contrast is reduced, to allow for an assessment of the performance of the method on drug-occupancy studies.

7.1 Validation of GIR using simulated $[^{11}\text{C}]\text{-(+)-PHNO}$ dopamine D2/D3 data

7.1.1 Validation data-sets

For the purpose of having the ground truth, simulated $[^{11}\text{C}]\text{-(+)-PHNO}$ brain images with known subject motion that were generated in Sec. 6.1 were used for validating the proposed spatio-temporal registration methods. Only data sets with high ($\sim 10\text{mm}$) and medium ($\sim 5\text{mm}$) motion levels were selected, with 10 simulations of the various rigid motions applied on the PET frames. Data sets with all three noise levels as noise free ($c = 0$), noise medium ($c = 16$, normal level of noise in clinical data) and noise high ($c = 64$, high level of noise for robustness testing) were chosen, where c scales the noise level in Equation 4.8 and 5 simulations were generated at each noise level, thus leading to $(1 + 5 + 5) \times 2 \times 10 = 220$ simulated data sets.

7.1.2 Relaxation parameter μ for basis pursuit denoising

As described in Sec. 5.1.1, for basis pursuit denoising, the constraint on sparsity of the solution is determined through the selection of a relaxation parameter. In this work it is proposed that a fixed value for this relaxation parameter μ can be determined for a particular tracer and target. This can be obtained from prior knowledge of the

tracer, using PET data with no motion artefacts that characterises the tracer’s true behaviour. Therefore the value for μ in the validation and evaluation experiments was determined using a motion-free numerical phantom of $[^{11}\text{C}]\text{-(+)-PHNO}$ in healthy subjects.

A set of time activity curves (TACs) $\mathbb{T}$, $n(\mathbb{T}) = 3000$, was derived from the noiseless motion-free phantom generated in Sec. 6.1. A mask was applied to discard background voxels outside the field of view of the brain tissue itself. 50 values for μ were logarithmically spaced on the interval $[10^{-2}, 10^2]$. The average squared error L_μ was calculated following the application of basis pursuit denoising to all TACs for each value of μ and is shown in Fig. 7.1. The average squared error L_μ is consistent with a histogram of μ that minimises the fitting error for each data point in $\mathbb{T}$. A value of $\mu = 8.6850$ was chosen to be optimal for $[^{11}\text{C}]\text{-(+)-PHNO}$.

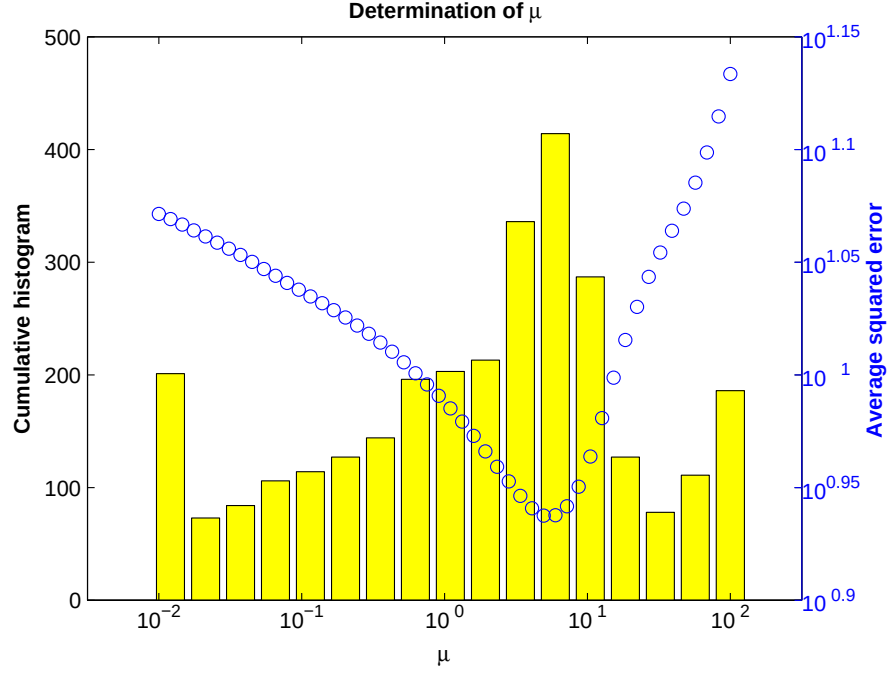


Figure 7.1: Determination of regularisation parameter μ for compartmental sparsity for basis pursuit denoising. For 50 μ values logarithmically spaced on the interval $[10^{-2}, 10^2]$, the average squared error L_μ (in blue) is consistent with the histogram of μ minimising the fitting error for each data point in $\mathbb{T}$ (in yellow) for an optimal value of $\mu = 8.6850$.

7.1.3 Simulation-based validation

In the simulation-based validation, the motion correction was conducted and compared by using five methods: the frame-by-frame registration of each PET frame to the one with highest uptake based on normalised mutual information (FBF_{NMI}), the frame-by-frame registration of the consecutive time frames using sum-of-squared-differences (FBF_{SSQ}), the groupwise registration of all frames with spectral analysis that requires the blood input (GIR_{SA}), the reference tissue groupwise registration of all frames using basis pursuit (GIR_{BP}), and the reference tissue groupwise registration of all frames using the simplified reference tissue model (GIR_{SRTM}). GIR_{BP} and

GIR_{SRTM} both avoid the need for any blood data. The motion correction accuracy is quantified as the target registration error (TRE) (Fitzpatrick et al. 1998), using the same computation as presented in Sec. 6.2.2. This is shown in Figure 7.2.

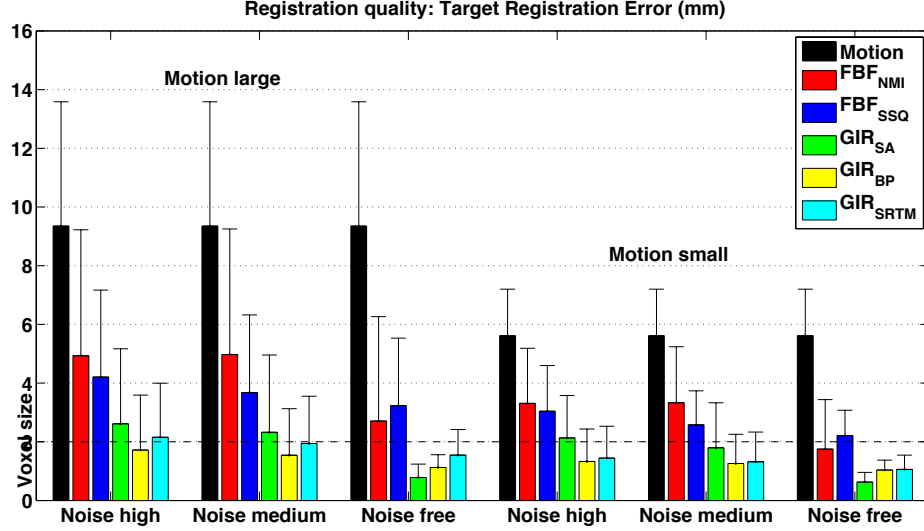


Figure 7.2: Registration accuracy, quantified as target registration error (TRE, in mm) of the spatio-temporal groupwise image registration with basis pursuit (GIR_{BP}), with simplified reference tissue model (GIR_{SRTM}) with spectral analysis (GIR_{SA} , required blood input) and frame-by-frame registration based on normalised mutual information (FBF_{NMI}) and based on sum-of-squared-differences (FBF_{SSQ}) on simulated data sets. The dashed line indicates the voxel size. For each simulation, the TREs were averaged over all time frames. The mean TREs at each motion level and noise level before and after correction are shown, along with the standard deviations as error bars.

For the groupwise image registration methods proposed in this work based on the spatio-temporal constraints imposed by the tracer pharmacokinetics, Figure 7.3 gives the frame-by-frame comparison of the GIR_{SA} (based on spectral analysis with blood input), GIR_{BP} (based on basis pursuit denoising with reference input), and GIR_{SRTM} (based on simplified reference tissue model with reference input).

The frame index in Figure 7.3 corresponding to mid-frame times is given in Ta-

ble 7.1.

Table 7.1: *Mid-frame times*

Frame index	Mid-frame time	Frame index	Mid-frame time
1	0.125 (min)	14	10 (min)
2	0.375 (min)	15	12 (min)
3	0.625 (min)	16	14 (min)
4	0.875 (min)	17	17.5 (min)
5	1.125 (min)	18	22.5 (min)
6	1.375 (min)	19	27.5 (min)
7	1.625 (min)	20	32.5 (min)
8	1.875 (min)	21	37.5 (min)
9	2.5 (min)	22	45 (min)
10	3.5 (min)	23	55 (min)
11	4.5 (min)	24	65 (min)
12	6 (min)	25	75 (min)
13	8 (min)	26	85 (min)

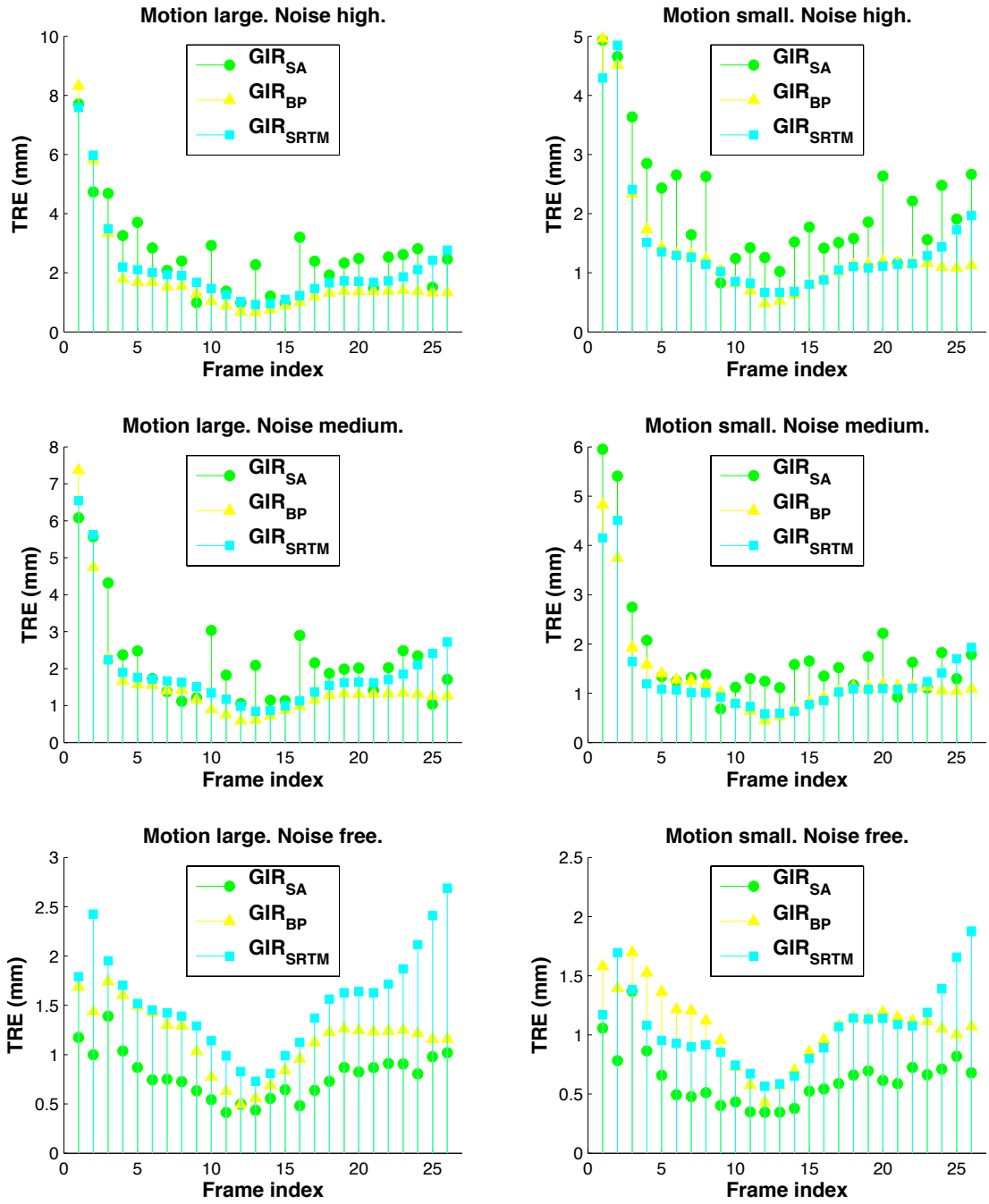


Figure 7.3: Target registration error (TRE , in mm) of GIR_{SA} , GIR_{BP} , and GIR_{SRTM} . For each PET temporal frame, the TRE s were averaged over all simulations.

For the groupwise registration methods GIR_{SA} , GIR_{BP} , and GIR_{SRTM} , Figure 7.3 illustrates that:

- 1) in noise free cases, both GIR_{SA} and GIR_{BP} led to sub-voxel ($< 2mm$) registration accuracy for all PET frames. GIR_{SA} had the lowest registration error for the first few frames;
- 2) in noisy cases, GIR_{BP} was in general more robust than GIR_{SA} ;
- 3) GIR_{SRTM} had consistently higher registration errors for the last few frames in all cases.

Here the performance of these methods on the early and late temporal PET frames may be explained by the limitations of the pharmacokinetic models. Spectral analysis (SA), basis pursuit denoising (BP) and the simplified reference tissue model (SRTM) were tested for modelling real $[^{11}\text{C}]\text{-(+)-PHNO}$ PET data.

Both GIR_{BP} and GIR_{SRTM} model the PET data using basis functions generated from the reference input, which is the response of the non-specific binding compartment to the PET tracer influx from artery, and is mathematically a delayed signal in the form of the convolution of a decay exponential with the plasma input. Therefore GIR_{BP} and GIR_{SRTM} cannot model the tracer uptake in the blood, and the lack of internal carotid artery present in the model-predicted PET data results in the inaccurate registration for the early PET temporal frames (0 to 1 min) in which the internal carotid artery is a dominant structure. However for dynamic PET tracer kinetics, the first few PET frames are not essential since there is no actual PET signal from tracer-target interaction. As such the registration for these frames will not significantly affect the estimation of the kinetic parameters of interest.

The consistently larger registration errors for the last few PET frames of GIR_{SRTM} might be explained as a result of SRTM failing to model the late $[^{11}\text{C}]\text{-(+)-PHNO}$ kinetics, due to the fact that the model requires more than one compartment in these regions and therefore the reduced model order of SRTM is unable to capture the kinetics perfectly. Registration results shown in Figure 7.3 suggests this model data mismatch mostly affects late $[^{11}\text{C}]\text{-(+)-PHNO}$ kinetics which are dominated by specific binding. As such motion correction conducted by the GIR_{SRTM} for $[^{11}\text{C}]\text{-(+)-PHNO}$ PET has the potential to lead to a bias in the subsequent tracer kinetic estimation of the outcome measure of interest (BP_{ND}).

7.2 Impact on clinical receptor occupancy studies

The groupwise image registration approaches that employ reference tissue kinetic models (basis pursuit denoising or simplified reference tissue model) show the ability to correct for subject motion using only dynamic PET data, as demonstrated by their performance in the simulation-based validation with realistic $[^{11}\text{C}]\text{-(+)-PHNO}$ PET data. It should be noted that, in the dopamine receptor system, $[^{11}\text{C}]\text{-(+)-PHNO}$ has two binding sites (D2 and D3) so that just a single compartment model may not be sufficient. This may affect the registration approach incorporated with SRTM, as supported by the registration accuracy from the simulation-based validation with $[^{11}\text{C}]\text{-(+)-PHNO}$ data, such that the registration with basis pursuit denoising (GIR_{BP}) has smaller registration error than (GIR_{SRTM}) for each noise level or motion level. Therefore in the clinical evaluation on a receptor occupancy study with $[^{11}\text{C}]\text{-(+)-PHNO}$, only GIR_{BP} was involved as the reference input based approach, to demonstrate the

impact on realistic data.

7.2.1 Background of the study

Drug dosing for studies in humans is an important step in drug development, and determining the dose-related occupancy of a specific target by the administered drug under test is important for the clinical development programme of a novel therapeutic approach. If a suitable radioactive tracer is available, PET can give quantitative information on the relationship between target occupancy and drug concentration in plasma. This is based on the fact that the binding of the radioactive tracer can be reduced by introducing a competing non-radioactive drug candidate into the system if it binds to the same target in sufficient amounts such that the available concentration of sites for the radiotracer to bind to is reduced. PET methods used to measure the receptor occupancy have been reviewed in (Laruelle 2000; Passchier et al. 2002; Zhang and Fox 2012).

The data used here for motion correction evaluation was from a dopamine D3 receptor occupancy study with PET. There has been significant interest in imaging the dopamine D3 receptor, both to study the relevance in conditions such as schizophrenia and addiction, and also to help the development of drugs which have the mechanisms of interacting with D3 receptors. This clinical study was designed to evaluate the relationship between the plasma concentration and target occupancy of a D3 antagonist as part of a drug development programme. The details about this study have been reported in (Searle et al. 2013). Human [^{11}C]-(+)-PHNO PET data was taken from a group of subjects with a wide dose range of the antagonist *GSK618334* to estimate the drug's potency. All the subjects were healthy, male, drug-free, non-smoking vol-

unteers between 25 and 55 years of age, with body weights and BMI in the normal range. All subjects gave written informed consent, and their eligibility was confirmed via medical history, physical examinations and standard tests. Further details of the inclusion and exclusion criteria can be found on www.clinicaltrial.gov by reference to *NCT00814957* and the study was approved by the local ethics committees.

Each subject received a baseline PET scan, then a single oral dose of 5 – 550mg of *GSK618334* followed by two further PET scans performed between 1.5 and 29 hours after administration of *GSK618334*. Venous blood was sampled for measurements of *GSK618334* plasma concentration. The dynamic [^{11}C]-(+)-PHNO PET scans were acquired using a Siemens Biograph 6 PET-CT with Truepoint gantry in 3D-mode, and then reconstructed using 2D filtered back projection with corrections for attenuation (based on a low-dose CT acquisition) and scatter. Dynamic data were binned into 26 frames (durations: 8×15 s, 3×1 min, 5×2 min, 5×5 min, 5×10 min). To enable plasma-input based modelling techniques, arterial blood data were also acquired as part of this study. Each subject also received a high resolution T1-weighted magnetic resonance imaging (MRI) scan with a Siemens Tim Trio 3T scanner (Siemens Healthcare, Erlangen, Germany).

Data from 8 subjects in this study were used here to test the performance of different motion correction algorithms. For each dynamic PET scan, motion correction was conducted and compared for the proposed GIR_{BP} algorithm and also using the conventional FBF_{NMI} method. The FBF_{NMI} method used one of the PET frames (highest uptake) in the scan as the reference and normalised mutual information cost function. For the GIR_{BP} method, cerebellum grey matter was used as the reference region to derive the input function for basis pursuit denoising. The reference region

was segmented by nonlinearly warping a predefined brain atlas (Tziortzi et al. 2011) into the individual subjects space using the associated T1 MRI. Both the GIR_{BP} and FBF_{NMI} algorithms were implemented in MATLAB 7.7. The image registration was conducted based on functions available within Statistical Parametric Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm/>) using the same settings for the optimisation, interpolation, image smoothing and histogram smoothing as described in Sec. 6.2.1. The PET data for motion correction was decay-corrected and reconstructed with attenuation correction as described above. Regional analysis of BP_{ND} and occupancy analysis were subsequently performed on the following PET datasets:

- 1) without motion correction,
- 2) after motion correction with the conventional FBF_{NMI} method,
- 3) after motion correction with the proposed GIR_{BP} method.

7.2.2 Outcome measures of interest

Regional calculation of $[^{11}\text{C}]\text{-(+)-PHNO}$ BP_{ND}

After motion correction, $[^{11}\text{C}]\text{-(+)-PHNO}$ kinetics were analysed for six target regions-of-interest (ROIs): substantia nigra (SN), globus pallidus (GP), ventral striatum (VST), dorsal caudate (CD), dorsal putamen (PU), thalamus (TH). These target ROIs were defined manually according to the guidelines described previously in (Tziortzi et al. 2011) GP, VST, CD, PU, TH were delineated on each subject's structural T1-weighted magnetic resonance image (MRI). SN was defined on each subject's baseline PET integral image given the insufficient contrast available from

MRI data. Regional time-activity curves (TACs) were then derived for each ROI from the [^{11}C]-(+)-PHNO PET data.

A two-tissue compartmental (2TC) plasma input model was applied to the regional time activity curves to appropriately quantify [^{11}C]-(+)-PHNO in the basal ganglia ROIs (Searle et al. 2013) and enable derivation of V_T as,

$$V_T = \frac{K_1}{k_2} \cdot \left(1 + \frac{k_3}{k_4}\right) \quad (7.1)$$

The model also included a fixed blood volume correction of 5%. Regional BP_{ND} estimates were then derived for each of the target regions using cerebellum as the reference region, as:

$$BP_{ND}^{ROI} = \frac{V_T^{ROI} - V_T^{CER}}{V_T^{CER}} \quad (7.2)$$

Competitive binding of drug and [^{11}C]-(+)-PHNO

The dopamine D2 and D3 receptors are members of the D2-like receptor family. [^{11}C]-(+)-PHNO is a dopamine D2/D3 receptor agonist radioligand with preferential affinity for D3 over D2. In the human brain, D2 receptors are expressed in significantly higher numbers than D3 in many regions including basal ganglia. This requires the application of a two-site competitive binding model. Furthermore, recent work in (Searle et al. 2013) considered that [^{11}C]-(+)-PHNO PET scans might be routinely performed in non-tracer conditions with respect to D3 receptors, and therefore the PHNO mass dose effect on D3 receptor needs to be considered. In addition, in (Searle et al. 2013) it is also reported that the cerebellum, used as a reference region, might manifest some displaceable binding signal that needs correction. As such, for quantification of [^{11}C]-(+)-PHNO kinetics with differing doses of *GSK618334*, the 2-site

competitive binding model with PHNO mass dose effect correction on D3 and cerebellum specific binding correction was used. The model is described below.

Firstly, if only the 2-site competitive receptor binding is considered, the model can be written as:

$$BP_{ND}^{drug} = BP_{ND}^{base} \left(\frac{f_{PHNO}^{D3}}{1 + \frac{C_p^{drug}}{EC_{50}^{drug,D3}}} + \frac{1 - f_{PHNO}^{D3}}{1 + \frac{C_p^{drug}}{EC_{50}^{drug,D2}}} \right) \quad (7.3)$$

where

- BP_{ND}^{base} - the binding potential measured in the baseline $[^{11}\text{C}]\text{-(+)-PHNO}$ PET data
- BP_{ND}^{drug} - the binding potential measured in $[^{11}\text{C}]\text{-(+)-PHNO}$ after a dose of *GSK618334*
- C_p^{drug} - the concentration of the drug *GSK618334* measured in sampled venous blood
- f_{PHNO}^{D3} - the regional fraction of baseline $[^{11}\text{C}]\text{-(+)-PHNO}$ BP_{ND} corresponding to D3 receptors
- $EC_{50}^{drug,D2}$ - the plasma concentrations of drug that would result in 50% occupancy of D2 receptors
- $EC_{50}^{drug,D3}$ - the plasma concentrations of drug that would result in 50% occupancy of D3 receptors

BP_{ND}^{base} and BP_{ND}^{drug} were estimated from the measured $[^{11}\text{C}]\text{-(+)-PHNO}$ PET data. C_p^{drug} was measured from the venous blood samples from the subject. f_{PHNO}^{D3} was taken from (Searle et al. 2013) and had values of 0.87 for SN, 0.66 for GP, 0.39

for VST, 0.69 for TH, 0.21 for CD, 0.14 for PU. $EC_{50}^{drug,D2}$ and $EC_{50}^{drug,D3}$ were the outcome measures of interest estimated from the competitive modelling.

When considering the PHNO mass dose effect on D3, Equation 7.3 becomes:

$$BP_{ND}^{drug} = BP_{ND}^{base} \left(\frac{f_{PHNO}^{D3}}{1 + \frac{C_p^{drug}}{EC_{50}^{drug,D3}} + \frac{D^{PHNO}}{ED_{50}^{PHNO,D3}}} + \frac{1 - f_{PHNO}^{D3}}{1 + \frac{C_p^{drug}}{EC_{50}^{drug,D2}}} \right) \quad (7.4)$$

where

- D^{PHNO} - the administered dose of [^{11}C]-(+)-PHNO
- $ED_{50}^{PHNO,D3}$ - the mass dose of [^{11}C]-(+)-PHNO that results in 50% occupancy of D3 receptor

and the value of 40 ng/kg (Searle et al. 2013) was used for $ED_{50}^{PHNO,D3}$. The mass dose has been shown not to be an issue at the D2 site given the lower affinity of [^{11}C]-(+)-PHNO for the D2 site.

Meanwhile, the non-zero specific binding in CER modulated by the presence of drug and [^{11}C]-(+)-PHNO can also be accounted for by Equation 7.4, as:

$$BP_{ND}^{CER,drug} = BP_{ND}^{CER,base} \left(\frac{f_{PHNO}^{D3,CER}}{1 + \frac{C_p^{drug}}{EC_{50}^{drug,D3}} + \frac{D^{PHNO}}{ED_{50}^{PHNO,D3}}} + \frac{1 - f_{PHNO}^{D3,CER}}{1 + \frac{C_p^{drug}}{EC_{50}^{drug,D2}}} \right) \quad (7.5)$$

where $f_{PHNO}^{D3,CER}$ is the fraction of baseline [^{11}C]-(+)-PHNO BP_{ND} corresponding to D3 receptors in cerebellum. According to (Searle et al. 2013), $f_{PHNO}^{D3,CER} = 1$.

Then with the specific binding in CER, the model is corrected as:

$$BP_{ND}^{ROI,drug}(corrected) = \frac{BP_{ND}^{ROI,drug} - BP_{ND}^{CER,drug}}{1 + BP_{ND}^{CER,drug}} \quad (7.6)$$

with Equation 7.5 and $f_{PHNO}^{D3,CER} = 1$, it becomes:

$$\begin{aligned}
 BP_{ND}^{ROI,drug} = & \frac{BP_{ND}^{ROI,base} \left(\frac{f_{PHNO}^{D3}}{1 + \frac{C_p^{drug}}{EC_{50}^{drug,D3}} + \frac{D^{PHNO}}{ED_{50}^{PHNO,D3}}} + \frac{1 - f_{PHNO}^{D3}}{1 + \frac{C_p^{drug}}{EC_{50}^{drug,D2}}} \right)}{1 + \frac{BP_{ND}^{CER,base}}{1 + \frac{C_p^{drug}}{EC_{50}^{drug,D3}} + \frac{D^{PHNO}}{ED_{50}^{PHNO,D3}}}} \\
 & - \frac{\frac{BP_{ND}^{CER,base}}{1 + \frac{C_p^{drug}}{EC_{50}^{drug,D3}} + \frac{D^{PHNO}}{ED_{50}^{PHNO,D3}}}}{1 + \frac{BP_{ND}^{CER,base}}{1 + \frac{C_p^{drug}}{EC_{50}^{drug,D3}} + \frac{D^{PHNO}}{ED_{50}^{PHNO,D3}}}} \quad (7.7)
 \end{aligned}$$

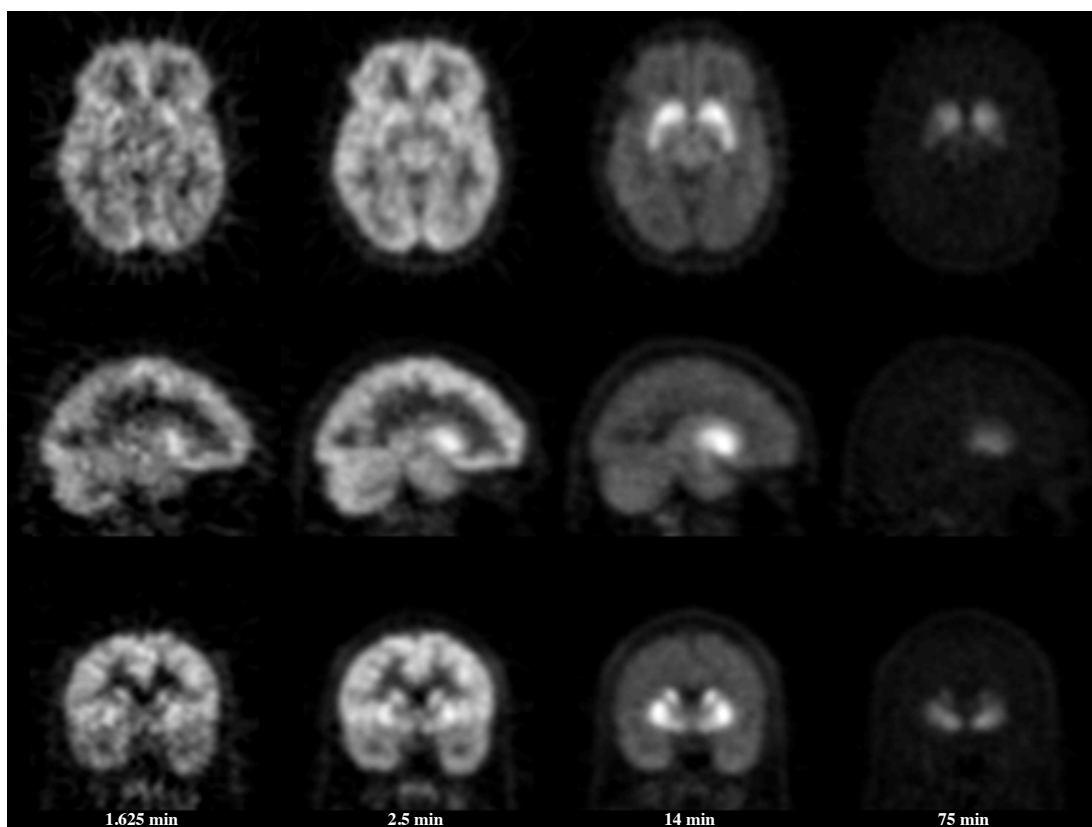
It should be noted that all regions $BP_{ND}^{ROI,base}$ and $BP_{ND}^{ROI,drug}$ were fitted simultaneously and the $EC_{50}^{drug,D2}$ and $EC_{50}^{drug,D3}$ parameters were assumed to be constant across regions and subjects (Searle et al. 2013).

7.2.3 Results

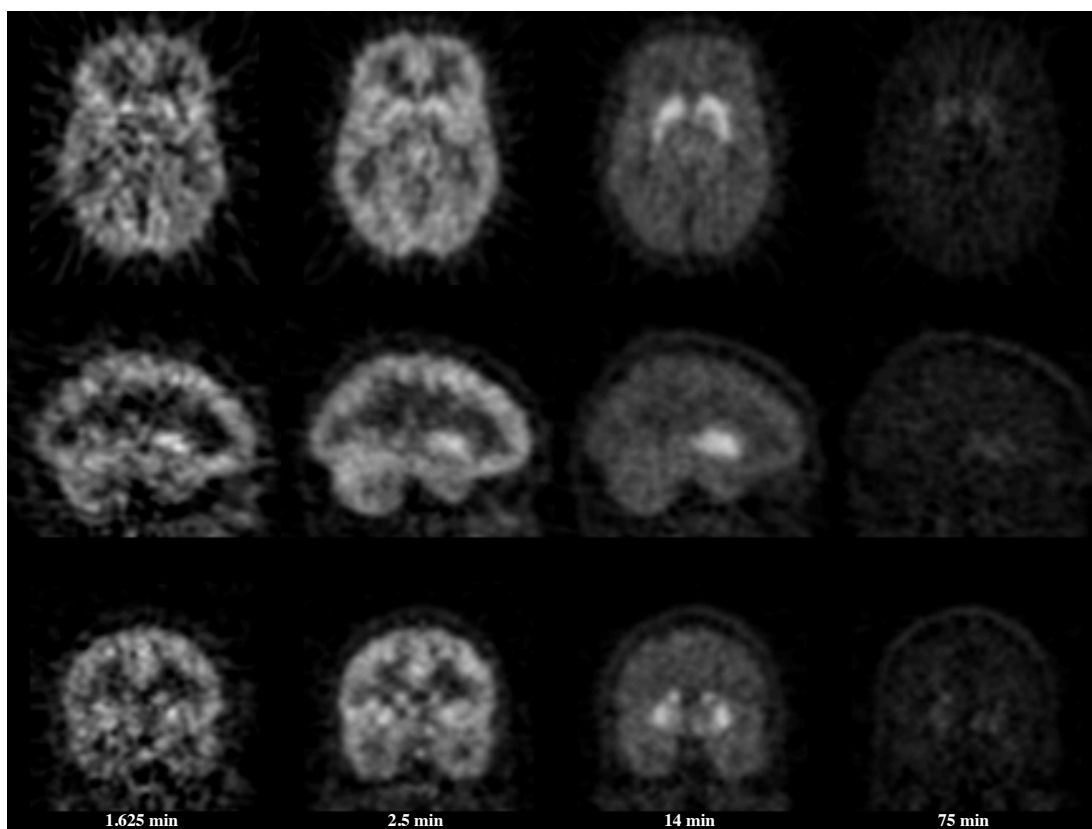
Motion correction in the [^{11}C]-(+)-PHNO PET data

The GIR_{BP} and FBF_{NMI} algorithms were applied on reconstructed [^{11}C]-(+)-PHNO PET data to address inter-frame misalignment caused by subject motion. PET data with attenuation correction was used. PET data from the 24 scans used had varying contrast and SNR due to different doses of [^{11}C]-(+)-PHNO and *GSK618334*. Figure 7.4 shows 1 baseline scan and 1 post *GSK618334* scan, to illustrate the differing PET signal present in the occupancy study.

Firstly, visual inspection using the movie mode in FSLview (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) was performed on the 24 scans obtained from the 8 healthy subjects without motion correction to derive an initial qualitative assessment of mo-



(a)



(b)

Figure 7.4: $[^{11}\text{C}]$ -(+)-PHNO data of two PET scans from the D3 receptor occupancy study. Selected temporal frames (times are mid-frame times) are shown in orthogonal views for (7.4a) baseline scan (GSK618334 plasma concentration: 0 mg/ml), and (7.4b) post-dose scan (GSK618334 plasma concentration: 526 mg/ml).

tion. In 4 scans, there was severe motion with up to 10 degree rotations or 40mm translations. In 8 scans there was motion at the level of the voxel size (2mm), and in 12 scans the motion was difficult to detect. Using the translation and rotation parameters for each time frame, a metric summarising the displacement was calculated for each time frame as:

$$displacement = \sqrt{\frac{1}{M} \sum_{j=1}^M \|\mathbf{T}(\mathbf{x}_j) - \mathbf{x}_j\|^2}, \quad (7.8)$$

where $\mathbf{T}$ is the rigid transformation determined by the translations and rotations and M is the number of voxels. Figure 7.5 shows a summary of the displacements introduced by both GIR_{BP} and FBF_{NMI} motion correction algorithms for the 24 scans.

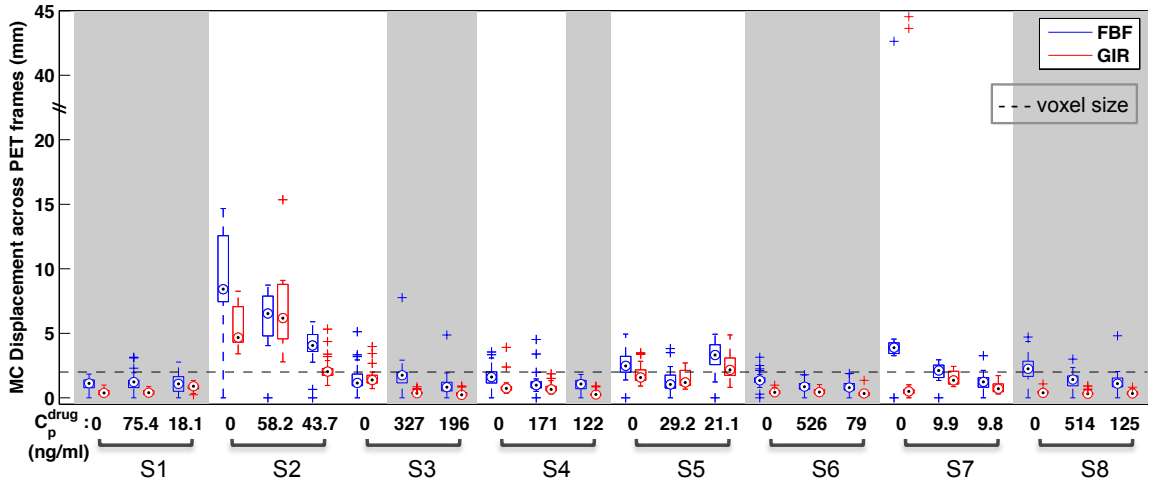


Figure 7.5: Summary of displacements introduced by the GIR_{BP} and FBF_{NMI} motion correction methods for the $[^{11}C]$ -(+)-PHNO PET occupancy study data. Subjects (S1-S8) exhibited various degrees of motion during the scans. The scans marked with grey background had visually negligible motion following assessment by an observer viewing the data in the movie mode in FSLview. For these scans the FBF_{NMI} method introduced up to 5mm displacement, whereas the displacement introduced by the GIR_{BP} method was at a sub-voxel level. Plasma concentration of GSK618334 is also shown for each scan.

The computation time of the GIR_{BP} motion correction algorithm depended on the amplitude of the motion and the image noise. On a desktop workstation (CPU 3.20GHz, 16GB RAM) with MATLAB 7.7, it took between 20 and 90 mins of computation time for each 26-frame dynamic image.

Figure 7.6 illustrates the performance of the proposed GIR_{BP} algorithm when registering dynamic $[^{11}\text{C}]\text{-(+)-PHNO}$ PET data having visually obvious inter frame motion (subject S2's baseline scan).

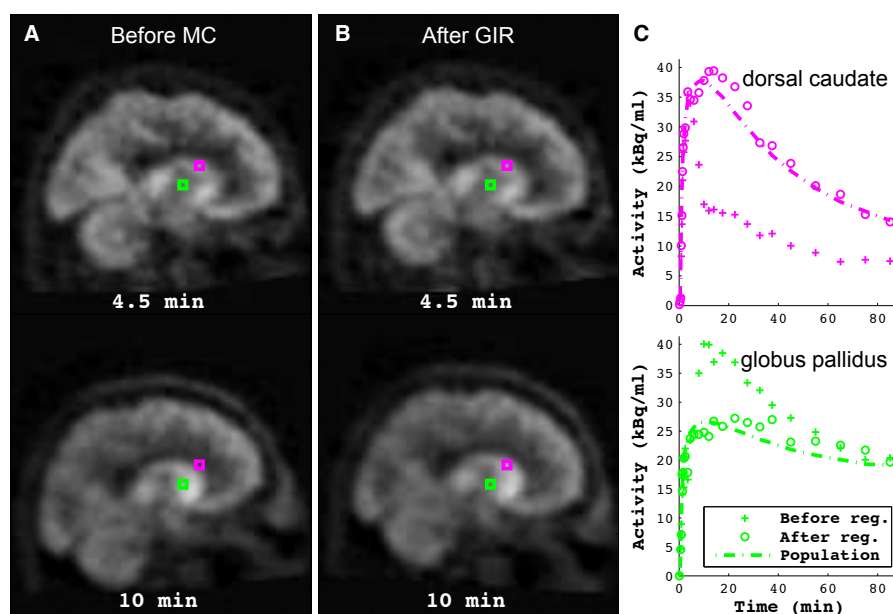


Figure 7.6: Selected temporal frames (times are mid-frame times) from a sagittal slice from baseline $[^{11}\text{C}]\text{-(+)-PHNO}$ data A) without motion correction B) after motion correction by the proposed GIR_{BP} algorithm. C) TACs from voxels in dorsal caudate and globus pallidus, depicted in colours corresponding to the voxels shown in A) and B), which are spatially fixed to demonstrate the displacement. The subject exhibited obvious rotation of ~ 10 degree which was corrected by the proposed method, as shown on the sagittal slice. The TACs for these regions were also obtained from all the eight healthy subjects' baseline data after motion correction, and the population TACs were generated by averaging TACs normalised for $[^{11}\text{C}]\text{-(+)-PHNO}$ dose and subject weight to show the kinetics in these regions. The population TACs were scaled to match this subject and also shown in C). The tracer kinetics showed consistency with the population data after GIR_{BP} motion correction.

Figure 7.6 shows that the motion artefacts were well corrected by the GIR_{BP} algorithm as indicated by the sagittal view of the PET data. Furthermore, the voxel-based TACs from dorsal caudate and globus pallidus shown on the sagittal slice are displayed before and after GIR_{BP} motion correction together with the normalised population TACs for these ROIs. The population TACs were generated by averaging the baseline $[^{11}\text{C}]\text{-(+)-PHNO}$ PET data after motion correction over the eight healthy subjects, and were scaled according to dose and subject weight. The consistency with the normalised population data after motion correction by the GIR_{BP} algorithm provides supporting evidence for the successful removal of the inter-frame misalignment caused by motion.

Binding potential of $[^{11}\text{C}]\text{-(+)-PHNO}$

Regional nondisplaceable binding potentials (BP_{ND}) were derived from the $[^{11}\text{C}]\text{-(+)-PHNO}$ baseline and followup PET data for the ROIs SN, GP, VST, CD, PU and TH after motion correction.

During the 2TC kinetic parameter estimation, 2 unrealistically large V_T values (> 100) were obtained for the data without motion correction, 3 unrealistically large V_T values (> 100) were obtained after motion correction by FBF_{NMI} , whereas none were obtained after motion correction by GIR_{BP} . Corresponding V_T values for baseline and follow-ups are shown in Figure 7.7 with unrealistic values shown above the line breaks.

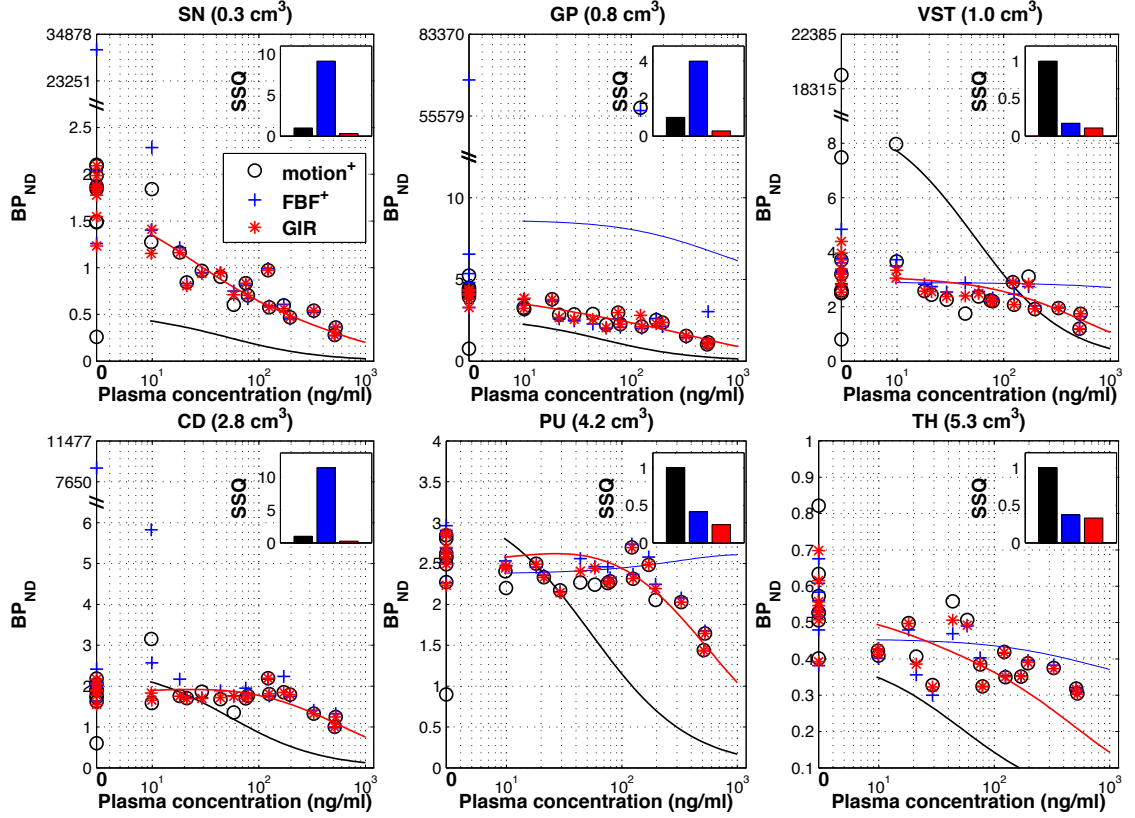


Figure 7.7: Fits (shown as curves) to the baseline and follow-up data before and after motion correction by FBF_{NMI} and GIR_{BP} (shown as circles, crosses and stars) using a competitive binding model (Equation 7.6). The sum of squared differences (SSQ), scaled to the SSQ of data before motion correction so that $SSQ_{motion} = 1$, is shown inset for each fit. Both the motion and motion correction by the FBF_{NMI} algorithm resulted in unrealistic estimates of the BP_{ND} that affected the fits, whereas GIR_{BP} algorithm successfully reduced the variability in the data after motion correction. For data points where the subject motion was visually negligible, the GIR_{BP} algorithm did not introduce additional misalignment to the data during registration whereas the conventional FBF_{NMI} algorithm was possible to distort the data by registering all frames to a common reference.

After excluding the unrealistic data points considered as convergence failure, the inter-subject variability was assessed on baseline BP_{ND} by the coefficient of variation

(C_v) as:

$$C_v = \frac{\sigma(BP_{ND})}{\mu(BP_{ND})} \quad (7.9)$$

where σ and μ are the standard deviation and mean across the 8 subjects.

The C_v values without motion correction, after motion correction by the FBF_{NMI} algorithm and by the proposed GIR_{BP} algorithm are shown in Table 7.2, together with the ROI volume in cm^3 . These data provide further evidence for the improved registration with GIR_{BP} through the significant reduction in the C_v of baseline BP_{ND} data across all regions. It was also apparent that the conventional FBF_{NMI} algorithm could lead to subsequent convergence problems in the kinetic fitting, whereas the proposed GIR_{BP} algorithm avoided such problems, thus eliminating the need to exclude outliers due to unsuccessful motion correction. The conventional FBF algorithm produced less of a reduction in C_v (even after excluding unrealistic data).

Table 7.2: *The inter-subject variability in baseline BP_{ND} before and after motion correction (C_v), with the removal of unrealistically large V_T values due to unsuccessful convergence in 2TC kinetic parameter estimation as a result of uncorrected motion artefacts. ROI volumes are given in cm^3 .*

ROI	SN ($0.3cm^3$)	GP ($0.8cm^3$)	VST ($1.0cm^3$)
w/o ¹	0.3699	0.3405	0.6345
FBF _{NMI} ²	0.1785	0.7411	0.2857
GIR _{BP}	0.1523	0.0896	0.1822
ROI	CD ($2.8cm^3$)	PU ($4.2cm^3$)	TH ($5.3cm^3$)
w/o ¹	0.2825	0.2627	0.5172
FBF _{NMI} ²	0.1173	0.0848	0.1630
GIR _{BP}	0.0962	0.0772	0.1606

¹2 outlier values removed

²3 outlier values removed

Occupancy and estimation of the EC_{50} of *GSK618334*

The BP_{ND} of [^{11}C]-(+)-PHNO measured in the follow up PET data, after dosing with *GSK618334*, was modelled using Equation 7.6. The two-site competitive binding model, including correction for PHNO mass on D3 binding and specific signal in the cerebellum, was applied to the measured data before and after motion correction. The BP_{ND} values obtained without motion correction, and after applying the FBF_{NMI} and GIR_{BP} algorithms, are shown in Figure 7.7 for each of the six target ROIs, together with the competitive binding model fits. Motion correction using the proposed GIR_{BP} algorithm avoided the convergence problems that led to data points with unrealistic values, which occurred with the uncorrected and FBF_{NMI} corrected PET data.

In practice, to maintain the integrity at the study level, it is possible (though not

ideal) to remove the outliers with appropriate testing. Furthermore, the BP_{ND} estimation following the FBF_{NMI} method could be enhanced by applying a time stability criterion to remove the unsuccessfully registered PET frames. Here after the motion correction by FBF_{NMI} method, the time stability check was conducted to improve the BP_{ND} estimation, and BP_{ND} values greater than 10 were considered as outliers. In Figure 7.8, the competitive binding model fits are also shown using BP_{ND} before motion correction with the exclusion of outliers, BP_{ND} after FBF_{NMI} with time stability check and the exclusion of outliers, and BP_{ND} estimates obtained directly after applying the proposed GIR_{BP} algorithm for motion correction with no further corrections. Even with all this extra help for the other methods, GIR_{BP} still produced the best fit to the competitive binding data as judged by its ability to achieve the smallest SSQ.

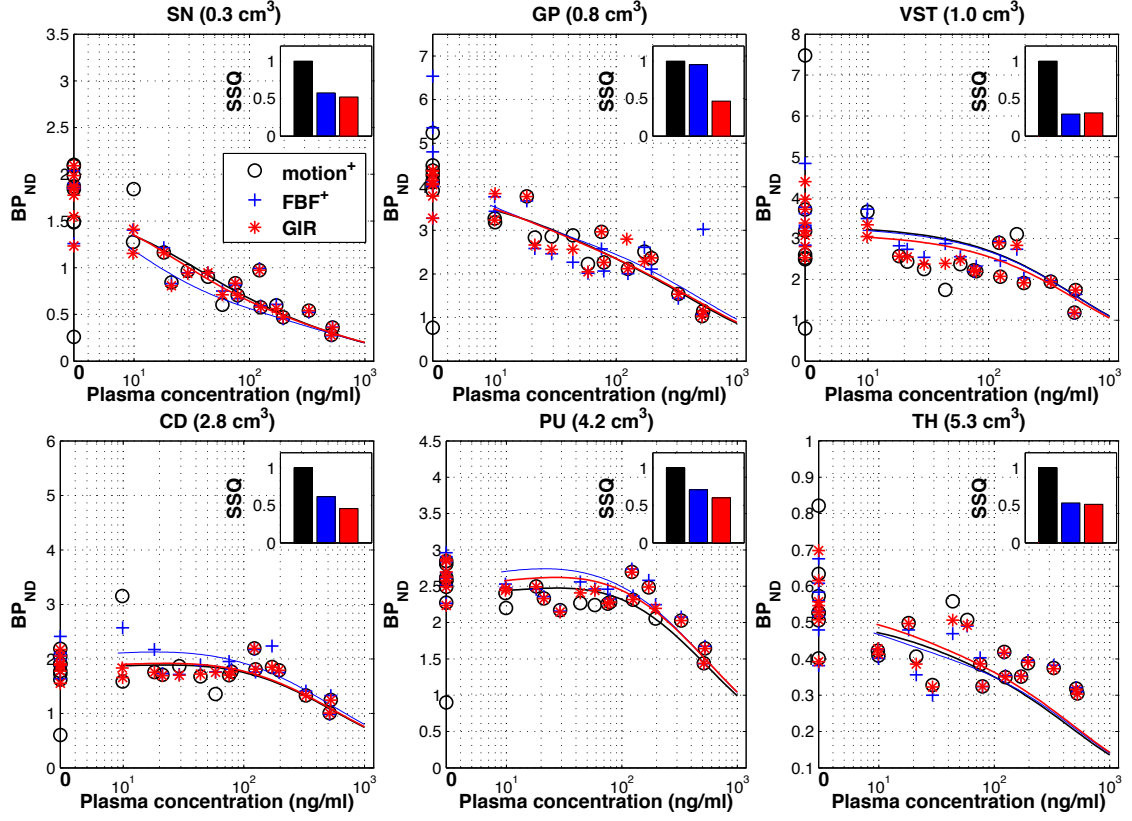


Figure 7.8: Competitive model fits (shown as curves) of BP_{ND} data points derived from PET data without motion correction (shown as circles) with removal of unrealistic values; after motion correction by FBF_{NMI} (shown as crosses) with time stability check and removal of unrealistic values; after only motion correction by the proposed GIR_{BP} (shown as stars).

The primary outcome measures of this study, $EC_{50}^{drug,D2}$ and $EC_{50}^{drug,D3}$ of *GSK618334*, estimated using Equation 7.6, are presented along with the 95% confidence intervals in Table 7.3.

Table 7.3: $EC_{50}^{drug,D2}$ and $EC_{50}^{drug,D3}$ of *GSK618334* estimates before and after motion correction. Values in brackets indicate 95% confidence intervals associated with the parameter estimates.

	Time stability check	Removal of BP_{ND} outliers	$EC_{50}^{drug,D3}$ of <i>GSK618334</i> (ng/ml)	$EC_{50}^{drug,D2}$ of <i>GSK618334</i> (ng/ml)
w/o	No	Yes	15 (−6, 37)	529 (206, 852)
FBF _{NMI}	Yes	Yes	4 (0, 8)	492 (327, 658)
GIR _{BP}	No	No	10 (5, 15)	539 (419, 660)

The EC_{50} estimates obtained following GIR were consistent with the values obtained before MC with the removal of unrealistic BP_{ND} data points (the ones with significant subject motion) during competitive binding modelling

The EC_{50} estimates from [^{11}C]-(+)-PHNO PET data corrected by the proposed GIR_{BP} method were consistent with the values reported in (Searle et al. 2013) ($EC_{50}^{drug,D2}$ of *GSK618334* (ng/ml): 494.2 (332, 656), $EC_{50}^{drug,D3}$ of *GSK618334* (ng/ml): 9.8 (4.3, 15.3)), and achieved tighter confidence intervals. In (Searle et al. 2013) the EC_{50} estimates were derived using the same competitive binding model with cerebellum specific binding correction and [^{11}C]-(+)-PHNO mass dose effect correction, and the BP_{ND} estimates were derived from the same 2TC model using the same ROI segmentation, but involved about 50% more scans. Motion correction was performed in (Searle et al. 2013) by the FBF_{NMI} method and BP_{ND} data points considered as outliers based on a semi-subjective assessment of time stability criterion were removed for the competitive binding analysis. In this work, the reliable motion correction achieved by the proposed GIR_{BP} method avoided the use of a time stability criterion

to remove outlying BP_{ND} values and led to improved occupancy estimates.

7.2.4 Discussion

Here the motion correction performance of the groupwise image registration method based on basis pursuit denoising GIR_{BP} was evaluated on a dopamine D3/D2 receptor clinical occupancy study with *GSK618334*. Reference tissue based pharmacokinetic models that do not require any blood data were used. It had been demonstrated that an improved ability to estimate the efficacy of the drug can be achieved by using GIR_{BP} for reducing motion artefacts without any subjective data selection for improving tracer kinetic analysis or the modelling of competitive binding.

The GIR_{BP} approach incorporates a pharmacokinetic model into the registration process so as to provide additional temporal constraints in the registration process over just spatial image similarity maximisation. The input function for the pharmacokinetic model is derived directly from the tomographic PET data using a reference region and therefore the GIR_{BP} method does not require any arterial blood sampling. The chosen pharmacokinetic model is generic allowing for different compartmental topologies at individual voxels. Furthermore, it is not necessary for the reference region to be devoid of the target biology, as the data can be quantified subsequently, and a region with the fastest kinetics could be used as the reference region. Thus, the method should be generally applicable to dynamic brain PET data (except perhaps when significant metabolite components contribute to the data). Further extension to the deformation motion model could also allow application to dynamic imaging outside the brain.

Performance of the proposed GIR_{BP} method was evaluated using data from a

dopamine D3/D2 receptor occupancy study in humans with [^{11}C]-(+)-PHNO. In the PET data there were different levels of subject motion and a range of signal-to-noise ratios (SNR) due to competitive binding of the drug at varying doses. The performance was assessed directly by visual inspection of the PET data, and indirectly by assessing the inter-subject variability in baseline BP_{ND} , convergence and residuals of the competitive binding modelling, as well as the drug EC_{50} estimation. In addition to the visually improved removal of subject motion, the proposed GIR_{BP} method led to more reliable estimates with reduced variation and bias at baseline BP_{ND} and when modelling competitive binding of *GSK618334* as compared to the conventional FBF_{NMI} method. It also provided estimates of *GSK618334* that were consistent with a previously published study that had employed time-stability check and outlier removal techniques (Searle et al. 2013). These convergent data all provide evidence that the proposed GIR_{BP} method yields improved registration for dynamic PET data. On the study level, it increases the statistical power by reducing the motion-introduced variability, and in practice fewer PET scans would be required to achieve the same outcome parameter precision once the motion correction is accurately conducted using the proposed GIR_{BP} method.

Chapter 8

Discussion and Future Work

8.1 Contributions

The research presented in this thesis contributes to PET motion correction, which is one of the fundamental issues in PET imaging, and provides a novel solution based on groupwise registration with the incorporation of kinetic modelling (spatio-temporal registration). The computational framework is formulated using the generative model of dynamic PET data, and the subject motion and tracer kinetics are estimated iteratively by maximising the likelihood of tomographic PET data. The tracer kinetics are modelled based on the compartment theory. The generic models are implemented in the spatio-temporal registration framework so that the approach is in principle applicable to any tracer. The kinetic parameters are solved using basis functions (spectral analysis (SA) for plasma input and basis pursuit denoising (BP) for reference input) to achieve computational efficiency and robust estimation for the motion correction task. In addition, the simplified tissue compartment model (SRTM), which strictly

constrains the number of kinetic model compartments, as opposed to the generic models which allow undefined compartment number and configuration, is also implemented in the registration framework. The motion correction performance of the kinetics-based spatio-temporal registration is assessed by simulation-based validation. Compared with the alternative dynamic PET registration methods based on solely the image intensity, the proposed methodology significantly reduces the registration error, and can achieve motion correction accuracy at sub-voxel level. Performance of these 3 kinetic models (SA, BP and SRTM) in the motion correction is also compared and discussed. The clinical impact of the improved motion correction performed by the proposed spatio-temporal registration is evaluated in both neurology and oncology studies. It is demonstrated that, on a study level, the variability in the kinetic analysis of the clinical PET data is reduced by conducting motion correction using the proposed method, and this improves the confidence of deriving outcome measures from PET studies and therefore reduces the need for large numbers of costly scans.

8.2 Future directions

In this thesis, the reconstructed [^{11}C]-(+)-PHNO PET data following attenuation correction, which represents a very common clinical workflow, was used. In practice, the continuous subject motion would also introduce intra-frame blurring and mismatch for attenuation correction, which would not be addressed using such an approach. However, the proposed method is readily applicable to non-attenuation corrected PET data to further improve the motion correction performance, as suggested in (Jin et al. 2013). In the image domain the effect of attenuation can be described as a

linear transformation of the image, therefore the application of a linearised kinetic model to the dynamic PET data without attenuation correction is still valid. Spectral analysis and basis pursuit denoising utilised in the proposed framework in this thesis both model the temporal PET data on each voxel as a weighted linear combination of the basis functions, and is thus suitable for attenuated dynamic PET data. With the motion parameters estimated, the attenuation map can be transformed and the PET data can be reconstructed again with improved attenuation alignment. Moreover, the proposed method describes the measured PET data with the underlying tracer kinetics and subject motion. With reconstructed PET data it operates in the image space, and it can be implemented to operate on the LOR data for sinogram or list-mode PET data to account for the intra-frame motion. In the following, the formulation using raw PET data will be presented.

8.2.1 Kinetics based motion correction in PET reconstruction

Formulation of the generative model

Returning to the probability of the system observing counts z given the activity y :

$$p(z|y) = \prod_{i=1}^{N_{det}} \mathcal{P}(\bar{z}_i, z_i) = \prod_{i=1}^{N_{det}} \mathcal{P}\left(\sum_{j=1}^{N_{vox}} \mathbf{P}_{i,j} \bar{y}_j, z_i\right), \quad (8.1)$$

the expected activity $\bar{y}$ can be further expressed by the tracer kinetics and subject motion with the parameter Φ and $\mathbf{T}$. The kinetic parameter Φ varies on spatial positions and the motion function $\mathbf{T}$ varies over time. Denote the coordinate of voxel

j by x_j , and motion function at time t by $\mathbf{T}^{[t]}$, then $\bar{y}_j$ at time t can be expressed as:

$$\bar{y}_j^{[t]} = \Phi(\mathbf{T}^{[t]}(x_j))\mathbf{B}^{[t]}, \quad (8.2)$$

where $\mathbf{B}$ is the matrix of basis functions of time for representing the kinetic activity. Note that Equation 8.2 simplifies the formation of the activity y with respect to the kinetic parameter Φ by ignoring the uncertainties between them, otherwise $\bar{y}$ can be formulated as a Gaussian of unknown parameter conditionally to Φ that $p(\bar{y}_j) = \mathcal{N}(\Phi(\mathbf{T}(x_j))\mathbf{B}, \sigma(\Phi))$.

Then the probability of the system observing counts z given the kinetics Φ and motion $\mathbf{T}$ is

$$p(z|\Phi, \mathbf{T}) = \prod_t p(z^{[t]}|\Phi, \mathbf{T}^{[t]}) = \prod_t \prod_{i=1}^{N_{det}} \mathcal{P}\left(\sum_{j=1}^{N_{vox}} \mathbf{P}_{i,j} \Phi(\mathbf{T}^{[t]}(x_j))\mathbf{B}^{[t]}, z_i^{[t]}\right). \quad (8.3)$$

The system matrix $\mathbf{P}$ and basis functions $\mathbf{B}$ can be predetermined for the reconstruction task. With $\mathbf{P}$ and $\mathbf{B}$, the forward projection can be calculated as the expected photon counts that

$$\bar{z}_i^{[t]} = \sum_{j=1}^{N_{vox}} \mathbf{P}_{i,j} \Phi(\mathbf{T}^{[t]}(x_j))\mathbf{B}^{[t]}. \quad (8.4)$$

Iterative optimisation

To correct subject motion, the goal here becomes to estimate the motion function $\mathbf{T}$. Given the kinetics Φ , $\mathbf{T}$ can be obtained by maximising the partial probability distribution $p(\mathbf{T}|\Phi, z)$.

From Bayes' theorem, it can be written that

$$p(\mathbf{T}|\Phi, z) = \frac{p(z|\Phi, \mathbf{T})p(\mathbf{T}|\Phi)}{p(z|\Phi)}. \quad (8.5)$$

Note that $p(\mathbf{T}|\Phi)$ represents the *a priori* knowledge on $\mathbf{T}$ given that $\mathbf{T}$ is independent of Φ , which can be provided by for example motion tracking. When it is absent, this term can be considered as a constant for estimating $\mathbf{T}$. Also in Equation 8.5, $p(z|\Phi)$ is independent of $\mathbf{T}$. Therefore

$$\hat{\mathbf{T}} := \operatorname{argmax}_{\mathbf{T}} p(\mathbf{T}|\Phi, z) = \operatorname{argmax}_{\mathbf{T}} p(z|\Phi, \mathbf{T}). \quad (8.6)$$

To maximise $p(z|\Phi, \mathbf{T})$, it is algebraically more convenient to use its log. Expanding the log and ignoring the constant gives

$$\log p(z|\Phi, \mathbf{T}) = \sum_t \sum_{i=1}^{N_{det}} \log \mathcal{P}(\bar{z}_i^{[t]}, z_i^{[t]}) \quad (8.7)$$

$$= \sum_t \sum_{i=1}^{N_{det}} (z_i^{[t]} \log \bar{z}_i^{[t]} - \bar{z}_i^{[t]}). \quad (8.8)$$

The motion function $\mathbf{T}$ can be estimated by maximising Equation 8.8 by a gradient-based algorithm. Transferring the dependence on $\mathbf{T}$ from the parameter space to the activity space gives

$$\bar{z}_i^{[t]} = \sum_{j=1}^{N_{vox}} \mathbf{P}_{i,j} \Phi(\mathbf{T}^{[t]}(x_j)) \mathbf{B}^{[t]} = \sum_{j=1}^{N_{vox}} \mathbf{P}_{i,j} \Phi \mathbf{B}^{[t]}(\mathbf{T}^{[t]}(x_j)), \quad (8.9)$$

then the transformation takes place in the image space instead of in the kinetic parameter space. Denote $\mathbf{T}^{[t]}$ as the motion function parameterised by the vector

$\mathbf{q}^{[t]} = [q_1^{[t]} \dots q_r^{[t]} \dots]$. Differentiating Equation 8.8 with respect to the transformation parameters and applying the chain rule, the gradient is:

$$\frac{\partial \log p(z|\Phi, \mathbf{T})}{\partial q_r^{[t]}} = \sum_t \sum_{i=1}^{N_{det}} \left(\frac{z_i^{[t]}}{\bar{z}_i^{[t]}} - 1 \right) \cdot \frac{\partial \bar{z}_i^{[t]}}{\partial q_r^{[t]}} \quad (8.10)$$

$$= \sum_t \sum_{i=1}^{N_{det}} \left(\frac{z_i^{[t]}}{\bar{z}_i^{[t]}} - 1 \right) \cdot \sum_{j=1}^{N_{vox}} \mathbf{P}_{i,j} \frac{\partial \Phi \mathbf{B}^{[t]}(\mathbf{T}^{[t]}(x_j))}{\partial q_r^{[t]}}, \quad (8.11)$$

where

$$\frac{\partial \Phi \mathbf{B}^{[t]}(\mathbf{T}^{[t]}(x_j))}{\partial q_r^{[t]}} = \nabla(\Phi \mathbf{B}^{[t]}(\mathbf{T}^{[t]}(x_j))) \cdot \left(\frac{\partial \mathbf{T}^{[t]}(x_j)}{\partial q_r^{[t]}} \right). \quad (8.12)$$

To update Φ given $\mathbf{T}^{[t]}$, similarly from the Bayesian inference it can be achieved by maximising $\log p(z|\Phi, \mathbf{T})$. If Φ can be determined directly using a gradient-based algorithm, then it becomes a problem of reconstructing the parametric image Φ from counts z with known motion $\mathbf{T}^{[t]}$. It is straightforward to write the derivation:

$$\frac{\partial \log p(z|\Phi, \mathbf{T})}{\partial \Phi} = \sum_t \sum_{i=1}^{N_{det}} \left(\frac{z_i^{[t]}}{\bar{z}_i^{[t]}} - 1 \right) \cdot \frac{\partial \bar{z}_i^{[t]}}{\partial \Phi} \quad (8.13)$$

$$= \sum_t \sum_{i=1}^{N_{det}} \left(\frac{z_i^{[t]}}{\bar{z}_i^{[t]}} - 1 \right) \cdot \sum_{j=1}^{N_{vox}} \mathbf{T}^{[t]}(\mathbf{P}_{i,j}) \frac{\partial \Phi \mathbf{B}^{[t]}(x_j)}{\partial \Phi}, \quad (8.14)$$

where the motion function $\mathbf{T}^{[t]}$ is operating on the system matrix $\mathbf{P}$, so that the emissions are realigned as a result of motion compensation on the scanner.

If Φ needs a specific form of constraint as the basis functions $\mathbf{B}$ are overcomplete to ensure the sufficient coverage of kinetics, then the ordinary gradient-based algorithms might not be directly appropriate for the optimisation. In such a case, Φ can be updated using the intermediate variable $\bar{y}$. Then it becomes a two-step procedure

where firstly $\hat{y} := \operatorname{argmax}_y p(y|z, \mathbf{T})$ and secondly $\hat{\Phi} := \operatorname{argmax}_{\Phi} p(\Phi|y)$. For estimating Φ from the activity y , it is necessary to have rebinned time frames $y^{[t']}$. The first step can be considered as reconstructing the activity from emission events with known motion. Since the motion information is used to modify the system matrix $\mathbf{P}$, therefore the rebinning of counts z into the time series is independent of the timing determined by $\mathbf{T}^{[t]}$, i.e. t' is independent of t . If modifying the system matrix $\mathbf{P}$ by the motion $\mathbf{T}$ is not feasible due to computational issues, $\mathbf{T}$ can be applied on the emission counts z by reprojecting the LORs using $\mathbf{T}$, in this way t' is also independent of t so that the frame timing does not depend on the motion timing. The activity y can be estimated using the EM algorithm for Poisson likelihood, which guarantees the non-negativity of the solution. In the M-step the One Step Late approximation can be adopted to give a closed-form solution. Given y , the kinetic parameter Φ can then be estimated by performing kinetic modelling.

Table 8.1 shows a comparison of the reconstruction with kinetics based motion correction (recon-mc) which is an extension of the work presented in this thesis, the image-based spatio-temporal registration for dynamic PET motion correction (img-mc) which is the work presented in this thesis, and the alternative motion-tracking based motion correction for PET (track-mc), such as with a Microsoft Kinect.

Table 8.1: *Comparison of motion correction methods for PET*

	img-mc	recon-mc	track-mc
need additional devices	no	no	yes
need special lighting	no	no	yes
need calibration	no	no	yes
need synchronisation	no	no	yes
need reconstruction	no	yes	yes
correct attenuation mismatch	possible	yes	yes
correct intra-frame motion	difficult	yes	yes
compatible with a PET/MR scanner	yes	yes	difficult
derive 3D deformable motion field	yes	yes	difficult

8.2.2 The input function for kinetic modelling

This work uses the kinetic model as a constraint for estimating the motion in dynamic PET scan. The kinetic analysis can be considered as determining the system response function by known output and input data. The system is the biological target of

interest in the PET study, and the output data is the measured PET activity in the subject. The input data is the measured PET activity in the plasma and can be replaced by the activity in a reference region. The measurement of plasma input from blood samples is invasive and sometimes infeasible, and the reference region does not exist for a variety of biological targets. This motivates the elimination of the input function for modelling tracer kinetics for the registration task. To impose a constraint on the activity data, the kinetic model does not have to quantify the system response function and instead, it gives a description of the expected activity. For this purpose, it is possible to use an input function that is not directly measured from the plasma activity but can describe the response activity well.

To find the suitable substitute for the measured plasma input function, there have been approaches proposed that extract the blood/plasma input function from the measured PET data in the subject, based on the assumption that the blood/plasma activity is measured by the PET scanner, either in an artery that can be segmented in the image or as an activity component in all the voxels. However, such image-based plasma input extractions are sensitive to the signal-to-noise ratio, motion artefacts, and the partial volume effect in the PET image and therefore have limited accuracy. Alternative methods consider the input function unknown, and estimate it together with the system response function from several output signals. These methods require the output signals to be "orthogonal" enough to determine the input function, which may not be the case, e.g. for a tracer that has less various kinetics.

Potential approaches to provide the input function for kinetics based registration may involve employing a population plasma input function and the incorporation of a mathematical model for the plasma input.

8.2.3 Complex motion and multi-modal estimation

In this work, the subject motion has been considered as rigid. For neurological PET studies the head motion during a dynamic PET scan is rigid. However for other applications, such as in oncology and cardiology, the tissues and organs can exhibit more complicated movements which may require a nonrigid deformation model. In Sec. 6.4 it has been demonstrated that for solid breast tumours when the regional analysis is conducted instead of the voxel-by-voxel analysis, the motion correction for the rigid misalignment is sufficient for improving the outcome measure estimation of the study. This is because the extraction of the tumour's time activity as a whole is affected by the global translation and rotation of the tumour due to the body motion but not the local deformation inside the tumour. In (Grgic et al. 2011) it is also found that using nonrigid motion models will not improve the regional analysis of FDG uptake in lung cancer. However if the analysis is to study the local kinetics within the tumour or an organ (such as the heart), only the rigid motion model will not be appropriate.

Given the low SNR and spatial resolution (compared to MRI and CT), the dynamic PET data may not allow for nonrigid motion estimation. In addition the partial volume effect imposes challenges for estimating the local deformations on the tumour or the organ boundary. Therefore nonrigid motion correction for dynamic PET data may require further information for determining a large number of parameters in the deformable motion model. Recently, based on the development of hybrid PET-MR scanner, nonrigid motion correction approaches (Chun et al. 2012; Grimm et al. 2013) have been proposed using the MRI images acquired simultaneously with the PET data to derive the nonrigid motion. For such multi-modal imaging, the

kinetics based registration framework proposed in this work can be readily extended to account for the complementary image data. A joint generative model can be used to formulate the likelihood function of the observed PET data and, for example, the MRI data, in which the subject motion and tracer kinetics are unknown parameters, determined by maximising the likelihood. From the logarithm of the joint probability it can be seen that the image data from another modality will be added to the tracer kinetic term, therefore provide additional constraint for estimating the nonrigid motion parameters.

8.2.4 Investigation of the parametric maps derived from the motion correction framework

In practice the outcome measures of interest could be derived directly from the kinetic model employed in the GIR method. However, within this work we have chosen to employ previously identified parsimonious compartmental models to subsequently derive the parameter values. In future work, it would be interesting to compare the results obtained by the GIR employed kinetic models (i.e. spectral analysis and basis pursuit denoising in this work) with those from the particular compartmental models. It will be necessary to investigate the bias and variance of these parameters to determine whether the basis function methods provide a viable one-stop-shop in terms of registration and modelling.

List of publications and presentations

PUBLICATIONS

- **Jiao, J.**, Searle, G.E., Schnabel, J.A., Gunn, R.N.: Groupwise Image Registration for Improved Motion Correction of dynamic PET data and its Impact on Receptor Occupancy Studies. *Journal of Cerebral Blood Flow & Metabolism* (under review)
- **Jiao, J.**, Searle, G.E., Tziortzi, A.C., Salinas, C.A., Gunn, R.N., Schnabel, J.A.: Spatio-temporal pharmacokinetic model based registration of 4D PET neuroimaging data. *NeuroImage* (2013)
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- Oral presentation at **The XXVIth International Symposium on Cerebral Blood Flow, Metabolism and Function & XIth International Conference on Quantification of Brain Function with PET**, Shanghai, China, 21 May 2013. (**ISCBFM Young Investigator Travel Bursary**)
- Oral presentation at **MICCAI 2012 Workshop on Spatiotemporal Image Analysis for Longitudinal and Time-Series Image Data**, Nice, France, 1 October 2012. (**Guarantors of Brain Student Grant**)
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